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Beta agonists, inhaled steroids, and the risk of intensive care unit admission for asthma

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ABSTRACT: Although inhaled corticosteroid (ICS) use is associated with a decreased risk of hospitalization for asthma, the impact of ICS on the risk of life-threatening asthma exacerbation is less clear. The effect of ICS and inhaled beta agonist (IBA) dispensing on the risk of intensive care unit admission for asthma, a surrogate for life-threatening exacerbation, is evaluated.

Using computerized International classification of diseases (ICD)-9 discharge diagnoses, a cohort of all 2,344 adult Northern California members of a health maintenance organization hospitalized for asthma over a 2-yr period were identified. Computerized pharmacy data was used to ascertain asthma medications dispensed during the 3-, 6-, and 12-month intervals preceding index hospitalization for asthma.

During the 3-months preceding hospitalization, a minority of subjects had no IBA units dispensed (34%), with 14% receiving low level (1 unit), 20% medium level (2–3 units), and 32% high level (⩾4 units) therapy. A substantial proportion received no ICS units (55%), whereas 13% had low, 16% medium, and 15% high level therapy. In multiple logistic regression analysis, high level IBA use was associated with a greater risk of intensive care unit (ICU) admission for asthma after controlling for asthma severity. There was no relationship, however, between low or medium level IBA use and ICU admission. Conversely, medium level and high level ICS use were associated with a reduced risk of ICU admission. Analysing 6- and 12-month medication dispensing data, similar risk patterns were observed.

Inhaled corticosteroid dispensing was associated with reduced risk of intensive care unit admission among adults hospitalized for asthma, whereas the opposite applied for high dose beta agonist usage. This suggests that ICS prescription to adults with moderate-to-severe asthma could reduce the risk of life-threatening exacerbation.
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Despite the availability of effective medications, asthma mortality continues to increase in the USA and other industrialized nations [1]. Although inhaled corticosteroid (ICS) use appears to reduce hospitalization for asthma [2, 3] the impact on life-threatening asthma exacerbation is less clear. In a population-based study, investigators demonstrated an association between ICS dispensing and decreased risk of death or near-death from asthma [4]. Other studies, however, have shown no reduction of asthma-related respiratory failure [5], intensive care unit admission [6, 7], or mortality [8–11] among ICS users. Because clinicians prescribe ICS more frequently to adults with severe asthma [3, 4, 12, 13], inadequate adjustment for asthma severity may explain this lack of observed benefit.

According to some investigators, excess inhaled beta agonist (IBA) use may explain the rising asthma mortality [8–11, 14]. Supporting this contention, observational studies have found a strong association between greater IBA use and mortality [8–11, 14–16]. Both fenoterol, a high dose IBA not available in the USA, and albuterol have been associated with greater asthma mortality [15–17]. As with ICS, preferential prescribing of IBA to persons with severe asthma could underlay this association [15–19]. Alternatively, excess IBA use may exert toxic effects, directly resulting in death [8–11, 14].

In a retrospective cohort study of adult health maintenance organization (HMO) members hospitalized for asthma, the impact of ICS and IBA dispensing on the risk of intensive care unit admission, a surrogate for life-threatening asthma exacerbation, was studied [20, 21]. Using multivariate analysis, the potential confounding effect of asthma severity was controlled for.

Methods

Overview

Using computerized utilization data, all adult members of a closed panel HMO who were hospitalized

for asthma over a 2-yr period were identified. For each subject, asthma medications dispensed during the three-month, six-month, and twelve-month intervals preceding the index hospitalization were retrospectively ascertained. Based on these data, the impact of ICS and inhaled beta agonist (IBA) use on the risk of intensive care unit (ICU) admission and endotracheal intubation during the hospitalization were studied.

Study subjects

Members of Kaiser Permanente (KP), the USA's largest nonprofit HMO were studied. In Northern California, USA, KP provides the full spectrum of primary-to-tertiary care to ~2.7 million members *via* 17 hospital-based medical centres and 14 medical office buildings. In Northern California, KP's share of the regional population ranges 20–35%. The demographic characteristics of KP membership are similar to the overall Northern California population [22]. Of 2.1 million adult KP members (≥18 yrs), an estimated 101,110 (4.9%) persons have asthma [23].

