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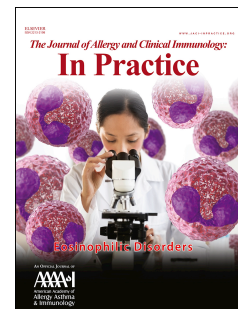
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ABSTRACT

Background: Hospitalization for asthma exacerbation is an opportune setting for initiating preventive efforts. However, hospital-initiated preventive asthma care remains underdeveloped and its effectiveness is uncertain.

Objective: To examine the effectiveness of a hospital-initiated asthma care bundle on post-hospitalization asthma care and clinical outcomes.

Methods: Prospective multicenter study of adults (18-54 years) hospitalized for asthma exacerbation in 2017-2019. During the hospitalization, we implemented an asthma-care bundle (inpatient laboratory testing, asthma education, and discharge care), and prospectively measured chronic asthma care (e.g., IgE testing, specialist care) and asthma exacerbation (i.e., systemic corticosteroid use, emergency department visit, hospitalizations) outcomes. By applying a self-controlled case series method, we examined within-person changes in these outcomes before (2-year period) and after (1-year period) the bundle implementation.

Results: Of 103 adults hospitalized for asthma exacerbation, the median age was 40 years and 72% were female. Compared to the pre-implementation period, the post-implementation period had improved post-hospitalized asthma care, including serum specific IgE testing (rate ratio [RR] 2.18, 95%CI 0.99-4.84; $P=0.051$) and evaluation by asthma specialist (RR 2.66; 95%CI 1.77-4.04; $P<0.001$). Likewise, after care bundle implementation, patients had significantly lower annual rates of systemic corticosteroid use (4.2 vs. 2.9 per person-year; RR 0.70; 95%CI 0.61-0.80; $P<0.001$), emergency department visits (3.2 vs. 2.7 per person-year; RR 0.83; 95%CI 0.72-0.95; $P=0.008$), and hospitalizations (2.1 vs. 1.8 per person-year; RR 0.82; 95%CI 0.69-0.97; $P=0.02$). Stratified analyses by sex, race/ethnicity, and health insurance yielded consistent results.

Conclusion: After hospital-initiated care bundle implementation, patients had improved post-hospitalization care and reduced rates of asthma exacerbation.

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Highlights Box

What is already known about this topic?

Hospitalization for asthma exacerbation is an opportune setting for initiating preventive care for high-risk patients. However, little is known about the effect of implementing an evidence-based preventive care bundle during hospitalization on subsequent risk of asthma exacerbation.

What does this article add to our knowledge?

In this study of adults hospitalized for asthma exacerbation, implementation of a hospital-initiated care bundle not only improved the quality of post-hospitalization asthma care but also reduced the rate of severe asthma exacerbation up to 30%.

How does this study impact current management guidelines?

The present study underscores the importance of implementing evidence-based preventive asthma care in patients hospitalized with asthma exacerbation.

Keywords: asthma exacerbation, hospitalization, quality of care, asthma management, outcomes

85 **Abbreviations:** RR, rate ratio; CI, confidence interval; ED, emergency department; EPR, Expert
86 Panel Report; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; MARC-41,
87 the 41st Multicenter Airway Research Collaboration; RCT, randomized controlled trial

INTRODUCTION

Asthma is a significant health problem in the U.S. In 2018, 25 million individuals had asthma,¹ with an estimated direct health cost of \$50 billion.² Asthma exacerbations contribute to a substantial portion of this problem—e.g., approximately 1.7 million emergency department (ED) visits and 180,000 hospitalizations in 2016 alone.³ In this context, the U.S. government has identified improving asthma care as an objective in *Healthy People 2030*, with a goal to reduce asthma exacerbations, ED visits, and hospitalizations.⁴

Despite its clinical and public health importance, recent studies have demonstrated a suboptimal quality of ED,⁵⁻⁹ inpatient,¹⁰⁻¹² and transitional^{12, 13} care in patients with asthma exacerbation. For example, a retrospective study of hospitalized patients with asthma reported that guideline-recommended transition of care to specialists was suboptimal (only 27% of hospitalized adults received a referral to an asthma specialist at hospital discharge).¹⁰ Within the sparse literature, clinical trials of adults with asthma exacerbation have examined the effect of single or limited elements of asthma care—such as asthma education,¹⁴⁻¹⁶ individual action plan,¹⁷⁻¹⁹ or facilitated referral²⁰—on subsequent asthma outcomes. Although hospitalization for asthma exacerbation is an opportune setting for initiating high-quality asthma care for these costly and high-risk patients, little is known about the effect of implementing an evidence-based preventive care “bundle”²¹ during hospitalization on subsequent risk of asthma exacerbation.

To address the knowledge gap, we conducted a prospective multicenter study of adults hospitalized for asthma exacerbation to examine the effectiveness of a hospital-initiated asthma care bundle on post-hospitalization asthma care and clinical outcomes.

METHODS

Study design, setting, and participant

This is a multicenter, prospective, “before-after” study—the 41st Multicenter Airway Research Collaboration (MARC-41)—that investigates the effectiveness of the hospital-initiated preventive care bundle in adults hospitalized for asthma exacerbation. By applying a self-controlled case series design, we compared each participant’s rate of outcomes over a 3-year period (i.e., the 2 years before vs. 1 year after the implementation of the care bundle). This design enables each participant to function as his/her own control.²² Accordingly, it has a major advantage that effects of any time-invariant covariates (e.g., the genetics, sex, race/ethnicity, site) are implicitly controlled, thereby mitigating unmeasured confounding.²²⁻²⁵

In 2017-2019, we enrolled adults (aged 18-54 years) with a physician-diagnosis of asthma, current use of inhaled corticosteroids (ICS), and a history of frequent severe exacerbations (defined by ≥ 2 bursts of systemic corticosteroids [≥ 3 days each] in a one-year period²⁶) who were hospitalized for asthma exacerbation at one of the five geographically-diverse U.S. hospitals—Henry Ford Hospital (Detroit, MI), Massachusetts General Hospital (Boston, MA), University of Arkansas for Medical Science (Little Rock AR), University of Chicago Medical Center (Chicago, IL), and Virginia Commonwealth University Medical Center (Richmond, VA). We limited patients to be aged 18-54 years in order to minimize misspecification with chronic obstructive pulmonary disease, according to previous studies.^{6, 10} We excluded patients with non-adherence to ICS (i.e., use of ICS $\leq$ once a week—based on the screening interview and medical record review at enrollment) and those without a permanent address or phone number. The institutional review board at each of the participating hospitals

approved the study (as a quality improvement study). Informed consent was obtained from all study participants.

Exposure—Hospital-initiated asthma care bundle

Immediately after hospital admission, the participating site implemented the inpatient asthma care bundle consisting of three major areas with a total of ten core elements (**Table E1**): 1) laboratory testing (serum total IgE as well as complete blood count with differential [including eosinophil quantification]); 2) education (development of written action plan, education of inhaler use technique, issuing peak flow meter, and smoking cessation assistance [for smokers]); 3) hospital discharge (or transitional) care (prescription of systemic corticosteroids, modification of ICS, and instruction/scheduling of follow-up by asthma specialist). In addition to these core (mandatory) elements, the sites also implemented optional elements (e.g., pharmacy, asthma care manager consult) based on the availability of resources at each site. These optional elements did not contribute to the overall bundle examined. The item selection of the care bundle was based on the national and international asthma guidelines,^{27, 28} systematic literature review of high-quality evidence (including the Cochrane Database of Systematic Reviews and meta-analysis of clinical trials), and input from the multidisciplinary project team (e.g., allergists, emergency physicians, internists, pulmonologists). The overall goal of the bundle was to reduce the risk of severe asthma exacerbations after the index hospitalization.

