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Impact of Age and Gender on Response to Asthma Therapy

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Title: Impact of Age and Gender on Response to Asthma Therapy

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At a Glance Commentary:

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

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

This article has an online data supplement, which is accessible from this issue's table of contents online at www.atsjournals.org.

Abstract

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

Objectives: Determine if age and gender associate with distinct phenotypes and a variable response to therapy in mild-moderate asthmatics.

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

Measurements and Main Results: 1,200 subjects were identified [median age = 30.4 years, male = 520 (43.3%), female = 680(56.7%)] and analyzed. A higher proportion of subjects ≥30 years old experienced treatment failures (17.3% vs. 10.3%; OR=1.82, CI=1.30-2.54; P < 0.001); and rates increased proportionally with increasing age above 30 across the cohort [OR per year = 1.02, CI=1.01-1.04), OR per 5-year = 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 failure. A higher proportion of subjects ≥30 years old receiving controller therapy experienced treatment failures. When stratified by specific therapy, treatment failures increased consistently for every year above age 30 in subjects on inhaled corticosteroids [OR per year = 1.03 (CI 1.01-1.07)]. Females had a slightly higher FEV1% 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).

Conclusion: 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 genders.

Word Count: 249

Keywords: asthma, inhaled corticosteroid, age, gender, treatment failure.

Introduction:

Over the last two decades, much progress has been made in recognizing the heterogeneity of asthma. Cluster analysis and observational data have suggested that factors such as environment, genetics, race, obesity, gender, and specific endotypes may have important implications for asthma symptoms and management. (1, 2). Gender 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 asthmatics (3). Asthma in older patients is also associated with a more rapid decline in FEV_1 with age when compared to aging healthy controls (4). Older asthmatics 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 asthmatics. Older asthmatics 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 to 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 asthmatics to conventional asthma therapies is also not well characterized as the majority of patients enrolled in clinical asthma trials are less than 35 years old (12-14).

The influence of gender 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 gender 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(18-27). The high quality, detailed patient data acquired during these studies allow for a thorough analysis of the impact of age and gender on response to specific treatments in this group of mild-moderate asthmatics.

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) (18-27). We excluded smokers or patients who withdrew prior to starting treatment. Subjects who participated in multiple trials were only counted once (see supplementary appendix for full details on subject selection). 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, gender, self-reported race, peak expiratory flows (PEF), forced expiratory volume in 1 second (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 (28), 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. In order to distinguish important differences across age groups, we separated the cohort at the 50^{th} and 75^{th} 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 genders 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 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. To look for differences in the reasons for treatment failures between age groups, a Fisher's exact test was applied (Table 2). Finally, differences in treatment failure rates between the age groups over all therapy types and within therapy types was analyzed with logistic regression. Treatment failure was the binary dependent variable and age group was the independent variable. To compare odds ratios for treatment types, we used a logistic regression model that included age group, treatment type, and the interaction between the two variables. Odds ratios 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 above, 303 (25.3%) aged 38 and above and 680 (57.7%) were female. 795 patients were self-reported White, 233 were Black and 172 were other races. Baseline demographics separated by age group and gender are shown in Table 3 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 under age 30.

Age

Of the 579 subjects aged 30 and above, absolute measures of lung function including AM and PM peak flows, forced expiratory volume (FEV_1) and FEF_{25-75} 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 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. Body mass index (BMI) slightly higher in the older aged cohort (28.2 vs. 25.1 p <0.001) while exhaled nitric oxide was slightly lower (15.70 ppb vs. 13.65 ppb, p = 0.009).

Subjects aged 30 and above 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-year increase, OR 1.13 (1.04-1.22) for 5-year increase and OR 1.27 (1.09-1.49) for 10-year 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 to the youngest age quartile (age <25) the risk of treatment failure continued to increase after age 30 in both the 3rd quartile (ages 30-37) and 4th quartile (age ≥ 38) with the

greatest odds of treatment failure among those in the oldest age group (see supplementary appendix Table 2). 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 > 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. less than 10 years, 10-19 years etc.). No specific decade of asthma onset was found to be significantly associated with treatment failure (see supplementary appendix Table 3). BMI, daily β-agonist use, exhaled NO 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 ICS, alone or in combination, had greater than twice the odds of experiencing a treatment failure as subjects younger than 30 to [OR 2.79 (1.40-5.58), P = 0.0037]. 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 3). Although not statistically different across age groups or gender, 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 (supplementary appendix Table 1).

Gender

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 symptoms 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 genders were not statistically significantly different although there was a strong trend towards 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 gender, there was no difference in risk of treatment failures between females aged 30 and above versus their male counterparts (18.8% vs. 15.3% P = 0.267).

