Impact of Race on Asthma Treatment Failures in the Asthma Clinical Research Network

Michael E. Wechsler¹, Mario Castro², Erik Lehman³, Vernon M. Chinchilli³, E. Rand Sutherland⁴, Loren Denlinger⁵, Stephen C. Lazarus⁶, Stephen P. Peters⁷, Elliot Israel¹, and the NHLBI Asthma Clinical Research Network*

¹Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; ²Washington University School of Medicine, St. Louis, Missouri; ³Penn State University College of Medicine, Hershey, Pennsylvania; ⁴National Jewish Medical Center, Denver, Colorado; ⁵University of Wisconsin Medical School, Madison, Wisconsin; ⁶University of California, San Francisco, San Francisco, California; and ⁷Wake Forest University School of Medicine, Winston-Salem, North Carolina

Rationale: Recent studies suggest that people with asthma of different racial backgrounds may respond differently to various therapies. **Objectives:** To use data from well-characterized participants in prior Asthma Clinical Research Network (ACRN) trials to determine whether racial differences affected asthma treatment failures.

Methods: We analyzed baseline phenotypes and treatment failure rates (worsening asthma resulting in systemic corticosteroid use, hospitalization, emergency department visit, prolonged decrease in peak expiratory flow, increase in albuterol use, or safety concerns) in subjects participating in 10 ACRN trials (1993–2003). Self-declared race was reported in each trial and treatment failure rates were stratified by race.

Measurements and Main Results: A total of 1,200 unique subjects (whites = 795 [66%]; African Americans = 233 [19%]; others = 172 [14%]; mean age = 32) were included in the analyses. At baseline, African Americans had fewer asthma symptoms ($P < 0.001$) and less average daily rescue inhaler use ($P = 0.007$) than whites. There were no differences in baseline FEV₁ (% predicted); asthma quality of life; bronchial hyperreactivity; or exhaled nitric oxide concentrations. A total of 147 treatment failures were observed; a significantly higher proportion of African Americans (19.7%; $n = 46$) experienced a treatment failure compared with whites (12.7%; $n = 101$) (odds ratio = 1.7; 95% confidence interval, 1.2–2.5; $P = 0.007$). When stratified by treatment, African Americans receiving long-acting β -agonists were twice as likely as whites to experience a treatment failure (odds ratio = 2.1; 95% confidence interval, 1.3–3.6; $P = 0.004$), even when used with other controller therapies.

Conclusions: Despite having fewer asthma symptoms and less rescue β -agonist use, African-Americans with asthma have more treatment failures compared with whites, especially when taking long-acting β -agonists.

Keywords: asthma; long-acting β -agonist; African Americans; race; treatment failure

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* A complete list of members may be found before the beginning of the REFERENCES.

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Correspondence and requests for reprints should be addressed to Michael E. Wechsler, M.D., M.M.Sc., Brigham & Women's Hospital, 15 Francis Street, Boston, MA 02115. E-mail: mwechsler@partners.org

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

In Asthma Clinical Research Network trials, a greater proportion of African Americans experienced asthma treatment failures than whites despite having fewer asthma symptoms and less rescue β -agonist use.

What This Study Adds to the Field

The increased rate of treatment failures was related to increased rates of treatment failure occurring in African Americans being treated with long-acting β -agonists, suggesting that these medications should be used with caution in these patients.

Environmental and genetic factors have been shown to significantly influence response to medications in patients with asthma. Among these factors, it has been speculated that race contributes to differential response to pharmacologic therapies. In this regard, several studies have demonstrated that African Americans have worse asthma control than whites, and a disproportionately higher rate of asthma-related emergency department visits, hospitalizations, and deaths (1). Although genetic, environmental, and socioeconomic factors, including disparities in access to care and quality of care, have been implicated in these differential outcomes (2), it is also possible that there are inherent pathophysiologic or even pharmacogenomic differences between whites and African Americans that result in these discrepancies.

Over the last few years, several reports have associated specific asthma therapies with adverse responses including life-threatening asthma and asthma-related deaths, particularly among African Americans (3, 4). Because of these discrepancies in asthma control in patients with asthma of different racial backgrounds, we hypothesized that patients with asthma of different racial backgrounds respond differently to specific asthma pharmacologic therapies.