Outcome measures

The primary clinical outcome was severe asthma exacerbation—i.e., the use of systemic corticosteroids for ≥ 3 days, ED visit, or hospitalization for asthma exacerbation—during the pre-

and post-implementation periods, according to previous studies.²⁹⁻³¹ The secondary (process measure) outcomes were asthma care, including laboratory testing (total and specific IgE measurement, environmental allergen skin testing), adjustment to long-term controller medications (e.g., initiation of biologic agents), and evaluation by an asthma specialist (e.g., allergist, pulmonologist). We measured these outcomes—both in the pre-implementation period (retrospectively) and post-implementation period (prospectively)—through structured interviews and medical record review by non-blinded investigators using a standardized protocol, which has been used in previous studies.^{6, 10, 32} Structured interviews and medical record review was conducted at enrollment and during hospitalization as well as at 1 month, 6 months, and 12 months after enrollment to abstract the data on asthma care (including the electronic documentation of medication use), clinical outcomes, medical history, and laboratory testing during the pre- and post-implementation periods. All data were reviewed at the EMNet Coordinating Center at Massachusetts General Hospital (Boston, MA), and site investigators were queried about missing data and discrepancies identified by data checks.

Statistical analysis

In the current study, we applied a self-controlled case series method to multicenter data. This design relies on *within*-individual comparisons in a study sample with both the exposure and outcomes of interest.²² Specifically, to examine the effectiveness of the care bundle on the post-hospitalization asthma care and clinical outcomes, we examined the within-individual changes for each outcome between the pre- and post-implementation periods. We fit conditional Poisson regression models to estimate rate ratios (RRs) with 95% confidence intervals (95% CIs)—with the pre-implementation period (2-year period) as the reference period—for the

post-implementation 1-year period. To account for the difference in period intervals, the model incorporated an offset term (i.e., natural logarithm of the interval). Because each patient is matched to his/her own reference period, the RRs from the conditional Poisson regression model are equivalent to having fixed effects in the model.

We conducted a series of sensitivity analyses. First, in the stratified analyses that examine the potential heterogeneity in the effect of care bundle,³³⁻³⁶ we repeated the analysis with stratification by sex, race/ethnicity, insurance, baseline smoking status, obesity (body mass index ≥ 30 kg/m²), history of intubation, recent oral corticosteroid use, and initial disposition (i.e., ED observation unit, hospital ward or stepdown, and intensive care unit). Second, to minimize the potential misclassification with chronic obstructive pulmonary disease (COPD), we have conducted a subgroup analysis excluding patients with a history of COPD. Third, to address the potential effect of increased availability of biologic agents in recent years, we repeated the analysis by excluding patients who initiated anti-IL-4/IL-5 therapy after hospital discharge. Fourth, we repeated the analysis by dividing the post-implementation period into two 6-month intervals (1-6 months and 7-12 months after the index hospitalization). Lastly, to address the point that exacerbations events are recurrent and non-independent, we modeled the outcome events as binary variables. The original target sample size was 90 patients hospitalized for asthma exacerbation. We estimated that the study would have had a power of >80% to detect a 30% decrease in the incidence of severe asthma exacerbation, from 2.40 per year in the pre-implementation period to 1.68 per year in the post-implementation period at a two-sided significance level of 0.05. We analyzed the data using R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). All P-values were two-tailed, with $P < 0.05$ considered statistically significant.

RESULTS

Patient characteristics

The MARC-41 study enrolled 103 adults hospitalized for asthma exacerbation at one of the five participating hospitals during 2017-2019. Data of the 12-month post-implementation period were available in 102 patients (99%), with the other patient contributing to 6-month post-implementation period data due to loss to follow-up (i.e., a total of 1,230 person-month follow-up). In this cohort, the median age was 40 years (interquartile range, 32-49 years); 72% were women, 67% non-Hispanic black, and 12% Hispanic (**Table I**). Additionally, 60% had public health insurance while 3% had no insurance. As expected, the study patients had a large asthma burden in the pre-implementation period, reflected by 93% having at least one ED visit and 77% having hospitalization for asthma exacerbation; the index hospitalization was consistent with their chronic asthma trajectory. Despite their substantial morbidity, patients reported suboptimal quality of asthma care components in the pre-implementation period, such as only 46% of patients having an asthma action plan prior to their index hospitalization. At the index hospitalization, 53% were admitted to the observation unit, 35% to the ward or stepdown unit, and 11% to the intensive care unit.

Comparisons of asthma care between the pre- and post-implementation of care bundle

After implementation of hospital-initiated asthma care bundle during the index hospitalization, the patients had improved quality of chronic asthma care (**Figure 1**). For example, after the implementation of the care bundle, there was a non-significant increase in the rate of specific IgE measurement (RR 2.18, 95%CI 0.99-4.84; P=0.051) and a significant increase in the rate both for anti-IL-4/IL-5 therapies (RR 10.1; 95%CI 1.62-192.4; P=0.04) and

asthma specialist visit (RR 2.66; 95%CI 1.77-4.04; $P<0.001$) with adjusting for the difference in the period interval. In the sensitivity analyses, despite their limited statistical power, the association of care bundle implementation with an increased rate of asthma specialist visits was similar across sex (**Table E2**), race/ethnicity (**Table E3**), and health insurance (**Table E4**) strata.

Comparisons of clinical outcomes between the pre- and post-implementation of care bundle

After the implementation of the in-hospital care bundle, the study patients had a significantly lower rate of severe asthma exacerbation (**Figure 2**). Specifically, the annualized rate of systemic corticosteroid use decreased from 4.2 per person-year in the pre-implementation period to 2.9 per person-year in the post-implementation period, with a corresponding RR 0.70 (95%CI 0.61-0.80; $P<0.001$). Likewise, there was a significant reduction in the rate for both ED visits (3.2 vs. 2.7 per person-year; RR 0.83; 95%CI 0.72-0.95; $P=0.008$) and hospitalizations (2.1 vs. 1.8 per person-year; RR 0.82; 95%CI 0.69-0.97; $P=0.02$) after implementation of the asthma care bundle.

In the sensitivity analyses, despite the relatively limited sample size, the relationship between care bundle implementation and decreased rate of severe asthma exacerbation was generally consistent across the sex (**Table E5**), race/ethnicity (**Table E6**), and health insurance (**Table E7**) strata. For example, the rate of ED visits and hospitalizations significantly decreased in both non-Hispanic white and Hispanic individuals, while the estimated effect was not significant in non-Hispanic black individuals ($P_{\text{interaction}}<0.01$ and $P_{\text{interaction}}=0.02$, respectively; **Table E6**). With stratification by insurance, the estimated downward effects were also consistent with the main analysis in both public and private insurance strata. Likewise, similar relationships were observed in the stratified analysis by smoking status (**Table E8**), obesity (**Table E9**),

intubation history (**Table E10**), oral systemic corticosteroid use (**Table E11**), and disposition (**Table E12**). In the subgroup analysis of patients without COPD, the findings did not materially change (**Table E13**). In the sensitivity analysis excluding patients who initiated anti-IL-4/IL-5 therapy during the post-implementation period, the primary inference did not change materially—e.g., the annualized rate of systemic corticosteroid use decreased, with corresponding RR 0.71 (95%CI 0.62-0.81; $P < 0.001$; **Table E14**). In the analysis dividing the post-implementation into two 6-month periods, the rate reduction remained significant during the 7-12 months after the index hospitalization. (**Tables E15 and E16**). Lastly, in the analysis modeling the outcome events as binary variables, the findings were also consistent—e.g., reduced rate of ED visits with a corresponding RR of 0.21 (95%CI 0.07-0.70; $P = 0.01$; **Table E17**).

DISCUSSION

In this self-controlled case series analysis of a multicenter prospective study of 103 adults hospitalized for asthma exacerbation, the implementation of a hospital-initiated care bundle was associated with a significant improvement in post-hospitalization asthma care. Specifically, our data demonstrated an increase in the rate of biologic agent use and asthma specialist visit. Furthermore, there was a significant improvement in the clinical outcomes—an approximately 20%-30% decrease in the rate of subsequent severe asthma exacerbations, defined by the use of systemic corticosteroids, ED visits, or hospitalizations. The current study demonstrated the effectiveness of an evidence-based, hospital-initiated care bundle on both chronic asthma care and clinical outcomes in adults with severe asthma exacerbation.