In this retrospective cohort study, previously described methods were employed to identify adults hospitalized for asthma [23, 24]. All adult KP members (≥18 yrs) hospitalized at any Northern California KP hospital between 1996–1998 were identified with a principal Ninth International Classification of Diseases (ICD-9) discharge diagnosis code for asthma (codes 493.00–493.99). KP members hospitalized with a secondary ICD-9 discharge diagnosis code for asthma and a principal ICD-9 code for acute asthma-related respiratory conditions (pneumonia, influenza with pneumonia, acute upper respiratory infection, acute bronchitis and bronchiolitis, pulmonary collapse, respiratory failure, other pulmonary insufficiency, pneumothorax, and viral infection) were also included. A previous KP-based study indicates that hospital discharge diagnoses have acceptable validity for ascertaining asthma cases [25].

Using computerized discharge diagnoses, 2,694 adults hospitalized for asthma over a 2-yr period were identified. Two-hundred and fifty persons (9.3%) without KP pharmacy coverage were excluded because computerized pharmacy data were not available. Also excluded were 100 subjects (3.7%) with any secondary ICD-9 discharge diagnoses for chronic obstructive pulmonary disease (codes 490, 491.0–491.9, 492.0–492.9). Therefore, the final cohort comprised 2,344 adults hospitalized for asthma (87% of those initially identified).

Predictor variables

Demographic data, including age, sex, and race, were obtained from KP computerized databases. Using computerized pharmacy data, medications dispensed during the three-month, six-month, and twelve-month periods preceding index hospitalization for asthma were retrospectively ascertained. These medications included IBA, inhaled corticosteroids (ICS), inhaled nonsteroidal anti-inflammatory agents (*e.g.* cromolyn sulphate), inhaled anticholinergic agents (*e.g.* ipratroprium bromide), methylxanthines, oral corticosteroids, and oral beta agonists. For medications delivered by metered-dose inhaler (MDI), each dispensed MDI was defined as one unit. For other medications, including solutions intended for home nebulizer devices, each prescription dispensed was defined as one unit (an ~one-month supply).

Previous investigators have observed a "U-shaped" relationship between IBA and ICS dispensing rates and the risk of hospitalization for asthma [2]. To address this potentially nonlinear relationship between predictor and outcome, four categories of IBA units dispensed during the three-month period preceding hospitalization were defined: none, low level (1 unit), medium level (2–3 units), and high level (≥4 units). A previous population-based study demonstrated a dramatic increase in asthma mortality among persons receiving >1.4 MDI canisters·month^{-1} [16]. Consistent with this finding, the highest dispense category was defined to reflect this threshold of increased risk (~1.3 MDI units·month^{-1}). Parallel medication dispensing categories for the six- and twelve-month intervals preceding hospitalization were also defined.

Similarly, four categories of ICS units dispensed during the three months prior to hospitalization were defined: none, low level (1 unit), medium level (2–3 units), and high level (≥4 units). The lowest category corresponds approximately to the minimal clinically effective ICS dose (~0.5 canisters·month^{-1}) [3, 26]. In addition, this dose has been associated with a decreased risk of hospitalization [2]. The high dispense category, ~≥1,000 μg·day^{-1} or more, corresponds to clinical recommendations for high dose ICS therapy [26]. Furthermore, this cut-point is similar to the ICS level associated with reduced risk of fatal or near-fatal asthma in the Saskatchewan Asthma Epidemiology Project [4]. Since the relative efficacy of different ICS preparations has not been well-defined, the study was not adjusted for relative ICS preparation potency [27]. As with IBA dispensing, parallel categories of medication dispensing during the six- and twelve-month intervals preceding hospitalization were also defined.

Three categories of oral corticosteroid dispensing during the three months prior to hospitalization were delineated: none, 1 prescription, and ≥2 prescriptions. To reflect longer-term oral corticosteroid requirements, patients who received 3 or more oral corticosteroid prescriptions during the previous 12 months were defined as "steroid dependent". Using a similar definition, previous studies have found an association between steroid dependency and both greater asthma severity and asthma-related health care utilization [12, 13, 28, 29].

Exploratory analyses revealed no "U-shaped" or nonlinear relationships between other asthma medication use and outcome. Therefore, these asthma medications (oral beta agonists, inhaled nonsteroidal anti-inflammatory agents, inhaled anticholinergic agents, and methylxanthines) were treated as dichotomous indicator variables (any dispensed during the interval *versus* none). Because there was no apparent relationship between number of beta agonist solution units dispensed and outcome, nebulized medications

were also treated as a dichotomous predictor variable (any nebulized medications *versus* none).

