



Adherence with controller medication in adults with asthma – impact of hospital admission for acute exacerbation

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ABSTRACT

Objective: Uncontrolled asthma is associated with higher risk of hospital admissions and death. Low adherence to inhaled corticosteroid (ICS), the cornerstone of asthma therapy, is well-documented. Our aim was to investigate if hospital admission with an acute exacerbation of asthma changes ICS adherence.

Methods: This retrospective cohort study comprises 241 patients hospitalized with an asthma exacerbation over 12 months (May 2019–April 2020). The primary outcome was proportion of ICS adherent patients, defined as Medication Possession Ratio (MPR) $\geq 80\%$, in the six-month period before and after admission.

Results: The pre- to post-admission proportion of ICS adherent patients increased from 10% to 13% ($p=0.25$) and the mean ICS MPR increased from 34% to 42% ($p<0.001$). Different patterns of post-discharge adherence were observed, as adherent patients remained adherent, while patients with poor pre-admission adherence increased their adherence during two months after discharge followed by a decline in MPR. Co-variables such as sex, age, body mass index (BMI), GINA 2020-treatment step did not predict improvement in adherence after discharge.

Conclusions: Admission with an asthma exacerbation did not increase the proportion of patients adherent with controller medication, primarily ICS. Although an improvement in adherence was initially seen primarily in previously poorly adherent patients, this increase was transient as it decreased over time post-discharge.

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Introduction

Controller medication for asthma, primarily inhaled corticosteroids (ICS), improves symptoms and reduces risk of acute exacerbations, but only if taken on a regular basis (1). Poor adherence with ICS is the major challenge in asthma management, with adherence ranging from 15–63% in adults (2–4). Good adherence, defined as $\geq 80\%$ of prescribed doses taken, reduces risk of exacerbations, use of oral corticosteroids (OCS), hospitalization and death (2,3,5–7). A plethora of known and unknown factors affect adherence, such as age, sex, cultural background, socio-economic status, satisfaction with inhaler device, perceived quality of life and level of disease insight (3,8–10). Lack of adherence is further divided into intentional (e.g. fear of side-effects, lack of perceived

effect, miscommunication) and non-intentional (e.g. forgetfulness, costs) (1).

Adherence in asthma patients can be measured with a variety of both self-reported and objective methods (2). The gold standard for monitoring adherence to inhalers is electronic monitoring devices, but is often costly (2,11,12). Medication possession ratio (MPR), based on pharmacy records, is a common estimate of objective adherence as it is easily accessible in registries and less expensive. However it does not ensure actual dose administration or offer information about patterns of use over shorter time periods (2). Another method is patient-assessed adherence, using questionnaires filled by the patients or requested during a consultation, but adherence is often overestimated by patients (13,14).

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Previous studies have shown that living with uncontrolled asthma, apart from increasing risk of exacerbations, admissions and death, also has detrimental psychological effects and impacts on quality of life (2,3,7,15,16). Patients experiencing asthma exacerbations are often feeling distressed and even scared of dying, leading professionals to assume patients should become further motivated for increasing adherence to controller medication following exacerbation to prevent reexacerbations (17). However, this assumption is challenged by the “poor perceiver” phenomenon, both in terms of potential disease severity, dyspnea, and airway obstruction, and its presence within asthma populations (18). As such, the effect of asthma-related hospitalization on adherence is yet to be fully elucidated, despite a vicious circle between nonadherence and poor asthma control typically being described.

The aim of this study was to assess the impact of hospitalization-requiring asthma exacerbations on adherence with controller medication, both in total and when differentiated based on previous adherence.

Materials and methods

Study population

Patients eligible for inclusion in the present retrospective cohort study comprises all patients admitted with an exacerbation of asthma (ICD-10: J45, J46) between May 1, 2019 and April 30, 2020 to the Emergency Department, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark. Data was obtained from electronic medical records (Sundhedsplatformen, Epic Systems Inc.) and the National Common Medication Card (CMC, Det Faelles Medicinkort, MedCom A/S).