In agreement with our findings, previous studies—mostly focusing on individual elements of asthma care—have reported reductions in asthma disease burden.^{14, 37-39} For example, in a single-center randomized clinical trial (RCT) of children and adults with asthma exacerbation in the ED, Zeiger *et al.* found that, compared to continued management from non-specialists, facilitated asthma specialist care not only increased the use of ICS but also decreased the frequency of asthma exacerbations and ED revisits.³⁸ Furthermore, in another single-center RCT of adults hospitalized for asthma exacerbation in 1996-1999, Castro *et al.* reported that, compared to conventional care, multifaceted asthma care intervention (based on the 1997 EPR-2 guidelines) reduced readmissions for asthma as well as healthcare (both direct and indirect) costs.³⁹ In contrast, earlier reports have also shown no significant change in clinical outcomes.^{17, 40-42} For example, a Cochrane systematic review of 12 RCTs of educational intervention on adults with asthma exacerbation in the ED did not show a significant reduction in ED revisits.⁴⁰ These apparent discrepancies may be attributable to the differences in study design, setting,

target populations, interventions of interest, or any combination of these factors. Regardless, the validity of our inference is strengthened by the self-controlled case series design. Its major advantage is that each individual serves as her/his own control, and hence mitigate any time-invariant confounding, which cannot be addressed in conventional observational studies.²² Additionally, the study design removes between-individual variations, thereby yielding more precise estimates despite the relatively small sample size. The current study meets the assumptions of self-controlled case series in which we modeled transient exposures (i.e., implementation of care bundle) and acute outcome events (i.e., asthma exacerbations).²² The current multicenter study builds on these prior reports, and extends them by demonstrating the effectiveness of evidence-based care bundle on both chronic asthma care and clinical outcomes in patients hospitalized with asthma exacerbation.

There are several potential explanations for the observed reductions in the frequency of severe asthma exacerbation after implementation of the hospital-initiated care bundle. First, the care “bundle” was, by definition, multifaceted (not as an isolated item) and was implemented in the inpatient setting—a time of heightened awareness and interest in health matters—reducing the outcome rates, at least partially, through an improvement in both inpatient and post-hospitalization care. Indeed, our data showed that the implementation of the bundle significantly improved post-hospitalization asthma care (e.g., the modest increase in biologic agent use and improved follow-up rate by an asthma specialist). Second, it is also possible that, after the implementation of asthma education, the patients changed their health behaviors (e.g., better medication adherence) which the current study did not directly measure after the hospital discharge. Third, non-bundle elements of the study (e.g., follow-up interviews) might have had an incremental benefit while its contribution is unlikely to have been substantial. However,

despite the observed benefit of the care bundle, the morbidity burden of these patients remained large. This is partly because the implementation and effectiveness of the care bundle were imperfect in this real-world setting. Indeed, the implementation rate of some bundle elements was relatively low—e.g., 67% for instruction for a follow-up visit with an asthma specialist and 31% for an appointment of a follow-up visit with an asthma specialist. Only 52% had a specialist visit during the post-implementation period while the rate significantly increased after the care bundle implementation. A prompt referral to a specialist at hospital discharge continued to be a challenge for administrative, financial, system-wide, and transportation reasons.⁴³ Additionally, the current study did not directly intervene on post-discharge asthma care during the follow-up period (e.g., guideline-concordant use of chronic asthma medications by the primary care physician). Furthermore, the observed heterogeneity of the effect between the race/ethnicity groups also suggests the potential need for context-specific implementations;⁴⁴ it also could have been due to the small subgroup sample sizes. Notwithstanding the complexity, the identification of an effective hospital-initiated preventive care bundle is an important finding. Our data, along with the previous studies, present cautious optimism that implementation of evidence-based hospital-initiated asthma care bundle can not only improve the quality of asthma care but also reduce asthma morbidity burden.

Limitations

The study has several potential limitations. First, the data measurement relied, in part, on medical record review for the assessment of bundle implementation, asthma care, and outcomes; consequences of under-documentation are possible. However, a prior study demonstrated that our data ascertainment methods had a high inter-rater agreement, including k

coefficient of 0.95 (almost perfect) for clinical outcomes.⁶ Second, we retrospectively measured the outcomes during the pre-implementation period while we prospectively measured the outcome during the post-implementation period. This might have up- or downwardly biased the risk in the pre-implementation period. Nevertheless, the measurement for both periods was performed using a standardized protocol. Third, the implementation of the bundle was imperfect and varied across the participating sites. Identifications of the barriers to its implementation merit further investigations. Fourth, as with any observational study, the causal inference might have been confounded by time-varying factors (e.g., an increase in comorbidities over time). A randomized controlled trial—with perfect adherence to the assigned intervention, no selection bias due to a differential loss to follow-up, and no post-randomization confounding—would yield a consistent estimate for the causal effect of interest. Fifth, the secular trend in asthma management may have affected the observed improvement in the patient outcomes. However, the observed 30% reduction in the primary outcome is unlikely to be fully explained by the secular change in asthma management alone. Sixth, in this current study, the sample size was not large. Regardless, we successfully identified significant effects of the bundle on the rate of severe asthma exacerbation. Lastly, our study sample comprised patients with frequent severe exacerbations in inner-city settings and excluded those with suboptimal medication adherence. Therefore, our inference might not be generalized to patients with mild-to-moderate asthma exacerbations or those with suboptimal adherence in non-urban or non-academic hospitals. Nonetheless, our target population has a substantial asthma morbidity burden,⁴⁵ and hence is the one for which targeted interventions are most urgently needed.

Conclusion

In sum, by applying a self-controlled case series method to prospective multicenter data of adults hospitalized for asthma exacerbation, we found that the implementation of an evidence-based asthma care bundle during hospitalization—an important opportunity for preventive care—was associated with significantly improved quality of asthma care and reduced rate of severe asthma exacerbation over the 1-year post-implementation period. These findings support a cautious optimism that the quality of asthma care can be further improved and asthma morbidity mitigated. For researchers, our study should advance research into building more robust evidence on hospital-initiated asthma care and identifying barriers for its implementation. For clinicians and hospitals, our data underscore the importance of continued efforts on the development and implementation of high-quality asthma care, which will, in turn, improve the outcomes of this population with large morbidity burden.

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REFERENCES

1. Most recent national asthma data. *Centers for Disease Control and Prevention*. Available at https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm. Accessed February 23, 2021.
2. Nurmagambetov T, Kuwahara R, Garbe P. The economic burden of asthma in the United States, 2008-2013. *Ann Am Thorac Soc* 2018; 15:348-56.
3. HCUPnet. Healthcare cost and utilization project (HCUP). 2016. *Agency for Healthcare Research and Quality, Rockville, MD*. Available at <https://hcupnet.ahrq.gov/>. Accessed February 23, 2021.
4. U.S. Department of Health and Human Services. Healthy People 2030. Washington (DC). *U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion*. Available at <https://health.gov/healthypeople>. Accessed February 23, 2021.
5. Hasegawa K, Sullivan AF, Tovar Hirashima E, Gaeta TJ, Fee C, Turner SJ, et al. A multicenter observational study of US adults with acute asthma: who are the frequent users of the emergency department? *J Allergy Clin Immunol Pract* 2014; 2:733-40.
6. Hasegawa K, Chiba T, Hagiwara Y, Watase H, Tsugawa Y, Brown DF, et al. Quality of care for acute asthma in emergency departments in Japan: a multicenter observational study. *J Allergy Clin Immunol Pract* 2013; 1:509-15.e1-3.
7. Waseem M, Leber MJ, Wasserman EJ, Sullivan AF, Camargo CA, Jr., Hasegawa K. Factors associated with concordance with the non-level-A guideline recommendations for emergency department patients with acute asthma. *J Allergy Clin Immunol Pract* 2015; 3:618-20.e2.
8. Craig S, Kuan WS, Kelly AM, Van Meer O, Motiejunaite J, Keijzers G, et al. Treatment

and outcome of adult patients with acute asthma in emergency departments in Australasia, South East Asia and Europe: Are guidelines followed?

AANZDEM/EuroDEM study. *Emerg Med Australas* 2019; 31:756-62.

9. Tsai CL, Sullivan AF, Gordon JA, Kaushal R, Magid DJ, Blumenthal D, et al. Quality of care for acute asthma in 63 US emergency departments. *J Allergy Clin Immunol* 2009; 123:354-61.

10. Hasegawa K, Tsugawa Y, Clark S, Eastin CD, Gabriel S, Herrera V, et al. Improving quality of acute asthma care in US hospitals: changes between 1999-2000 and 2012-2013. *Chest* 2016; 150:112-22.