Asthma severity

Asthma severity can confound the relationship between medication use and health outcomes [4, 16, 17]. Simply stated, patients with severe asthma are more likely to receive aggressive pharmacological treatment with ICS and IBA. To study the impact of these medications on the risk of ICU admission for asthma, inherent disease severity must be taken into account.

In the present study, asthma severity was controlled for by both study design and analysis. All subjects in the current study were hospitalized for asthma, suggesting a comparable level of asthma severity. Asthma medication use was also controlled for, including inhaled medications and oral corticosteroids. Previous investigators have successfully performed similar severity adjustments using asthma hospitalization and medication use [2–4, 8–11, 15–17].

Outcome variables

The primary study outcome was ICU admission among adults hospitalized for asthma. Using computerized hospitalization data, all subjects admitted to an intensive care unit (ICU) during the index hospitalization for asthma were identified. The total and ICU lengths of stay were also ascertained. As secondary outcome measures, ICD-9 procedure codes were identified for endotracheal intubation and mechanical ventilation from computerized hospital discharge data (ICD-9 procedure codes 960.4 and 967.00–967.99, respectively).

Statistical analysis

The principal analysis examines the association between IBA and ICS dispensing during the three-month interval preceding hospitalization and the subsequent risk of ICU admission and endotracheal intubation for asthma. The authors selected the three-month category *a priori* to best reflect asthma status prior to hospitalization. To capture longer-term medication usage, the impact of IBA and ICS dispensing during the six- and twelve-month intervals preceding hospitalization were also analysed.

Data were analysed with SAS 6.12 (SAS Institute, Cary, NC, USA). Bivariate analyses were performed using the Chi-squared test for categorical variables, t-test for continuous normally distributed variables, and Wilcoxon rank-sum test for continuous non-normally distributed variables. Multiple logistic regression analysis was employed to examine the association between ICS and IBA dispensing and the risk of ICU admission among all hospitalized subjects, after controlling for demographic characteristics and other asthma medication use. Similarly, multiple logistic regression analysis was used to examine the relationship between ICS and IBA dispensing and endotracheal intubation. As described above, the authors controlled for asthma severity by including oral corticosteroid and other asthma medications in all multivariate models. Because all patients were hospitalized for asthma, they all had moderate-to-severe asthma. Furthermore, analyses controlled for age, sex, and race in all models. Logistic regression model goodness-of-fit was tested using the Hosmer-Lemeshow test [30]. In all cases, model fit was adequate ($p > 0.50$).

As discussed previously, IBA use has been related to a higher risk of asthma mortality [8–11, 14–16]. The causal mechanism could reflect beta agonist toxicity or severe, poorly controlled asthma. The hypothesis that IBA use would be associated with ICU admission for asthma was further tested by stratifying subjects based on whether they received any ICS therapy during the previous three months (*i.e.* ICS "users" and "nonusers"). If IBAs confer toxicity, then we should observe the association between greater IBA use and ICU admission among both ICS users and nonusers. Alternatively, if this association was observed only among ICS nonusers, then greater IBA use may indicate severe, poorly controlled asthma rather than exerting a toxic effect. In these stratified analyses, multiple logistic regression was used to control for other markers of asthma severity and demographic characteristics. To evaluate the exposure-response relationship within each stratum, the logistic regression analysis was repeated using incremental (nested) coding for IBA use [31]. In this fashion, each level of IBA dispensing can be compared to the prior category (*e.g.* high level *versus* medium level).

Results

Demographic characteristics and mortality

During the 2-yr study period, 2,344 adult KP members were hospitalized for asthma. Of these hospitalized adults, 309 persons (13.2%, 95% confidence interval (CI) 11.8–14.6%) were admitted to an intensive care unit (ICU). As shown in table 1, there were no statistical differences in age or sex between subjects admitted to the ICU compared with those hospitalized on general medical wards. In contrast, subjects admitted to the ICU were more likely to be nonwhite. Adults admitted to the ICU for asthma also had less favourable health outcomes, with greater length of hospital stay and inpatient mortality (table 1).