Discussion:

In this large group of mild-moderate asthmatics who participated in ACRN trials, the risk of treatment failures was increased in those subjects aged 30 and above and the risk increased directly with age across the whole cohort. The effect of gender 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. While 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 et al. (29). 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 mild-moderate asthmatics is a novel finding that warrants further study. The decline in FEV_1% predicted in older aged asthma subjects was not surprising and is consistent with other observational data (30-32), suggesting that asthmatics with long-standing disease have an increased decline in their FEV_1 when compared to healthy controls. This may be a reflection of airway remodeling that may contribute to the increased risk of treatment failures in older asthmatics even though baseline measures of asthma control (ACQ and beta-agonist use) and the AQLQ 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 felt 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(33). Whether this applies to humans or not is unclear, but it has been reported that middle-aged and elderly asthmatics 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, as 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 NO was slightly lower in the older age group though this small difference is not likely clinically relevant. More recently recognized Th2 biomarkers, such as periostin, DPP4, and interleukins (in both serum and BAL)(34, 35) may help further delineate if older asthmatics have less active Th2 driven inflammation and thus potentially a reduced response to ICS.

While subjects aged 30 and above who were on long-acting beta-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 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 asthmatics. 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.

While increased risk of treatment failures in older asthmatics likely has an associated biological mechanism, it is also possible that there were socioeconomic, geographic, or medication adherence differences between the older and younger asthmatics 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 asthmatics but this was not likely clinically significant. While racial differences are also potential confounders, the percentage of patients classified as “non-white” was not statistically different in the two age groups.

The lack of differences across gender was surprising given the significant amount of observational data suggesting differences across gender in prevalence, comorbidities (obesity), severity, response to therapy and mortality (2, 17, 36). However, given the relatively mild disease severity in this ACRN cohort, differences due to gender may not be fully appreciated. Furthermore, it appears that at least among this population of mild-moderate asthmatics there was not a differential response to individual therapies across genders. Further population-based studies will be required among asthmatics of varying severity to determine if there are important differences across gender not recognized in this analysis.

One limitation of this analysis is the relatively young age patient population. The majority of the patients in the ACRN trials were under age 45 with the median age of 30. Fewer than 10% of patients were aged 50 or above. There was a very small number of patient's 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 will be 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 non-Caucasian 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 (SES), specifically would have been helpful given that age and gender differences may be associated with differences in SES that could impact asthma control. There is also a

potential selection bias given that the majority of these patients are recruited from large, academic medical centers and not necessarily from the general community. Lastly, since this is a retrospective cohort analysis, it is subject to a number of 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 (28, 37). Specifically, Blacks have been shown to have an increased risk of treatment failures when treated with long-acting beta-agonist and potentially an increased mortality when receiving long-acting beta-agonist therapy alone (37). Our data suggest that age may also be an important phenotype to consider when predicting response to therapy even among mild-moderate asthmatics. 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 will be required to determine if older patients may benefit from a different treatment approach than younger patients.

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Table 1. Total subjects by study and treatment

Unique Subjects Across Studies					
Study	**Arm**	**Total N**	**Age (years) Mean ± SD**	**Age < 30 N**	**Age ≥ 30 N**
BAGS	Albuterol	120	28.4 ± 8.6	73	47
	Placebo	122	29.1 ± 9.3	76	46
SOCS	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*	Placebo+ICS (pre Taper)	14	33.8 ± 13.0	5	9
	Placebo Only (post Taper)	4	39.6 ± 18.7	1	3
	Sal+ICS (pre Taper)	43	33.5 ± 10.9	20	23
	Sal+ICS (Sham Taper)	72	36.3 ± 12.4	26	46
	Sal Only (post Taper)	24	35.7 ± 11.8	11	13
DICE	Placebo	8	31.9 ± 12.9	5	3
	ICS	100	30.6 ± 8.6	58	42
MICE	ICS	29	29.6 ± 7.2	18	11
BARGE*	Albuterol	29	30.3 ± 6.4	13	16
	Placebo	39	29.5 ± 9.7	24	15
IMPACT	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*	Montelukast	14	27.2 ± 3.5	12	2
	Beclomethasone	8	25.4 ± 5.1	7	1
SLIMSIT*	Salmeterol+Montelukast	91	34.2 ± 10.2	33	58
	Salmeterol+Beclomethasone	69	33.7 ± 10.6	29	40
PRICE	Placebo	27	32.3 ± 9.4	12	15
	ICS	30	32.7 ± 9.4	17	13
Total		1200	31.7 ± 10.1	621	579

* SLIC, BARGE, SMOG, and SLIMSIT were either crossover designs or designs that used multiple treatments over several study period

Table 2. 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

* p-value < 0.05, Fisher's Exact test

Table 3. 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
Non-white 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*
AM Peak Flow, L/min †	621	446.3 (437.8, 454.8)	578	423.3 (413.7, 432.9)	<0.001*
PM 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*

† Two-sample T-test, Mean (95% CI), ‡ Wilcoxon Rank Sum test, Median (Q1, Q3), + Chi-square test, Frequency (Percentage)
- 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.

