ORIGINAL ARTICLE

Impact of Age and Sex on Response to Asthma Therapy

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Abstract

Rationale: Age and sex are associated with differences in asthma prevalence and morbidity.

Objectives: To determine if age and sex associate with distinct phenotypes and a variable response to therapy in subjects with mild to moderate asthma.

Methods: We used Asthma Clinical Research Network data to determine the impact of age and sex on phenotypes and treatment failures among subjects participating in 10 trials from 1993 to 2003.

Measurements and Main Results: A total of 1,200 subjects were identified (median age, 30.4 yr; male, 520 [43.3%]; female, 680 [56.7%]) and analyzed. A higher proportion of subjects greater than or equal to 30 years old experienced treatment failures (17.3% vs. 10.3%; odds ratio [OR], 1.82; confidence interval [CI], 1.30–2.54; $P < 0.001$), and rates increased proportionally with increasing age older than 30 across the cohort (OR per yr, 1.02 [CI, 1.01–1.04]; OR per 5 yr, 1.13 [CI, 1.04–1.22]; $P < 0.001$). Lower lung function and longer duration of asthma were associated with a higher risk of treatment failures. A higher proportion of subjects greater than or equal to 30 years old receiving controller therapy experienced treatment failures. When stratified by specific therapy, treatment failures increased consistently for every year older than age 30 in subjects on inhaled corticosteroids (OR per year, 1.03; CI, 1.01–1.07). Females had a slightly higher FEV_1 % predicted (84.5% vs. 81.1%; $P < 0.001$) but similar asthma control measures. There was not a statistically significant difference in treatment failures between females and males (15.2% vs. 11.7%; $P = 0.088$).

Conclusions: Older age is associated with an increased risk of treatment failure, particularly in subjects taking inhaled corticosteroids. There was no significant difference in treatment failures between sexes.

Keywords: asthma; inhaled corticosteroid; age; sex; treatment failure

At a Glance Commentary

Scientific Knowledge on the Subject: There are important differences in asthma epidemiology across age and sex. The effect of age and sex on response to therapy is not well understood.

What This Study Adds to the Field: Among a large clinical trial cohort of subjects with mild to moderate asthma, age is associated with an increased risk of treatment failures particularly among subjects on inhaled corticosteroids. Sex did not affect the response to therapy.

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Over the last two decades, much progress has been made in recognizing the heterogeneity of asthma. Cluster analysis and observational data have suggested that such factors as environment, genetics, race, obesity, sex, and specific endotypes may have important implications for asthma symptoms and management (1, 2). Sex and aging have also been implicated to have effects on asthma pathophysiology, symptoms, and response to therapy, but these associations are poorly understood.

Data from the Centers for Disease Control and Prevention suggest that asthma morbidity and mortality are increased in middle-aged and older subjects with asthma (3). Asthma in older patients is also associated with a more rapid decline in FEV_1 with age when compared with aging healthy control subjects (4). Older subjects with asthma are more likely to be misdiagnosed, undertreated, and, in some studies, less likely to respond to emergency bronchodilator therapy (5, 6). From a physiologic standpoint, there are also important distinctions between younger and older subjects with asthma. Older subjects with asthma demonstrate enhanced bronchoconstriction to methacholine and a reduced awareness of bronchoconstriction (7, 8). More recent data suggest that older patients have increased "small airway" involvement, increased neutrophilic inflammation, and decreased eosinophil function and specific antibody response compared with younger cohorts (9–11). These important, but understudied age-related changes in pulmonary function, bronchial hyperresponsiveness, host defense, and inflammation highlight the need for more investigation into this important group of patients. The differential response of older subjects with asthma to conventional asthma therapies is also not well characterized because most patients enrolled in clinical asthma trials are less than 35 years old (12–14).

The influence of sex on asthma symptoms and management is another area that has been understudied. Among children less than age 12, asthma is more common in males but after the onset of puberty, it is observed more frequently in females (15). In adulthood, asthma continues to be more prevalent among females throughout the reproductive years and beyond (16). It is unknown if the factors that influence the differences in asthma prevalence across sex also influence the response to therapy.