Inhaled beta agonists and the risk of intensive care unit admission for asthma

IBA dispensing was related to an increased risk of ICU admission for asthma among all subjects hospitalized for asthma during the 2-yr period. Nearly two-thirds of subjects had received IBA units during the three months prior to hospitalization for asthma. As shown in table 2, 336 subjects received low level (14%), 462 subjects received medium level (20%), and 752 subjects received high level (32%) IBA therapy. Compared to no IBA dispensing, high level IBA

Table 1. – Demographic characteristics and hospital outcomes among 2,344 adult Northern California Kaiser Permanente members hospitalized for asthma

Characteristic	Hospital only	ICU admission	p-value
Subjects n	2035	309	
Age years*	55.5 ± 17.7	55.3 ± 17.5	0.90
Female sex[#]	1421 (70)	206 (67)	0.26
White race[#]	1394 (69)	186 (60)	0.004
Hospital length of stay days*,[¶]	3.2 ± 2.7	7.4 ± 7.0	
	3.0 (1.0 – 4.0)	5.0 (3.0 – 9.0)	< 0.0001
Inpatient mortality[#]	17 (0.8)	31 (10)	< 0.001

*: data presented as mean ± SD; [#]: data presented as n (%); [¶]: data presented as median, 25th – 75th interquartile range. P-values were determined by the following tests: age was analysed by t-test; sex, race, and mortality by Chi-squared test; length of stay by Wicoxon rank-sum test. ICU: intensive care unit.

therapy was associated with an increased risk of ICU admission after controlling for systemic corticosteroid use, other asthma medications, and demographic characteristics (odds ratio (OR) 1.4). The 95% CI, however, did not exclude "no association" (1.0 – 2.0).

Similarly, IBA dispensing was associated with an increased risk of endotracheal intubation and mechanical ventilation among adults hospitalized for asthma. Compared to no IBA units dispensed, medium level IBA use was associated with a greater risk of intubation after controlling for other asthma medication use and demographic characteristics (OR 1.6, 95% CI 1.0 – 2.7) (table 2). High level IBA dispensing was more strongly associated with intubation for asthma exacerbation (OR 1.9, 95% CI 1.2 – 3.1).

Salmeterol MDI dispensing was rare among study subjects, with 5.3% receiving one or more units during the three months prior to hospitalization. In multivariate analysis, treating these long-acting IBAs separately or together with short-acting IBAs did not appreciably affect the observed results. Furthermore, dispensing beta agonist solutions for home nebulizer devices was not statistically associated with the risk of ICU admission (OR 1.1, 95% CI 0.8 – 1.5) or endotracheal intubation (OR 1.0, 95% CI 0.7 – 1.6) after controlling for covariates.

In the 6- and 12-month intervals preceding hospitalization, most subjects received IBA units (73% and 80%, respectively). IBA dispensing during 6- and 12-month intervals was associated with an increased risk of ICU admission and endotracheal intubation (fig. 1). For 6-month IBA dispensing, the risks of ICU admission and intubation were similar to those for the 3-month interval. During the 12-month interval, the association between IBA dispensing and adverse outcomes was stronger.

Inhaled corticosteroids and the risk of intensive care unit admission

ICS dispensing was associated with a decreased risk of ICU admission among adult KP members hospitalized for asthma. Fewer than one-half of subjects had

Table 2. – Inhaled beta agonists, inhaled corticosteroids, and the risk of intensive care unit admission and endotracheal intubation for asthma: medications dispensed during the 3-month interval preceding hospitalization

Medication*	n (%)	Risk of ICU admission n = 309		Risk of intubation n = 155	
		Unadjusted OR (95% CI)	Adjusted OR (95% CI)[#]	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[#]
Inhaled beta agonists					
None	794 (34)	1.0	1.0	1.00	1.0
Low (1 unit)	336 (14)	0.7 (0.4 – 1.1)	0.8 (0.5 – 1.2)	0.7 (0.4 – 1.3)	0.8 (0.4 – 1.6)
Medium (2 – 3 units)	462 (20)	1.1 (0.8 – 1.5)	1.1 (0.8 – 1.7)	1.5 (0.9 – 2.3)	1.6 (1.0 – 2.7)
High (⩾4 units)	752 (32)	1.5 (1.1 – 1.9)	1.4 (1.0 – 2.0)	1.8 (1.2 – 2.7)	1.9 (1.2 – 3.1)
Inhaled corticosteroids					
None	1298 (55)	1.0	1.0	1.0	1.0
Low (1 unit)	305 (13)	0.7 (0.5 – 1.1)	0.7 (0.5 – 1.1)	0.7 (0.4 – 1.2)	0.7 (0.4 – 1.2)
Medium (2 – 3 units)	383 (16)	0.9 (0.7 – 1.3)	0.7 (0.5 – 1.0)	1.1 (0.7 – 1.7)	0.8 (0.5 – 1.3)
High (⩾4 units)	358 (15)	1.0 (0.7 – 1.4)	0.7 (0.4 – 0.96)	1.1 (0.7 – 1.8)	0.7 (0.4 – 1.1)
Oral corticosteroids					
None	1247 (53)	1.0	1.0	1.0	1.0
Low (1 unit)	624 (27)	0.7 (0.5 – 0.9)	0.6 (0.4 – 0.9)	0.8 (0.5 – 1.2)	0.7 (0.5 – 1.1)
High (⩾2 units)	473 (20)	0.9 (0.6 – 1.3)	0.8 (0.5 – 1.2)	0.9 (0.5 – 1.5)	0.8 (0.5 – 1.4)
Steroid dependant[¶]	568 (24)	1.7 (1.2 – 2.4)	1.4 (1.0 – 2.0)	1.7 (1.1 – 2.6)	1.3 (0.8 – 2.1)

