Evidence Table 16. Pharmacologic Therapy: Bronchodilators—Levalbuterol

Abbreviations used in table:

AE	**adverse event**	**LOS**	**length of stay**
ED	**emergency department**	**PEF**	**peak expiratory flow**
FEV_1	**forced expiratory volume in 1 sec.**	**RAC**	**racemic albuterol**
IB	**ipratopium bromide**	**SAE**	**severe adverse event**
LEV	**levalbuterol**		

*** 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)
Lotvall et al. The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients. J Allergy Clin Immunol 2001;108(5):726–731. (GlaxoWellcome Research & Development Limited)	Randomized, double-blind, placebo-controlled 4-way crossover study	20 (20)	**Age** 24–70 yr; mean = 50 yr **Gender** 60% male, 40% female **Ethnicity** Not reported **Smoking** 35% nonsmoker, 65% exsmoker	FEV_1 % pred. 60–94, mean = 73 FEV_1 reversibility 15%–29%, mean = 19%
Milgrom et al. Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. J Allergy Clin Immunol 2001;108(6):938–945. (Sepracor Inc.)	Multicenter, randomized, double-blind, parallel group study	338 (319 completers; intent-to-treat analysis)	**Age** 4–11 yr, mean = 8.5 yr **Gender** 58.3% male, 41.7% female **Ethnicity** 60.4% White, 23.1% Black, 10.7% Hispanic, 5.8% other	Chronic asthma $\geq$60 days Majority had mild-to-moderate persistent asthma FEV_1 % pred. mean = 73.5 FEV_1 % reversibility = 26.9 Concomitant medications: 50% steroids, 6% leukotriene modifiers 90% had histories of allergies
Carl et al. Comparison of racemic albuterol and levalbuterol for treatment of acute asthma. J Pediatr 2003;143(6):731–736. (Sepracor, Inc.)	Randomized, double-blind, controlled trial Block randomization stratified by age (<6 yr or $\geq$6 yr)	547 (547 enrollments based on presentation to the ED for 482 children)	**Age** 1–18 yr, mean = 7.1 yr **Gender** 67% male, 33% female **Ethnicity** 13.7% White, 85.6% Black, 0.7% other	Acute asthma Respiratory rate, mean = 35.1 73.4% with ED visits in past yr 43.5% hospitalized in past yr Medication use: 23% inhaled steroid, 20% cromolyn, 14% leukotriene receptor, 5% long-acting beta-agonist 6% oral steroid in past 24 hr
Hardasmalani et al. Levalbuterol versus racemic albuterol in the treatment of acute exacerbation of asthma in children. Pediatr Emerg Care 2005;21(7):415–419.	Randomized, double-blind, prospective trial	70 completed the study	**Age** $\geq$5 yr, mean = 12.1 yr **Gender** 55% male, 45% female **Ethnicity** Hispanics were the largest racial group. **Height** Mean = 59.3 inches	Moderate asthma, presenting to ED in acute exacerbation Oxygen saturation, mean = 96.67 Respiratory rate, mean = 25.96 Peak flow rate, mean = 168.7; 50%–80% of predicted

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Nowak et al. Levalbuterol compared with racemic albuterol in the treatment of acute asthma: results of a pilot study. Am J Emerg Med 2004;22(1):29–36. (Sepracor, Inc.)	Prospective, open-label, nonrandomized pilot study	91 (91)	**Age** 25–40 yr; mean = 33 yr **Gender** 46% male, 54% female **Ethnicity** 84% Black 16% other **Smoking** All had <10 pack-yr smoking history.	FEV_1 % pred., 20%–55%, median = 39.0 FEV_1 mean = 1.18 L Concomitant inhaled corticosteroids, 36% All had oxygen saturation ≥90%.
Qureshi et al. Clinical efficacy of racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. Ann Emerg Med 2005;46(1):29–36. (Sepracor, Inc.)	Prospective, double-blind, randomized controlled trial	139 (129)	**Age** 2–14 yr; median = 5.8 yr **Gender** 66% male, 34% female **Ethnicity** 84% Black 16% other **Weight** Median = 22 kg	Presenting to ED with acute, moderate (66%) or severe (34%) asthma exacerbation FEV_1 % pred., median = 26
Ralston et al. Comparison of levalbuterol and racemic albuterol combined with ipratropium bromide in acute pediatric asthma: a randomized controlled trial. J Emerg Med 2005;29(1):29–35.	Prospective, double-blind, randomized controlled trial (Tertiary hospital serving eligible Department of Defense beneficiaries)	154 (140)	**Age** 6–18 yr, mean = 11.6 yr **Gender** 54% male, 46% female **Ethnicity** 53% African American 37% Caucasian 5% Hispanic 5% other **Height** Mean = 148 cm **Weight** Mean = 47 kg	Acute moderate-to-severe asthma SaO_2 (room air), mean = 97% Heart rate, mean = 102 beats/min Respiration, mean = 24 beats/min PEF, mean = 171 L/min PEF % pred., mean = 50; <50% predicted, 49%; 50%–80% predicted, 51%