The Asthma Clinical Research Network (ACRN) is a consortium of asthma clinical research centers across the United States that has been funded by the National Heart, Lung, and Blood Institute since 1993 to perform asthma treatment trials. The diverse and large number of subjects with asthma studied by this network, using several different classes of asthma therapies, coupled with the rigorous standards of quality control, makes this cohort an ideal one to assess the effect of race on response to different therapies. In this analysis of 1,200 patients with asthma in 10 trials, we assessed the effect of race on the response

to commonly used asthma medications, as defined by treatment failure.

METHODS

Cohort and Outcomes

The study cohort consists of 1,200 unique randomized subjects from six centers across the United States participating in 10 different ACRN treatment trials. Trial subjects had limited comorbidities other than asthma. Socioeconomic status data were not captured but subjects were recruited from diverse neighborhoods and from databases of all of the network's participating asthma research centers, and from diverse practices affiliated with their institutions, which include primary care, hospital-based, academic centers, and specialty practices. Subjects were excluded from these studies if they had an asthma exacerbation within the month preceding the trial; no data were captured regarding exacerbations within the prior year. The studies analyzed had different run-in period durations, duration of therapy, and duration of follow-up; details of these trials can be found at www.acrn.org, at www.clinicaltrials.gov, and in the references (5–14). Table 1 lists the number of unique subjects of each race in each study arm.

For each trial, baseline characteristics for individuals of different self-reported races (based on National Institutes of Health categorization: white, black/African American, Asian, Native American, Hawaiian/Pacific Islander, or other) were examined and included PEF, FEV₁, asthma symptoms, asthma quality of life, use of asthma rescue medication, exhaled nitric oxide, and methacholine responsiveness (Table 2). Asthma treatment failure was defined as an asthma exacerbation, worsening lung function, increased use of asthma medication, or physician clinical judgment. Specific treatment failure criteria and types of treatment failure by race are reported in Table 3. Definitions of other specified phenotypes are in the online supplement.

Statistical Analysis

Details of statistical analysis are in the online supplement. Analyses were performed using SAS 9.2 software (SAS Institute, Inc., Cary, NC). Comparisons were made between races in terms of age using an analysis of variance and in terms of sex and treatment failure using a Pearson chi-square test. Comparisons between races at baseline for these outcomes adjusted for age, sex, center, and study were made using a linear mixed-effects model.

A comparison between races (self-reported) in terms of the rate of treatment failure was made using two different methods. Primary analysis involved logistic regression that was used to test the difference in the treatment failure rate between races. This was a cross-sectional analysis that only used one observation per subject. Treatment failure rates, odds ratios, and *P* values from this analysis are listed in Table 4. A secondary analysis adjusting for baseline characteristics that demonstrated differences between whites and African Americans (i.e., FEV₁, body-mass index, daily symptom scores, and daily β -agonist rescue puffs) was completed, but there were no notable differences between the unadjusted and adjusted results. Kaplan-Meier survival curves were constructed and a generalized Wilcoxon test was applied to test the difference in survival curves between races (Figures 1–5).

All observations used in each comparison were from unique subjects over all of the study treatment groups involved in each comparison, with no repeated measures. All of these comparisons were made within treatment types and within combinations of treatments (*see RESULTS* and Table 4).

RESULTS

A total of 1,200 unique subjects with asthma were enrolled in 10 randomized, double-blind, placebo-controlled trials in the ACRN between 1993 and 2003. Of this group, 795 subjects were self-reported white, 233 were African American, and 172 other races. Other races included American Indian, Asian, South American, mixed races, or unreported; these other races were not analyzed because of small sample size and their broad

TABLE 1. CLINICAL TRIALS EXAMINED WITH TREATMENT ARMS AND NUMBER OF UNIQUE WHITES AND AFRICAN AMERICANS IN EACH STUDY'S ARM