Table 4. Baseline Comparisons across genders

Characteristic	Male (n=520)		Female (n=680)		P-value
	N	Mean (95% CI)	N	Mean (95% CI)	
Age, years †	520	31.3 (30.5, 32.2)	680	31.9 (31.2, 32.7)	0.304
Non-white 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
AM Peak Flow, L/min †	520	508.2 (498.8, 517.6)	679	379.4 (373.3, 385.4)	<0.001*
PM 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

* p-value < 0.05

† Two-sample T-test, Mean (95% CI), ‡ Wilcoxon Rank Sum test, Median (Q1, Q3), + Chi-square test, Frequency (Percentage)

- 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.

Table 5. Treatment failures separated by 50th , 75th percentile and with age as a continuous variable

All Treatments					
Age (5-year 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

* p-value < 0.05, all p-values and odds ratios 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 Long-acting Beta-agonist (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 Long-acting Beta-agonist	31/376	8.2	29/476	6.1	1.39 (0.82, 2.34)	0.224
All vs. No Long-acting Beta-agonist	comparison of odds ratios†					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 odds ratios†					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 odds ratios†					0.361
All Short-acting Beta-agonist (Only)	3/63	4.8	4/86	4.7	1.02 (0.22, 4.75)	0.975
No Short-acting Beta-agonist	97/516	18.8	60/535	11.2	1.83 (1.29, 2.59)	<0.001*
All vs. No Short-acting Beta-agonist	comparison of odds ratios†					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 odds ratios†					0.274

* p-value < 0.05, all p-values and odds ratios from logistic regression
† Tests the significance of the difference in odds ratios in the age group between the therapy groups
- significant exacerbations for DICE, IMPACT, SMOG, and PRICE (which had no treatment failures) were counted as treatment failures

Online Supplementary Data

Title: Impact of Age and Gender on Response to Asthma Therapy

Authors: Ryan M. Dunn, MD, Erik Lehman, MS, Vernon M. Chinchilli, PhD, Richard J. Martin, MD, Homer A. Boushey, MD, Elliot Israel4, MD, Monica Kraft, MD, Stephen C. Lazarus, MD, Robert F. Lemanske, MD, Njira L. Lugogo, MD, Stephen P. Peters, MD, PhD, Christine A. Sorkness, PharmD, Stanley Szefler, MD, Michael E. Wechsler, MD, MMSc on behalf of the NHLBI Asthma Clinical Research Network.

Supplementary Appendix:

METHODS

Subject Selection for analysis:

There were 1927 subjects enrolled in all included trials. Of these, non-randomized subjects (497 subjects), smokers (39 subjects) and all subjects who withdrew before getting treatment (34 subjects) were all excluded.

Of the remaining 1357 we limited data to unique subjects across by giving preference to subject data based upon the following selection criteria:

To limit the data to unique subjects ACROSS studies, we prioritized inclusion in our analysis based on the following:

#1 For any subject, we gave preference to treatment failures over non-treatment failures
#2 For any subjects who had more than one treatment failure, we gave preference to the trial in which the individual had the shortest time to treatment failure
#3 For subjects who never had a treatment failure, we gave preference to non-treatment failures with the longest time to the end of the study truncating it at 140 days.

This resulted in 1200 unique subjects across studies for inclusion in this analysis. Of the 1200 subjects, 127 participated in more than 1 study (anywhere from 2-5).

RESULTS

TABLE 1: Baseline Comparisons between subjects with and without treatment failures

Characteristic	Treatment Failure (n=164)		No Treatment Failure (n=1036)		P-value
	N	Mean (95% CI)	N	Mean (95% CI)	
Age ≥ 30 +	164	100 (61.0)	1036	479 (46.2)	<0.001*
Male +	164	61 (37.2)	1036	459 (44.3)	0.089
Non-white Race +	164	63 (38.4)	1036	342 (33.0)	0.175
BMI, kg/m^2 †	164	27.3 (26.2, 28.4)	1036	26.5 (26.2, 26.9)	0.123
AM Peak Flow, L/min †	164	403.6 (385.5, 421.7)	1035	440.3 (433.4, 447.1)	<0.001*
PM Peak Flow, L/min †	164	422.6 (405.1, 440.1)	1035	456.3 (449.5, 463.2)	<0.001*
FEV_1, L †	164	2.67 (2.56, 2.77)	1036	3.04 (2.99, 3.08)	<0.001*
FEV_1 % Predicted †	164	79.1 (77.0, 81.2)	1036	83.7 (82.8, 84.5)	<0.001*
Albuterol 2-Puff Reversibility ‡	15	10.0 (5.3, 19.3)	313	7.9 (3.8, 13.9)	0.260
Maximum Reversibility ‡	17	12.4 (7.5, 26.5)	366	10.3 (6.3, 17.0)	0.348
PC_{20}, mg/mL ‡	164	0.98 (0.44, 2.50)	955	1.18 (0.44, 3.37)	0.574
Daily Symptom Score, 0-absent – 3=severe ‡	164	0.20 (0.04, 0.49)	1034	0.20 (0.06, 0.43)	0.956
Daily β-agonist Rescue Puffs, # of puffs ‡	85	1.22 (0.21, 2.18)	222	0.54 (0.07, 1.86)	0.059
Exhaled Nitric Oxide, ppb ‡	116	16.4 (10.4, 24.8)	563	14.4 (9.4, 22.6)	0.408
Asthma Quality of Life Score, 1=worst – 7=best ‡	159	5.84 (5.0, 6.41)	876	5.84 (5.27, 6.31)	0.248
IgE, IU/mL ‡	59	190.0 (79.5, 754.0)	391	149.0 (61.4, 312.0)	0.003*
Sputum Eosinophils ‡	111	1.0 (0.20, 4.70)	493	0.50 (0.0, 2.10)	0.069
Blood Eosinophils ‡	63	267.0 (142.0, 382.0)	405	200.0 (110.0, 300.0)	0.021*