The National Heart, Lung and Blood Institute's Asthma Clinical Research Network (ACRN) was a consortium of multiple asthma clinical research centers that conducted 10 influential trials between 1993 and 2003(17–26). The high-quality, detailed patient data acquired during these studies allow for a thorough analysis of the impact of age and sex on response to specific treatments in this group of subjects with mild to moderate asthma.

Methods

Cohort

This analysis cohort consisted of 1,200 unique subjects who participated in 10 different ACRN treatment trials and were enrolled at six different centers across the United States (Table 1) (17–26). We excluded smokers or patients who withdrew before starting treatment. Subjects who participated in multiple trials were only counted once (*see* the online supplement for full details on subject selection).

Table 1. Total Subjects by Study and Treatment

Study (Reference)	Arm	Total (*n*)	Age (*yr*) (*Mean* ± *SD*)	Age < 30 (*n*)	Age ⩾ 30 (*n*)
BAGS (17)	Albuterol	120	28.4 ± 8.6	73	47
	Placebo	122	29.1 ± 9.3	76	46
SOCS (18)	Placebo	52	30.7 ± 10.4	28	24
	Salmeterol	49	31.1 ± 10.2	26	23
	ICS	49	31.3 ± 11.3	28	21
SLIC (19)*	Placebo + ICS (pretaper)	14	33.8 ± 13.0	5	9
	Placebo only (post-taper)	4	39.6 ± 18.7	1	3
	Salmeterol + ICS (pretaper)	43	33.5 ± 10.9	20	23
	Salmeterol + ICS (sham taper)	72	36.3 ± 12.4	26	46
	Salmeterol only (post-taper)	24	35.7 ± 11.8	11	13
DICE (20)	Placebo	8	31.9 ± 12.9	5	3
	ICS	100	30.6 ± 8.6	58	42
MICE (21)	ICS	29	29.6 ± 7.2	18	11
BARGE (22)*	Albuterol	29	30.3 ± 6.4	13	16
	Placebo	39	29.5 ± 9.7	24	15
IMPACT (23)	Budesonide	70	32.7 ± 9.3	33	37
	Placebo	68	32.2 ± 10.2	36	32
	Zafirlukast	69	33.4 ± 10.7	29	40
SMOG (24)*	Montelukast	14	27.2 ± 3.5	12	2
	Beclomethasone	8	25.4 ± 5.1	7	1
SLIMSIT (25)*	Salmeterol + montelukast	91	34.2 ± 10.2	33	58
	Salmeterol + beclomethasone	69	33.7 ± 10.6	29	40
PRICE (26)	Placebo	27	32.3 ± 9.4	12	15
	ICS	30	32.7 ± 9.4	17	13
Total		1,200	31.7 ± 10.1	621	579

Definition of abbreviation: ICS = inhaled corticosteroid.
All subjects were unique across studies.
*SLIC, BARGE, SMOG, and SLIMSIT were either crossover designs or designs that used multiple treatments over several study periods.

Subjects were recruited from primary care, specialty practices, and hospital-based academic centers. Socioeconomic data were not captured but patients were recruited from diverse neighborhoods. Subjects were excluded from these studies if they had an asthma exacerbation within a month of enrolling in the trial. The studies included in this analysis had different run-in durations, duration of therapy, and duration of follow-up.

Detailed demographic and baseline data were collected and included age, sex, self-reported race, peak expiratory flows, FEV_1, bronchial hyperresponsiveness, asthma symptoms, use of asthma rescue medication, and asthma quality-of-life scores. The primary dependent variable analyzed was asthma treatment failure as previously described (27), defined as any the following: an asthma exacerbation requiring oral corticosteroid or emergency room visit, worsening of lung function, increased use of asthma medication, or physician clinical judgment. To distinguish important differences across age groups, we separated the cohort at the 50th and 75th percentiles (aged 30 and 38). We also examined age as a continuous variable over 1-, 5-, and 10-year intervals.

Statistical Analysis

All analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC). Comparisons were made between age groups and sexes in terms of categorical baseline characteristics, such as race, using a Pearson chi-square test or in terms of continuous or ordinal baseline characteristics, such as body mass index (BMI), using a two-sample *t* test or a Wilcoxon rank sum test depending on the distribution of the variable. Logistic regression was used to determine associations between the primary outcome variable, treatment failure, and baseline characteristics (Table 2). To look for differences in the reasons for treatment failures between age groups, a Fisher exact test was applied (Table 3). Finally, differences in treatment failure rates between the age groups over all therapy types and within therapy types were analyzed with logistic regression. Treatment failure was the binary dependent variable and age group was the independent variable. To compare odds ratios (ORs) for treatment types, we used a logistic regression model that included age group, treatment type, and the interaction between the two variables. ORs were used to quantify the magnitude and direction of any significant associations.