*: medications dispensed during the 3 months prior to index hospitalization; for inhaled beta agonists and inhaled steroids, 1 unit = 1 metered dose inhaler; for oral steroids, 1 unit = 1 prescription filled (~1 month supply); [#]: odds ratios from multiple logistic regression analysis, adjusting for other variables shown in table, plus methylxanthines, oral beta agonists, ipratroprium bromide, inhaled nonsteroidal anti-inflammatory agents, nasal medications, nebulized beta agonists, age, sex, and race; [¶]: steroid dependant defined as ⩾3 prescriptions during the past 12 months.

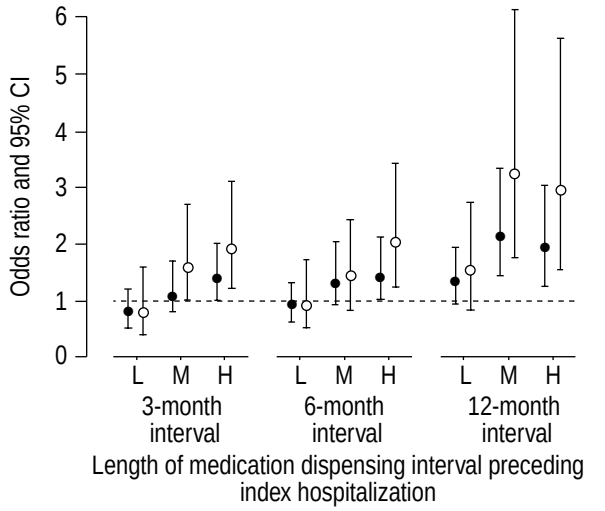

Fig. 1. – Inhaled beta agonists and the risk of intensive care unit (ICU) admission and endotracheal intubation for asthma. The figure depicts the risk of ICU admission (●) and endotracheal intubation (○) associated with inhaled beta agonists (IBA) dispensed during the 3-month, 6-month, and 12-month intervals preceding hospitalization. For each dispensing interval, the risk associated with low (L), medium (M), and high level (H) IBA dispensing is shown. The odds ratios and 95% confidence intervals (CI) are from multiple logistic regression analysis, adjusting for inhaled corticosteroids, oral corticosteroids, methylxanthines, oral beta agonists, ipratroprium bromide, inhaled nonsteroidal anti-inflammatory agents, nasal medications, nebulized beta agonists, age, sex, and race.

