Randomized Clinical Trial Comparing Breath-Enhanced to Conventional Nebulizers in the Treatment of Children with Acute Asthma

Mike A. Gardiner, MD[1], and Matthew H. Wilkinson, MD, MPH[2]

Objective To compare the efficacy of a breath-enhanced and a conventional jet nebulizer in the treatment of children with moderate to severe acute asthma.

Study design We enrolled subjects between 6 and 18 years of age presenting to the emergency department (ED) with acute asthma and an initial forced expiratory volume in 1 second (FEV_1) <70% of predicted. We excluded patients with chronic disease, who required immediate resuscitation, or failed spirometry. Subjects were randomized to breath-enhanced or conventional jet delivery of a 5-mg albuterol treatment. Our primary outcome was change in FEV_1, and secondary outcomes included change in clinical asthma scores, ED length of stay, disposition, and side effects. Student *t* test and multivariable linear regression were used to evaluate the primary outcome.

Results In total, 497 patients were assessed for eligibility with 118 enrolled and 107 subjects available for analysis of the primary outcome. Improvement in FEV_1 was significantly greater with conventional jet nebulizer (mean ΔFEV_1 +13.8% vs +9.1%, $P = .04$). This difference remained significant after adjustment for baseline differences. Subgroup analysis of 57 subjects with spirometry meeting American Thoracic Society/European Respiratory Society guidelines yielded similar results (mean ΔFEV_1 +14.5% vs +8.5%, $P=.03$). There were no significant differences in clinical asthma scores, ED length of stay, disposition, or side effects.

Conclusions Albuterol delivered via conventional jet nebulizer resulted in significantly greater improvement in FEV_1 than albuterol delivered by breath-enhanced nebulizer, without significant differences in clinical measures. Conventional jet nebulizers may deliver albuterol to children with acute asthma more effectively than breath-enhanced nebulizers. *(J Pediatr 2018;■■:■■-■■).*

Trial registration ClinicalTrials.gov: NCT02566902.

Asthma exacerbations are among the most frequent reasons for children to visit the emergency department (ED).[1] Current standard of care treatment of acute asthma includes administration of an inhaled short acting β_2-agonist, systemic glucocorticoids, and correction of hypoxemia.[2] Although it has long been accepted that the use of inhaled short acting β_2-agonist is efficacious, there have been efforts to develop more effective and efficient means of delivering aerosolized medications.

Breath-enhanced nebulizers are one of several new technology nebulizers designed to more effectively deliver aerosolized medication. Breath-enhanced nebulizers continuously nebulize medication into a holding chamber, using a system of 1-way valves to direct exhaled air away from the holding chamber. This design minimizes medication loss upon exhalation and allows delivery of a bolus dose of nebulized aerosol.[3-5] Although breath-enhanced nebulizer studies on in vitro lung models and healthy adult subjects have demonstrated improved lung deposition of aerosol,[3-8] study in children with acute asthma is lacking. To our knowledge, only 1 prior study has evaluated breath-enhanced nebulizers in pediatric patients with acute asthma.[9] This study demonstrated that a breath-enhanced treatment algorithm was noninferior to a conventional jet algorithm, however, was limited by small sample size and did not evaluate spirometry data.

We performed a prospective blinded-observer randomized clinical trial to test the hypothesis that the use of a breath-enhanced nebulizer for albuterol delivery leads to a greater improvement in forced expiratory volume in 1 second (FEV_1) than use of a conventional jet nebulizer in children presenting to a pediatric ED with a moderate to severe acute asthma exacerbation. Prior to implementation into practice, this study of breath-enhanced nebulizers was necessary to evaluate

ATS	American Thoracic Society
ED	Emergency department
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second
MDI	Metered-dose inhaler
PAS	Pediatric Asthma Score
PASS	Pediatric Asthma Severity Score

From the [1]Department of Pediatrics, University of California, San Diego, Rady Children's Hospital—San Diego, La Jolla, CA; and [2]Department of Pediatrics, University of Texas at Austin, Dell Children's Medical Center of Central Texas, Austin, TX

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whether they provide improved bronchodilation compared with less expensive conventional jet nebulizers.