Citation (Sponsor)	Study Characteristics			Findings			Adverse Events
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Rescue Medication Use	Lung Function	Exacerbations/ Symptoms	
Lotvall et al. The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients. J Allergy Clin Immunol 2001; 108(5):726–731. (GlaxoWellcome)	**Purpose/Objective:** To compare the local bronchodilating and systemic pharmacodynamic effects of R- and RS-albuterol and the effects of S-albuterol and placebo			Both R- and RS-albuterol produced significant and dose-dependent increases in FEV_1. S-albuterol did not show any consistent effect on FEV_1 compared with placebo. Geometric mean potency ratio for R-albuterol/RS-albuterol effects on FEV_1 was 1.9 (95% CI 1.3–2.8).	Doses of R-albuterol ≥200 mcg and doses of RS-albuterol ≥400 mcg showed dose-dependent increases in heart rate and decreases in plasma K^+ level. Geometric mean potency ratio for R-albuterol/RS-albuterol effects on heart rate was 1.9 (95% CI 1.3–2.9) and on plasma K^+ level was 1.7 (95% CI 1.3–2.1).		No SAE and no withdrawal because of drug-related AE occurred.
	Arm 1 R-albuterol **Arm 2** S-albuterol **Arm 3** RS-albuterol **Arm 4** Placebo	6.25, 12.5, 25, 50, 100, 200, 400, 800, and 1,600 mcg for S- or R-albuterol 12.5, 25, 50, 100, 200, 400, 800, 1,600, and 3,200 mcg for RS-albuterol	One medication was given per day for 4 study days, with a minimum 3-day washout period between crossovers. Medications were administered 1 per study day in a cumulative fashion.				
Milgrom et al. Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. J Allergy Clin Immunol 2001;108 (6):938–945. (Sepracor Inc.)	**Purpose/Objective:** To evaluate the safety and efficacy of chronic treatment with nebulized LEV in 4- to 11-yr-old children with chronic asthma			*All treatments improved FEV_1 as compared with placebo on day 21 ($p < 0.019$). The effect on FEV_1 of 0.32 mg LEV did not differ from the effect of 2.5 mg RAC at either day 0 or day 21. Clinically significant changes (≥15% median change) from baseline FEV_1 occurred immediately on days 0 and 21 for all groups except placebo and 1.25 mg RAC.	0.63 mg LEV and the 2 RAC doses increased heart rate significantly. 2.5 mg RAC consistently caused greater increases in heart rate than did either of the LEV doses. All treatments decreased serum potassium vs. placebo ($p < 0.002$). Exposure to S-albuterol was about 4-fold greater than exposure to R-albuterol at equivalent doses.	No differences were found among treatments for overall asthma symptom score, symptom-free days, and quality-of-life score. Rescue medication use was comparable in all treatment groups over the course of the study. 0.31 mg LEV achieved greater change in asthma control days than 0.63 mg LEV and 1.25 mg RAC during the last 7 days (median = 1.6, 0.25, and 0 days, respectively, $p < 0.04$).	No treatment-related SAE occurred. An AE was reported by 43% taking 0.31 mg LEV, 53% taking 0.63 mg LEV, 34% taking 1.25 mg RAC, 52% taking 2.5 mg RAC, and 34% taking placebo.
	Arm 1 LEV (n=70)	0.31 mg 3 times/day	21 days of 3 times/day treatment after 1-week single-blinded placebo run-in period Ventolin MDI and Ventolin nebules were used as rescue medication.				
	Arm 2 LEV (n=70)	0.63 mg 3 times/day					
	Arm 3 RAC (n=67)	1.25 mg 3 times/day					
	Arm 4 RAC (n=66)	2.5 mg 3 times/day					
	Arm 5 Placebo (n=70)						