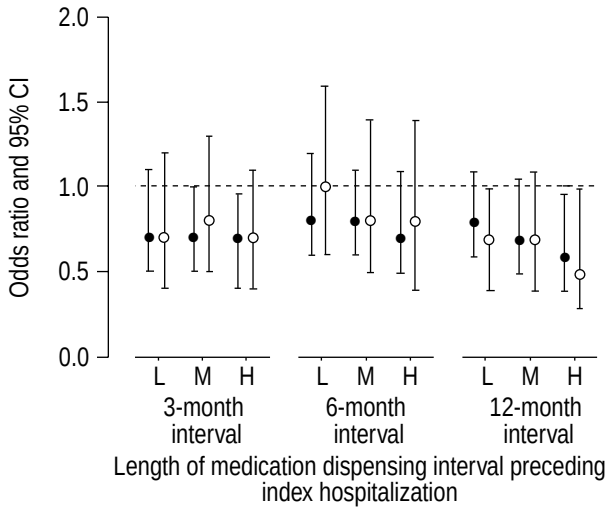

Fig. 2. – Inhaled corticosteroids and the risk of intensive care unit (ICU) admission and endotracheal intubation for asthma. The figure depicts the risk of ICU admission (●) and endotracheal intubation (○) associated with inhaled corticosteroids (ICS) dispensed during the 3-month, 6-month, and 12-month intervals preceding hospitalization. For each dispensing interval, the risk associated with low (L), medium (M), and high level (H) ICS dispensing is shown. The odds ratios and 95% confidence intervals (CI) are from multiple logistic regression analysis, adjusting for inhaled beta agonists, oral corticosteroids, methylxanthines, oral beta agonists, ipratroprium bromide, inhaled nonsteroidal anti-inflammatory agents, nasal medications, nebulized beta agonists, age, sex, and race.

ICS units dispensed during the three months prior to hospitalization, with 305 subjects receiving low level (13%), 383 subjects receiving medium level (16%), and 358 subjects receiving high level (15%) ICS therapy (table 2). Adults hospitalized for asthma who received ICS had a lower risk of ICU admission, after controlling for other asthma medication use and demographic covariates. Although the confidence intervals did not exclude "no association" in the low and medium level categories, the high level group had a statistically significant reduction in ICU admission risk (OR 0.7, 95% CI 0.4 – 0.96). The risk of intubation was also reduced, but the 95% CI did not exclude "no relationship". Furthermore, ICS dispensing during the 6- and 12-month intervals preceding hospitalization was associated with a similar reduction in the risks of ICU admission and intubation (fig. 2).

In contrast to ICS, oral corticosteroid dependent patients had a higher risk of ICU admission (OR 1.4, 95% CI 1.0 – 2.0) (table 2). However, patients dispensed only one oral corticosteroid prescription during the previous three months manifested a lower risk of ICU admission (OR 0.6, 95% CI 0.4 – 0.9). There was no statistical relationship between high level oral corticosteroid dispensing during the previous 3-months and either ICU admission or intubation.

Stratified analysis: risk of beta agonists among users and nonusers of inhaled corticosteroids

To examine whether the association between IBA dispensing and risk of ICU admission (or intubation) reflected toxic medication effects or uncontrolled asthma, analyses were stratified by ICS use during the 3-months preceding hospitalization. Among ICS users, there was no apparent bivariate association between IBA use and either ICU admission or intubation ($p > 0.2$). After adjustment for systemic corticosteroids, other asthma medications, and demographic characteristics, there was still no statistical association between IBA dispensing and either adverse outcome (table 3).

Among ICS nonusers, however, a strong association was observed between IBA dispensing and adverse outcomes. In bivariate analysis, high level IBA users were nearly twice as likely to undergo ICU admission compared to nonusers (20% *versus* 12%, $p < 0.001$). Compared to nonusers, high level IBA users had an approximate two-fold greater risk of intubation for asthma (12% *versus* 5%, $p < 0.0001$). After controlling for other asthma medication use and demographic covariates, high level IBA use was associated with a greater risk of ICU admission (OR 1.6, 95% CI 1.02 – 2.4) (table 3). Similarly, both medium and high level IBA use were strongly associated with a greater risk of endotracheal intubation (OR 2.2, 95% CI 1.1 – 4.1 and OR 2.6, 95% CI 1.4 – 4.7, respectively). When stratified analyses were performed using the 6-month and 12-month medication dispensing interval, the same pattern of risks was observed (unpublished data).

In the stratum of ICS nonusers, a nonmonotonic exposure-response trend was observed between IBA use and the risk of ICU admission after adjusting for covariates. Compared to low level IBA dispensing,

Table 3. – Inhaled beta agonists and the risk of intensive care unit (ICU) admission and endotracheal intubation for asthma in users and nonusers of inhaled steroids: multivariate analysis

Inhaled beta agonists units dispensed during 3-months preceding admission	No inhaled steroids dispensed during previous 3 months (n = 1298)			Any inhaled steroids dispensed during previous 3 months (n = 1046)		
	n	OR (95% CI)		n	OR (95% CI)	
		ICU admission	Intubation		ICU admission	Intubation
None	648	1.0	1.0	146	1.0	1.0
Low dose (1 unit)	179	0.6 (0.3 – 1.2)	0.5 (0.2 – 1.3)	157	0.9 (0.4 – 1.9)	1.0 (0.4 – 2.6)
Medium dose (2 – 3 units)	189	1.4 (0.9 – 2.2)	2.2 (1.1 – 4.1)	273	0.9 (0.5 – 1.7)	1.0 (0.4 – 2.3)
High dose (⩾4 units)	282	1.6 (1.02 – 2.4)	2.6 (1.4 – 4.7)	470	1.1 (0.6 – 2.1)	1.1 (0.5 – 2.4)