Methods

This study was performed as a blinded-observer randomized clinical trial at a large urban pediatric ED with an annual volume of approximately 80 000 visits. The study was approved by the hospital's Institutional Review Board and registered on www.clinicaltrials.gov (NCT02566902). We enrolled a convenience sample of children with physician-diagnosed asthma, age 6 and 18 years with English or Spanish speaking guardian(s), presenting to the pediatric ED with symptoms of acute asthma, objective signs of acute asthma (pediatric asthma score >0), and an FEV_1 less than 70% predicted on initial spirometry (moderate to severe asthma exacerbation).[2,10,11] Potential subjects were excluded if they were unable to perform initial spirometry, had chronic diseases other than asthma, required immediate resuscitation at the discretion of the treating physician, received albuterol in the ED prior to enrollment, or if there were not 2 available study personnel at the time of ED arrival.

Written informed consent and Health Insurance Portability and Accountability Act authorization were obtained from each subject's parent or guardian, and written assent was obtained from all subjects aged seven years or older. This study received funding from a small institutional grant, which was used for purchase of study supplies.

Potential subjects were identified and enrolled at the time of ED triage, prior to administration of albuterol in the ED. Enrolling study personnel remained blinded to group allocation throughout the study (blinded-observer) and were responsible for data collection. At the time of enrollment baseline spirometry measurement, initial vital signs, and clinical asthma severity were recorded. Clinical asthma severity was assessed using 2 previously validated clinical asthma scores, the Pediatric Asthma Score (PAS) and Pediatric Asthma Severity Score (PASS) (**Appendix 1**; available at www.jpeds.com).[12,13] Study subjects were randomized to receive treatment with either the experimental (breath-enhanced) or control (conventional jet) nebulizer. A parallel study design with 1:1 group allocation was used. A second unblinded member of the study team revealed group allocation by opening a pre-assigned study box containing either the control or experimental nebulizer and administered a 5-mg nebulized albuterol treatment to the subject via the provided nebulizer. Ten minutes following completion of the study treatment, the blinded enrolling study personnel completed a post-treatment assessment of the subject including spirometry, vital signs, clinical asthma severity, and treatment side effects. Subjects who required further treatment were released to standard of care treatment at the discretion of the treating emergency physician, with further treatments delivered by conventional jet nebulizer. This single-treatment study design was chosen to allow for equal treatments to all subjects regardless of whether they only required a single ED treatment, or several treatments and hospital admission. In addition, there was concern that if the breath-enhanced nebulizer led to greater lung deposition, that larger or repeated doses of albuterol delivered by breath-enhanced nebulizers may result in unacceptable side effects.

Patients randomized to the breath-enhanced group received therapy with a NebuTech HDN, Breath-Enhanced High-Density Jet Nebulizer (Salter Labs, Arvin, California) via mouthpiece. Patients randomized to the conventional jet arm received therapy with a Hudson RCI Micro Mist nebulizer (Teleflex Medical, Research Triangle Park, New Jersey) via mouthpiece. Both study arms received 5-mg nebulized albuterol diluted to 3.5 mL with 0.9% normal saline. Nebulizers were attached to wall oxygen at a flow rate of 8 liters per minute and treatment was continued until solution was completely nebulized. Steroid administration and other therapies were used per ED protocol at treating physician discretion and were not included as a part of study protocol.

Computerized 1:1 randomization was completed prior to the start of the study. Blinding of the enrolling personnel was accomplished by creating identical opaque study boxes for each subject, labeled only with the subject identification, prior to the start of the study. These boxes contained the subject's pre-assigned nebulizer (breath-enhanced or conventional jet) and were only opened by the study personnel administering study medication. Boxes were created and sealed by a participant not otherwise involved with the study and maintained in a locked office and until the time of randomization so as to not reveal group allocation until the time of enrollment. Study boxes were identical in appearance and had similar weight regardless of nebulizer type contained. Adequacy of blinding was assessed after study completion by asking the blinded study personnel to predict which nebulizer was used and comparing this prediction with the assigned study arm by χ^2 analysis.

Study personnel consisted of pediatric emergency medicine fellows and attending physicians, with 1 research nurse who was trained on study enrollment. All study personnel underwent a training session detailing consent and enrollment for this study. As a part of this training, proper spirometry technique and methods for encouraging spirometry effort were reviewed, with all personnel required to demonstrate the ability to perform beside spirometry and medication administration prior to being cleared for participation.

