

Letters

RESEARCH LETTER

Clinical Outcomes After Bilevel Positive Airway Pressure Treatment for Acute Asthma Exacerbations

Guidelines for the management of acute asthma exacerbations recommend noninvasive ventilation as an “experimental approach for treatment of respiratory failure due to severe asthma exacerbation.”^{1(p398)} Clinicians in our tertiary pediatric emergency department have the option to use bilevel positive airway pressure (BiPAP) as treatment for children with asthma exacerbations who have no signs of respiratory failure. We sought to examine whether these patients have improved clinical outcomes.

Methods | The study protocol was approved by the institutional review board of Vanderbilt University. Written informed consent was obtained from the parents and verbal assent from the participants. We performed a secondary analysis of data (which were not deidentified) from a prospective observational study of 933 children and adolescents aged 5 to 17 years who were admitted to our pediatric emergency department with acute asthma exacerbations. The objective of the

parent study was to develop a clinical prediction rule for acute asthma exacerbations.² For each participant, we performed a comprehensive pulmonary examination and calculated the Acute Asthma Intensity Research Score (AAIRS) before treatment.³ The clinical team was not provided with the results of the pulmonary examination or the AAIRS.

Our primary predictor variable was BiPAP treatment (yes or no) among participants who did not have signs of respiratory failure.¹ Outcomes included hospital admission, admission to the pediatric intensive care unit (PICU), hospital length of stay, and time to spacing of albuterol inhalation to every 4 hours (hereinafter referred to as time to albuterol Q4h) (a metric of exacerbation resolution) based on severity scoring by respiratory therapists.

Individual clinicians may, for a given patient, have different preferences for use of BiPAP treatment and different likelihoods for hospital or PICU admission. These preferences may result in confounding by indication, in which BiPAP-treated patients have a risk for relevant outcomes dependent on non-independent clinician characteristics. Estimating associations of BiPAP treatment with these outcomes in multivariable regression models may not adjust for this confounding.

Table 1. Characteristics of 933 Participants Aged 5 to 17 Years With Acute Asthma Exacerbations in a Pediatric Emergency Department

Characteristic	BiPAP Treatment Status ^a		P Value
	Treated (n = 45)	Not Treated (n = 888)	
Age, median (IQR), y	8.3 (6.9-10.7)	8.8 (6.9-11.2)	.48 ^b
Male sex	29 (64.4)	540 (60.8)	.63 ^c
Race			
African American	31 (68.8)	520 (58.5)	.003 ^c
White	12 (26.7)	363 (40.9)	
Other	2 (4.4)	5 (0.6)	
Hispanic ethnicity ^d	1 (2.2)	67 (7.5)	.18 ^c
Medicaid insurance	30 (66.7)	556 (62.6)	.73 ^c
Prior PICU admission for asthma	18 (40.0)	185 (20.8)	.002 ^c
Prior respiratory failure owing to asthma	3 (6.7)	39 (4.4)	.47 ^c
AAIRS before treatment, median (IQR) ^e	9 (7-10)	5 (1-8)	<.001 ^b
Clinician deciding whether to use BiPAP			
PEM physician	31 (68.9)	415 (46.7)	.02 ^c
EM physician	4 (8.9)	250 (28.2)	
PEM fellow or EM chief resident	8 (17.8)	168 (18.9)	
Nurse practitioner	2 (4.4)	55 (6.2)	
Disposition decision of clinical team			
Hospital admission	43 (95.6)	172 (19.4)	<.001 ^c
PICU admission ^f	24 (53.3)	27 (3.0)	<.001 ^c
Hospitalized participants			
Length of stay, median (IQR), d	41 (20-47)	31 (19-43)	.10 ^b
Time to albuterol sulfate Q4h, median (IQR), h ^g	10 (6-19)	7 (3-13)	.06 ^b
Respiratory failure	0	0	NA

Abbreviations: AAIRS, Acute Asthma Intensity Research Score; BiPAP, bilevel positive airway pressure; EM, emergency medicine; IQR, interquartile range; NA, not applicable; PEM, pediatric emergency medicine; PICU, pediatric intensive care unit; Q4h, every 4 hours.

^a Unless otherwise indicated, data are expressed as number (percentage) of patients.

^b Calculated using the Wilcoxon rank sum (2-sample) test.

^c Calculated using the Pearson test.