All analyses adjusted for oral steroid use, methylxanthines, oral beta agonists, ipratroprium bromide, inhaled nonsteroidal anti-inflammatory agents, nasal medications, nebulized beta agonists, age, sex and race. OR: odds ratio; 95% CI: 95% confidence interval.

medium level IBA use was associated with a greater risk of ICU admission (OR 2.2, 95% CI 1.1 – 4.4) and intubation (OR 4.7, 95% CI 1.5 – 14.5). Relative to medium level IBA dispensing, high level IBA use was not associated with further incremental risk of ICU admissions (OR 1.1, 95% CI 0.7 – 1.9) or intubation (OR 1.2, 95% CI 0.6 – 2.3). In the ICS user stratum, there was no clear exposure-response trend.

Younger patients hospitalized for asthma

Although patients with concommittant discharge diagnoses of chronic obstructive pulmonary disease (COPD) were excluded, some possibility of asthma misclassification remained. For this reason, the association between 3-month IBA and ICS dispensing and ICU admission among subjects < 50 yrs (n = 901), a group less likely to have COPD, was re-analysed. As before, the risk of ICU admission (OR 1.5, 95% CI 0.9 – 2.6) and endotracheal intubation (OR 3.5, 95% CI 1.6 – 8.1) were elevated among high level IBA users after controlling for medication and demographic covariates. Similarly, high level ICS use was associated with a reduced risk of ICU admission (OR 0.6, 95% CI 0.3 – 1.3) and intubation (OR 0.5, 95% CI 0.1 – 1.8). In these analyses, the risk estimates (ORs) were similar to those obtained in initial logistic regression models (table 2). However, the smaller number of subjects analysed resulted in wider confidence intervals.

Discussion

Intensive care unit (ICU) admission indicates severe asthma exacerbation and portends a substantial risk of adverse health outcomes, such as rehospitalization and death [20, 21 32, 33]. In a population-based study, nearly 10% of patients admitted to the ICU for asthma died during the next two years [20]. Similarly, a significant proportion (15%) of 121 patients discharged from an ICU following mechanical ventilation died from asthma within six years [21]. Furthermore, the sociodemographic characteristics of adults admitted to the ICU for asthma are similar to those dying from asthma, indicating that both groups represent the same high risk population [20].

Among adult HMO members hospitalized for asthma, ICS and IBA dispensing were significantly related to the risk of severe asthma exacerbation requiring ICU admission or endotracheal intubation. Specifically, dispensing of medium-to-high level ICS therapy was associated with a reduced risk of ICU admission. A parallel pattern of risk reduction for endotracheal intubation was observed among ICS users. In contrast, high level IBA dispensing was associated with an increased risk of both ICU admission and endotracheal intubation for asthma. Importantly, stratified analysis indicated that this excess risk was observed only among patients not receiving ICS therapy. Overall, these results support the effectiveness of ICS therapy in reducing the risk of severe, life-threatening asthma exacerbation.

The current study strongly suggests that ICS therapy is effective in preventing severe asthma exacerbation, resulting in ICU admission. Previous observational studies demonstrated an association between ICS use and decreased risk of hospitalization [2] and rehospitalization for asthma [3]. Whether or not ICS use reduces the risk of life-threatening asthma exacerbation has been less certain. The Saskatchewan Asthma Epidemiology Project investigators found a relationship between ICS use and decreased risk of fatal or near-fatal asthma, defined as hypercapnoea or nonelective intubation [4]. A series of case-control studies from New Zealand, however, have found no reduction in mortality among ICS users [8 – 11]. Similarly, epidemiological studies have not established this medication′s salutory effect on ICU admission rates [6, 7] or respiratory failure [5]. In these studies, confounding by asthma severity may explain the apparent lack of ICS effectiveness. Controlling for asthma severity, the present study supports the effectiveness of ICS in preventing severe, life-threatening exacerbation.

