Evidence Table 20. Managing Exacerbations: Heliox

Abbreviations used in table:

CI	**confidence interval**	**PEF**	**peak expiratory flow**
ED	**emergency department**	**PEFR**	**peak expiratory flow rate**
FEV_1	**forced expiratory volume in 1 sec.**	**PI**	**pulmonary index**
H	**helium-oxygen (heliox)**	**RCT**	**randomized control trial**
ICS	**inhaled corticosteroid**	**RR**	**relative risk**
O	**oxygen**	**SMD**	**standardized mean difference**
OR	**odds ratio**	**WMD**	**weighted mean difference**

*** indicates primary outcome**

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Citation (Sponsor)	Study Design	Study Population		
		Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if reported)
Ho et al. Heliox vs. air–oxygen mixtures for the treatment of patients with acute asthma. Chest 2003;123(3):882–890.	Meta-analysis of studies published between 1966 and 2002	15 articles (8 randomized control trials (RCTs) (n ranged from 11 to 205), 1 nonrandomized prospective controlled trial (n=27), 1 retrospective case-match controlled trial (n=22), 4 before–after case series, and 1 case report)	**Age** Months to 70 yr **Gender** Not reported **Ethnicity** Not reported	Acute asthma
Rodrigo et al. Heliox for nonintubated acute asthma patients. Cochrane Database Syst Rev 2003;(4):CD002884.	Meta-analysis of studies published between 1966 and 2002	6 RCTs with 369 acute asthma patients; 5 studies involved adults and 1 study dealt with children.	**Age** Mean age of samples: 12.3, 28.5, 32.3, 32.5, 37.0, and 44.5	Patients with clinical diagnosis of acute asthma who were seen in emergency departments (EDs)
Kim et al., Helium/oxygen-driven albuterol nebulization in the treatment of children with moderate to severe asthma exacerbations: a randomized, controlled trial. Pediatrics 2005;116(5):1127–1133. (Praxair Corporation)	Randomized, single-blind, controlled trial	31 (30)	**Age** 2–18 yr, mean = 7.4 yr Gender 50% male, 50% female Ethnicity 60% Black, 37% White, 3% not given	Moderate–to-severe asthma Patients presented to urban, pediatric ED Pulmonary index (PI) score of >8 out of 15; mean = 10.2 at entry Beta$_2$-agonist, 50% 1 hour before, 87% 24 hours before Corticosteroids, 87% in the past, 17% in past 4 weeks Inhaled steroids, 43% Other controller therapies, 33% Mean initial oxygen (O) saturation on room air, 92.3% Previous hospitalizations, mean = 2.3

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Lee et al. Beneficial effects of albuterol therapy driven by heliox versus by oxygen in severe asthma exacerbation. Acad Emerg Med 2005;12(9):820–827. (Kaohsiumg Veterans General Hospital, Taiwan)	Two randomized, double-blind, controlled trials (ED of a university-affiliated tertiary care medical center)	Trial 1: 80 (80) Trial 2: 80 (80)	**Trial 1** **Age** 18–50 yr, mean = 34.6 yr **Gender** 27% male, 73% female **Ethnicity** Not reported **Smoking** 14% tobacco smoking **Trial 2** **Age** >40 yr, mean = 54 yr **Gender** 35% male, 65% female **Ethnicity** Not reported **Smoking** 12.5% tobacco smoking **Trial 2** **Age** >40 yr, mean = 54 yr **Gender** 35% male, 65% female **Ethnicity** Not reported **Smoking** 12.5% tobacco smoking	**Trial 1** Asthma diagnosed by American Thoracic Society criteria History of reversible airway obstruction as manifested by episodes of cough, dyspnea, and wheeze interspersed with symptom-free periods; 35% with history of asthma admission and 6% with history of mechanical ventilation for asthma Pretreatment PEF <50%, mean = 35.2% pred. Infectious exacerbation, 47% Days of exacerbation before ED visit, mean = 2.9 days Ipratropium, 22.5%; $beta_2$-agonist, 72.5%; oral corticosteroids, 17.5%; inhaled corticosteroid (ICS), 42.5%; methylxanthine, 36%; antileukotriene, 17.5% Heart rate, mean = 100 beats/min (104 for heliox group, 97 for O group, p <0.01) Respiratory rate, mean = 25.5 breaths/min SpO_2, mean = 94.8% **Trial 2** Asthma diagnosed by American Thoracic Society criteria History of reversible airway obstruction as manifested by episodes of cough, dyspnea, and wheeze interspersed with symptom-free periods; 35% with history of asthma admission and 6% with history of mechanical ventilation for asthma Pretreatment PEF<40%, mean = 26.4% pred. Baseline FEV_1 % pred., mean = 35.4 Ipratropium, 14%; $beta_2$-agonist, 84%; systemic corticosteroids, 17.5%; ICS, 42.5%; methylxanthine, 29%; antileukotriene, 15% Heart rate, mean = 95 beats/min Respiratory rate, mean = 23.5 breaths/min SpO_2, mean = 95.4%