^d Defined according to the National Institutes of Health Policy on Reporting Race and Ethnicity Data release NOT-OD-01-053.

^e Scores ranging from 1 to 6 indicate mild; 7 to 11, moderate; and 12 to 16, severe.

^f Also included in the hospital admission category.

^g Indicates time to spacing of albuterol inhalation to Q4h (a metric of exacerbation resolution).

Table 2. Adjusted Associations of BiPAP Treatment With Clinical Outcomes Assessed Using Propensity Score Matching and Propensity Score-Adjusted Multiple Regression Analyses in Participants With Acute Asthma Exacerbations

Outcome	Propensity Score Matching (1:3) ^a			Propensity Score-Adjusted Multiple Regression Models (n = 933)	
	BiPAP Treatment Status		P Value	Adjusted OR (95% CI) ^b	P Value
	Treated (n = 45)	Not Treated (n = 135)			
Disposition decision of clinical team, No. (%)					
Hospital admission	43 (96)	19 (42)	<.001	48.1 (11.1-208.0) ^c	<.001
PICU admission ^d	24 (53)	3 (7)	<.001	15.0 (6.9-32.8) ^c	<.001
Hospitalized participants, median (IQR), d ^e					
Length of stay	41 (20-47)	40 (32-42)	.90	1.3 (0.7-2.5) ^g	.46
Time to albuterol sulfate Q4h, median (IQR), h ^f	10 (6-19)	11 (6-16)	.30	1.4 (0.8-2.7) ^g	.25

Abbreviations: BiPAP, bilevel positive airway pressure; OR, odds ratio; PICU, pediatric intensive care unit; Q4h, every 4 hours.

^a Analyzed using conditional logistic regression for binary and proportional odds mixed models for continuous outcomes.

^b Calculated for outcome after BiPAP treatment, adjusted for propensity score, age, sex, race, and pretreatment Acute Asthma Intensity Research Score.

^c Analyzed using logistic regression models.

^d Also included in the hospital admission category.

^e Includes 43 participants treated and 62 participants not treated with BiPAP.

^f Indicates time to spacing of albuterol inhalation to Q4h (a metric of exacerbation resolution).

^g Analyzed using ordinal logistic regression models owing to skewness of these outcome variables; adjusted ORs are for a 1-hour increase in time for outcome of interest.

To adjust for confounding by indication, we used propensity scoring that fitted a multiple regression model, with BiPAP treatment as the dependent variable.⁴⁻⁶ Model predictors included the following covariates that might influence clinician decisions for BiPAP treatment: the individual pretreatment AAIRS components, age, sex, race, Hispanic ethnicity (per the National Institutes of Health Policy on Reporting Race and Ethnicity Data release NOT-OD-01-053, defined by the parent), symptom duration, prior PICU admission for asthma, prior respiratory failure due to asthma, insurance type, and clinician type deciding whether to use BiPAP treatment. The output of this model was a propensity score ranging from 0 to 1 that estimated the adjusted probability of being treated with BiPAP.

We then performed propensity score-matching analysis in which BiPAP-treated participants were matched 1:3 by the propensity score with participants not treated with BiPAP, without replacement. We also fitted multiple regression models adjusted for the propensity score and other covariates to examine adjusted associations of BiPAP treatment with each outcome of interest.

Results | Characteristics and univariate associations for the 933 participants are displayed in **Table 1**. The median AAIRS in participants treated with BiPAP (n = 45) indicated episodes of moderate severity; the median AAIRS in those not treated with BiPAP (n = 888) indicated episodes of mild to moderate severity. No participant had signs of respiratory failure. The propensity score model yielded a C statistic of 0.895, and the matched groups were very well balanced on the covariates. Results of propensity score matching and propensity score-adjusted multivariable regression models are presented in **Table 2**. Those participants treated with BiPAP were more likely to be admitted to the hospital or to the PICU and did not differ in length of stay or time to albuterol Q4h.

Discussion | Our results indicate that BiPAP treatment of children and adolescents with acute asthma exacerbations who have no signs of impending respiratory failure is associated with a greater likelihood of hospital and PICU admission and no apparent benefit in decreased length of stay or time to albuterol Q4h. Propensity score analyses have been proposed as a method to estimate the causal effect of an exposure.^{4,6} Nonetheless, this study is limited because it cannot resolve whether these findings are a consequence of clinical momentum after positive pressure ventilation or of increased air trapping and ventilation-perfusion mismatch, derangements that worsen an exacerbation. A randomized clinical trial should be performed before BiPAP is used in children with acute asthma exacerbations without respiratory failure.