Results

In this cohort of 1,200 subjects, 579 (48.3%) of them were aged 30 and older, 303 (25.3%) aged 38 and older, and 680 (57.7%) were female. A total of 795 patients were self-reported white, 233 were black, and 172 were other races. Baseline demographics separated by age group and sex are shown in Tables 2 and 4. Of the medication adherence data that were collected in 4 of 10 trials, older patients had a slightly higher median average adherence (92.5% vs. 89.9%; $P < 0.001$) than those younger than age 30.

Age

Of the 579 subjects aged 30 and older, absolute measures of lung function including A.M. and P.M. peak flows, FEV_1, and forced expiratory flow, midexpiratory phase were slightly lower, reflecting the older age of the subjects. Notably, FEV_1 % predicted was also slightly lower in the older aged patients (80.2%; 95% confidence interval, 79.1–81.3) than in their younger

Table 2. Baseline Demographics

Characteristic	Age <30 (*n* = 621)		Age ⩾30 (*n* = 579)		*P* Value
	n	Mean (95% CI)	n	Mean (95% CI)	
Male*	621	271 (43.6)	579	249 (43.0)	0.825
Nonwhite race*	621	203 (32.7)	579	202 (34.9)	0.421
BMI, kg/m^2†	621	25.1 (24.7–25.5)	579	28.2 (27.7–28.7)	<0.001‡
A.M. peak flow, L/min†	621	446.3 (437.8–454.8)	578	423.3 (413.7–432.9)	<0.001‡
P.M. peak flow, L/min†	621	464.2 (455.7–472.7)	578	438.4 (428.8–447.9)	<0.001‡
FEV_1, L†	621	3.20 (3.14–3.26)	579	2.76 (2.70–2.82)	<0.001‡
FEV_1 % predicted†	621	85.7 (84.6–86.8)	579	80.2 (79.1–81.3)	<0.001‡
Albuterol 2-puff reversibility§	197	7.63 (3.97–13.42)	131	7.98 (4.11–14.75)	0.526
Maximum reversibility§	202	10.27 (6.29–16.97)	181	10.47 (6.56–17.33)	0.629
PC_{20}, mg/ml§	573	1.04 (0.39–3.05)	546	1.20 (0.49–3.59)	0.082
Daily symptom score, 0 = absent–3 = severe§	620	0.20 (0.06–0.43)	578	0.20 (0.06–0.45)	0.685
Daily β-agonist rescue puffs, # of puffs§	145	0.54 (0.08–1.69)	162	0.88 (0.11–2.14)	0.123
Exhaled nitric oxide, ppb§	325	15.70 (10.60–24.30)	354	13.65 (8.90–22.10)	0.009‡
Asthma quality-of-life score, 1 = worst–7 = best§	529	5.88 (5.34–6.34)	506	5.77 (5.10–6.31)	0.072
IgE, IU/ml§	213	164.0 (74.3–365.0)	237	141.0 (53.9–309.0)	0.160
Sputum eosinophils§	279	0.40 (0.0–2.0)	325	0.70 (0.20–2.50)	0.056
Blood eosinophils§	217	200.0 (120.0–330.0)	251	200.0 (110.0–300.0)	0.543
Treatment failure*	621	64 (10.3)	579	100 (17.3)	<0.001‡

Definition of abbreviations: BMI = body mass index; CI = confidence interval; PC_{20} = methacholine provocative concentration required to produce a 20% decline in FEV_1.

All baseline comparisons are based on unique subjects across all studies using the most recent study data for subjects in multiple studies, with treatment failures taking precedence.

*Chi-square test, frequency (percentage).

†Two-sample *t* test, mean (95% CI).

‡$P < 0.05$.

§Wilcoxon rank sum test, median (quartile 1–quartile 3).