* p-value < 0.05, all p-values from Logistic Regression using treatment failure as the outcome variable
† Mean (95% CI), ‡ Median (Q1, Q3), + Frequency (Percentage)
- 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.

Table 2:
Treatment failures by age quartile:

Quartiles	Age	Treatment Failures (%)	Odds Ratio when compared to youngest quartile	Confidence Interval
First	< 25	10.8	N/A	N/A
Second	25-29	9.7	0.88	(0.52, 1.49)
Third	30-37	16.7	1.65	(1.04, 2.63)
Fourth	≥38	17.8	1.79	(1.14, 2.81)

P-value = 0.0062 for quartile comparisons

Table 3:

Percentage treatment failure for asthma age of onset age groups and the p-value testing for a difference.

Age of onset <10 (N=595) vs. ≥ 10 (N=595): 15.3% vs. 12.3%, p=0.131
Age of onset <20 (N=898) vs. ≥ 20 (N=292): 13.1% vs. 15.8%, p=0.261
Age of onset < 30 (N=1072) vs. ≥ 30 (N=118): 14.1% vs. 11.0%, p=0.360
Age of onset < 40 (N=1156) vs. ≥ 40 (N=34): 13.8% vs. 11.8%, p=0.810

There were missing data from 10 subjects

Title: Impact of Age and Gender on Response to Asthma Therapy

Authors: Ryan M. Dunn[1], MD, Erik Lehman[2], MS, Vernon M. Chinchilli[2], PhD, Richard J. Martin[1], MD, Homer A. Boushey[3], MD, Elliot Israel4, MD, Monica Kraft[5], MD, Stephen C. Lazarus[3], MD, Robert F. Lemanske[6], MD, Njira L. Lugogo[5], MD, Stephen P. Peters[7], MD, PhD, Christine A. Sorkness[6], PharmD, Stanley Szefler[8], MD, Michael E. Wechsler[1], MD, MMSc on behalf of the NHLBI Asthma Clinical Research Network.

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Author Contributions: All of the authors participated in the study's conception and design, analysis and interpretation of data, preparation and editing of manuscript and in recruiting and analysis of the primary research studies.

Running Head: Impact of Age and Gender Among Mild-moderate Asthmatics

Description Number: Adult Asthma: Outcomes

Word Count: 2878

At a Glance Commentary:

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

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

This article has an online data supplement, which is accessible from this issue's table of contents online at www.atsjournals.org.

Abstract

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

Objectives: Determine if age and gender associate with distinct phenotypes and a variable response to therapy in mild-moderate asthmatics.

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

Measurements and Main Results: 1,200 subjects were identified [median age = 30.4 years, male = 520 (43.3~~2~~%), female = 680(56.7~~8~~%)] and analyzed. A higher proportion of subjects ≥30 years old experienced treatment failures (17.3% vs. 10.3%; OR=1.82, CI=1.30-2.54; P < 0.001); and rates increased proportionally with increasing age~~10-year increments of age~~ above 30 across the cohort [OR per year = ~~=~~1.02~~27~~, CI=1.01~~9~~-1.04~~49~~), OR per 5-year = 1.13 (CI 1.04-1.22), P<0.001]. ~~There were similar proportions of females and Caucasians in both age groups.~~ Lower lung function and longer duration of asthma were associated with a higher risk of treatment failures. A higher proportion of subjects ~~-~~≥30 years old receiving controller therapy~~inhaled corticosteroids, long-acting beta-agonists and leukotriene modifiers~~ experienced treatment failures. When stratified by specific therapy, treatment failures increased consistently ~~across~~ for every year above age 30~~10-year~~

~~increments of age~~ in ~~the~~ subjects on inhaled corticosteroids [OR ~~-~~per year = 1.03~~40~~ (CI 1.01~~5~~-1.0~~8~~7)~~].].~~ Females ~~across ages~~ had a slightly higher FEV_1% predicted ~~than males~~ (84.5% vs. 81.1%; P <0.001) but similar asthma control measures. There ~~was were not not a~~was not a ~~s~~tatistically significant difference in treatment failures between ~~females and males~~females and males (15.2% vs. 11.7%, P =0.088).

Conclusion: 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 genders.