Study Name (reference)	Arm	Number of Whites	Number of African Americans
BAGS (5)	Albuterol	81	23
	Placebo	81	26
SOCS (6)	Placebo	35	9
	Sal	39	4
	ICS	35	6
SLIC (7)	Placebo + ICS (pretaper)	7	5
	Placebo only (posttaper)	4	0
	Sal + ICS (pretaper)	23	11
	Sal + ICS (sham taper)	49	14
	Sal only (posttaper)	17	5
DICE (8)	Placebo	5	1
	ICS	76	16
MICE (9)	ICS	22	4
BARGE* (10)	Albuterol	18	7
	Placebo	22	6
IMPACT (11)	Budesonide	57	9
	Placebo	52	10
	Zafirlukast	45	11
SMOG* (12)	Montelukast	5	6
	Beclomethasone	5	1
SLIMSIT* (13)	Sal + montelukast	42	29
	Sal + beclomethasone	47	18
PRICE (14)	Placebo	18	2
	ICS	10	10
Total		795	233

Definition of abbreviations: ICS = inhaled corticosteroids; Sal = salmeterol.

*Denotes crossover trial in which individuals may have participated in more than one trial arm.

representation. Demographics are shown in Table 2. Most of the subjects participating in the ACRN trials were female and young to middle age with similar demographic distribution between races. Of note, in the trials reported, adherence rates were 87.5% and 91%, respectively, for African Americans and whites, and there was no difference in adherence between those who had treatment failures and those who did not (90% adherence in both; *see online supplement*).

In ACRN trials, baseline absolute values for spirometric measurements were lower in African Americans with asthma compared with whites. However, when FEV₁ was presented as percent predicted, African Americans showed similar results (82.8%; 95% confidence interval, 81.1–84.4) as whites (81.0%; 95% confidence interval, 79.9–82.1). There was no significant difference in exhaled nitric oxide, methacholine bronchial reactivity, or asthma-related quality of life between whites and African Americans. When adjusted for age, sex, site of enrollment, and trial, daily asthma symptoms and use of supplemental rescue short-acting β -agonists were significantly greater in whites compared with African Americans.

Overall, African Americans were more likely to have a treatment failure than whites (46 of 233 [19.7%] vs. 101 of 795 [12.7%]; *P* = 0.0074) (Table 4), and also had a shorter time to treatment failure (Figure 1).

Table 4 lists all of the comparisons between African Americans and whites with respect to treatment failure rates for various asthma therapies (*P* values based on logistic regression analyses). Figures 1–5 display the Kaplan-Meier survival curves of African Americans and whites with respect to time to treatment failure rates for selected asthma therapies (*P* values based on generalized Wilcoxon tests). The two different analyses yield very similar *P* values. When stratified by treatment received, there were no differences between races when subjects did not receive long-acting β -agonist (LABA) therapy. However, when

TABLE 2. BASELINE CHARACTERISTICS

Characteristic	African American (n = 233)		White (n = 795)		P Value
	N	Mean (95% CI)	N	Mean (95% CI)	
Age, yr*	233	31.9 (30.5–33.2)	795	31.8 (31.1–32.5)	0.9458
Male†	233	95 (40.8)	795	343 (43.1)	0.5196
AM peak flow, L/min*	232	438.5 (425.3–451.6)	795	451.5 (442.9–460.2)	0.0891
FEV ₁ , L*	233	2.72 (2.64–2.79)	794	3.10 (3.06–3.15)	<0.0001‡
FEV ₁ % predicted*	233	82.8 (81.1–84.4)	794	81 (79.9–82.1)	0.0782
PC ₂₀ , mg/m ³ §	218	1.24 (1–1.53)	728	1.21 (1.05–1.4)	0.8562
Daily symptom scores§,	232	0.67 (0.64–0.7)	794	0.75 (0.72–0.77)	0.0001‡
Daily β-agonist rescue puffs§	229	1 (0.87–1.1)	794	1.2 (1.13–1.31)	0.0016‡
Exhaled nitric oxide, ppb§	125	16.2 (14.2–18.5)	437	14.5 (13.4–15.7)	0.1516
Asthma quality of life score§,¶	202	5.7 (5.62–5.87)	683	5.7 (5.62–5.79)	0.5812
Treatment failure†	233	46 (19.7)	795	101 (12.7)	0.0074‡

Definition of abbreviation: CI = confidence interval.

All baseline comparisons are based on unique subjects across all studies using the latest study data for subjects in multiple studies.

