Dyspnea and Inhaled Corticosteroid and Long-acting β-Agonist Therapy in an Occupational Cohort: A Longitudinal Study

To the Editor:

Inhaled corticosteroids in combination with long-acting β-agonists (ICS/LABA) are commonly used to treat fixed and variable obstructive lung diseases (1–6). Current treatment guidelines are based on clinical trials with restricted data before ICS/LABA initiation. Research on the trajectories of respiratory symptoms before and after ICS/LABA initiation is limited. Fire Department of the City of New York (FDNY) rescue/recovery workers experienced a massive irritant exposure after the collapse of the World Trade Center (WTC) on September 11, 2001 (9/11), resulting in increased rates of respiratory symptoms, as well as an acute drop in lung function associated with reactive airway disease and fixed airflow obstruction (7–13). Using longitudinal data on respiratory symptoms, the aims of the present study were to analyze changes in dyspnea before and after ICS/LABA initiation and to determine whether time between WTC exposure and treatment initiation was associated with treatment response.

Methods

The source population consisted of 9,638 male firefighters who were employed by FDNY on 9/11, first arrived at the WTC site between 9/11 and September 24, 2001, and underwent at least three routine medical monitoring examinations between 9/11 and September 10, 2018. The study population ($N = 1{,}073$; 11% of the source population) consisted of those who had ICS/LABA

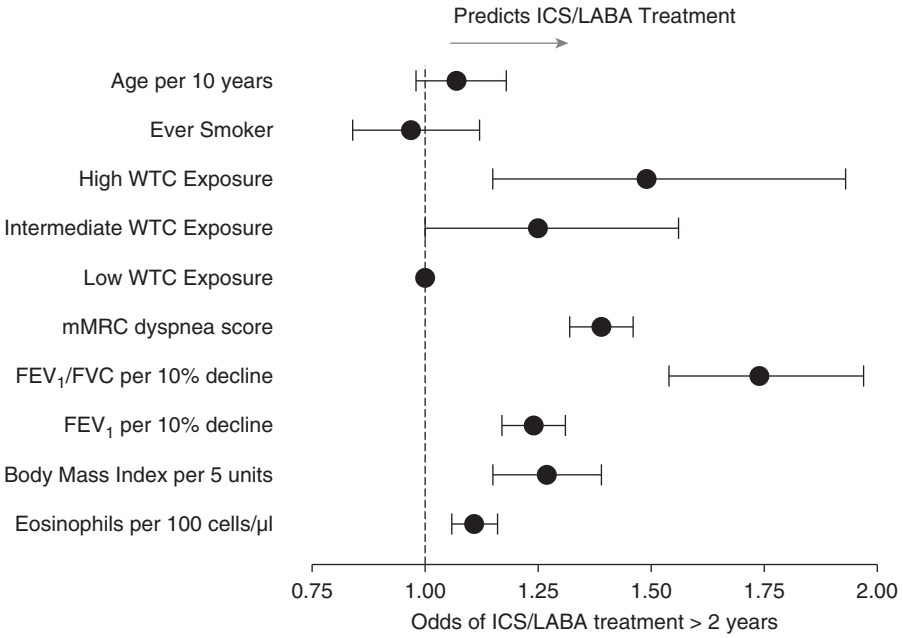

Figure 1. Forest plot showing variables associated with being included in the study population and receiving inhaled corticosteroid (ICS)/long-acting β-agonist (LABA) treatment for longer than 2 years versus not receiving ICS/LABA treatment ($n = 7{,}777$). Results shown are from a multivariable logistic regression analysis performed to determine the associations between first post-9/11 medical monitoring data and ICS/LABA treatment for longer than 2 years (odds ratios and 95% confidence intervals [bars]); data are also adjusted for race. FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; mMRC = modified Medical Research Council dyspnea scale; WTC = World Trade Center.

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Author Contributions: M.D.W. had full access to all of the data in the study and agrees to be accountable for all aspects of the work so that questions related to the accuracy and integrity of the research are appropriately investigated and resolved. B.P. and M.D.W. conceived of the study and designed it in conjunction with L.L., R.Z.-O., C.B.H., and D.J.P. B.P., A.S., R.Z.-O., T.S., and M.D.W. analyzed and interpreted the data. B.P. and M.D.W. drafted the first manuscript with critical revisions from L.L., A.S., R.Z.-O., C.B.H., M.J.F., T.S., M.P.W., H.W.C., and D.J.P. All authors approved the final manuscript.

treatment for longer than 2 years after 9/11 and had at least one modified Medical Research Council (mMRC) dyspnea scale score (14) before and at least two mMRC scores after ICS/LABA initiation. The study population completed 7,835 medical monitoring questionnaires, including mMRC scores, between August 1, 2005 and September 10, 2018. Written informed consent was provided by all participants.