11. Press VG, Hasegawa K, Heidt J, Bittner JC, Camargo CA, Jr. Missed opportunities to transition from nebulizers to inhalers during hospitalization for acute asthma: A multicenter observational study. *J Asthma* 2017; 54:968-76.

12. Morse RB, Hall M, Fieldston ES, McGwire G, Anspacher M, Sills MR, et al. Hospital-level compliance with asthma care quality measures at children's hospitals and subsequent asthma-related outcomes. *JAMA* 2011; 306:1454-60.

13. Hasegawa K, Ahn J, Brown MA, Press VG, Gabriel S, Herrera V, et al. Underuse of guideline-recommended long-term asthma management in children hospitalized to the intensive care unit: a multicenter observational study. *Ann Allergy Asthma Immunol* 2015; 115:10-6.e1.

14. Khmour MR, Elyan SO, Hallak HO, Jarab AS, Mukattash TL, Astal A. Pharmaceutical care for adult asthma patients: A controlled intervention one-year follow-up study. *Basic Clin Pharmacol Toxicol* 2020; 126:332-40.

15. Abdulwadud O, Abramson M, Forbes A, James A, Walters EH. Evaluation of a

- randomised controlled trial of adult asthma education in a hospital setting. *Thorax* 1999; 54:493-500.
16. Atmann O, Werner C, Linde K, Schneider A. Health literacy and eHealth among adult asthma patients - results of a cross sectional survey. *J Asthma* 2019;Oct 17;1-9.
17. Gatheral TL, Rushton A, Evans DJ, Mulvaney CA, Halcovitch NR, Whiteley G, et al. Personalised asthma action plans for adults with asthma. *Cochrane Database Syst Rev* 2017; 4:CD011859.
18. Cowie RL, Revitt SG, Underwood MF, Field SK. The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. *Chest* 1997; 112:1534-8.
19. Powell H, Gibson PG. Options for self-management education for adults with asthma. *Cochrane Database Syst Rev* 2003:CD004107.
20. Cloutier MM, Salo PM, Akinbami LJ, Cohn RD, Wilkerson JC, Diette GB, et al. Clinician agreement, self-efficacy, and adherence with the guidelines for the diagnosis and management of asthma. *J Allergy Clin Immunol Pract* 2018; 6:886-94.e4.
21. Verhaegh KJ, MacNeil-Vroomen JL, Eslami S, Geerlings SE, de Rooij SE, Buurman BM. Transitional care interventions prevent hospital readmissions for adults with chronic illnesses. *Health Aff (Millwood)* 2014; 33:1531-9.
22. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ* 2016; 354:i4515.
23. Hasegawa K, Tsugawa Y, Chang Y, Camargo CA, Jr. Risk of an asthma exacerbation after bariatric surgery in adults. *J Allergy Clin Immunol* 2015; 136:288-94.e8.
24. Goto T, Hirayama A, Faridi MK, Camargo CA, Jr., Hasegawa K. Association of bariatric surgery with risk of infectious diseases: a self-controlled case series analysis. *Clin Infect*

- Dis 2017; 65:1349-55.
25. Raita Y, Camargo CA, Jr., Faridi MK, Brown DFM, Shimada YJ, Hasegawa K. Risk of acute myocardial infarction and ischemic stroke in patients with asthma exacerbation: a population-based, self-controlled case series study. *J Allergy Clin Immunol Pract* 2020; 8:188-94.e8.
26. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43:343-73.
27. Expert panel report 3: guidelines for the diagnosis and management of asthma. Full report 2007. *National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program*. Available at https://www.nhlbi.nih.gov/sites/default/files/media/docs/EPR-3_Asthma_Full_Report_2007.pdf Accessed February 22, 2021
28. Global strategy for asthma management and prevention, 2020. *Global Initiative for Asthma*. Available at https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf. Accessed February 22, 2021
29. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43:343-73.
30. Liu MC, Chipps B, Munoz X, Devouassoux G, Bergna M, Smith SG, et al. Benefit of switching to mepolizumab from omalizumab in severe eosinophilic asthma based on patient characteristics. *Respir Res* 2021; 22:144.
31. Pelaia C, Pelaia G, Crimi C, Maglio A, Gallelli L, Terracciano R, et al. Tezepelumab: A

potential new biological therapy for severe refractory asthma. *Int J Mol Sci* 2021; 22.

32. Hasegawa K, Mansbach JM, Ajami NJ, Espinola JA, Henke DM, Petrosino JF, et al. Association of nasopharyngeal microbiota profiles with bronchiolitis severity in infants hospitalised for bronchiolitis. *Eur Respir J* 2016; 48:1329-39.

33. Goto T, Tsugawa Y, Camargo CA, Jr., Hasegawa K. Sex differences in the risk of hospitalization among patients presenting to US emergency departments with asthma exacerbation, 2010-2012. *J Allergy Clin Immunol Pract* 2016; 4:149-51.e2.

34. Chasm RM, Pei YV, Pallin DJ, Shapiro N, Snyder B, Sullivan AF, et al. Sex differences in risk of hospitalization among emergency department patients with acute asthma. *Ann Allergy Asthma Immunol* 2015; 115:70-2.e1.

35. Venkat A, Hasegawa K, Basior JM, Crandall C, Healy M, Inboriboon PC, et al. Race/ethnicity and asthma management among adults presenting to the emergency department. *Respirology* 2015; 20:994-7.

36. Hasegawa K, Stoll SJ, Ahn J, Kysia RF, Sullivan AF, Camargo CA, Jr. Association of insurance status with severity and management in ED patients with asthma exacerbation. *West J Emerg Med* 2016; 17:22-7.

37. Freitas PD, Passos NF, Carvalho-Pinto RM, Martins MA, Cavalheri V, Hill K, et al. A behaviour change intervention aimed at increasing physical activity improves clinical control in adults with asthma: a randomised controlled trial. *Chest* 2020;Sep 12;S0012-3692(20)34492-5.

38. Zeiger RS, Heller S, Mellon MH, Wald J, Falkoff R, Schatz M. Facilitated referral to asthma specialist reduces relapses in asthma emergency room visits. *J Allergy Clin Immunol* 1991; 87:1160-8.

39. Castro M, Zimmermann NA, Crocker S, Bradley J, Leven C, Schechtman KB. Asthma intervention program prevents readmissions in high healthcare users. *Am J Respir Crit Care Med* 2003; 168:1095-9.
40. Tapp S, Lasserson TJ, Rowe B. Education interventions for adults who attend the emergency room for acute asthma. *Cochrane Database Syst Rev* 2007:CD003000.
41. Knibb RC, Alviani C, Garriga-Baraut T, Mortz CG, Vazquez-Ortiz M, Angier E, et al. The effectiveness of interventions to improve self-management for adolescents and young adults with allergic conditions: A systematic review. *Allergy* 2020; 75:1881-98.
42. Velsor-Friedrich B, Militello LK, Richards MH, Harrison PR, Gross IM, Romero E, et al. Effects of coping-skills training in low-income urban African-American adolescents with asthma. *J Asthma* 2012; 49:372-9.
43. Bloom CI, Walker S, Quint JK. Inadequate specialist care referrals for high-risk asthma patients in the UK: an adult population-based cohort 2006-2017. *J Asthma* 2019;Oct 9;1-7.
44. McCallum GB, Morris PS, Brown N, Chang AB. Culture-specific programs for children and adults from minority groups who have asthma. *Cochrane Database Syst Rev* 2017; 8:CD006580.
45. Keet CA, Matsui EC, McCormack MC, Peng RD. Urban residence, neighborhood poverty, race/ethnicity, and asthma morbidity among children on Medicaid. *J Allergy Clin Immunol* 2017; 140:822-7.