Patients aged 18 or above, residing in Denmark, with at least one medication order for ICS made six months both before and after index admission were included in the present analyses, provided they had not opted out of research and/or quality assessment access to electronic patient records. Exclusion criteria were no medication order to ICS treatment for asthma still valid on the CMC six months pre- and post-admission and/or death during index admission.

Medication prescriptions were collected from the CMC. Smoking-status, body mass index (BMI), forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC) and asthma control questionnaire (ACQ) data were registered from medical record entries closest to admission date (max. six months). The CMC contains national information of prescriptions 24 months

retrospectively, which defined the timeframe of the study (12 months inclusion and 6 months prior and post-admission). The CMC offers complete and accurate information about prescriptions and claims, explaining no missing values due to medication in analysis.

Definitions

Good adherence to controller medication was defined as having filled prescription for at least 80% of the medication order (2,3,7). Adherence was measured as MPR, defined as percentage claimed ICS doses (number of doses claimed, divided by prescribed doses during the observation window) (19). Observation windows were six months prior to hospital admission to six months after discharging due to data for the CMC being complete in 24 months retrospectively. Moderate exacerbation was defined as < 24 h in hospital or not hospital-requiring exacerbation and ≥ 3 days prescribed ≥ 25 mg of oral corticosteroids (OCS) (1). Severe exacerbation was defined as ≥ 24 h in hospital and/or mechanical ventilation needed and ≥ 3 days prescribed ≥ 25 mg OCS (1). ICS doses were defined as prescribed ICS doses at the admission date according to Global Initiative for Asthma (GINA) 2020 (1). Excessive use of short-acting beta-agonists (SABA) was defined as ≥ 600 doses/year evaluated in the year prior to admission (20).

Outcomes

The primary outcome was the proportion of asthma patients with good adherence, defined as MPR ≥ 80% with controller medication, before compared to after hospital admission.

The secondary outcomes included change in ICS MPR following hospital admission due to exacerbation of asthma, risk of hospital readmission with asthma as primary cause and all-cause mortality from the day of discharge within adherent and non-adherent patients. Additional secondary outcomes comprised predictors of increasing adherence following hospital admission due to asthma exacerbation and correlations between ICS MPR before admission and change in MPR after discharge.

Statistical methods

The exposure variable in the primary analysis was a severe asthma exacerbation. The exposure variable in the secondary analysis (Cox-regression) was poor

adherence (< 80%) in six months following index admission.

For group comparisons, Chi-square or McNemar's test were used, where appropriate. Paired t-test was used to compare continuous data supplemented by Wilcoxon signed rank test for non-normally distributed data. For continuous data, Pearson's correlation-analysis was used to analyze correlation. Cox-proportional hazards model was used to analyze possible differences in time to event, covariates included in the analysis were sex, age, smoking-status, blood eosinophil count at admission, BMI, GINA 2020-step and history of any exacerbation within 12 months before index admission, regardless of severity. Multivariable logistic regression was used to analyze predictors of changing from non-adherent to adherent, variables included were identical to the variables included in the cox-proportional hazards model. Two-sided p values were used, $p < 0.05$ were defined as statistically significant. Regression analyses presented as Hazards or Odds Ratio (HR, OR) with 95% Confidence Intervals (CI). Statistical analyses were performed using R for Windows v3.6.0 (The R Foundation, AU).

Results

Cohort characteristics

A total of 369 patients were admitted during the study period due to an asthma exacerbation. Of these, 241 patients fulfilled all inclusion and no exclusion criteria, and by that comprises the final study cohort. Of note, 115 of the admitted patients did not have a pre-admission ICS-prescription and were, therefore, not eligible for the present study (Figure 1).