Demographics, height, weight, smoking status, initial arrival time at the WTC site (WTC exposure level), and spirometric measurements were retrieved from the FDNY employee database and/or assessed during routine medical monitoring examinations. Medication data were obtained from the FDNY electronic medical record and/or pharmacy claims data. Treatment duration was defined as the interval between first and latest fill dates of ICS/LABA. Multivariable-adjusted logistic regression determined variables associated with being in the study population of ICS/LABA-treated individuals versus not receiving ICS/LABA treatment ($n = 6{,}721$). Individuals classified as "responders" to ICS/LABA were those who had an mMRC slope less than 0 after treatment initiation; "nonresponders" had an mMRC slope greater than or equal to 0. Longitudinal mMRC scores in responders and nonresponders were estimated using linear mixed effects models with random intercepts, with categorized year from ICS/LABA initiation, age, body mass index (BMI), and race as fixed effects. Multivariable logistic regression assessed pretreatment mMRC and time from 9/11 to treatment initiation as predictors for treatment response, adjusting for age and BMI pretreatment, race, ever-smoking status, and WTC exposure level.

Data analyses were performed using SAS version 9.4 software (SAS Institute). Figures were created with Prism 8 software (GraphPad Software).

Results

The study population included 1,073 individuals who received ICS/LABA therapy for more than 2 years and had at least one mMRC score before and two mMRC scores after ICS/LABA initiation. The mean (± standard deviation) numbers of mMRC scores were 4 (±2) before ICS/LABA initiation and 6 (±3) after ICS/LABA initiation. Individuals from the study population had higher WTC exposure, first post-9/11 mMRC score, blood eosinophils, and BMI and lower first post-9/11 lung function than those who did not receive ICS/LABA treatment (Figure 1).

Responders (571 of 1,073; 53%) were more likely to be ever-smokers (36% vs. 33%) but had pretreatment lung function similar to that of nonresponders (forced expiratory volume in 1 second [FEV_1] percent predicted, 89.3 ± 4% vs. 89.2 ± 13.7%; FEV_1/FVC forced vital capacity, 77.3 ± 6.0% vs. 76.8 ± 6.4%). Nonresponders (502 of 1,073; 47%) had a gradual rise in mMRC scores starting 11 years after WTC exposure (Figure 2A), culminating in worse dyspnea score at the end of longitudinal follow-up (1.55; 95% confidence interval [CI], 1.40–1.70; vs. 0.79; 95% CI, 0.64–0.94, respectively). When we assessed dyspnea trajectory relative to treatment initiation (Figure 2B), we observed that responders had a sharp increase in mMRC scores before treatment and a subsequent decrease. Nonresponders, however, had a gradual rise in mMRC scores before treatment initiation, which continued to increase during treatment.

In an adjusted multivariable model, increased time between 9/11 and treatment initiation was a strong predictor of nonresponse to therapy (Table 1). A higher pretreatment mMRC, however, was significantly associated with a favorable response to treatment.