Citation (Sponsor)	Study Design	Study Population		
		Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if reported)
Rivera et al. Albuterol nebulized in heliox in the initial ED treatment of pediatric asthma: a blinded, randomized controlled trial. Am J Emerg Med 2006;24(1):38–42.	Blinded, randomized controlled trial (pediatric ED of a tertiary care, urban, university-based children's hospital)	41 (41)	**Age** 3–16 yr, median 8 in heliox group, 7 in O group **Gender** 61% male, 39% female **Ethnicity** Not reported	Moderately severe asthma exacerbation with modified dyspnea index of 4 or higher on admission (median 6 for heliox group and 5 for O group, p=0.936) Previous history of at least 3 prior episodes of reversible bronchospasm

Citation (Sponsor)	Study Characteristics			Findings			
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Severity/ Admissions	Safety
Ho et al. Heliox vs. air–oxygen mixtures for the treatment of patients with acute asthma. Chest 2003;123(3): 882–890.	**Purpose/Objective:** To evaluate the efficacy of heliox on respiratory mechanics and outcomes in patients with acute asthma			There was no significant difference in PEF between interventions (WMD +3%, 95% CI –2% to +8%; 4 RCTs) within the first hour. The level of confidence was 92% that heliox provides a benefit as an adjunct to standard medical care in acute asthma. Based on weighted linear regression, patients with <43% PEF may benefit more from heliox vs. patients with less severe acute asthma. Overall, all studies showed results in favor of heliox except 1 RCT and 1 case series that showed no improvement, 1 RCT that showed possible detrimental effect, and 1 small RCT that was inconclusive.			
	Arm 1 Any mixture of helium and O with or without concurrent beta-agonists, para-sympatholytics and corticosteroids, and with or without invasive ventilation **Arm 2** Oxygen (O)						

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Rodrigo et al. Heliox for nonintubated acute asthma patients. Cochrane Database Syst Rev 2003;(4): CD002884. NOTE: Includes Henderson et al. study.	**Purpose/Objective:** To determine the effect of the addition of heliox to standard medical care on the course of acute asthma, as measured by pulmonary function testing and clinical endpoints			There were no group differences in pulmonary function (SMD=0.13, 95% CI –0.09 to 0.34) based on 4 studies with n=127.	Heliox produced greater increase in heart rate than oxygen/air (SMD=7.67, 95% CI 0.79 to 14.55). There was no difference in O saturation (SMD=0.04, 95% CI –1.10 to 1.09) based on 3 studies with n=97.	There was no difference in Borg dyspnea score (WMD= –0.11, 95% CI –1.27 to 1.04) based on 3 studies with n=81.	There was no difference in hospital admissions (relative risk (RR) 1.02, 95% CI 0.58 to 1.81) based on 4 studies with n=324.
	Arm 1 Helium-oxygen (H) **Arm 2** Placebo (O or air)	Four trials used 70:30; 2 trials used 80:29					
Kim et al. Helium/oxygen-driven albuterol nebulization in the treatment of children with moderate to severe asthma exacerbations: a randomized, controlled trial. Pediatrics 2005;116(5): 1127–1133. (Praxair Corporation)	**Purpose/Objective:** to evaluate the efficacy of heliox versus O in driving continuous albuterol nebulization in children with moderate to severe asthma			*The mean change in PI score from baseline to 240 minutes was 6.67 for heliox vs. 3.33 for O ($p < 0.001$). At 125 minutes, heliox group showed clinically significant absolute mean PI improvement vs. O group ($p < 0.05$) that was sustained at 150, 180, and 240 minutes.		67% of heliox group were discharged from ED compared with 33% of O group (p=0.07). 73% of heliox group were discharged from hospital in <12 hours vs. 33% in O group ($p < 0.05$).	
	Arm 1 Heliox via compressed gas association 280 regulator driven by pressure of 50 lb per square inch gauge (n=16; n=15 completers) **Arm 2** O (n=15)	Flow of 16 L/min Flow of 10 L/min	All received 20 minutes of nebulized albuterol treatment (5 mg) driven by 100% O, and oral steroids followed by nebulized albuterol (15 mg/hour) by heliox or O using nonrebreathing face mask up to 3 hours or until ED discharge.				