Of the 241 patients included, the mean age was 47 years, 176 (73%) were women and 70 (30%) were active smokers, further demographic data given in Table 1.

Despite having at least one prescription of ICS, 65 patients (27%) had ICS MPR of 0.0% at admission (and a post-admission MPR of 7.2%). At the time of admission, 75 patients (31%), 97 patients (40%) and 69 patients (29%) were prescribed high, medium and low dose ICS, respectively. Further characteristics regarding ICS and second controllers are shown in Table 2.

A total of 70 patients (29%) had an excessive use of SABA (≥ 600 doses/year), and 117 patients (49%) had a history of any exacerbation (moderate or severe) in the 12 months prior to index admission. Table 2 provides further details related to disease control.

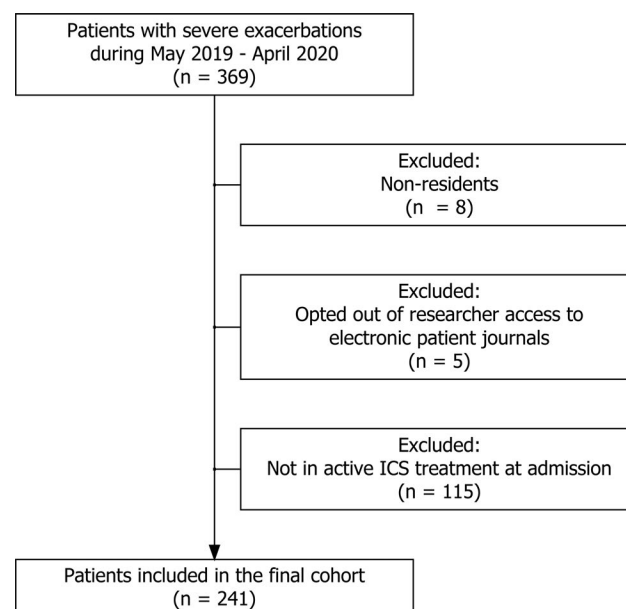


Figure 1. Flowchart of 369 screened patients admitted with asthma exacerbation.

Table 1. Baseline characteristics of 241 patients admitted with an exacerbation with asthma.

Characteristic	(n = 241)	Missing data
Age (years, median, IQR)	47 (32–61)	0
Sex (n female (%)/n male(%))	176 (73)/65 (27)	0
Active smokers, n (%)	70 (30)	5
BMI (kg/m ² , mean, SD)	29.83 (7.23)	103
FEV ₁ female (L, mean, SD)	2.07 (0.79)	63
FEV ₁ male (L, mean, SD)	2.64 (0.81)	30
FEV ₁ predicted female (% mean, SD)	76.81 (19.30)	
FEV ₁ predicted male (% mean, SD)	69.91 (15.52)	
FVC female (L, mean, SD)	2.82 (0.92)	63
FVC male (L, mean, SD)	3.88 (1.18)	30
FVC predicted female (% mean, SD)	88.86 (19.57)	
FVC predicted male (% mean, SD)	82.49 (19.19)	
FEV ₁ /FVC female (% mean, SD)	0.73 (0.13)	63
FEV ₁ /FVC male (% mean, SD)	0.69 (0.12)	30
Admission blood eosinophils (cells/ μ L, median, IQR)	210 (80–390)	4

IQR, interquartile range; BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity. Data for smoking-status, BMI, FEV₁ and FVC registered closest to admission date and maximally 6 months from admission date.

Changes in adherence after hospitalization with acute asthma exacerbation

Prior to a severe asthma exacerbation, 23 patients (9.5%) fulfilled the criteria of being adherent to ICS ($\geq 80\%$). A non-significant increase in number of adherent patients to 31 (12.9%) was observed six months after discharge compared to pre-admission ($p = 0.25$). In logistic regression, sex, age, smoking-status, ACQ-score, FEV₁, blood eosinophils at admission, BMI, GINA 2020-treatment step and history of exacerbation within 12 months before index admission, regardless of severity, were not significantly associated with a post-admission change in adherence.