Spirometry was performed in the ED with a handheld spirometer (ndd EasyOne Plus, ndd Medical Technologies, Inc, Andover, Massachusetts). This spirometer has been previously validated compared with formal spirometry in adult subjects.[14] In keeping with the most recent American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines, participants performed a minimum of 3 and maximum of 8 forced expiratory maneuvers to obtain 1-3 adequate samples.[15] FEV_1 calculation was performed by the spirometer based on National Health and Nutrition Examination Survey III study data.[10] The highest recorded FEV_1 was used for analysis. Adequacy of spirometry maneuvers was assessed by the spirometer which provided letter grades A-F based on acceptability of maneuvers (**Appendix 2**; available at www.jpeds.com). For the purposes of this study, grades A-D were deemed adequate for enrollment. This acceptability range was chosen

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to include all subjects able to perform at least 1 acceptable maneuver. Subjects with pre and post-treatment spirometry of grades A or B met stricter ATS/ERS guidelines for acceptable spirometry and were evaluated by subgroup analysis. Spirometry attempts were deemed subjectively unacceptable by study personnel if the subject demonstrated immediate cough, glottis closure, significant leak, mouthpiece obstruction, or early termination of exhalation.

The primary outcome measure was improvement in FEV_1 as measured by absolute improvement in percent of predicted. Measurement of FEV_1 has been used throughout prior asthma literature as a reliable measure of airway obstruction and effectiveness of treatment in patients with acute asthma.[16-19] FEV_1 measurement has been recommended by the National Heart, Lung, and Blood Institute as a means of assessing the degree of airway obstruction, and response to therapy in acute asthma.[2] Secondary outcomes included change in asthma severity scores (PAS and PASS), ED length of stay, admission rate, and side effects.

By evaluating data from previously performed studies,[16-18,20] a sample size calculation was performed with a 2-sided α of 0.05, β of 0.20. With the assumptions that control group would experience an absolute improvement in FEV_1 of 10% predicted, with a standard deviation of 10% predicted, it was calculated that 128 subjects with adequate spirometry would be needed to detect an improvement differential of 5% of predicted between treatment arms.

Treatment groups were analyzed on an intention-to-treat basis. The primary outcome of change in FEV_1 was analyzed using a 2-tailed Student *t* test. A multivariable linear regression model was used to assess for the potential confounding effect of differences in baseline demographic and illness characteristics on the primary outcome. Our regression model was created using purposeful variable selection with an entry criterion of $P < .2$ and $P < .05$ required for final model retention. Changes in clinical asthma scores were evaluated by Mann-Whitney U test, admission rate and medication side effects by χ^2 or Fisher exact tests, and ED length of stay by 2-tailed Student *t* test. All statistical analyses were performed using STATA 15 (StataCorp LLC, College Station, Texas).

Results

Subjects were enrolled over a 20-month period from October 2015 to May 2017 at which time the principal investigator changed institutions and study was stopped. In total, 497 potential subjects were screened for eligibility. Of those screened, 118 subjects met inclusion criteria and were randomized. Of these subjects, 107 were analyzed for the primary outcome and 115 subjects analyzed for secondary outcomes (**Figure**; available at www.jpeds.com). The baseline demographics and characteristics of the acute asthma episode are detailed in **Table I**. Subjects in the breath-enhanced arm were less commonly male, had lower baseline asthma severity, received more albuterol in the 24 hours prior to arrival to the ED, and had a lower proportion of subjects who had received oral steroids prior to ED arrival. The 2 groups were otherwise similar.

Table I. Baseline characteristics at study enrollment

Variables	Conventional jet	Breath-enhanced
Number analyzed, total no (1° outcome)	58 (55)	57 (52)
Age, y, mean (SD)	9.8 (2.6)	10.1 (3.0)
Sex, male, no (%)	37 (63.8)	27 (47.4)
Baseline severity, no (%)		
Mild intermittent	20 (34.5)	27 (47.4)
Mild persistent	11 (19.0)	12 (21.0)
Moderate persistent	20 (34.5)	14 (24.6)
Severe persistent	7 (12.0)	4 (7.0)
Ethnicity, no (%)		
Hispanic	30 (51.7)	33 (57.9)
African American	25 (43.1)	21 (36.8)
Caucasian	3 (5.2)	3 (5.3)
Weight, kg, mean (SD)	39.5 (16.4)	41.1 (16.5)
BMI, mean (SD)	19.7 (5.7)	19.7 (5.0)
Duration of symptoms, d, median (IQR)	2 (1-3)	2 (2-3)
Albuterol last 24 h, doses, median (IQR)	2 (0-4)	4 (2-6)
Nebulized, doses	0 (0-1)	1 (0-3)
MDI, doses	1 (0-2.75)	2 (2-4)
Pre-arrival steroids, no (%)	8 (13.8)	2 (3.5)
ED steroids prior to study treatment, no (%)	37 (63.8)	38 (66.7)
Initial RR, breaths/min, mean (SD)	28.1 (9.4)	28.9 (7.6)
Initial O_2, % saturation, mean (SD)	96.0 (2.1)	95.7 (2.6)
Initial PAS score, median (IQR)	4 (3-5)	4 (2-5)
Initial PASS score, median (IQR)	2 (2-3)	2 (1-3)
Initial FEV_1, % predicted, mean (SD)	39.4 (13.4)	42.0 (14.8)