*Analysis of variance on original data adjusted for age, body mass index, sex, center, and study except for the analysis of age, which is not adjusted for any factors.

†Chi-square test, frequency (percentage) listed instead of mean (95% CI).

‡P value < 0.05.

§Analysis of variance on log-transformed data adjusted for age, sex, center, and study.

||Symptoms were rated daily on a four-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe).

¶Quality of life is based on the 32-question Asthma Quality of Life Questionnaire [27], with a seven-point scale (1 = totally limited, 2 = extremely limited, 3 = very limited, 4 = moderate limitation, 5 = some limitation, 6 = a little limitation, 7 = not at all limited).

individuals with asthma received LABA, African Americans were more than twice as likely to experience a treatment failure ($P = 0.0017$) despite similar baselines when these subgroups were treated with LABA (data not shown). This difference in both treatment failure rate and time to treatment failure (Figures 2–5) was apparent when LABA were used concurrently with other asthma controller therapies, including inhaled corticosteroids (ICS) ($P = 0.0385$ [Wilcoxon]; $P = 0.0661$ [logistic regression]) and leukotriene receptor antagonists (LTRA) ($P = 0.0001$ [Wilcoxon]; $P = 0.0007$ [logistic regression]). There was also a higher rate of asthma treatment failures in African Americans using ICS or LTRA compared with whites. However, this increased rate was only appreciated when individuals were concomitantly receiving LABA, but not when they received ICS or LTRA as monotherapy.

DISCUSSION

This analysis compared African Americans and whites who participated in clinical trials, and thus had equal access to asthma caregivers and asthma medications. It was found that in controlled clinical trials of adults with asthma, in which individuals were provided free access to clinicians and asthma medications, and in which subjects were monitored for medication adherence (87.5% and 91%, respectively, for African Americans and

whites), African Americans experienced a higher rate of asthma treatment failures than whites.

The increased rate of treatment failures seemed to occur in African Americans being treated with LABAs, without a protective effect by the concomitant use of either ICS or LTRA. Indeed, in treatment arms in which LABA were not used, (i.e., when subjects received only ICS, LTRA, or even just placebo), there was no significant difference between African Americans and whites. Although not necessarily causative, the association of increased treatment failures with LABA in African Americans, even in the setting of concurrent controller use, is particularly important given the widespread use of this class of therapy, and the Food and Drug Administration's mandated boxed warning suggesting that this class may pose some increased risks in a subset of the population.

Our data stress the importance of studying response to specific therapies using race as a phenotype. Although differences within racial groups can further discriminate between differential ethnicities, specific phenotypes, and drug responsiveness (15, 16), there has been little study of asthma therapies in study populations limited to African Americans or other ethnicities (17, 18). However, data from the SMART study (a large multicenter trial examining safety of salmeterol) (3) and the current findings suggest that differential response to LABAs in African Americans exist.

TABLE 3. CAUSES OF TREATMENT FAILURES IN AFRICAN AMERICANS AND WHITES IN ACRN STUDIES

Reason	African American (n = 46)		White (n = 101)		P Value
	N (%)		N (%)		
Asthma exacerbation	21 (45.7)		61 (60.4)		0.1091
Use of inhaled, oral, parental steroids for increased asthma symptoms	20 (43.5)		60 (59.4)		0.0776
Emergency treatment or hospitalization at a medical facility for an acute asthma exacerbation	5 (10.9)		6 (5.9)		0.3205
Decreased lung function (defined as 20% fall in FEV ₁ from baseline or a 35% fall in peak expiratory flow from baseline on two of three consecutive [twice daily] measurements)	7 (15.2)		23 (22.8)		0.3791
Increased asthma rescue medication use (defined as use of 8 puffs per 24 h over baseline use for a period of 48 h, or ≥ 16 puffs per 24 h for 48 h)	32 (69.6)		47 (46.5)		0.0123*
Physician clinical judgment for safety reasons	16 (34.8)		50 (49.5)		0.1098

Definition of abbreviation: ACRN = Asthma Clinical Research Network.

Data are not mutually exclusive. Each individual treatment failure could have been attributable to more than one reason.

*P value < 0.05, Fisher exact test.