Table 2. Prescribed asthma therapy, adherence and disease control among 241 patients with hospital admission due to exacerbation of asthma.

Treatment, adherence and disease control	(n = 241)	Missing data
ICS daily dose n (%)		0
High	75 (31)	
Medium	97 (40)	
Low	69 (29)	
LABA treatment n (%)	199 (83)	0
LAMA treatment n (%)	60 (25)	0
LTRA treatment n (%)	37 (15)	0
Biologic therapy n (%)	4 (1.66)	0
GINA-treatment step n (%)		0
1	0 (0)	
2	37 (15)	
3	34 (14)	
4	95 (39)	
5	75 (31)	
ACQ (median, IQR)	2.14 (1.43–3.14)	139
Excessive SABA use, ≥ 600 /yearly, n (%)	70 (29)	0
Number of moderate exacerbations in previous year n (%)		0
0	142 (59)	
1	49 (20)	
≥ 2	50 (21)	
Number of severe exacerbations in previous year n (%)		0
0	193 (80)	
1	35 (15)	
≥ 2	13 (5)	
Number of patients with "dysregulated asthma" n (%)*	160 (66)	139
Baseline MPR (median, IQR)	33.33 (0.00–55.56)	0

ICS, inhaled corticosteroids; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists; GINA, global initiative for asthma. ACQ, asthma control questionnaire; SABA, short-acting beta-agonists; MPR, medication possession ratio. *Defined as SABA > 600 doses/year and/or ACQ ≥ 2 and/or any exacerbation (moderate or severe) in previous year. Data for ICS daily dose, LAMA, LTRA, biological medicine and GINA-treatment step registered on the admission date. Data for ACQ registered closest to admission date and maximally 6 months from admission date.

The overall mean ICS MPR prior to hospitalization was 33.8%, increasing to 41.6% in the six months following discharge ($p < 0.001$).

Risk of re-exacerbation in adherent and non-adherent patients

No difference in risk of a severe re-exacerbation was found between non-adherent and adherent patients (HR 1.98, 95%-CI 0.68–5.77, $p = 0.21$) within six months after index admission. Additionally, neither did they differ in risk of any re-exacerbation (moderate or severe) (HR 1.27, 95%-CI 0.54–3.04, $p = 0.58$). In multivariable models, the analyses were adjusted for sex, age, smoking-status, blood eosinophil count at admission, BMI, GINA 2020-step and history of any exacerbation within 12 months before index admission, regardless of severity. History of any exacerbation (moderate or severe) within 12 months before index admission predicted risk of severe re-exacerbation

with admission within six months after index admission (HR 5.41, 95%-CI 1.68–17.48, $p < 0.005$) and risk of any re-exacerbation (HR 12.28, 95%-CI 4.16–36.32, $p < 0.001$). None of the other covariates predicted any or severe re-exacerbation within six months after index admission. No significant interactions were found.

Due to the low number of severe re-exacerbation events, the analysis of difference in risk of re-exacerbation between adherent and non-adherent was additionally carried out using logistic regression with identical covariates. Still, the risk of severe re-exacerbation did not differ between adherent and non-adherent patients (OR 0.71, 95%-CI -0.62 – 1.96 , $p = 0.27$). Difference in risk of any re-exacerbation (moderate or severe) between adherent and non-adherent patients was not predicted either (OR 0.39, 95%-CI -0.88 – 1.68 , $p = 0.54$). On the other hand, history of any exacerbation (moderate or severe) within 12 months before index admission predicted risk of severe re-exacerbation in six months following discharge (OR 1.86, 95%-CI 0.71–3.27, $p < 0.005$) and risk of any re-exacerbation (moderate or severe) in six months after index admission (HR 2.95, 95%-CI 1.83–4.33, $p < 0.001$). None of the other covariates were found to predict any or severe re-exacerbation within six months after discharge.