Table I. Characteristics of adults hospitalized for asthma exacerbation

Characteristics	n=103
Patient characteristics	
Demographics	
Age (year), median (IQR)	40 (32-49)
Female sex	74 (72)
Race/ethnicity	
Non-Hispanic white	19 (18)
Non-Hispanic black	69 (67)
Hispanic ethnicity	12 (12)
Others	3 (3)
Health insurance	
Private	38 (37)
Public	62 (60)
No insurance	3 (3)
Household income (\$), median (IQR)*	37,942 (27,540-54,164)
Having primary care physician	95 (92)
Current smoking†	22 (21)
BMI (kg/m ²), median (IQR)‡	35 (28-43)
Medical history	
History of eczema	32 (31)
History of allergic rhinitis	66 (64)
Coexistent illnesses§	
COPD	13 (13)
Gastroesophageal reflux	12 (12)
Psychiatric disorder	10 (10)
Congestive heart failure	7 (7)
Pneumonia	6 (6)
Asthma-related history	
ED visit for asthma in the pre-implementation period	96 (93)
Hospitalized for asthma in the pre-implementation period	79 (77)
Frequency of hospitalizations, median (IQR)	2 (1-5)
History of intubation for asthma	30 (29)
Current use of oral corticosteroids	45 (44)

Current use of inhaled corticosteroids	103 (100)
Current use of long-acting beta-agonist	70 (68)
Current use of leukotriene receptor antagonists or modifiers	54 (52)
Asthma Control Test in the past 4 weeks, median (IQR)	9 (7-12)
Having PEF meter	76 (74)
Having PEF measured in the past 4 weeks	42 (55)
Having asthma action plan	47 (46)
Laboratory values during hospitalization	
WBC (cells/ μ L), mean (SD)	10,480 (4130)
Eosinophils (cells/ μ L), mean (SD)	297 (430)
Serum total IgE level (IU/ μ L), mean (SD)¶	412 (880)
Presentation and inpatient course	
Initial hospitalization location	
ED observation unit	55 (53)
Hospital ward or stepdown unit	36 (35)
ICU	12 (11)
Mechanical ventilation**	12 (12)
Disposition	
Discharged to home	101 (98)
Left against medical advice	2 (2)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ED, emergency department; ICU, intensive care unit; IQR, interquartile range; PEF, peak expiratory flow; WBC, white blood cell

Data were expressed as n (%) unless otherwise indicated. Percentages are not equal 100 because of missing.

* Estimated from patient's residence ZIP code

† Among 97 patients who have the information of the smoking status

‡ Among 90 patients who have the information of body height and weight

§ Including chronic obstructive pulmonary disease, pneumothorax, pneumonia, nasal polyps, rhinitis, sinusitis, vocal cord dysfunction, significant arrhythmia, congestive heart failure, psychiatric disorder (e.g., schizophrenia), and gastroesophageal reflux

|| Among 76 patients who had a PEF meter before the index hospitalization

¶ Among 77 patients who underwent serum total IgE measurement during the index hospitalization

** Including non-invasive and invasive positive pressure ventilation

FIGURE LEGEND**Figure 1. Within-individual comparisons of chronic asthma care between pre- and post-implementation periods**

Arrow indicates that the confidence interval of the rate ratio exceeds the lower or higher limit of the x-axis.

* Averaged over the 2-year period (a total of 206 person-years) before the implementation of the hospital-initiated care bundle

† In the 1-year period (a total of 102.5 person-years) after the implementation of hospital-initiated care bundle (including the index hospitalization)

‡ RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

§ Serum total IgE measurement during or after the index hospitalization

|| Serum specific IgE measurement after the index hospitalization

¶ Including dupilumab, benralizumab, mepolizumab, and reslizumab

Abbreviations: RR, rate ratio; CI, confidence interval; IgE, immunoglobulin E; IL-4, interleukin-4; IL-5, interleukin-5

Figure 2. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods

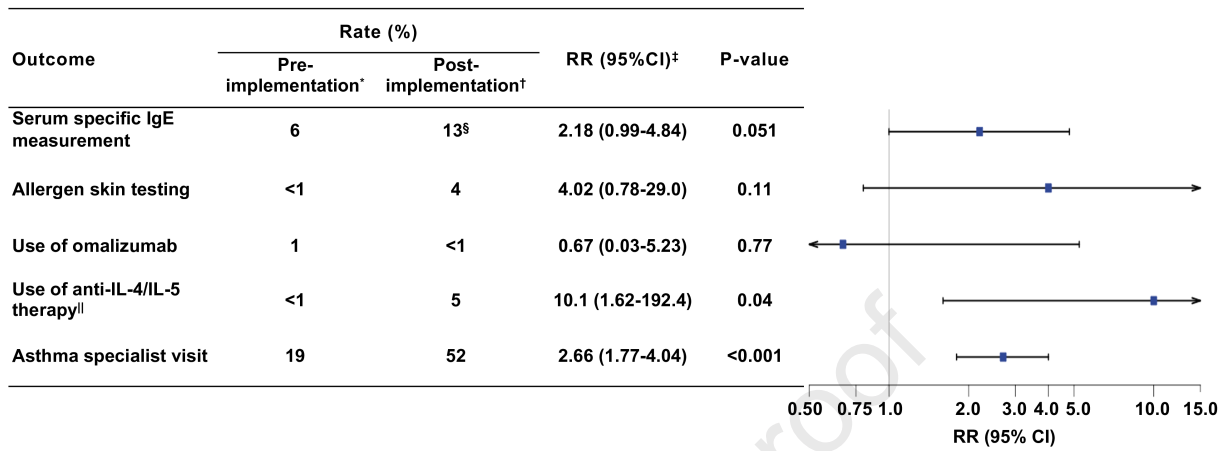
* Averaged over the 2-year period (a total of 206 person-years) before the implementation of hospital-initiated care bundle.

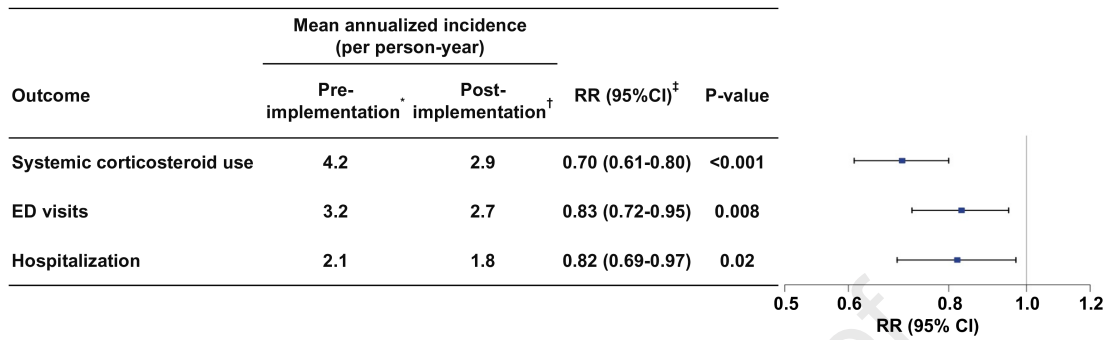
† In the 1-year period (a total of 102.5 person-years) after the implementation of hospital-initiated care bundle.

‡ RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals.

Abbreviations: RR, rate ratio; CI, confidence interval; ED, emergency department

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1 **Hospital-initiated care bundle, post-hospitalization care, and outcomes in adults with**

2 **asthma exacerbation**

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6

CONTENTS

Table E1. Implementation of hospital-initiated care bundle by item in patients hospitalized for asthma exacerbation..	4
Table E2. Within-individual comparisons of chronic asthma care between pre- and post-implementation periods, by sex.....	5
Table E3. Within-individual comparisons of chronic asthma care between pre- and post-implementation periods, by race/ethnicity.....	6
Table E4. Within-individual comparisons of chronic asthma care between pre- and post-implementation periods, by primary health insurance.....	7
Table E5. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by sex	8
Table E6. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by race/ethnicity.....	9
Table E7. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by primary health insurance.....	10
Table E8. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by smoking status.....	11
Table E9. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by obesity status.....	12
Table E10. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by history of intubation for asthma	13
Table E11. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by use of oral corticosteroids before index hospitalization.....	14
Table E12. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by initial hospitalization location	15
Table E13. Within-individual comparisons of the annualized incidence of severe asthma exacerbations between pre-and post-implementation periods in patients without chronic obstructive pulmonary disease (COPD).....	16
Table E14. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods in patients who did not initiate new biologic agents in post-implementation period.....	17
Table E15. Within-individual comparisons of the annualized incidence of severe asthma exacerbations between pre-and post-implementation (0-6 months after index hospitalization) periods.....	18