Table 3. Reasons for Treatment Failures

Reason	Age < 30 (*n* = 64) [*n* (%)]	Age ⩾ 30 (*n* = 100) [*n* (%)]	*P* Value
Asthma exacerbation	41 (64.1)	49 (49.0)	0.077
Use of inhaled, oral, parental steroids	40 (62.5)	47 (47.0)	0.056
Emergency treatment or hospitalization	8 (12.5)	6 (6.0)	0.162
Decreased lung function	34 (53.1)	58 (58.0)	0.629
Increased asthma rescue medication use	9 (14.1)	26 (26.0)	0.080
Physician clinical judgment for safety reasons	32 (50.0)	37 (37.0)	0.108

counterparts (85.7%; 95% confidence interval, 84.6–86.8). There were no significant differences in methacholine bronchial reactivity, daily symptom score, daily β-agonist use, or asthma quality-of-life scores. BMI was slightly higher in the older aged cohort (28.2 vs. 25.1; $P < 0.001$), whereas exhaled nitric oxide was slightly lower (15.70 vs. 13.65 ppb; $P = 0.009$).

Subjects aged 30 and older were more likely to experience treatment failures than younger adult subjects (100 of 579 [17.3%] vs. 64 of 621 [10.3%]; $P < 0.001$). When age was examined as a continuous variable, every year increase in age was associated with an increased odds of treatment failure (OR, 1.02 [1.01–1.04] for 1-yr increase; OR, 1.13 [1.04–1.22] for 5-yr increase; and OR, 1.27 [1.09–1.49] for 10-yr increase; $P = 0.003$). When separated at the 75th percentile of age (age 38), this trend continued to be statistically significant (Table 5). When compared with the youngest age quartile (age <25) the risk of treatment failure continued to increase after age 30 in both the third (ages 30–37) and fourth quartile (age ⩾38) with the greatest odds of treatment failure among those in the oldest age group (*see* Table E2 in the online supplement). Besides age, the primary variables associated with treatment failures included lower peak expiratory flows ($P < 0.001$), lower FEV_1 ($P < 0.001$), and asthma duration greater than 15 years (OR, 1.48; $P = 0.032$) all of which were significant when corrected for age. Age of asthma onset was measured from questionnaires that documented the decade of onset (i.e., <10 yr, 10–19 yr, and so forth). No specific decade of asthma onset was found to be significantly associated with treatment failure (*see* Table E3). BMI, daily β-agonist use, and exhaled nitric oxide levels were not risk factors for treatment failures in this cohort of patients.

There was no significant difference in the reasons for treatment failures between the two age groups (Table 3). However, there was a trend toward older subjects treatment failures being reported as an increase in rescue medication use and younger subjects having more asthma exacerbations. When the groups were stratified by treatment received (Table 6), we noted that subjects aged 30 and older who received inhaled corticosteroids (ICS), alone or in combination, had greater than twice the odds of experiencing a treatment failure as subjects younger than 30 (OR, 2.79 [1.40–5.58]; $P = 0.0037$). When age was analyzed as a continuous variable, individuals above age 30 on inhaled corticosteroids had a significantly increased risk of treatment failure (OR, 1.03 [1.01–1.07]). Interestingly, there was no significant difference in treatment failures among the patients who received placebo, when stratified by age.

Although not measured in all ACRN studies, when serum IgE levels and blood and sputum eosinophils in both groups of patients were compared, there was no statistically significant difference in any of these measures between the younger and older cohorts (Table 2). Although not statistically different across age groups or sex, median IgE levels (190 vs. 149 IU/ml; $P = 0.003$) and blood eosinophil counts (267 vs. 200 cells/μl; $P = 0.021$) were slightly higher in subjects who experienced a treatment failure (*see* Table E1).

Sex

Females enrolled in the ACRN actually had slightly higher FEV_1 % than their male counterparts (84.5% vs. 81.1%; $P < 0.001$) (Table 4). There were no other statistically significant differences regarding daily symptom score, β-agonist use, exhaled nitric oxide levels, IgE levels, or blood eosinophils.

Treatment failures were more common among females (103 of 680 [15.2%] vs. 61 of 520 [11.7%]) than males, although this difference was not statistically significant. The features associated with treatment failures between sexes were not statistically significantly different, although there was a strong trend toward increased use of asthma rescue medication in females (36.2% vs. 13.1%; $P = 0.051$).