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Published Online: December 29, 2014. doi:10.1001/jamapediatrics.2014.2767.

Author Contributions: Dr Arnold had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Obtained funding: Arnold.
Administrative, technical, or material support: Golden.
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Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by grant K23 HL80005 from the National Institutes of Health (Dr Arnold) and Clinical and Translational Science Award UL1 RR024975 (Vanderbilt Institute for Clinical and Translational Research).

Role of the Funder/Sponsor: The funding sources 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.

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Accuracy of Bayley Scores as Outcome Measures in Trials of Neonatal Therapies

Long-term follow-up of extremely preterm infants is essential because the proportion of infants who survive is increasing while neurodevelopmental impairment rates remain high.¹ Psychometric tests, such as the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III),² are commonly used to measure early childhood outcomes in obstetric and neonatal randomized trials.^{3,4} However, the composite scores on psychometric tests can be inaccurate because of administrative and technical errors. To determine the magnitude of this problem, we performed a post hoc review of all errors detected by central source document verification of Bayley-III assessments during the 18-month follow-up of the Canadian Oxygen Trial (COT).⁵

Table. Type and Frequency of Errors in Bayley-III Assessments

Type of Error	No. (%)	
	Total Independent Errors	Changed Outcome of Cognitive or Language Delay
Corrected age calculation	165 (42.6)	20 (12.1)
Documenting/applying scoring rules	47 (12.1)	5 (10.6)
Raw score addition	83 (21.4)	2 (2.4)
Table look-ups	48 (12.4)	10 (20.8)
Data entry	44 (11.4)	5 (11.4)
Total	387 (99.9%)	42 (10.9)

Abbreviation: Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition.

Methods | Extremely preterm COT participants in 25 centers in 6 countries were randomly assigned to 2 oxygen saturation target ranges. The primary outcome at a corrected age of 18 to 21 months was death or survival with neurodevelopmental disability. Cognitive or language composite scores of less than 85 on the Bayley-III scales were included in the primary outcome.⁵ The research ethics boards of all clinical centers approved the protocol, and written informed consent was obtained from a parent or guardian of every study infant.

Original Review Process During COT. Experienced examiners administered the Bayley-III test and submitted copies of the source documents to the coordinating center. Between October 15, 2008, and August 15, 2012, trained staff (J.D. and L.C.) reviewed the source documents for accuracy, completeness, and agreement with the electronic database entries. Discrepancies were identified and corrected through a formal data clarification process with input from Bayley-III examiners at the respective study sites. A small number of queries (n = 36) could not be resolved directly with the clinical centers and were referred to an adjudication committee consisting of a developmental pediatrician (D.M.) and a neurodevelopmental consultant (K.P.).

Post Hoc Analysis. In this study, 1 assessor (J.D.) reexamined all Bayley-III source documents and classified the errors that were identified during the original review process into 5 categories: calculation of the child’s corrected age, documenting or applying scoring rules, raw score addition, look-up of scaled scores and composite scores in normative tables, and electronic data entry. A 15% random sample was independently classified by a second assessor (L.C.) to ensure consistent classification of error types. Only 2 disagreements were found and resolved through consensus. The error categories are hierarchical in nature. An early mistake—for example, calculation of the corrected age—may affect all subsequent steps. We counted such errors only once, assigned them to the category in which they first occurred, and summarized the frequency of independent errors in each of the 5 categories.

Results | During COT follow-up, the source documents for 936 of 954 (98.1%) Bayley-III assessments were submitted to the coordinating center. Eighteen children could not be evaluated because of severe developmental delay or autism. Of 936 source documents, 576 (61.5%) contained no errors. The remaining 360 (38.5%) contained at least 1 error, and the total number of independent errors was 387 (Table). None of the 25 clinical centers were completely error free. The best and worst center-specific error rates were 8 of 61 (13.1%) and 14 of 16 (87.5%), respectively. Had they not been detected during the original review process, 41 of 387 (10.6%) incorrectly reported composite scores would have changed the determination of the composite primary outcome in COT.

Discussion | Experienced Bayley-III examiners made numerous administrative, scoring, and reporting errors in this inter-