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Nowak et al. Levalbuterol compared with racemic albuterol in the treatment of acute asthma: results of a pilot study. Am J Emerg Med 2004;22(1):29–36. (Sepracor, Inc.)	**Purpose/Objective:** To determine the most effective dose of LEV for treating acute bronchospasm and to evaluate its side-effect and safety profile			After 1 dose, median percentage change in FEV_1 was greater for 1.25 mg LEV (56%) vs. 2.5 mg RAC (6%), 5.0 mg RAC, (14%), 0.63 mg LEV (13%), and 3.75 mg LEV (13%) ($p < 0.05$). After 3 doses, median percentage change in FEV_1 was greater for 1.25 mg LEV (74%) vs. 2.5 mg RAC (39%), 0.63 mg LEV (37%), and 3.75 mg LEV (26%) ($p < 0.05$). Compared with baseline, 1.25, 2.5, and 5.0 mg LEV improved median % predicted FEV_1 at 60 min by 33%–38%. RAC at 2.5 and 5.0 mg and LEV at 0.63 and 3.75 mg improved median % predicted FEV_1 by 12%–24%.	Changes in glucose, potassium, and heart rate were proportional to the dose of RAC and were similar after matched doses of LEV and RAC. LEV, at 5.0 mg, caused the greatest median peak change in heart rate (35 beats/min); median peak changes for 1.25 mg LEV and 2.5 mg RAC were similar (15 and 17 beats/min). Baseline plasma levels of (R)-albuterol did not differ, but (S)-albuterol level was higher for 3.75 mg LEV vs. 0.63, 1.25, and 5.0 mg LEV ($p < 0.05$). (S)-albuterol was inversely correlated with baseline FEV_1 ($r=–0.30$, $p=0.004$) and % change in FEV_1 60 min postdose ($r=–0.30$, $p=0.006$).		
	Cohorts of 12–14 patients were sequentially entered into dose cohorts of LEV or RAC.	LEV doses were 0.63, 1.25, 2.5, 3.75, and 5 mg. RAC doses were 2.5 and 5 mg.	2 hr: 1 dose every 20 min for 3 doses followed by a 60-min observation period No other bronchodilator was administered during the study period. All received prednisone (60 mg orally or equivalent) at baseline.				

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Carl et al. Comparison of racemic albuterol and levalbuterol for treatment of acute asthma. J Pediatr 2003;143 (6):731–736. (Sepracor, Marlborough, MA)	**Purpose/Objective:** To determine whether LEV resulted in fewer hospital admissions than RAC resulted in when used for treatment of acute asthma				No difference in mean heart rate (130.1, LEV group; 129.7 RAC group), respiratory rate (37.0 LEV group; 35.8 RAC group), or oxyhemoglobin saturation (96.3% LEV group; 96.3% RAC group)	*Hospital admission rate was 36.3% for children treated with LEV and 45.4% for those treated with RAC (p=0.02). Controlling for age, treatment with >3 aerosols in past 12 hr, and oral corticosteroid use in the previous 24 hr, relative risk of admission in the RAC group compared with the LEV group was 1.25 (95% CI 1.01–1.51, p=0.04). ED LOS for those discharged to home did not differ between the 2 groups. Number of aerosols administered in the ED and to inpatients did not differ between the groups.	No SAE occurred in either group in either the ED or hospital.
	Arm 1 LEV (n=278) **Arm 2** RAC (n=269) Children <6 yr of age received treatments via face mask; those ≥6 yr of age received treatments via mouthpiece.	1.25 mg at 20-min intervals 2.5 mg at 20-min intervals All patients failing to meet discharge criteria after first treatment were given oral prednisone (2 mg/kg/day, 60 mg maximum).	Until patients met discharge criteria or reached a maximum of 6 treatments within 2 hr, at which time they were admitted to hospital.				