When stratified by therapy and treatment failure, there was no significant difference between females and males based on any individual therapy (data not shown). In a combined model that looked at age group and sex, there was no difference in risk of treatment failures between females aged 30 and older and their male counterparts (18.8% vs. 15.3%; $P = 0.267$).

Discussion

In this large group of subjects with mild to moderate asthma who participated in ACRN trials, the risk of treatment failures was increased in those subjects aged 30 and older and the risk increased directly with age across the whole cohort. The effect of sex on risk of treatment failure was negligible. The primary predictors of treatment failure in the older age subjects were lower lung function, longer duration of asthma, and earlier onset of asthma. Although BMI was slightly higher in the older cohort, BMI was not a risk factor for treatment failure in this cohort, consistent with previously published data by Sutherland and colleagues (28). Although not assessed in all ACRN subjects, there were no differences in blood or sputum eosinophils, nor in IgE levels between the two cohorts.

The decreased responsiveness to therapy with increasing age among subjects with mild to moderate asthma is a novel finding that warrants further study. The

Table 4. Baseline Comparisons across Sexes

Characteristic	Male (*n* = 520)		Female (*n* = 680)		*P* Value
	n	Mean (95% CI)	n	Mean (95% CI)	
Age, yr*	520	31.3 (30.5–32.2)	680	31.9 (31.2–32.7)	0.304
Nonwhite race†	520	177 (34.0)	680	228 (33.5)	0.853
BMI, kg/m^2*	520	26.3 (25.9–26.7)	680	26.8 (26.3–27.4)	0.131
A.M. peak flow, L/min*	520	508.2 (498.8–517.6)	679	379.4 (373.3–385.4)	<0.001‡
P.M. peak flow, L/min*	520	526.4 (517.2–535.7)	679	394.5 (388.6–400.4)	<0.001‡
FEV_1, L*	520	3.45 (3.39–3.51)	680	2.63 (2.59–2.68)	<0.001‡
FEV_1 % predicted*	520	81.1 (80.0–82.2)	680	84.5 (83.5–85.6)	<0.001‡
Albuterol 2-puff reversibility§	142	8.78 (4.79–13.47)	186	7.41 (3.64–14.39)	0.406
Maximum reversibility§	163	10.57 (6.92–18.31)	220	9.82 (5.82–16.56)	0.170
PC_{20}, mg/ml§	475	1.23 (0.54–3.27)	644	1.0 (0.38–3.34)	0.029‡
Daily symptom score, 0 = absent–3 = severe§	520	0.20 (0.06–0.42)	678	0.20 (0.06–0.47)	0.407
Daily β-agonist rescue puffs, # of puffs§	128	0.86 (0.11–1.96)	179	0.57 (0.08–2.0)	0.555
Exhaled nitric oxide, ppb§	276	14.3 (9.0–21.7)	403	15.0 (10.3–24.3)	0.100
Asthma quality-of-life score, 1 = worst–7 = best§	432	5.85 (5.28–6.38)	603	5.82 (5.16–6.31)	0.074
IgE, IU/ml§	176	176.5 (67.5–355.0)	274	147.5 (51.0–318.0)	0.164
Sputum eosinophils§	258	0.80 (0.20–2.90)	346	0.40 (0.0–1.60)	0.017‡
Blood eosinophils§	185	200.0 (120.0–312.0)	283	200.0 (103.0–310.0)	0.315
Treatment failure†	520	61 (11.7)	680	103 (15.2)	0.088

Definition of abbreviations: BMI = body mass index; CI = confidence interval; PC_{20} = methacholine provocative concentration required to produce a 20% decline in FEV_1.
All baseline comparisons are based on unique subjects across all studies using the most recent study data for subjects in multiple studies, with treatment failures taking precedence.
*Two-sample *t* test, mean (95% CI).
†Chi-square test, frequency (percentage).
‡$P < 0.05$.
§Wilcoxon rank sum test, median (quartile 1–quartile 3).

decline in FEV_1% predicted in older aged subjects with asthma was not surprising and is consistent with other observational data (29–31), suggesting that subjects with asthma with long-standing disease have an increased decline in their FEV_1 when compared with healthy control subjects. This may be a reflection of airway remodeling that may contribute to the increased risk of treatment failures in older subjects with asthma even though baseline measures of asthma control (Asthma Control Questionnaire scores and β-agonist use) and Asthma Quality of Life Questionnaire scores were not different. However, the observation that the increased risk of treatment failures was only seen in primarily those subjects on ICS and less so on other therapies, or even placebo, suggests that other factors may have contributed.