45	Table E16. Within-individual comparisons of the annualized incidence of severe asthma	
46	exacerbations between pre-and post-implementation (7-12 months after index hospitalization)	
47	periods.....	19
48	Table E17. Within-individual comparisons of the proportion of severe asthma exacerbations	
49	occurrence between pre-and post-implementation periods, modeling outcomes as binary	
50	variables.....	20

Table E1. Implementation of hospital-initiated care bundle by item in patients hospitalized for asthma exacerbation

Bundle item	% (95% CI)
Core elements	
<i>Inpatient laboratory testing</i> [*]	97 (92-99)
Serum total IgE measurement	75 (65-83)
CBC with differential measurement	93 (87-97)
<i>Inpatient asthma education</i> [†]	82 (73-89)
Development of written action plan	54 (44-64)
Education of inhaler use technique	44 (34-54)
Provision of peak flow meter [‡]	54 (33-73)
Smoking cessation assistance [§]	59 (36-79)
<i>Hospital discharge care</i>	96 (90-99)
Prescription of systemic corticosteroids	92 (85-97)
Modification of inhaled corticosteroids	23 (16-33)
Instruction for follow-up visit to asthma specialist	67 (57-76)
Appointment of follow-up visit to asthma specialist	31 (22-41)
Optional elements	38 (29-48)
Pharmacy consult	15 (8-23)
Asthma case manager consult	31 (22-41)

Abbreviations: CBC, complete blood count; CI, confidence interval; IgE, immunoglobulin E

^{*} Any of the following two items

[†] Any of the following four items; Asthma education was performed by the multidisciplinary project team (e.g., emergency physicians, internists, allergists/immunologists, pulmonologists, respiratory therapists, advanced practice providers, study staff) during the index hospitalization.

[‡] Among 26 patients who did not have a peak flow meter at hospitalization

[§] Among 22 patients who were current smoker

^{||} Any of the following four items

Table E2. Within-individual comparisons of chronic asthma care between pre- and post-implementation periods, by sex

Outcome by sex	Rate (%)		RR (95%CI) [‡]	P-value
	Pre-implementation [*]	Post-implementation [†]		
Female (n=74)				
Serum specific IgE measurement	7	11	1.45 (0.56-3.59)	0.42
Allergen skin testing	1	1	1.00 (0.05-10.5)	0.99
Use of omalizumab	<1	0	n/a	n/a
Use of anti-IL-4/IL-5 therapy [§]	<1	5.4	8.00 (0.89-71.6)	0.06
Asthma specialist visit	20	54	2.76 (1.72-4.49)	<0.001
Male (n=29)				
Serum specific IgE measurement	2	17	10.2 (1.64-194.7)	0.03
Allergen skin testing	0	0	n/a	n/a
Use of omalizumab	3	3	1.02 (0.05-10.6)	0.99
Use of anti-IL-4/IL-5 therapy [§]	0	3	n/a	n/a
Asthma specialist visit	19	45	2.41 (1.08-5.48)	0.03

Abbreviations: RR, rate ratio; CI, confidence interval; IgE, immunoglobulin E; IL-4, interleukin-4; IL-5, interleukin-5

n/a: Not estimated given the absence of an outcome in a period.

^{*} Averaged over the 2-year period (a total of 206 person-years) before the implementation of hospital-initiated care bundle

[†] In the 1-year period (a total of 102.5 person-years) after the implementation of hospital-initiated care bundle (including the index hospitalization)

[‡] RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

[§] Including dupilumab, benralizumab, mepolizumab, and reslizumab

^{||} Including allergists, pulmonologists, and asthma clinic providers

Table E3. Within-individual comparisons of chronic asthma care between pre- and post-implementation periods, by race/ethnicity

Outcome by race/ethnicity	Rate (%)		RR (95% CI) [‡]	P-value
	Pre-implementation [*]	Post-implementation [†]		
Non-Hispanic white (n=19)				
Serum specific IgE measurement	5	16	3.07 (0.51-23.3)	0.22
Allergen skin testing	3	0	n/a	n/a
Use of omalizumab	3.0	0	n/a	n/a
Use of anti-IL-4/IL-5 therapy [§]	0	16	n/a	n/a
Asthma specialist visit	32	58	1.88 (0.82-4.30)	0.13
Non-Hispanic black (n=69)				
Serum specific IgE measurement	7	12	1.78 (0.67-4.65)	0.24
Allergen skin testing	<1	0	n/a	n/a
Use of omalizumab	<1	0	n/a	n/a
Use of anti-IL-4/IL-5 therapy [§]	<1	3	4.00 (0.38-86.0)	0.26
Asthma specialist visit	18	54	2.96 (1.79-4.97)	<0.001
Hispanic (n=12)				
Serum specific IgE measurement	4	8	2.00 (0.08-50.5)	0.62
Allergen skin testing	0	8	n/a	n/a
Use of omalizumab	4	0	n/a	n/a
Use of anti-IL-4/IL-5 therapy [§]	0	0	n/a	n/a
Asthma specialist visit	8	25	3.00 (0.50-22.8)	0.23

Abbreviations: RR, rate ratio; CI, confidence interval; IgE, immunoglobulin E; IL-4, interleukin-4; IL-5, interleukin-5

n/a: Not estimated given the absence of an outcome in a period.

There were only 3 patients in the other race/ethnicity category; therefore, no statistical inference was made.

^{*} Averaged over the 2-year period (a total of 206 person-years) before the implementation of hospital-initiated care bundle

[†] In the 1-year period (a total of 102.5 person-years) after the implementation of hospital-initiated care bundle (including the index hospitalization)

[‡] RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

[§] Including dupilumab, benralizumab, mepolizumab, and reslizumab

^{||} Including allergists, pulmonologists, and asthma clinic providers

Table E4. Within-individual comparisons of chronic asthma care between pre- and post-implementation periods, by primary health insurance

Outcome by insurance	Rate (%)		RR (95% CI) [‡]	P-value
	Pre-implementation [*]	Post-implementation [†]		
Public insurance (n=62)				
Serum specific IgE measurement	7	11	1.76 (0.62-4.91)	0.27
Allergen skin testing	<1	2	2.02 (0.08-50.9)	0.62
Use of omalizumab	2	2	1.01 (0.05-10.5)	0.99
Use of anti-IL-4/IL-5 therapy [§]	<1	3	4.03 (0.39-86.7)	0.26
Asthma specialist visit	19	47	2.44 (1.42-4.22)	0.001
Private insurance (n=38)				
Serum specific IgE measurement	5	16	3.00 (0.86-11.7)	0.09
Allergen skin testing	1	0	n/a	n/a
Use of omalizumab	1	0	n/a	n/a
Use of anti-IL-4/IL-5 therapy [§]	0	8	n/a	n/a
Asthma specialist visit	21	58	2.75 (1.45-5.32)	0.002

Abbreviations: RR, rate ratio; CI, confidence interval; IgE, immunoglobulin E; IL-4, interleukin-4; IL-5, interleukin-5

n/a: Not estimated given the absence of an outcome in a period.

There were only 3 patients with no insurance; therefore, no statistical inference was made.

^{*} Averaged over the 2-year period (a total of 206 person-years) before the implementation of hospital-initiated care bundle

[†] In the 1-year period (a total of 102.5 person-years) after the implementation of hospital-initiated care bundle (including the index hospitalization)

[‡] RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

Table E5. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by sex

Outcome by sex [*]	Mean annualized incidence (per person-year)		RR (95%CI) [§]	P-value
	Pre-implementation [†]	Post-implementation [‡]		
Female (n=74)				
Systemic corticosteroid use	4.0	2.8	0.71 (0.60-0.83)	<0.001
ED visit	3.4	2.5	0.73 (0.62-0.86)	<0.001
Hospitalization	2.2	1.6	0.76 (0.61-0.93)	0.01
Male (n=29)				
Systemic corticosteroid use	4.7	3.2	0.69 (0.54-0.87)	0.002
ED visit	2.8	3.2	1.12 (0.87-1.45)	0.37
Hospitalization	2.1	2.0	0.97 (0.71-1.33)	0.87

Abbreviations: RR, rate ratio; CI, confidence interval; ED, emergency department

* Test for the interactions between the care bundle and sex: $P_{\text{interaction}}=0.86$ for systemic corticosteroid use, $P_{\text{interaction}}=0.01$ for ED visit, and $P_{\text{interaction}}=0.20$ for hospitalization