BMI, body mass index; *O_2*, oxygen saturation; *RR*, respiratory rate.

Three subjects were erroneously enrolled and randomized who did not meet the predefined inclusion and exclusion criteria (**Figure**). In the breath-enhanced group, 1 subject had an initial FEV_1 >70% of predicted, and in the conventional jet group 1 subject had an initial FEV_1 >70% of predicted, and another had been previously enrolled in this study. As these subjects objectively did not meet our enrollment criteria, they were excluded from the intention-to-treat analysis.[21]

Results for primary and secondary outcomes are detailed in **Table II**. Analysis of changes in FEV_1 demonstrated that subjects treated with the control conventional jet nebulizer had a statistically significantly greater improvement in FEV_1 than those treated with the breath-enhanced nebulizer (mean ΔFEV_1 +13.8% vs +9.1% of predicted, $P = .04$). This difference between groups remained statistically significant after multivariable linear regression ($P = .02$). All variables in **Table I** were evaluated for entry into the model and only initial respiratory rate ($P = .01$), asthma severity prior to acute exacerbation ($P = .05$), and steroid administration prior to ED arrival ($P = .001$) showed statistical significance and were retained in the final model. Subgroup analysis of the 57 subjects who met ATS/ERS spirometry guidelines showed a similar difference between groups (mean ΔFEV_1 +14.5% vs +8.5% of predicted, $P = .03$). There were no significant differences between groups in secondary outcomes including changes in PAS ($P = .29$), PASS ($P = .97$), ED length of stay ($P = .99$), or admission rate ($P = .96$). Observed side effects were nausea, vomiting, headache, dizziness, palpitations, tremor/shakiness, and weakness. These side effects were all transient and were not statistically different between groups. Assessment of blinding revealed no significant

Table II. Results for primary and secondary outcomes

Outcomes	Conventional jet n = 58*	Breath-enhanced n = 57†	*P* value
Δ FEV_1, % predicted, mean (95% CI)	13.8 (10.5-17.2)	9.1 (6.1-12.1)	.04
Δ FEV_1 (ATS/ERS‡), % predicted, mean (95% CI)	14.5 (10.2-18.7)	8.5 (5.5-11.4)	.03
Δ PAS score, median (IQR)	−1 (−2 to −1)	−2 (−2 to −1)	.29
Δ PASS score, median (IQR)	−1 (−1 to 0)	−1 (−1 to 0)	.97
ED length of stay, min, mean (95% CI)	246.3 (220.4-272.3)	246.2 (220.4-272.0)	.99
Admission rate, % (95% CI)	19.0 (10.6-31.5)	19.3 (10.8-32.0)	.96
Side effects, % (95% CI)	8.6 (3.5-19.5)	8.8 (3.6-19.9)	1.00

*n = 55 for primary outcome, n = 31 for Δ FEV_1 (ATS/ERS).
†n = 52 for primary outcome, n = 26 for Δ FEV_1 (ATS/ERS).
‡Spirometry meeting ATS/ERS Guidelines.[16]

association between predicted and actual group allocation ($P = .54$).

Discussion

In this blinded-observer, randomized clinical trial, we demonstrated that in children aged between 6 and 18 years with moderate to severe acute asthma, albuterol delivered with a conventional jet nebulizer resulted in greater improvement in FEV_1 than an equal treatment delivered by a breath-enhanced nebulizer. There were no observed differences in secondary outcomes between groups including changes in clinical asthma severity scores. These results may indicate that in this patient population, a breath-enhanced nebulizer may not deliver albuterol as effectively as a conventional jet nebulizer. Strengths of this study include the larger sample size than prior studies, the equal treatment of the 2 groups, and successful blinding of assessors.