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Lee et al. Beneficial effects of albuterol therapy driven by heliox versus by oxygen in severe asthma exacerbation. Acad Emerg Med 2005;12(9): 820–827. (Kaohsiumg Veterans General Hospital, Taiwan)	**Purpose/Objective (Trial 1):** To compare the efficacy of albuterol therapy driven by heliox versus by O and determine factors that were associated with beneficial response to heliox-driven albuterol therapy **Purpose/Objective (Trial 2):** To compare the efficacy of albuterol therapy driven by heliox versus by O in older patients			**Trial 1** *Both groups improved in PEF (p <0.001) with increase in H approximately twofold those in O. After first treatment, PEF increased by 17.5% in O and 35.7% in H (p <0.005); after third treatment, PEF increased from baseline by 39.7% in O vs. 71.4% in H (p <0.01). More in H vs. O reached PEF >60% pred. at end of third treatment (OR 2.58, 95% CI 1.03 to 6.46). Age (p=0.035) and pretreatment PEF (p=0.010) were associated with response to heliox; respiratory rate (p=0.13), heart rate (p=0.544), and smoking status (p=0.170) were not associated. **Trial 2** Improvement in PEF in H vs. O was greatest (23% pred.) for those in first quartile of pretreatment PEF (p <0.05). There were greater decreases in dyspnea score for H vs. O for those in lower 2 quartiles vs. upper 2 quartiles of pretreatment PEF.		**Trial 1** There was no difference in admission rates (18/40 in O vs. 12/40 in H, p=0.16). Among those discharged from ED, shorter stay for H vs. O (76 min vs. 86 min, p=0.007)	
	Arm 1 Heliox (H) (n=40; n=40 completers)	Albuterol (2.5 mg) in 3 mL of 0.9% saline via a nebulizer powered by helium/oxygen 80%/20%	**Trial 1** 3 treatments with 15-minute washout periods				
	Arm 2 Oxygen (O) (n=40; n=40 completers)	Albuterol (2.5 mg) in 3 mL of 0.9% saline via a nebulizer powered by air, O	**Trial 2** 2 treatments with 15-minute washout periods				

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Rivera et al. Albuterol nebulized in heliox in the initial ED treatment of pediatric asthma: a blinded, randomized controlled trial. Am J Emerg Med 2006;24(1):38–42.	**Purpose/Objective:** To determine if delivery of continuous nebulized albuterol with heliox led to greater clinical improvement over nebulized albuterol delivered with O						
	Arm 1 Heliox (H) (n=20; n=20 completers)	Continuous albuterol therapy (0.45 mg/kg, maximum dose 15 mg/h) delivered by nonrebreather face mask nebulized with helium/oxygen, 70%/30%	All patients received 3 doses of aerosolized albuterol (2.5 mg/treatment given with 8 L of O), intravenous (IV) fluids at a weight-based maintenance rate, and 2 mg/kg IV methylprednisolone. After third albuterol treatment, they were randomized to H or O, with assessment at 10 and 20 minutes after randomization.			*Median modified dyspnea index scores improved for both groups, with no clinical (≥2 points) or statistical difference (p=0.169 after 10 minutes; p=0.062 after 20 minutes) between groups. Rate of admission was 60% for H and 81% for O (p=0.181).	
	Arm 2 Oxygen (O) (n=21; n=21 completers)	Continuous albuterol therapy (0.45 mg/kg, maximum dose 15 mg/hour) delivered by nonrebreather face mask nebulized with air/oxygen, 70%/30%					