[†] Averaged over the 2-year period (a total of 206 person-years) before the implementation of hospital-initiated care bundle

[‡] In the 1-year period (a total of 102.5 person-years) after the implementation of hospital-initiated care bundle

[§] RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

Table E6. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by race/ethnicity

Outcome by race/ethnicity*	Mean annualized incidence (per person-year)		RR (95% CI) [§]	P-value
	Pre-implementation [†]	Post-implementation [‡]		
Non-Hispanic white (n=19)				
Systemic corticosteroid use	3.8	3.1	0.85 (0.63-1.15)	0.31
ED visit	4.0	2.1	0.51 (0.35-0.72)	<0.001
Hospitalization	2.8	1.5	0.54 (0.35-0.81)	0.004
Non-Hispanic black (n=69)				
Systemic corticosteroid use	4.2	3.1	0.74 (0.63-0.86)	<0.001
ED visit	3.1	3.1	0.99 (0.84-1.16)	0.87
Hospitalization	2.2	2.1	0.96 (0.79-1.17)	0.69
Hispanic (n=12)				
Systemic corticosteroid use	5.3	1.8	0.35 (0.22-0.54)	<0.001
ED visit	3.0	1.2	0.38 (0.21-0.66)	0.001
Hospitalization	1.3	0.4	0.32 (0.11-0.76)	0.02

Abbreviations: RR, rate ratio; CI, confidence interval; ED, emergency department

* There were only 3 patients in the other race/ethnicity category; therefore, no statistical inference was made. Test for the interactions between the bundle and race/ethnicity: In non-Hispanic black patients, $P_{\text{interaction}}=0.39$ for systemic corticosteroid use, $P_{\text{interaction}}<0.001$ for ED visit, and $P_{\text{interaction}}=0.02$ for hospitalization; In Hispanic patients, $P_{\text{interaction}}=0.001$ for systemic corticosteroid use, for $P_{\text{interaction}}=0.41$ for ED visit, and $P_{\text{interaction}}=0.32$ for hospitalization

[†] Averaged over the 2-year period (a total of 206 person-years) before the implementation of hospital-initiated care bundle

[‡] In the 1-year period (a total of 102.5 person-years) after the implementation of hospital-initiated care bundle

[§] RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

Table E7. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by primary health insurance

Outcome by insurance*	Mean annualized incidence (per person-year)		RR (95%CI)§	P-value
	Pre-implementation†	Post-implementation‡		
Public insurance (n=62)				
Systemic corticosteroid use	4.7	3.0	0.64 (0.54-0.75)	<0.001
ED visit	3.8	3.1	0.81 (0.68-0.95)	0.01
Hospitalization	2.8	2.4	0.85 (0.70-1.03)	0.10
Private insurance (n=38)				
Systemic corticosteroid use	3.4	2.8	0.81 (0.64-1.01)	0.06
ED visit	2.3	2.0	0.88 (0.67-1.15)	0.35
Hospitalization	1.1	0.8	0.73 (0.48-1.09)	0.13

Abbreviations: RR, rate ratio; CI, confidence interval; ED, emergency department

* There were only 3 patients with no insurance; therefore, no statistical inference was made. Test for the interactions between the care bundle and primary health insurance: $P_{\text{interaction}}=0.04$ for systemic corticosteroid use, $P_{\text{interaction}}=0.58$ for ED visit, and $P_{\text{interaction}}=0.40$ for hospitalization

† Averaged over the 2-year period (a total of 206 person-years) before the implementation of hospital-initiated care bundle

‡ In the 1-year period (a total of 102.5 person-years) after the implementation of hospital-initiated care bundle

§ RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

Table E8. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by smoking status

Outcome by smoking status*	Mean annualized incidence (per person-year)		RR (95%CI) §	P-value
	Pre-implementation†	Post-implementation‡		
Non-smoking (n=75)				
Systemic corticosteroid use	4.4	3.3	0.75 (0.65-0.86)	<0.001
ED visit	3.4	3.0	0.89 (0.76-1.03)	0.13
Hospitalization	2.2	2.0	0.93 (0.76-1.12)	0.45
Smoking (n=22)				
Systemic corticosteroid use	3.3	1.7	0.52 (0.36-0.74)	<0.001
ED visit	2.4	1.9	0.78 (0.54-1.11)	0.18
Hospitalization	1.9	1.2	0.62 (0.39-0.95)	0.03

Abbreviations: RR, rate ratio; CI, confidence interval; ED, emergency department

* Among 97 patients who had the information of smoking status. Test for the interactions between the care bundle and smoking status: $P_{\text{interaction}}=0.08$ for systemic corticosteroid use, $P_{\text{interaction}}=0.53$ for ED visit, and $P_{\text{interaction}}=0.10$ for hospitalization

† Averaged over the 2-year period (a total of 150 person-years in the non-smoking group and a total of 44 person-years in the smoking group) before the implementation of hospital-initiated care bundle.

‡ In the 1-year period (a total of 75 person-years in the non-smoking group and a total of 21.5 person-years in the smoking group) after the implementation of hospital-initiated care bundle.

§ RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals.

Table E9. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by obesity status

Outcome by obesity status*	Mean annualized incidence (per person-year)		RR (95%CI) §	P-value
	Pre-implementation†	Post-implementation‡		
Non-obesity (n=28)				
Systemic corticosteroid use	4.8	3.6	0.75 (0.59-0.94)	0.02
ED visit	2.5	3.5	1.38 (1.06-1.78)	0.02
Hospitalization	1.9	2.0	1.04 (0.75-1.43)	0.83
Obesity (n=62)				
Systemic corticosteroid use	4.2	2.8	0.68 (0.57-0.80)	<0.001
ED visit	3.8	2.7	0.72 (0.60-0.85)	<0.001
Hospitalization	2.5	2.0	0.77 (0.62-0.94)	0.01

Abbreviations: RR, rate ratio; CI, confidence interval; ED, emergency department

* Among 90 patients who had the information of body height and weight. Obesity was defined by BMI of ≥ 30 kg/m². Test for the interactions between the care bundle and obesity status: $P_{\text{interaction}}=0.49$ for systemic corticosteroid use, $P_{\text{interaction}}<0.001$ for ED visit, and $P_{\text{interaction}}=0.12$ for hospitalization

† Averaged over the 2-year period (a total of 56 person-years in the non-obesity group and a total of 124 person-years in the obesity group) before the implementation of hospital-initiated care bundle.

‡ In the 1-year period (a total of 28 person-years in the non-obesity group and a total of 61.5 person-years in the obesity group) after the implementation of hospital-initiated care bundle.

§ RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals.

Table E10. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by history of intubation for asthma

Outcome by history of intubation for asthma [*]	Mean annualized incidence (per person-year)		RR (95%CI) [§]	P-value
	Pre-implementation [†]	Post-implementation [‡]		
No history of intubation (n=72)				
Systemic corticosteroid use	4.0	2.7	0.68 (0.57-0.79)	<0.001
ED visit	2.6	2.2	0.88 (0.73-1.05)	0.16
Hospitalization	1.5	1.3	0.83 (0.65-1.06)	0.14
History of intubation (n=30)				
Systemic corticosteroid use	4.7	3.5	0.76 (0.60-0.94)	0.01
ED visit	4.9	3.8	0.77 (0.62-0.96)	0.02
Hospitalization	3.6	3.0	0.81 (0.63-1.04)	0.10

Abbreviations: RR, rate ratio; CI, confidence interval; ED, emergency department

^{*} Among 102 patients who have the information of history of intubation for asthma. Test for the interactions between the care bundle and history of intubation for asthma: $P_{\text{interaction}}=0.42$ for systemic corticosteroid use, $P_{\text{interaction}}=0.39$ for ED visit, and $P_{\text{interaction}}=0.90$ for hospitalization

[†] Averaged over the 2-year period (a total of 144 person-years in the no-history of intubation group and a total of person-years in the history of intubation group) before the implementation of hospital-initiated care bundle

[‡] In the 1-year period (a total of 71.5 person-years in the no-history of intubation group and a total of 30 person-years in the history of intubation group) after the implementation of hospital-initiated care bundle

[§] RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

Table E11. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by use of oral corticosteroids before index hospitalization