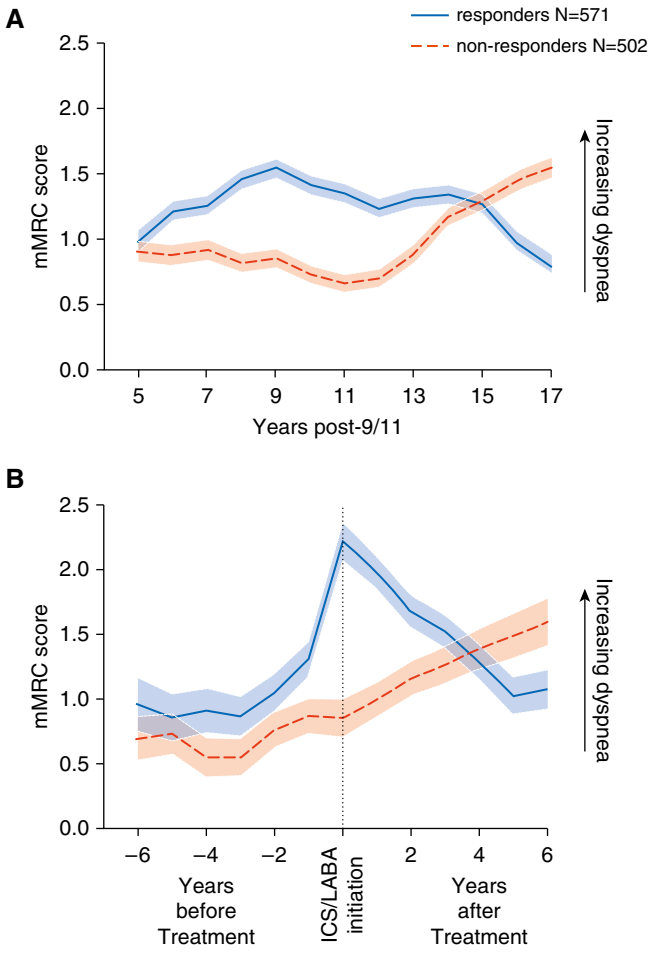

Figure 2. Longitudinal modified Medical Research Council (mMRC) dyspnea scale scores and 95% confidence intervals in linear mixed effects models, stratified by responder type. mMRC scores were estimated using linear mixed effects models with random intercepts, with categorized year, age, body mass index, and race as fixed effects. The trajectory of the responder group is shown as a solid blue line, and the trajectory in the nonresponders is shown as a broken red line. (*A*) Trajectories of mMRC scores relative to September 11, 2001 (9/11). Nonresponders had a gradual rise in mMRC scores starting 11 years after WTC exposure, culminating in worse dyspnea score at the end of longitudinal follow-up. (*B*) Trajectories of mMRC scores relative to treatment initiation. Responders had a sharp increase in mMRC scores before treatment, followed by a subsequent decrease. Nonresponders, however, had a gradual rise in mMRC scores before treatment initiation, which continued to increase after inhaled corticosteroid/long-acting β-agonist (ICS/LABA) initiation.

Discussion

This study produced longitudinal, patient-reported data on dyspnea from 1,073 previously healthy WTC-exposed firefighters who received more than 2 years of ICS/LABA treatment. The risk factors for treatment were similar to risk factors for obstructive airway disease in this cohort (7–10). We observed heterogeneity in

Table 1. Multivariable logistic regression predicting response to ICS/LABA treatment ($N = 1,073$)

Variable	Odds Ratio	95% CI		P Value
Time from 9/11 to treatment initiation, per 5 yr	0.43	0.34	0.55	<0.001
mMRC score*, per 1 point	1.21	1.10	1.33	<0.001
Age*, per 10 yr	1.06	0.87	1.28	0.60
Smoking, ever vs. never	1.17	0.89	1.53	0.26
BMI*, per 5 units	1.05	1.01	1.08	0.005
WTC exposure (reference = low exposure)				
High exposure	0.74	0.45	1.22	0.24
Intermediate exposure	0.74	0.48	1.13	0.16

Definition of abbreviations: 9/11 = September 11, 2001; BMI = body mass index; CI = confidence interval; ICS/LABA = inhaled corticosteroid and long-acting β agonist therapy; mMRC = modified Medical Research Council dyspnea scale; WTC = World Trade Center.
*Pretreatment.

dyspnea response, with only 53% of treated individuals responding to treatment. We found that responders had rapidly increasing dyspnea, as defined by mMRC score, in the 3 years before treatment initiation. Notably, in responders, dyspnea improved for 5 years after treatment initiation, returning to a level similar to baseline. Nonresponders had gradually increasing dyspnea in the 3 years before treatment, which continued to increase during the first 5 years after treatment initiation. This finding suggests that clinical trials with patient-reported outcomes may benefit from longer follow-up than that used in most randomized clinical trials.

Our study revealed pronounced differences in the trajectory of dyspnea in responders and nonresponders to ICS/LABA treatment. Responders presented earlier after WTC exposure, and higher pretreatment mMRC score predicted favorable treatment response, whereas nonresponders had a longer time between WTC exposure and symptom onset or treatment initiation. This difference in onset of symptoms suggests that nonresponders might have a different endotype of obstructive airway disease that is less responsive to ICS/LABA therapy. The lack of response to ICS/LABA therapy in those with later-onset dyspnea might be indicative of a less inflammatory type of disease.