Word Count: 24~~954~~

Keywords: asthma, inhaled corticosteroid, age, gender, treatment failure.

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Introduction:

Over the last two decades, much progress has been made in recognizing the heterogeneity of asthma. Cluster analysis and observational data have suggested that factors such as environment, genetics, race, obesity, gender, and specific endotypes may have important implications for asthma symptoms and management. (1, 2). Gender 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 asthmatics (3). Asthma in older patients is also associated with a more rapid decline in FEV_1 with age when compared to aging healthy controls (4). Older asthmatics 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 asthmatics. Older asthmatics demonstrate enhanced bronchoconstriction to methacholine and a reduced awareness of bronchoconstriction(7, 8). More recent data suggest that older patients have ~~more~~ increased "small airway" involvement, increased neutrophilic inflammation and decreased eosinophil function and specific antibody response compared to younger cohorts(9-11). ~~Immunologically, there are important age-related changes in innate and adaptive immunity, including an increase in neutrophilic airway inflammation but a decrease in eosinophil effector function and~~

~~specific antibody response(10, 11) that may affect the response to therapy and susceptibility to exacerbation.~~ 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 asthmatics to conventional asthma therapies ~~, including long-acting and short-acting β-agonists, leukotriene modifiers and inhaled corticosteroids (ICS),~~ is also not well characterized as the majority of patients enrolled in clinical asthma trials are less than 35 years old (12-14).

The influence of gender 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). ~~While some of the gender differences in asthma prevalence are thought to be related to the smaller airway caliber in females (17), hormonal differences are also felt to play a role.~~ It is unknown if the ~~differences~~factors that influence the differences in asthma prevalence across gender also ~~that make females more likely to have asthma also~~ influence the~~ir~~ response to therapy~~reatment~~.

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(18-27). The high quality,

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detailed patient data acquired during these studies allow for a thorough analysis of the impact of age and gender on response to specific treatments in this group of mild-moderate asthmatics.

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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~~see Table 1~~) (18-27). We excluded smokers or patients who~~m~~ withdrew prior to starting treatment. Subjects who~~m~~ participated in multiple trials were only counted once (see supplementary appendix for full details on subject selection). –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, gender, self-reported race, peak expiratory flows (PEF), forced expiratory volume in 1 second (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 (28),

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. In order 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 genders 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 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. To look for differences in the reasons for treatment failures between age groups, a Fisher's exact test was applied (Table 23). Finally, differences in treatment failure rates between the age groups over all therapy types and within therapy types was analyzed with logistic regression ~~(Table 5)~~. Treatment failure was the binary dependent variable and age group was the independent variable. To compare odds ratios for treatment types, we used a logistic regression model that included age

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group, treatment type, and the interaction between the two variables. Odds ratios were used to quantify the magnitude and direction of any significant associations.

Results:

In this cohort of 1,200 subjects, 579 (48.3%~~25%~~) of them were aged 30 and above, 303 (25.3~~25~~%) aged 38 and above and 680 (57.7%) were female. 795 patients were self-reported White, 233 were Black and 172 were other races. Baseline demographics separated by age group and gender are shown in Table 3~~2~~ and 4~~6~~. Of the medication adherence data that were collected in 4 of 10 trials, older patients had a slightly higher median average adherence (92.5~~49~~% vs. 89.9~~0~~%, P<0.001) than those under age 30.

Age

Of the 579 subjects aged 30 and above, absolute measures of lung function including AM and PM peak flows, forced expiratory volume (FEV_1) and FEF_{25-75} 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 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. Body mass index (BMI) slightly higher in the older aged cohort (28.2 vs. 25.1 p <0.001) while exhaled nitric oxide was slightly lower (15.70 ppb vs. 13.65 ppb, p = 0.009).

Subjects aged 30 and above 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 ~~10-year increase in age~~ was associated with an increased odds of treatment failure [OR 1.02 (1.01-1.04) for 1-year increase, OR 1.13 (1.04-1.22) for 5-year increase and OR 1.27 (1.09-1.49) for 10-year increase, P = 0.003]. When separated at the 75th percentile of age (age 38), this trend continued to be statistically significant (T~~t~~able 5~~4~~). -When compared to the youngest age quartile (age <25) the risk of treatment failure continued to increase after age 30 in both the 3rd quartile (ages 30-37) and 4th quartile (age ≥ 38) with the greatest odds of treatment failure among those in the oldest age group (see supplementary appendix Table 2). 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 > 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. less than 10 years, 10-19 years etc.). No specific decade of asthma onset was found to be significantly associated with treatment failure (see supplementary appendix Table 3). BMI, daily β-agonist use, exhaled NO 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~~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 ~~When~~ the groups were stratified by treatment received (Table 6~~5~~), we noted that subjects aged 30 and older who received ICS, alone or in combination, had greater than twice the odds of experiencing a treatment failure as subjects younger than 30 to [OR 2.79 (1.40-5.58), P = 0.0037]. 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 (T~~t~~able 3~~2~~). Although not statistically different across age groups or gender, 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~~ supplementary appendix Table 1).