TABLE 4. TREATMENT FAILURES IN AFRICAN AMERICAN AND WHITE SUBJECTS ACCORDING TO ASTHMA THERAPIES RECEIVED IN ACRN TRIALS BY LOGISTIC REGRESSION

Therapy	African American		White		African American vs. White	
	Failures/Total	% Failure	Failures/Total	% Failure	Odds Ratio (95% confidence interval)	P Value
All treatments	46/233	19.7	101/795	12.7	1.69 (1.15–2.48)	0.0074*
All LABA	36/81	44.4	55/217	25.4	2.36 (1.38–4.02)	0.0017*
LABA + ICS	10/43	23.3	13/114	11.4	2.35 (0.95–5.87)	0.0611
LABA + leukotriene	20/29	69	13/47	27.7	5.81 (2.11–16.02)	0.0007*
LABA only	6/9	66.7	29/56	51.8	1.86 (0.42–8.19)	0.4109
No LABA	10/152	6.6	46/578	8	0.81 (0.40–1.65)	0.5702
All vs. no LABA			Comparison of odds ratios			0.0190*
All ICS	13/95	13.7	22/327	6.7	2.20 (1.06–4.55)	0.0339*
LABA + ICS			See above LABA section			
ICS only	3/52	5.8	9/213	4.2	1.39 (0.36–5.32)	0.6326
No ICS	33/138	23.9	79/468	16.9	1.55 (0.98–2.45)	0.0627
All vs. no ICS			Comparison of odds ratios			0.4244
All leukotriene	20/46	43.5	14/97	14.4	4.56 (2.02–10.28)	0.0003*
LABA + leukotriene			See above LABA section			
Leukotriene only	0/17	0	1/50	2	n/a	n/a
No leukotriene	26/187	13.9	87/698	12.5	1.13 (0.71–1.82)	0.6006
All vs. no leukotriene			Comparison of odds ratios			0.0037*
All short-acting β -agonist (only)	2/29	6.9	5/98	5.1	1.38 (0.25–7.50)	0.7109
No short-acting β -agonist	44/204	21.6	96/697	13.8	1.72 (1.16–2.56)	0.0073*
All vs. no short-acting β -agonist			Comparison of odds ratios			0.8019
All placebo (only)	5/54	9.3	31/217	14.3	0.61 (0.23–1.66)	0.3341
No placebo	41/179	22.9	70/578	12.1	2.16 (1.40–3.31)	0.0004*
All vs. no placebo			Comparison of odds ratios			0.0228*

Definition of abbreviations: ACRN = Asthma Clinical Research Network; ICS = inhaled corticosteroids; LABA = long-acting β -agonists; n/a = not enough events in each category for analysis.

Significant exacerbations for DICE, IMPACT, SMOG, and PRICE (which had no treatment failures) were counted as treatment failures; *P* values differ from Figures 1–5 because logistic regression is used in Table 4 and survival analysis is used for the figures. The subset of subjects used for each treatment in each analysis is the same.

* *P* value < 0.05.

Indeed, despite the fact that multiple studies of similar and smaller size in predominantly white populations had demonstrated superiority of added salmeterol in exacerbations, symptom control, and medication use (19–21), the only prospective asthma study in African Americans to date (salmeterol or ICS vs. ICS alone in 475 African Americans) (22) revealed a blunted response to LABA in African Americans. That study failed to demonstrate that exacerbations were decreased or that asthma control (except night-time awakenings) was improved by the addition of salmeterol.

The reason for the observed association of differential response to LABAs in African Americans is unclear. Although

there was no difference in baseline lung function (FEV₁% predicted) between African Americans and whites in these studies, similar to other reports (23), whites had more symptoms and used more rescue inhaler at baseline than African Americans. This difference supports prior reports suggesting that African Americans may have differential perception of their asthma symptoms and perhaps their asthma severity, compared with whites, similar to other ethnicities (18). Because LABA use has been reported to attenuate asthma symptom perception (24), it is possible that in this population of individuals who already report fewer symptoms and use less asthma rescue medication, this class of therapy may be potentially detrimental and

Figure 1. Treatment failure Kaplan-Meier survival curves for whites (*n* = 795) and African Americans (*n* = 233) participating in all Asthma Clinical Research Network trials independent of treatment group assignment.