One limitation of this study may include generalizability to other affected individuals, because this single-center study of a massively dust-exposed cohort included only previously healthy males. We also acknowledge that there may be unmeasured confounding, which is possible in all observational studies. In addition, although regression to the mean might also contribute to the difference in symptom score trajectories between responders and nonresponders, the greater symptom burden of nonresponders at the end of follow-up suggests that regression to the mean is unlikely to be the sole or even main explanation for the observed effect.

Conclusions. This longitudinal study showed that almost half of irritant-exposed patients had worsening dyspnea after ICS/LABA initiation. Treatment benefited more symptomatic individuals who initiated ICS/LABA treatment sooner after WTC exposure.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Vasopressor Dosing in Septic Shock Clinical Trials: A Systematic Review and Ecologic Study

To the Editor:

Predictive and prognostic enrichment have been proposed as strategies to improve clinical trials in sepsis (1). By selecting patients more likely to respond to treatment, or by identifying patients at higher risk for a given outcome (up to 50% risk), smaller sample sizes are needed to detect differences between treatment groups.

Patient factors associated with increased mortality in septic shock trials have been assessed, including presence or absence of vasopressors and Sequential Organ Failure Assessment score (2). However, even after accounting for these factors, there remains wide variation in mortality rates between septic shock trials. We hypothesized that higher vasopressor dose rate on enrollment, which has been previously used for prognostic enrichment in trials (3, 4), may serve as a marker of severity of shock, and may therefore be helpful as a simple prognostic enrichment tool in future trials.

Methods

We adapted a previous search strategy (2), extending the search period from January 2006 to September 2019 and including only trials that used norepinephrine as an inclusion criterion, and that reported 28/30-day, intensive care unit, in-hospital, or 90-day mortality. All stages of review were performed independently by two reviewers.

The primary exposure was the minimum vasopressor dose rate required for study inclusion. The secondary exposure was the average (mean/median) vasopressor rate given to patients on study inclusion. Studies that did not report the secondary exposure were excluded from the secondary analysis. All nonnorepinephrine vasopressor doses were converted into norepinephrine equivalents using either equivalence calculations provided in the study, or the table from Ranieri and colleagues (5). Doses of vasopressors, reported as micrograms per minute, were divided by 70 kg to calculate the approximate dose (μg/kg/min) for comparison. Our primary outcome was 28/30-day control-group mortality. When not present, 28/30-day mortality was estimated using previously published regression equations (2).

As sensitivity analyses, we excluded studies that did not report 28/30-day control-group mortality, repeated our secondary analysis using alternative equivalence conversions (6), and assessed sensitivity of our findings to exclusion of noncatecholamine vasopressors.

We used random-effects meta-analysis to calculate overall control group mortality and rate of multiple vasopressors, and random-effects metaregression to assess the association between vasopressor doses and mortality. Mortality rates were logit-transformed before meta-analysis and metaregression.

Results

A total of 30 septic shock trials met inclusion criteria (Table 1) (2, 7–10). A total of 10 trials specified a minimum fluid administration volume before enrollment, ranging from 500 ml to approximately 2,000 ml (30 ml/kg); 6 trials required central venous pressure ⩾8 mm Hg or pulmonary artery occlusion pressure ⩾12 mm Hg before enrollment; 9 studies with a total of 353 patients did not report 28/30-day mortality, but reported intensive care unit, in-hospital, or 90-day mortality, from which 28/30-day mortality was estimated (2).

Author Contributions: B.T. helped complete the systematic review, evaluated each article independently, and helped draft the manuscript; N.A.B. helped complete the systematic review, evaluated each article independently, and helped draft the manuscript; A.J.W. helped design the study and provided feedback on previous drafts of the manuscript; R.P. helped with all statistical analyses for the study and provided feedback on previous drafts of the manuscript; H.W. conceived the project, helped design the study, and provided feedback on previous drafts of the manuscript.

Registration and URL: This systematic review and ecologic study was registered on PROSPERO (registration ID: CRD42018100197; http://www.crd.york.ac.uk/prospero/display_record.php?id=crd42018100197).