Gender

Females enrolled in the ACRN actually had slightly higher FEV_1% than their male counterparts (84.5% vs. 81.1%, p <0.001) (T~~see t~~able 4~~6~~). There were no other statistically significant differences regarding daily symptoms 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 genders were not statistically significantly different although there was a strong trend towards 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 gender, there was no difference in risk of treatment failures between females aged 30 and above versus their male counterparts (18.879% vs. 15.326% P = 0.267).

Discussion:

In this large group of mild-moderate asthmatics who participated in ACRN trials, the risk of treatment failures was increased in those subjects aged 30 and above and the risk increased directly with age across the whole cohort. The effect of gender 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. While 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 et al. (29). 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 mild-moderate asthmatics is a novel finding that warrants further study. The decline in FEV_1% predicted in older aged asthma subjects was not surprising and is consistent with other observational data (30-32), suggesting that asthmatics with long-standing disease have an increased decline in their FEV_1 when compared to healthy controls. This may be a reflection of airway remodeling that may contribute to the increased risk of treatment failures in older asthmatics even though baseline measures of asthma control (ACQ and beta-agonist use) and the AQLQ 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 felt 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(33). Whether this applies to humans or not is unclear, but it has been reported that middle-aged and elderly asthmatics 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, as subjects were required to be well-controlled on entry into the trials, potential differences in asthma biomarkers and airway inflammation may have been suppressed. ~~Sputum and blood eosinophils and IgE level analysis, while not different between the older and younger subgroup, was limited by inconsistent collection across studies.~~ Exhaled NO was slightly lower in the older age group though this small difference is not likely clinically relevant. More recently recognized Th2 biomarkers, such as periostin, DPP4, and interleukins (in both serum and BAL)(34, 35) may help further delineate if older asthmatics have less active Th2 driven inflammation and thus potentially a reduced response to ICS.

While subjects aged 30 and above who were on long-acting beta-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 these groups, ~~this analysis have been~~these data are underpowered to show a more meaningful age-related difference in treatment failures if ~~it is~~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 asthmatics. 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.

While increased risk of treatment failures in older asthmatics likely has an associated biological mechanism, it is also possible that there were socioeconomic, geographic, or medication adherence differences between the older and younger asthmatics 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 asthmatics but this was not likely clinically significant. While racial differences are also potential

confounders, the percentage of patients classified as "non-white" was not statistically different in the two age groups.

The lack of differences across gender was surprising given the significant amount of observational data suggesting differences across gender in prevalence, comorbidities (obesity), severity, response to therapy and mortality (2, 17, 36). However, given the relatively mild disease severity in this ACRN cohort, differences due to gender may not be fully appreciated. Furthermore, it appears that at least among this population of mild-moderate asthmatics there was not a differential response to individual therapies across genders. Further population-based studies will be required among asthmatics of varying severity to determine if there are important differences across gender not recognized in this analysis.

One limitation of this analysis is the relatively young age patient population. The majority of the patients in the ACRN trials were under age 45 with the median age of 30. Fewer than 10% of patients were aged 50 or above. There was a very small number of patient's 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 will be 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 non-Caucasian 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 (SES), specifically would have been helpful given that age and gender differences may be associated with differences in SES that could impact asthma control. There is also a potential selection bias given that the majority of these patients are recruited from large, academic medical centers and not necessarily from the general community. Lastly, since this is a retrospective cohort analysis, it is subject to a number of 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 (28, 37). Specifically, Blacks have been shown to have an increased risk of treatment failures when treated with long-acting beta-agonist and potentially an increased mortality when receiving long-acting beta-agonist therapy alone (37). Our data suggest that age may also be an important phenotype to consider when predicting response to therapy even among mild-moderate asthmatics. 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 will be required to determine if older patients may benefit from a different treatment approach than younger patients.

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Table 1. Total subjects by study and treatment

Unique Subjects Across Studies					
		Total	Age (years)	Age < 30	Age ≥ 30
Study	Arm	N	Mean ± SD	N	N
BAGS	Albuterol	120	28.4 ± 8.6	73	47
	Placebo	122	29.1 ± 9.3	76	46
SOCS	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*	Placebo+ICS (pre Taper)	14	33.8 ± 13.0	5	9
	Placebo Only (post Taper)	4	39.6 ± 18.7	1	3
	Sal+ICS (pre Taper)	43	33.5 ± 10.9	20	23
	Sal+ICS (Sham Taper)	72	36.3 ± 12.4	26	46
	Sal Only (post Taper)	24	35.7 ± 11.8	11	13
DICE	Placebo	8	31.9 ± 12.9	5	3
	ICS	100	30.6 ± 8.6	58	42
MICE	ICS	29	29.6 ± 7.2	18	11
BARGE*	Albuterol	29	30.3 ± 6.4	13	16
	Placebo	39	29.5 ± 9.7	24	15
IMPACT	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*	Montelukast	14	27.2 ± 3.5	12	2
	Beclomethasone	8	25.4 ± 5.1	7	1
SLIMSIT*	Salmeterol+Montelukast	91	34.2 ± 10.2	33	58
	Salmeterol+Beclomethasone	69	33.7 ± 10.6	29	40
PRICE	Placebo	27	32.3 ± 9.4	12	15
	ICS	30	32.7 ± 9.4	17	13
Total		1200	31.7 ± 10.1	621	579