Epidemiological studies have demonstrated a strong association between high dose IBA use and mortality, even after adjustment for other markers of asthma severity [8 – 11, 15 – 17]. Although this relationship has been especially noted for fenoterol, excessive albuterol use has also been associated with increased mortality [8 – 11, 15 – 17]. The causal mechanism of this relationship, however, has not been clearly established [15, 16, 19, 34]. Excessive IBA use may exert toxic effects, resulting in death [8 – 11, 14] or it may be a marker for

severe, uncontrolled asthma [15, 16, 19]. In the present study, IBA therapy was associated with an increased risk of ICU admission and endotracheal intubation only among subjects receiving no recent ICS medication. In ICS-treated patients, moderate-to-high level IBA dispensing did not appear to confer excess risk. Therefore, the association between high level IBA use and adverse outcomes may reflect severe, uncontrolled asthma and not direct drug-related toxicity. Alternatively, IBA medications could exert deleterious effects, such as increasing bronchial hyperresponsiveness [14], that are mitigated by ICS use. Either way, patients using moderate-to-high level IBA require vigorous treatment with ICS.

The present study has several potential limitations. Confounding by asthma severity could have influenced the observed association between medication use and ICU admission. For example, health care providers are more likely to prescribe ICS therapy, especially high dose ICS therapy, to adults with severe asthma [2, 3, 12]. Similarly, adults with severe asthma are more likely to receive high dose IBA therapy than those with mild disease [15–17]. To address confounding, the study was adjusted for systemic corticosteroid and other asthma medication use. Furthermore, all subjects were hospitalized, indicating a comparable level of asthma severity. Finally, confounding by asthma severity would be expected to attenuate, not overestimate, the association between ICS use and ICU admission. Supporting this contention, the risk reduction associated with ICS use was greater after adjusting for asthma severity (*i.e.* farther from the null value).

The use of computerized pharmacy data could provide imprecise ascertainment of asthma medication use. During the study interval preceding hospitalization, the number of asthma medication units dispensed may not equate with medication consumption. Loss of dispensed medication could result in overestimation of consumption; home storage of previously received medication may lead to underestimation of actual usage. This misclassification may result in decreased measurement precision, but would be unlikely to introduce systematic bias.

Although the inclusion criteria require a hospital discharge diagnosis of asthma, misclassification of COPD as asthma could influence the findings. Previous investigations have utilized ICD-9 discharge diagnoses to define persons hospitalized for asthma [2, 15, 20, 23–25]. At Northwest Kaiser Permanente, OSBORNE *et al.* [25] demonstrated that hospital discharge diagnoses of asthma have acceptable validity, compared with asthma diagnosis based on chart review. Limiting key analyses to persons <50 yrs, a group unlikely to have smoking-related COPD, did not appreciably affect study conclusions.

A central issue is whether adult KP members with asthma are similar to the general US population of adults with asthma. Because KP members have established health care access, study results may not be generalized to populations without access to health care. In addition, excluding those subjects without KP prescription coverage may have further reduced generalizability, albeit to a limited extent. Even given these limitations, the demographic and socioeconomic characteristics of Northern California KP members are similar to those of the regional population [22]. There is also no evidence of systematic inclusion or exclusion of healthy persons into the KP system [35]. Also, the prevalence of asthma among Northern California KP members is similar to the general US population (4% *versus* 5%, respectively) [1]. Overall, KP members with asthma are probably similar to the general population of adults with asthma.

Outside the USA, the pattern of IBA and ICS prescribing may differ. In considering these results, health care providers may wish to compare their usual therapies to those used in the presented study subjects. Among KP members studied, the most commonly prescribed IBA metered dose inhaler was albuterol, which is supplied in 17 g canisters containing 200 metered inhalations of 100 μg. The other common IBA preparation was metaproterenol (200 inhalations of 150 mg), with fewer patients receiving salmeterol (120 inhalations of 25 μg). The most commonly prescribed ICS were triamcinolone acetonide (240 actuations of 100 μg delivered from the spacer-mouthpiece), flunisolide (100 inhalations of 250 μg), and beclomethasone (200 inhalations of 42 μg).

In adults with asthma, inhaled corticosteroid therapy appears to reduce the risk of intensive care unit admission. Treatment with inhaled corticosteroid, then, seems to attenuate the severity of asthma exacerbation, decreasing the likelihood of a life-threatening event. Since the presented study sample approximates the general population, efforts aimed at inhaled corticosteroid prescription to adults with moderate-to-severe asthma would probably reduce asthma morbidity and mortality in the USA and worldwide.

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