Outcome by use of oral corticosteroids*	Mean annualized incidence (per person-year)		RR (95%CI)§	P-value
	Pre-implementation†	Post-implementation‡		
No use of oral corticosteroids (n=57)				
Systemic corticosteroid use	4.7	3.1	0.67 (0.56-0.79)	<0.001
ED visit	3.6	2.9	0.79 (0.65-0.94)	0.009
Hospitalization	2.4	2.0	0.85 (0.68-1.06)	0.15
Use of oral corticosteroids (n=45)				
Systemic corticosteroid use	3.6	2.7	0.76 (0.62-0.93)	0.01
ED visit	2.8	2.5	0.90(0.72-1.12)	0.34
Hospitalization	1.9	1.4	0.76 (0.57-1.01)	0.07

Abbreviations: RR, rate ratio; CI, confidence interval; ED, emergency department

* Among 102 patients who have the information of use of oral corticosteroids before the index hospitalization. Test for the interactions between the care bundle and use of oral corticosteroids: $P_{\text{interaction}}=0.35$ for systemic corticosteroid use, $P_{\text{interaction}}=0.37$ for ED visit, and $P_{\text{interaction}}=0.56$ for hospitalization

[†] Averaged over the 2-year period (a total of 114 person-years in the non-use of oral corticosteroids group and a total of 90 person-years in the use of oral corticosteroids group) before the implementation of hospital-initiated care bundle

[‡] In the 1-year period (a total of 56.5 person-years in the non-use of oral corticosteroids group and a total of 45 person-years in the use of oral corticosteroids group) after the implementation of hospital-initiated care bundle

[§]RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

Table E12. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods, by initial hospitalization location

Outcome by initial hospitalization location*	Mean annualized incidence (per person-year)		RR (95%CI) [§]	P-value
	Pre-implementation [†]	Post-implementation [‡]		
ED observation unit (n=55)				
Systemic corticosteroid use	4.4	3.0	0.69 (0.57-0.82)	<0.001
ED visit	2.6	2.4	0.92 (0.75-1.13)	0.43
Hospitalization	1.4	1.3	0.90 (0.68-1.18)	0.45
Hospital ward or stepdown unit (n=36)				
Systemic corticosteroid use	4.1	3.0	0.73 (0.58-0.91)	0.01
ED visit	3.6	3.3	0.93 (0.75-1.16)	0.52
Hospitalization	3.0	2.4	0.80 (0.62-1.02)	0.08
Intensive care unit (n=12)				
Systemic corticosteroid use	3.4	2.3	0.69 (0.44-1.05)	0.09
ED visit	4.9	1.8	0.37 (0.23-0.58)	<0.001
Hospitalization	2.7	1.8	0.68 (0.41-1.08)	0.11

Abbreviations: RR, rate ratio; CI, confidence interval; ED, emergency department

* Test for the interactions between the bundle and initial hospitalization location: In Hospital ward or stepdown, $P_{\text{interaction}}=0.66$ for systemic corticosteroid use, $P_{\text{interaction}}=0.94$ for ED visit, and $P_{\text{interaction}}=0.55$ for hospitalization; In Intensive care unit, $P_{\text{interaction}}=0.97$ for systemic corticosteroid use, for $P_{\text{interaction}}<0.001$ for ED visit, and $P_{\text{interaction}}=0.32$ for hospitalization

[†] Averaged over the 2-year period (a total of 110 person-years in the ED observation unit group, a total of 72 person-years in the hospital ward or stepdown unit group, and a total of 24 person-years in the intensive care unit group) before the implementation of hospital-initiated care bundle

[‡] In the 1-year period (a total of 55 person-years in the ED observation unit group, a total of 35.5 person-years in the hospital ward or stepdown unit group, and a total of 12 person-years in the intensive care unit group) after the implementation of hospital-initiated care bundle

[§] RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

Table E13. Within-individual comparisons of the annualized incidence of severe asthma exacerbations between pre-and post-implementation periods in patients without chronic obstructive pulmonary disease (COPD)

Outcomes	Mean annualized incidence (per person-year)		RR (95%CI) [‡]	P-value
	Pre- implementation [*]	Post- implementation [†]		
Systemic corticosteroid use	3.9	2.6	0.68 (0.58-0.78)	<0.001
ED visit	3.3	2.4	0.74 (0.63-0.86)	<0.001
Hospitalization	2.0	1.5	0.75 (0.62-0.92)	0.01

Abbreviations: COPD, chronic obstructive pulmonary disease; RR, rate ratio; CI, confidence interval; ED, emergency department

^{*} Averaged over the 2-year period (a total of 180 person-years) before the implementation of the hospital-initiated care bundle

[†] In the 1-year period (a total of 90.5 person-years) after the implementation of the hospital-initiated care bundle

[‡] RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

Table E14. Within-individual comparisons of annualized incidence of severe asthma exacerbations between pre- and post-implementation periods in patients who did not initiate new biologic agents in post-implementation period*

Outcome	Mean annualized incidence (per person-year)		RR (95%CI) [§]	P-value
	Pre-implementation [†]	Post-implementation [‡]		
Systemic corticosteroid use	4.2	2.9	0.71(0.62-0.81)	<0.001
ED visit	3.1	2.7	0.76(0.72-1.02)	0.10
Hospitalization	2.0	1.8	0.88(0.73-1.05)	0.15

Abbreviations: RR, rate ratio; CI, confidence interval; ED, emergency department

* Defined as anti-IL-4/IL-5 therapy including dupilumab, benralizumab, mepolizumab, and reslizumab

[†] Averaged over the 2-year period (a total of 196 person-years) before the implementation of hospital-initiated care bundle

[‡] In the 1-year period (a total of 97.5 person-years) after the implementation of hospital-initiated care bundle

[§] RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

Table E15. Within-individual comparisons of the annualized incidence of severe asthma exacerbations between pre-and post-implementation (0-6 months after index hospitalization) periods

Outcome	Mean annualized incidence (per person-year)		RR (95%CI) [‡]	P-value
	Pre- implementation [*]	Post- implementation [†]		
Systemic corticosteroid use	4.2	3.1	0.74 (0.63-0.88)	<0.001
ED visit	3.2	2.8	0.88 (0.73-1.05)	0.15
Hospitalization	2.1	2.0	0.93 (0.75-1.15)	0.52

Abbreviations: RR, rate ratio; CI, confidence interval; ED, emergency department

* Averaged over the 2-year period (a total of 206 person-years) before the implementation of the hospital-initiated care bundle

[†] In the first 6-month period after the implementation of the hospital-initiated care bundle (a total of 51.5 person-years)

[‡] RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

Table E16. Within-individual comparisons of the annualized incidence of severe asthma exacerbations between pre-and post-implementation (7-12 months after index hospitalization) periods

Outcome	Mean annualized incidence (per person-year)		RR (95%CI) [‡]	P-value
	Pre- implementation [*]	Post- implementation [†]		
Systemic corticosteroid use	4.2	2.7	0.66 (0.55-0.79)	<0.001
ED visit	3.2	2.5	0.77 (0.64-0.93)	0.007
Hospitalization	2.1	1.5	0.70 (0.55-0.89)	0.004

Abbreviations: RR, rate ratio; CI, confidence interval; ED, emergency department

* Averaged over the 2-year period (a total of 206 person-years) before the implementation of the hospital-initiated care bundle

† In the second 6-month period after the implementation of the hospital-initiated care bundle (a total of 51 person-years)

‡ RRs are for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional Poisson regression models accounting for the difference in period intervals

Table E17. Within-individual comparisons of the proportion of severe asthma exacerbations occurrence between pre-and post-implementation periods, modeling outcomes as binary variables

Outcome	Proportion (%)		OR (95%CI)*	P-value
	Pre-implementation	Post-implementation		
Systemic corticosteroid use	100	73	N.A. †	N.A. †
ED visit	93	69	0.21 (0.07-0.70)	0.01
Hospitalization	77	58	0.59 (0.27-1.30)	0.19

Abbreviations: OR, odds ratio; CI, confidence interval; ED, emergency department

* ORs for the occurrence of outcome event (yes vs. no) for post- vs. pre- (reference) implementation periods within individuals, as estimated by conditional logistic regression models accounting for the difference in period intervals

† Not estimated because all patients had a systemic corticosteroid use in the pre-implementation period as an inclusion criterion