A potential reason for a decreased response to ICS could be explained by differences in type of airway inflammation in older patients. Th2-driven, eosinophilic inflammation is typically believed to be more responsive to corticosteroids than the Th1-driven phenotype, which may be characterized by more neutrophilic inflammation. Aged rodents have consistently been reported to have less Th2 cytokine expression than younger animals (32). Whether this applies to humans or not is unclear, but it has been reported that middle-aged and elderly subjects with asthma have an increase in airway neutrophils (11) suggestive of more Th1 inflammation. Inflammatory phenotyping of this set of subjects was limited by the absence of sputum cell measurements and other biomarkers now available for research purposes, inconsistent collection of biomarkers (blood eosinophils and serum IgE) across studies, and the relatively young age of the cohort. Furthermore, because subjects were required to be well-controlled on entry into the trials, potential differences in asthma biomarkers and airway inflammation may have been suppressed. Exhaled nitric oxide was slightly lower in the older age group, although this small difference is not likely clinically relevant. More recently recognized Th2 biomarkers, such as periostin, DPP4, and interleukins (in both serum and bronchoalveolar lavage) (33, 34), may help further delineate if older subjects with asthma have less active Th2-driven inflammation and thus potentially a reduced response to ICS.

Although subjects aged 30 and older who were on long-acting β-agonists and leukotriene modifiers also had an increased risk of treatment failures over age 30, age, when analyzed as a continuous variable, was not shown to be a risk factor for treatment failure in these subgroups. Given the lower number of subjects in

Table 5. Treatment Failures for All Treatments Separated by 50th and 75th Percentile and with Age as a Continuous Variable

Age (*5-yr Increase*)		Age (⩾*30 vs. <30*)		Age (⩾*38 vs. <38*)	
OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
1.13 (1.04–1.22)	0.0027*	1.82 (1.30–2.54)	0.0005*	1.55 (1.09–2.21)	0.0154*

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
*$P < 0.05$, all *P* values and ORs from logistic regression.

Table 6. Treatment Failure Odds by Specific Therapy

Therapy	Age ⩾30		Age <30		Age ⩾ 30 vs. Age < 30	
	Failures/Total	Failure (%)	Failures/Total	Failure (%)	OR (95% CI)	*P* Value
All treatments	100/579	17.3	64/621	10.3	1.82 (1.30–2.54)	<0.001*
All LABA	69/203	34.0	35/145	24.1	1.62 (1.0–2.61)	0.049*
LABA + ICS	22/109	20.2	7/75	9.3	2.46 (0.99–6.09)	0.052
LABA + leukotriene	28/58	48.3	10/33	30.3	2.15 (0.87–5.30)	0.098
LABA only	19/36	52.8	18/37	48.7	1.18 (0.47–2.96)	0.724
No LABA	31/376	8.2	29/476	6.1	1.39 (0.82–2.34)	0.224
All vs. no LABA			Comparison of ORs†			0.668
All ICS	31/243	12.8	12/241	5.0	2.79 (1.40–5.57)	0.004*
LABA + ICS			LABA section			
ICS only	9/134	6.7	5/166	3.0	2.32 (0.76–7.09)	0.140
No ICS	69/336	20.5	52/380	13.7	1.63 (1.10–2.42)	0.015*
All vs. no ICS			Comparison of ORs†			0.186
All leukotriene	29/99	29.3	11/75	14.7	2.41 (1.11–5.22)	0.026*
LABA + leukotriene			LABA section			
Leukotriene only	1/41	2.4	1/42	2.4	1.02 (0.06–16.95)	0.986
No leukotriene	71/480	14.8	53/546	9.7	1.61 (1.11–2.36)	0.013*
All vs. no leukotriene			Comparison of ORs†			0.361
All short-acting β-agonist (only)	3/63	4.8	4/86	4.7	1.02 (0.22–4.75)	0.975
No short-acting β-agonist	97/516	18.8	60/535	11.2	1.83 (1.29–2.59)	<0.001*
All vs. no short-acting β-agonist			Comparison of ORs†			0.469
All placebo (only)	18/138	13.0	19/182	10.4	1.29 (0.65–2.56)	0.471
No placebo	82/441	18.6	45/439	10.3	2.0 (1.35–2.96)	<0.001*
All vs. no placebo			Comparison of ORs†			0.274