Figure 2. Treatment failure Kaplan-Meier survival curves for whites (n = 578) and African Americans (n = 152) participating in Asthma Clinical Research Network trials who did not receive long-acting β -agonists.

put these individuals at increased risk of adverse outcomes. Although use of LABA monotherapy (previously demonstrated in the predominantly white study to be associated with increased asthma treatment failures independent of race [6]) was not associated with an increased risk of treatment failures in African Americans, the number of African Americans who received LABA monotherapy in these trials (n = 7) was too small to permit us to draw conclusions.

Possible explanations for our findings could include differences in socioeconomic status or geography between subjects, confounding by indication, differential medication adherence, or definitions of race in the studies analyzed. Although access to medications and clinicians was equal for all subjects and subjects were recruited from all center sites using similar recruitment methods, no data regarding household income, socioeconomic status, or baseline exacerbation rate were obtained in ACRN trials, thus limiting the study's generalizability. However, adherence rates in the trials reported were high (87.5% and 91%, respectively, for African Americans and whites), and there was no difference in adherence rates between those who had

treatment failures and those who did not (90% adherence in both), suggesting that differential adherence did not play a significant role. Although study populations are often racially admixed, self-identified racial and ethnic categories are crude descriptors of individual genetic ancestry; indeed, recent studies of African Americans suggest that fewer than 5% of self-reported African Americans get misclassified when race is analyzed using ancestry informative markers (15) and that genetic ancestry does not contribute to differences in response to asthma medications among African American patients with asthma (17).

Another possible explanation for the increased asthma treatment failures observed in African Americans receiving LABA is that some African Americans have a pharmacogenomic predisposition to either nonresponse or to adverse response with this class of therapy. Although associations are likely related to multiple loci, this hypothesis is suggested by our recent genotype-stratified randomized-controlled asthma study comparing LABA with placebo in users of ICS, in which African American subjects harboring the Arg/Arg polymorphism at the sixteenth amino acid position of the β -adrenergic receptor demonstrated

Figure 3. Treatment failure Kaplan-Meier survival curves for whites (n = 217) and African Americans (n = 81) participating in Asthma Clinical Research Network trials who received long-acting β -agonists.

Figure 4. Treatment failure Kaplan-Meier survival curves for whites ($n = 114$) and African Americans ($n = 43$) participating in Asthma Clinical Research Network trials who received long-acting β -agonists and inhaled corticosteroids (ICS) concurrently.

no incremental benefit of LABA with respect to lung function compared with placebo, whereas Gly/Gly African Americans did improve with LABA (25). This analysis was not designed to evaluate these possibilities, but additional studies evaluating whether these and other factors have an impact on serious asthma outcomes in some African Americans, and efforts to identify genetic loci that correlate with these findings (e.g., β -receptor or other polymorphisms), are currently under way.

Interestingly, although there were several reasons for treatment failures in both groups (Table 3), a greater proportion of African Americans than whites reported increased use of rescue medication ($P = 0.01$) and there was a trend of a greater proportion of whites than African Americans having treatment failures caused by asthma exacerbations ($P = 0.1$) or by physician judgment ($P = 0.1$). However, because many subjects had more than one reason for failing treatment, one cannot extrapolate that treatment failures in whites were more severe; indeed, there were similar proportions of African

Americans and whites receiving emergency room care or getting hospitalized.

It remains unclear whether populations other than African Americans, or whether other asthma outcomes besides treatment failures, are differentially affected by different asthma therapies. However, the results shed light onto the novel concept in recent iterations of asthma guidelines recommending individualized treatment paradigms for different patient populations (26). Although pooled analysis of studies with different trial designs and with diverse patient populations, that may not have represented the spectrum of asthma severity, may also limit the generalizability of the findings, until further trials are performed to prospectively assess the risk of LABAs in African Americans, both with and without concomitant use of ICS, these therapies should be used with caution in this patient population, with attentive monitoring and with consideration of alternative treatment options to maximize drug efficacy and patient safety.

Figure 5. Treatment failure Kaplan-Meier survival curves for whites ($n = 47$) and African Americans ($n = 29$) participating in Asthma Clinical Research Network trials who received long-acting β -agonists and leukotriene modifiers concurrently.

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