* SLIC, BARGE, SMOG, and SLIMSIT were either crossover designs or designs that used multiple treatments over several study period

Table 2. 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

* p-value < 0.05, Fisher's Exact test

Table 3. 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
Non-white 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*
AM Peak Flow, L/min †	621	446.3 (437.8, 454.8)	578	423.3 (413.7, 432.9)	<0.001*
PM 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*

† Two-sample T-test, Mean (95% CI), ‡ Wilcoxon Rank Sum test, Median (Q1, Q3), + Chi-square test, Frequency (Percentage)
- 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.

Table 4. Baseline Comparisons across genders

Characteristic	Male (n=520)		Female (n=680)		P-value
	N	Mean (95% CI)	N	Mean (95% CI)	
Age, years †	520	31.3 (30.5, 32.2)	680	31.9 (31.2, 32.7)	0.304
Non-white 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
AM Peak Flow, L/min †	520	508.2 (498.8, 517.6)	679	379.4 (373.3, 385.4)	<0.001*
PM 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

* p-value < 0.05
† Two-sample T-test, Mean (95% CI), ‡ Wilcoxon Rank Sum test, Median (Q1, Q3), + Chi-square test, Frequency (Percentage)
- 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.

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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

* p-value < 0.05, Fisher's Exact test

Table 54. Treatment failures separated by 50th , 75th percentile and with age as a continuous variable

All Treatments					
Age (5-10-year increase)		Age (≥30 vs. <30)		Age (≥38 vs. <38)	
OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
1.1327 (1.0409, 1.2249)	0.0027	1.82 (1.30, 2.54)	0.0005	1.55 (1.09, 2.21)	0.0154

* p-value < 0.05, all p-values and odds ratios from logistic regression

Table 65. 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 Long-acting Beta-agonist (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 Long-acting Beta-agonist	31/376	8.2	29/476	6.1	1.39 (0.82, 2.34)	0.224
All vs. No Long-acting Beta-agonist	comparison of odds ratios†					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 odds ratios†					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 odds ratios†					0.361
All Short-acting Beta-agonist (Only)	3/63	4.8	4/86	4.7	1.02 (0.22, 4.75)	0.975
No Short-acting Beta-agonist	97/516	18.8	60/535	11.2	1.83 (1.29, 2.59)	<0.001*
All vs. No Short-acting Beta-agonist	comparison of odds ratios†					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 odds ratios†					0.274

* p-value < 0.05, all p-values and odds ratios from logistic regression
† Tests the significance of the difference in odds ratios in the age group between the therapy groups
- significant exacerbations for DICE, IMPACT, SMOG, and PRICE (which had no treatment failures) were counted as treatment failures

Table 6. Baseline Comparisons across genders

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Characteristic	Male (n=520)		Female (n=680)		P-value
	N	Mean (95% CI)	N	Mean (95% CI)	
Age, years †	520	31.3 (30.5, 32.2)	680	31.9 (31.2, 32.7)	0.304
Non-white Race +	520	177 (34.0)	680	228 (33.5)	0.853
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AM Peak Flow, L/min †	520	508.2 (498.8, 517.6)	679	379.4 (373.3, 385.4)	<0.001*
PM 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
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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

* p-value < 0.05

† Two-sample T-test, Mean (95% CI), ‡ Wilcoxon Rank Sum test, Median (Q1, Q3), + Chi-square test, Frequency (Percentage)

– 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.

Online Supplementary Data

Title: Impact of Age and Gender on Response to Asthma Therapy

Authors: Ryan M. Dunn, MD, Erik Lehman, MS, Vernon M. Chinchilli, PhD, Richard J. Martin, MD, Homer A. Boushey, MD, Elliot Israel4, MD, Monica Kraft, MD, Stephen C. Lazarus, MD, Robert F. Lemanske, MD, Njira L. Lugogo, MD, Stephen P. Peters, MD, PhD, Christine A. Sorkness, PharmD, Stanley Szefler, MD, Michael E. Wechsler, MD, MMSc on behalf of the NHLBI Asthma Clinical Research Network.

Supplementary Appendix:

METHODS

Subject Selection for analysis:

There were 1927 subjects enrolled in all included trials. Of these, ~~is, we excluded any~~ non-randomized subjects (497 subjects), smokers (39 subjects) and all subjects who withdrew before getting treatment (34 subjects) were all excluded.