Definition of abbreviations: CI = confidence interval; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; OR = odds ratio.
Significant exacerbations for DICE, IMPACT, SMOG, and PRICE (which had no treatment failures) were counted as treatment failures.
*$P < 0.05$, all *P* values and ORs from logistic regression.
†Tests the significance of the difference in ORs in the age group between the therapy groups.

these groups, these data are underpowered to show a more meaningful age-related difference in treatment failures if such were indeed present. The lack of difference in treatment failures and slightly lower rate of treatment failures among aged patients on placebo were also not surprising given that the studies that had placebo-only arms generally enrolled more mild subjects with asthma. Lastly, although the treatment algorithms for treatment failures were similar, they were not identical across studies. It seems unlikely, however, that these small differences would significantly contribute to the risk of treatment failures.

Although increased risk of treatment failures in older subjects with asthma likely has an associated biologic mechanism, it is also possible that there were socioeconomic, geographic, or medication adherence differences between the older and younger subjects with asthma that may have contributed to the increased risk of treatment failures observed in this group of patients. Socioeconomic and geographic data unfortunately were not captured in the ACRN studies but there is no reason to assume that there would be a significant difference across age groups or therapies. Medication adherence was actually slightly higher in older subjects with asthma but this was not likely clinically significant. Although racial differences are also potential confounders, the percentage of patients classified as "nonwhite" was not statistically different in the two age groups.

The lack of differences across sex was surprising given the significant amount of observational data suggesting differences across sex in prevalence, comorbidities (obesity), severity, response to therapy, and mortality (2, 35, 36). However, given the relatively mild disease severity in this ACRN cohort, differences caused by sex may not be fully appreciated. Furthermore, it seems that at least among this population of subjects with mild to moderate asthma there was not a differential response to individual therapies across sexes. Further population-based studies are required among subjects with asthma of varying severity to determine if there are important differences across sex not recognized in this analysis.

One limitation of this analysis is the relatively young age patient population. Most of the patients in the ACRN trials were younger than age 45 with the median age of 30. Fewer than 10% of patients were aged 50 or older. There was a very small number of patients aged 65 or greater preventing any significant conclusions to be drawn from this age group in whom there is a significant morbidity and mortality. It is also possible that the effect of age is not linear across all age groups but further studies are needed to determine if this is true. There was also a lack of minority representation in this patient population precluding any conclusions regarding asthma in nonwhite populations.

Other limitations include lack of geographic, socioeconomic status, and in some studies laboratory data that would help characterize inflammatory subtype of asthma. Socioeconomic status specifically would have been helpful given that age and sex differences may be associated with differences in socioeconomic status that could impact asthma control. There is also a potential selection bias given that most of these patients are recruited from large, academic medical centers and not necessarily from the general community. Lastly, because this is a retrospective cohort

analysis, it is subject to several biases and may be confounded by the variation in average age across different trials that were studying different therapies.

Strengths of this analysis include the size of the cohort analyzed and the detailed and consistent clinical, physiologic, and demographic data acquired across these well-conducted ACRN trials. Additionally, the consistent definition of treatment failures and detailed medications use were imperative in allowing assessment of response to specific therapies across this patient population.

It has previously been shown that race is important in predicting response to therapy (27, 37). Specifically, black individuals have been shown to have an increased risk of treatment failures when treated with long-acting β-agonists and potentially an increased mortality when receiving long-acting β-agonist therapy alone (37). Our data suggest that age may also be an important phenotype to consider when predicting response to therapy even among subjects with mild to moderate asthma. The evolving recognition of the heterogeneity of asthma has suggested that specific patient populations may benefit from more individualized treatment paradigms. Future prospective well-designed trials are required to determine if older patients may benefit from a different treatment approach than younger patients. ■

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