The findings in this study are contrary to what has been demonstrated in breath-enhanced studies using lung models and healthy adult controls.[3-8] One potential explanation may be the mouthpiece design of the breath-enhanced nebulizer as it relates to the breathing pattern of children with acute asthma. The breath-enhanced mouthpiece separates the subject from the aerosol holding chamber, leaving a small volume of exhaled air that does not contain aerosol (dead-space). This dead-space volume is the first air inhaled by the subject with each breath. Although this dead-space volume is small in comparison with a healthy adult's inspiratory volume, it may be more important in children with acute asthma. Pediatric patients with moderate to severe bronchoconstriction typically demonstrate a rapid and shallow breathing pattern. It is possible that children in this setting gain benefit from the cloud of aerosolized albuterol that is continuously created by the conventional jet nebulizer and that the dead-space of the breath-enhanced nebulizer is more impactful in this patient population.

We identify several potential limitations of our study. The failure to demonstrate changes in secondary outcomes including clinical asthma scores, ED length of stay, and admission rates is likely related to the study design involving a single 5-mg albuterol treatment. This design gave us a clean comparison of the effect of a single albuterol treatment on spirometry measurements, though may limit the applicability of these results to clinical practice where multiple treatments and larger doses are typically utilized. Likewise, this study was not powered to address these secondary outcomes, and a larger sample size may be needed to evaluate these outcomes. Although we anticipate that the greater bronchodilation demonstrated by the conventional jet nebulizer group in this study would translate to improved or noninferior clinical outcomes in a larger study using multiple treatments, this cannot be determined from our data.

Although we effectively blinded the study personnel responsible for subject enrollment and assessment, a potential source of bias is the lack of blinding of parents, subjects, and study personnel delivering nebulized albuterol. We do not suspect that the majority of parents or subjects knew the difference between nebulizers and, if present, we would expect this potential bias to favor the newer technology breath-enhanced nebulizer.

In our study protocol, we administered albuterol without the addition of ipratropium bromide, it is unclear how the results of this study would be altered with the inclusion of ipratropium bromide. Likewise, the post-treatment assessment was performed 10 minutes following treatment completion. This time was chosen to minimize study-related delays for children requiring further treatment, though may have given inadequate time for complete bronchodilation. It is uncertain how a longer observation period would impact our results.

Although we attempted to account for spirometry effort through utilization of subjective assessment by study personnel and the spirometer's grading of curves, the encouragement and determination of spirometry effort in children proved difficult throughout the study. This was especially true of younger children. It is possible that variable spirometry effort may have impacted our results.

The clinical asthma pathway at our institution does not include metered-dose inhaler (MDI) albuterol in the ED, and all albuterol treatments are delivered by nebulizer. As such, conventional jet nebulizer was chosen as the control group for this study. We appreciate that MDIs have been demonstrated as noninferior to jet nebulizers,[16,17,20,22-24] and that there are EDs that use MDI albuterol regularly. It is unclear from these results how breath-enhanced nebulizers compare with MDIs and further study would be needed to address this.

Finally, this was a single-center trial performed at an urban tertiary care children's hospital with a large proportion of Hispanic subjects. The results of this study may not be generalizable to other clinical settings or different patient populations.

In conclusion, the results of this study indicate that breath-enhanced nebulizers may be less effective at delivering aerosol to pediatric patients with moderate to severe acute asthma compared with conventional jet nebulizers. Although this study was

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not designed to include a formal cost analysis, the less expensive conventional jet nebulizers provided greater improvement in FEV_1 with no difference in clinical outcomes. Given our findings and currently available data, we cannot recommend the use of breath-enhanced nebulizers as a replacement for conventional jet nebulizers. ■

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Reprint requests: Mike A. Gardiner, MD, Department of Pediatrics, University of California, San Diego, Rady Children's Hospital—San Diego, La Jolla, CA. E-mail: magardiner@ucsd.edu

Data Statement

Data will be made available on request.

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Appendix 1

Clinical asthma scores

PAS

categories	Definition	0	1	2
RR	Respiratory rate (30 s rate × 2)			
	6-12 y	≤26	27-30	≥31
	>12 y	≤23	24-27	≥28
O_2	Oxygen requirement (on RA × 2 min)	>95% RA	90%-95% RA	<90% RA
Appearance	Auscultation	Clear breath sounds to end expiratory wheeze only	Expiratory wheezes	Inspiratory and expiratory wheeze or diminished breath sounds
Work of breathing	Nasal flaring Suprasternal, intercostal, or subcostal muscle use	≤1 accessory muscle	2 accessory muscles	≥3 accessory muscles
Dyspnea		Speaks full sentences	Speaks partial sentences	Speaks short phrases, single words, grunting

PASS

clinical findings	Definition	0	1	2
Wheezing	High-pitched expiratory sound heard by auscultation	None or mild	Moderate	Severe wheezing or absent wheezing because of poor air exchange
Work of breathing	Observed use of accessory muscles or retractions	None or mild	Moderate	Severe
Prolongation of expiration	Ratio of duration of expiration to inspiration	Normal or mildly prolonged	Moderately prolonged	Severely prolonged

O_2, oxygen saturation; *RA*, room air; *RR*, respiratory rate.