Of the remaining 1357 we limited data to unique subjects across by giving preference to subject data based upon the following selection criteria:

To limit the data to unique subjects ACROSS studies, we prioritized inclusion in our analysis based on the following:

#1 For any subject, we gave preference to treatment failures over non-treatment failures
#2 For any subjects who had more than one treatment failure, we gave preference to the trial in which the individual had the shortest time to treatment failure
#3 For subjects who never had a treatment failure, we gave preference to non-treatment failures with the longest time to the end of the study truncating it at 140 days.

~~For any subject, give precedence to treatment failure over non-treatment failure~~
~~For subjects who have more treatment failures in more than one study give precedence to treatment failure with shortest duration~~
~~For subjects who never have a treatment failure, give precendence to non-treatment failures with the longest time to end of the study truncating at 140 days.~~

This resulted in 1200 unique subjects across studies for inclusion in this analysis. Of the 1200 subjects, 127 participated in more than 1 study (anywhere from 2-5).

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RESULTS

TABLE 1: Treatment failures by age quartile:

Quartiles	Age	Treatment Failures (%)	Odds Ratio when compared to youngest quartile	Confidence Interval
First	< 25	10.8	N/A	N/A
Second	25–29	9.7	0.88	(0.52, 1.49)
Third	30–37	16.7	1.65	(1.04, 2.63)
Fourth	≥38	17.8	1.79	(1.14, 2.81)

P-value = 0.0062 for quartile comparisons

Percentage treatment failure for asthma age of onset age groups and the p-value testing for a difference.

Age of onset <10 (N=595) vs. ≥ 10 (N=595): 15.3% vs. 12.3%, p=0.131
Age of onset <20 (N=898) vs. ≥ 20 (N=292): 13.1% vs. 15.8%, p=0.261
Age of onset ≤ 30 (N=1072) vs. ≥ 30 (N=118): 14.1% vs. 11.0%, p=0.360
Age of onset ≤ 40 (N=1156) vs. ≥ 40 (N=34): 13.8% vs. 11.8%, p=0.810

Missing data in 10 subjects

Baseline Comparisons between subjects with and without treatment failures

Characteristic	Treatment Failure (n=164) N	Treatment Failure (n=164) Mean (95% CI)	No Treatment Failure (n=1036) N	No Treatment Failure (n=1036) Mean (95% CI)	P-value
Age ≥ 30 +	164	100 (61.0)	1036	479 (46.2)	<0.001*
Male +	164	61 (37.2)	1036	459 (44.3)	0.089
Non-white Race +	164	63 (38.4)	1036	342 (33.0)	0.175
BMI, kg/m^2 †	164	27.3 (26.2, 28.4)	1036	26.5 (26.2, 26.9)	0.123
AM Peak Flow, L/min †	164	403.6 (385.5, 421.7)	1035	440.3 (433.4, 447.1)	<0.001*
PM Peak Flow, L/min †	164	422.6 (405.1, 440.1)	1035	456.3 (449.5, 463.2)	<0.001*
FEV_1, L †	164	2.67 (2.56, 2.77)	1036	3.04 (2.99, 3.08)	<0.001*
FEV_1 % Predicted †	164	79.1 (77.0, 81.2)	1036	83.7 (82.8, 84.5)	<0.001*
Albuterol 2-Puff Reversibility ‡	15	10.0 (5.3, 19.3)	313	7.9 (3.8, 13.9)	0.260
Maximum Reversibility ‡	17	12.4 (7.5, 26.5)	366	10.3 (6.3, 17.0)	0.348
PC_{20}, mg/mL ‡	164	0.98 (0.44, 2.50)	955	1.18 (0.44, 3.37)	0.574
Daily Symptom Score, 0-absent – 3=severe ‡	164	0.20 (0.04, 0.49)	1034	0.20 (0.06, 0.43)	0.956
Daily β-agonist Rescue Puffs, # of puffs ‡	85	1.22 (0.21, 2.18)	222	0.54 (0.07, 1.86)	0.059
Exhaled Nitric Oxide, ppb ‡	116	16.4 (10.4, 24.8)	563	14.4 (9.4, 22.6)	0.408
Asthma Quality of Life Score, 1=worst – 7=best ‡	159	5.84 (5.0, 6.41)	876	5.84 (5.27, 6.31)	0.248
IgE, IU/mL ‡	59	190.0 (79.5, 754.0)	391	149.0 (61.4, 312.0)	0.003*

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Sputum Eosinophils ‡	111	1.0 (0.20, 4.70)	493	0.50 (0.0, 2.10)	0.069
Blood Eosinophils ‡	63	267.0 (142.0, 382.0)	405	200.0 (110.0, 300.0)	0.021*

* p-value < 0.05, all p-values from Logistic Regression using treatment failure as the outcome variable
† Mean (95% CI), ‡ Median (Q1, Q3), + Frequency (Percentage)
- 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.

Table 2:
Treatment failures by age quartile:

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P-value = 0.0062 for quartile comparisons

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Table 3:

Percentage treatment failure for asthma age of onset age groups and the p-value testing for a difference.

Age of onset <10 (N=595) vs. ≥ 10 (N=595): 15.3% vs. 12.3%, p=0.131
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There were missing data from 10 subjects

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