Of note, no difference in adherence was seen in pre- and post-MPR in patients with re-exacerbations within 6 months after discharge (41.1% versus 41.6% in patients who did not re-exacerbate ($p = 0.91$)).

Correlation between prior adherence to ICS and change in adherence after discharge

A correlation between baseline adherence level and change in adherence after hospital admission due to an asthma exacerbation was observed, the correlation coefficient was -0.50 (95%-CI -0.59 to -0.40 , $p < 0.001$, $R^2 = 0.25$).

In terms of adherence patterns, the adherent patients at admission had an apparent decrease in ICS MPR in the two months after discharge, whereas the non-adherent patients had an increase in ICS MPR (Figure 2). After two months both groups had increased their MPR and kept it above baseline adherence level during the remaining follow-up period.

Pre- and post-admission adherence were calculated in two different ways, both with and without adjustment for in-hospital procurement of 30 days' worth of daily doses, a common practice during admission and not accounted for in national pharmacy records. The mean ICS MPR before admission among adherent

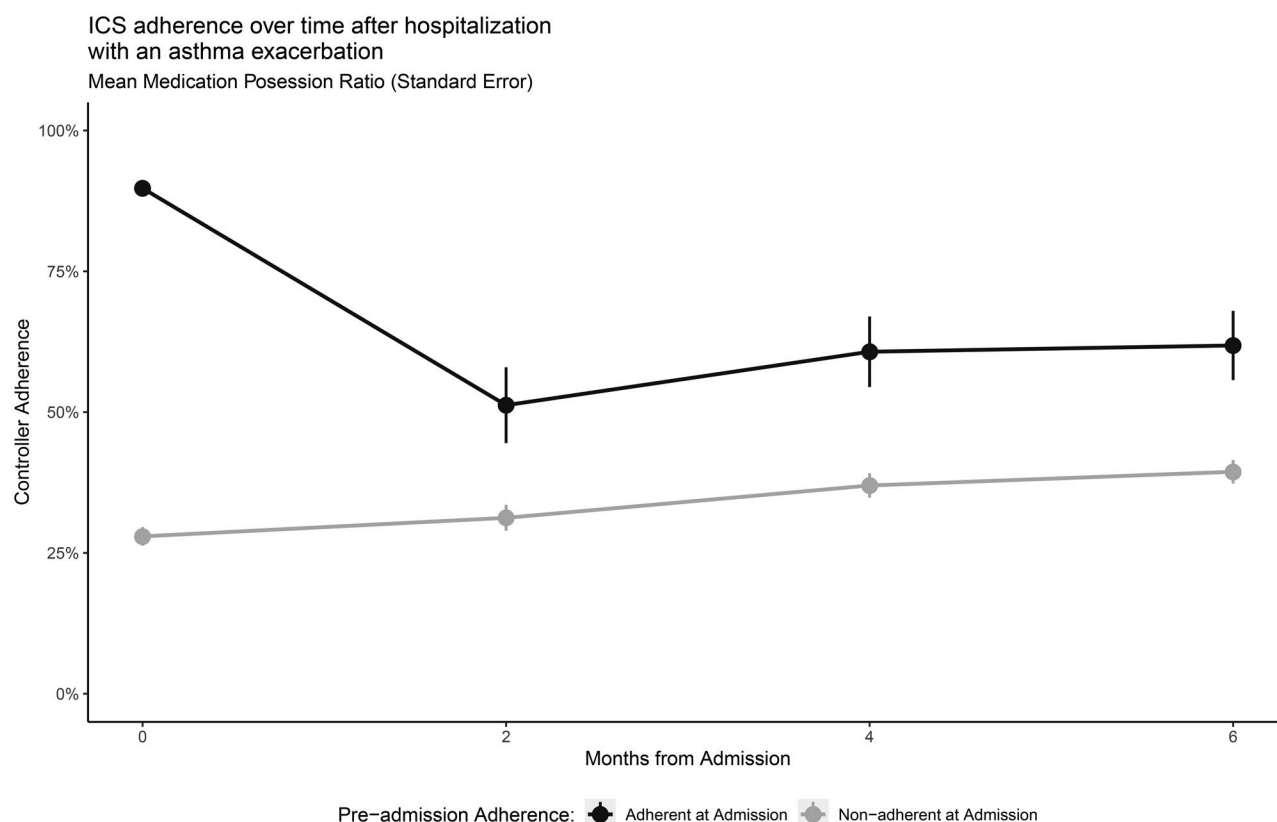


Figure 2. Adherence to inhaled corticosteroid treatment pre-admission, after two months, four months and six months in 241 patients admitted with asthma exacerbation. Adherent $\geq 80\%$ of medication possession ratio of inhaled corticosteroid; Non-adherent $< 80\%$ of Medication Possession Ratio of inhaled corticosteroid.

patients was 89.1%, with no statistically significant change after six months (77.3%, when adjusted ($p=0.11$)) (Figure 3). The mean ICS MPR prior to admission in the non-adherent patients was 27.9%, increasing to 62.5% two months after discharge when adjusted ($p<0.001$), after four months ICS MPR adjusted was 55.5% ($p<0.001$) and finally at six months ICS MPR adjusted was 49.3% ($p<0.001$).