Appendix 2

Spirometry grading criteria*

A	A: At least 3 acceptable tests AND the difference between the best 2 FEV_1 and FVC values is equal to or less than 100 mL (80 mL if FVC <1.0L)
B	At least 3 acceptable tests AND the difference between the best 2 FEV_1 and FVC values is equal to or less than 150 mL (100 mL if FVC <1.0L)
C	At least 2 acceptable tests AND the difference between the best 2 FEV_1 and FVC values is equal to or less than 200 mL (150 mL if FVC <1.0L)
D	At least 2 acceptable trials but the results are not reproducible OR only 1 acceptable trial
F	No acceptable test available

FVC, forced vital capacity.
*Reproduced from ndd EasyOne Plus Operator's Manual, ndd Medical Technologies, Inc, Andover, Massachusetts.

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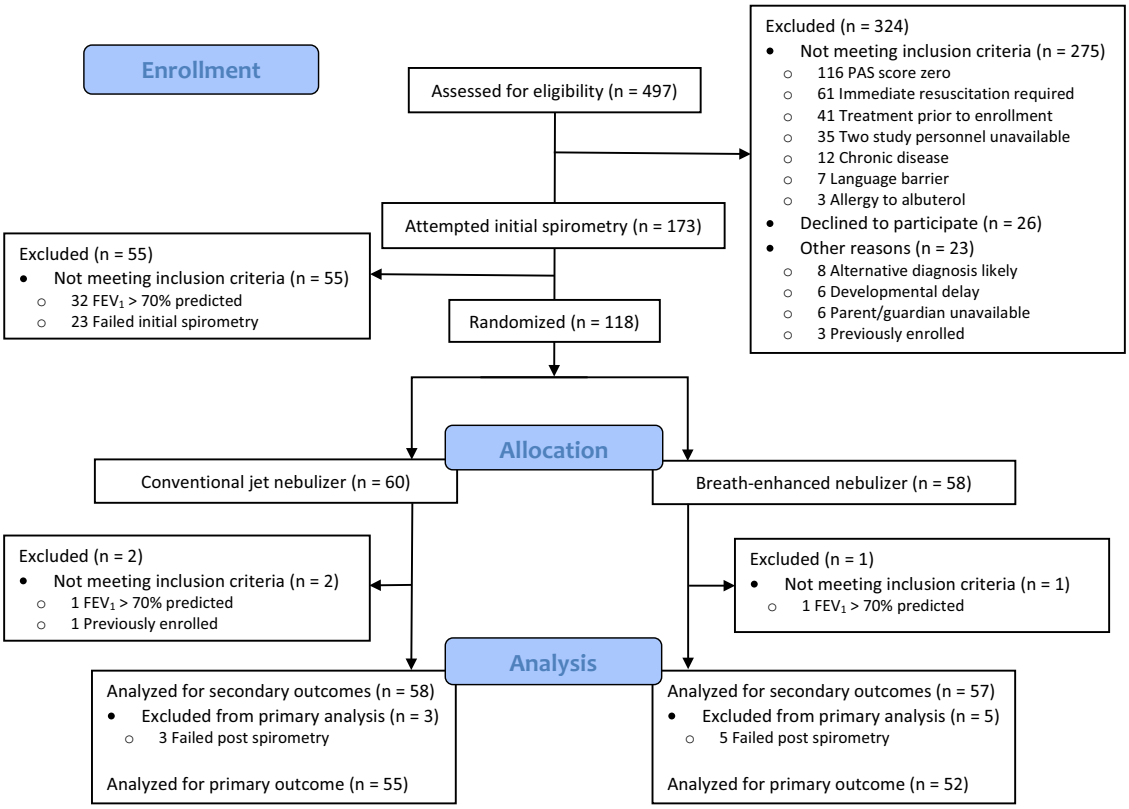

Figure. CONSORT flow diagram.