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Hardasmalani et al. Levalbuterol versus racemic albuterol in the treatment of acute exacerbation of asthma in children. Pediatr Emerg Care 2005;21(7): 415–419.	**Purpose/Objective:** To compare LEV versus RAC in treatment of acute exacerbation of asthma in pediatric population 5–21 yr of age			*After treatment, no difference was found between groups in oxygen saturation (p=0.99), respiratory rate (p=0.83), peak flow rate (p=0.896), or peak flow rate % change (p=0.707).		No difference in percentage of patients requiring >3 treatments (20.6% in RAC group vs. 13.9% in LEV group; p=0.535 by Fisher's Exact Test). No difference in percentage of patients requiring hospitalization (5.9% in RAC group vs. 8.3% in LEV group; p=1.00 by Fisher's Exact Test).	
	Arm 1 LEV (n=36) **Arm 2** RAC (n=34)	1.25 mg/3 mL 2.5 mg/3 mL All received IB (250 mcg in children weighing <30 kg and 500 mcg in children weighing >30 kg).	3 treatments as required at 20-min intervals Oral steroids (prednisone/ prednisolone in dose of 2 mg/kg, maximum dose 60 mg) were given after 2nd treatment.				

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Ralston et al. Comparison of levalbuterol and racemic albuterol combined with ipratropium bromide in acute pediatric asthma: a randomized controlled trial. J Emerg Med 2005; 29(1):29–35.	**Purpose/Objective:** To evaluate safety and efficacy outcomes of nebulized LEV compared to nebulized RAC combined with IB in the management of acute, moderate-to-severe pediatric asthma exacerbations in the ED			Measures of PEF were similar between the 2 groups (median increase in PEF, p=0.36; median maximum increase in PEF, p=0.42).	Difference between the RAC + IB group and the LEV group in increase in mean heart rate from initial to final (26 vs. 10 beats/min, p<0.001) and in mean increase from initial to maximum heart rate (29 vs. 16 beats/min, p <0.001)	*Median ED LOS for LEV group and RAC + IB group were comparable (80 min vs. 94 min, p=0.13). More patients in the RAC + IB group vs. LEV group were given oral steroids in the ED (87% vs. 70%, p=0.014).	No SAE was reported.
	Arm 1 LEV (n=78; n=72 received LEV)	Up to 6 nebulized treatments containing 1.25 mg LEV for total volume of 3.0 mL solution in vials 1–6	Number of treatments, interval between treatments, use of adjunctive medications, patient disposition, and discharge instructions were determined at the discretion of the treating physician. No nebulized treatments other than study medications were permitted.				
	Arm 2 RAC + IB (n=76; n=68 received RAC)	Up to 6 nebulized treatments containing 5.0 mg RAC mixed with 0.25 mg IB and 0.75 mL normal saline in vials 1–3; 5.0 mg RAC mixed with 2.0 mL normal saline in vials 4–6					

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Qureshi et al. Clinical efficacy of racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. Ann Emerg Med 2005;46(1):29–36. (Sepracor, Inc.)	**Purpose/Objective:** To determine whether LEV improved clinical asthma score and pulmonary function tests compared with RAC in children presenting to the ED with an acute, moderate-to-severe asthma exacerbation			No differences were found between groups in percentage of predicted FEV_1 after the 1st, 3rd, and 5th treatments.	No differences between groups after 1st, 3rd, and 5th treatments in changes in pulse rate, respiratory rate, and pulse oximetry readings	No differences between groups in number of treatments given, length of care, rate of hospitalization, and number who received IB after the 3rd treatment	No difference in prevalence of AE
	Arm 1 LEV (n=71; 65 completers)	1.25 mg for children weighing <25 kg; 2.5 mg for children weighing ≥25 kg	Up to 5 treatments per patient The first 3 treatments were given at 20-min intervals; subsequent treatments were given at 30- to 60-min intervals. All children received 2 mg/kg of prednisone or equivalent oral corticosteroids with 2nd treatment. IB therapy was delayed until after 3rd treatment.				
	Arm 2 RAC (n=68; 64 completers)	2.5 mg for children weighing <25 kg; 5 mg for children weighing ≥25 kg					