Discussion

In this retrospective study of 241 patients hospitalized with a severe asthma exacerbation, we found that our population had an overall poor adherence, with only 23 patients (9.5%) being adherent at admission. The proportion of patients with good adherence increased following the index admission, however not significantly. A history of any exacerbation within 12 months prior to the index admission predicted risk of re-exacerbation within six months after discharge. Analysis revealed a correlation between baseline adherence and change in adherence following discharge, as the non-adherent patients increased their adherence, in contrast the adherent patients had an unchanged adherence.

Changes in ICS adherence after hospitalization with an acute exacerbation

We defined *a priori* “good adherence” as MPR $\geq 80\%$ with respect to earlier studies showing evidence of best possible reduction in risk of exacerbations (5,6,21–23).

The proportion of asthma patients with good adherence increased in our population after a severe asthma exacerbation, as did the overall level of adherence, however not to the level of best possible reduction in risk of exacerbations. A similar pattern has been observed in other studies, such as Williams et al. (24), where comparable baseline adherence and increase in adherence following an asthma exacerbation were seen in a young population of African Americans. The combined studies might indicate that the increased adherence after an asthma exacerbation is a general phenomenon, or at least a phenomenon prevalent in these two diverse populations (24).

The absolute increase of ICS MPR of less than 10% was not of certain clinical importance, as the study by Williams et al. (24) only found a decrease in risk of asthma exacerbation when increasing adherence $> 25\%$. Indeed, in patients with critically low adherence, the relative benefit of re-initiation of

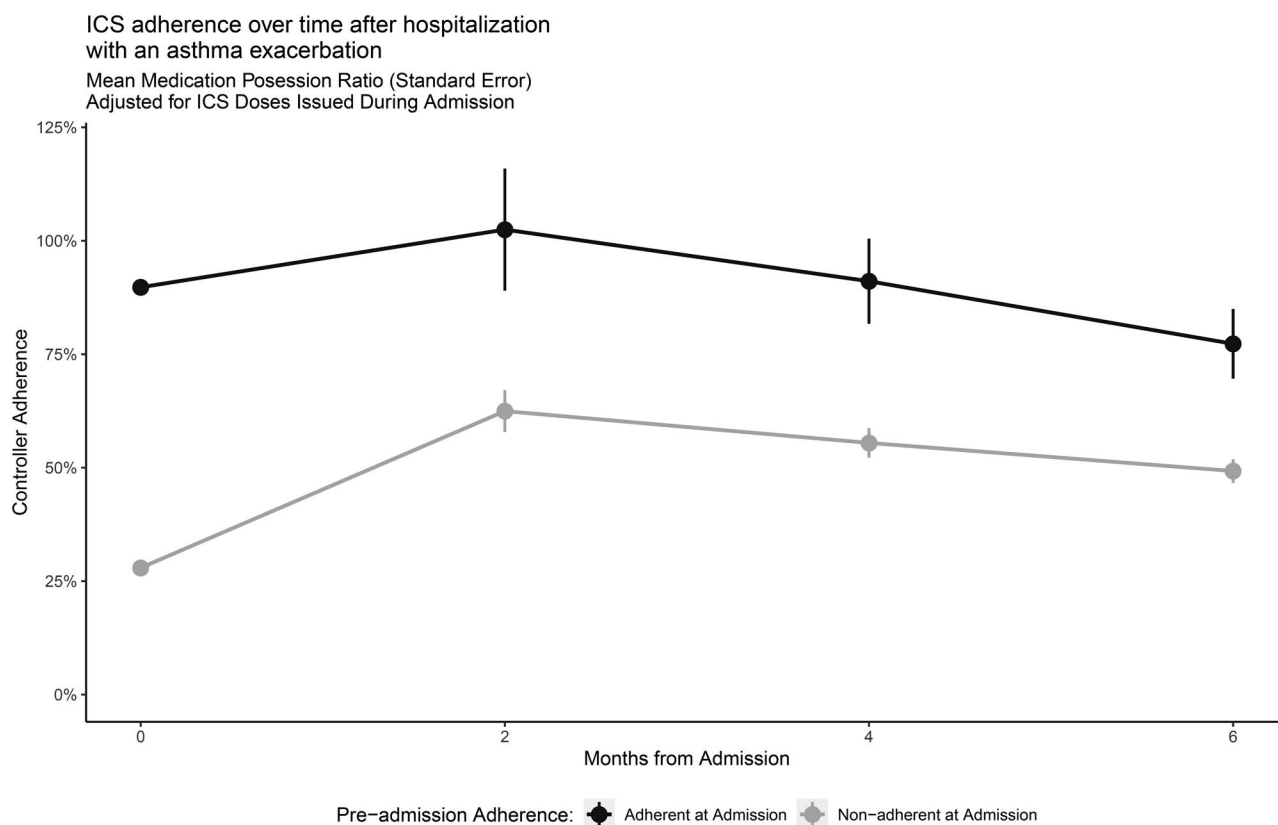


Figure 3. Adjusted adherence to inhaled corticosteroid treatment pre-admission, after two months, four months and six months in 241 patients admitted with asthma exacerbation. Adherent $\geq 80\%$ of medication possession ratio of inhaled corticosteroid; Non-adherent $< 80\%$ of Medication Possession Ratio of inhaled corticosteroid. The adjustment is 30 daily doses added, as they are not accounted for in medication orders due to in-hospital procurement.

ICS therapy could be assumed to be larger, as a dose-response relationship between adherence and the risk of severe exacerbations has been observed (25). Several studies have aimed at improving adherence after emergency care in both children and adults with mixed results (26–28). Overall, interventions focusing on patients-centered care, such as regular appointments with a healthcare worker discussing and educating the patient in asthma control, are seemingly the most effective intervention at increasing adherence to a clinically significant level (28–30).

Interestingly, we observed different patterns of change in adherence after discharge, as adherence increased only in patients who initially had low/moderate adherence ($\text{MPR} < 80\%$), suggesting that the group of patients were able to change their pattern of inhaler use. No previous studies found any differentiation between adherent and non-adherent patients in adherence measures after discharge. Our results did not identify any of the collected objective data to be predictors of increasing MPR after discharge, suggesting that subjective or non-asthma related factors are vital for understanding changes in adherence. This

is supported by a small, short-term study showing the depressive symptoms during asthma admission are major determinants of post-discharge adherence (31).

In terms of changes in adherence over time, patients who were adherent ($\text{MPR} \geq 80\%$) prior to admission, interestingly, reduced their adherence in the first two months following discharge (Figure 2). This stands in contrast to Williams et al. (24), who showed an increased adherence immediately after discharge. However, the literature is conflicting, as a smaller study ($n=60$) by Krishnan et al. (32) show an immediate decline in adherence to ICS after discharge. Of note, disparities between studies may in part be explained by patients receiving inhalers not accounted for by prescription registries during admission. Indeed, when adjusted for an assumed in-hospital procurement of 30 daily doses, the differences in pre-admission-MPR and MPR after six months was attenuated for patients previously adherent to ICS. In initially non-adherent patients, a significant, yet over time declining, increased MPR was seen after six months. However, the present study is limited by its six months follow-up, as previous studies have shown

the relapses to previous adherence patterns is common after 12 months (33).

ICS adherence and re-exacerbation risk

The level of adherence following a hospital admission did not predict the risk of re-exacerbation with asthma within six months from discharge, possibly due to a small number of events and resulting lack of power. Alternatively, patients who re-exacerbated could be patients with severe or difficult-to-treat asthma and thus be at an excess risk of re-exacerbation no matter adherence level. This hypothesis is supported by the approximate number of re-exacerbations matching the prevalence of difficult-to-treat asthma in Denmark (34). Our findings that a history of asthma exacerbations predicted a future exacerbation were in accordance to previous research (35).

Strengths and limitations of the study

A major strength in our study is the detailed registration of a variety of patient factors, due to the highly detailed nature of electronic patient records and the lack of loss to follow-up. Less than 35% of screened patients were not included, primarily due to not having an ICS prescription at baseline, but also due to opting out of research and/or quality assessment access to electronic patient records or non-residence in Denmark. The minor level of exclusion lessened the selection bias within the population.

A direct limitation is the single-center design and its inherent limitation to external validity and generalizability, as the study population could differ from the general population. However, the catchment area for Copenhagen University Hospital-Hvidovre is large and encompasses a broad socioeconomic spectrum. A second limitation is the relatively small population ($n=241$), however no loss to follow-up increases the validity.

Patients not included in the study

A considerable number of patients ($n=115$, 31%) hospitalized with a severe asthma exacerbation did not have a fill for an ICS recorded in the CMC during the 6 months preceding the hospitalization, though it is unknown whether due to no previous diagnosis of asthma or being regarded as having no indication for controller therapy. In accordance with our findings, a national British study found that 20% of patients with known asthma were not treated with controller

medication (36). Causes of non-prescription of controller medication in asthma are many, and not necessarily mutually exclusive, such as lack of subjective symptoms, underreporting of symptoms by the patients or even some degree of remission (37). The lack of medication order for an ICS prescription could have led to selection bias as patients without an active ICS prescription were excluded.

Conclusions

In our sample, an acute hospital admission with exacerbation of asthma was not associated with an increased proportion of ICS adherent patients but increases the overall adherence in non-adherent patients. However, the absolute increase in ICS MPR was less than 10%. Clinical factors such as age and sex failed to predict future adherence, suggesting that factors beyond clinical parameters such as psychological or socioeconomic factors should be accounted for during interventions aiming at improving adherence to ICS in patients with asthma.

Declaration of interest

The authors declare that they have no conflict of interest in relation to this study. KEJH reports personal fees from AstraZeneca, Chiesi and TEVA outside of the present work. CSU reports personal fees and/or grants from AstraZeneca, GSK, Chiesi, TEVA, Mundipharma, Novartis, ALK-Abello, SanofiGenzyme, Boehringer-Ingelheim, Orion Pharma and Actelion outside of the present work.

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