Pneumonia Risk in Asthmatic Children Using Inhaled Corticosteroids: A Nested Case-Control Study in a Birth Cohort

Pragya Shrestha MBBS[1], Chung Il Wi MD[1], Katherine S. King[2], Euijung Ryu Ph.D[2], Jungwon Yoon MD[1], Jung Hyun Kwon[3], Sunghwan Sohn Ph.D[2], Hongfang Liu Ph.D[2], Young Juhn MD MPH[1]

[1]Precision Population Science Lab, Department of Pediatrics and Internal Medicine, Mayo Clinic, Rochester, MN; [2]Department of Health Sciences Research, Mayo Clinic, Rochester, MN

[3]Department of Pediatrics, Korea University College of Medicine, Seoul, South Korea

Background

What is known?

- National Asthma Education and Practice Program (NAEPP) guidelines recommend inhaled corticosteroids (ICS) as a first-line controller medication as well as symptom reliever medication for asthma [Global Initiative for Asthma (GINA) 2019 guidelines]
- While ICS has reasonable safety profile, there is data suggesting association of long-term use of ICS with systemic adverse effects.
- Recently, risk of pneumonia associated with ICS was demonstrated in chronic obstructive pulmonary disease (COPD) patients which have led to similar concerns in asthmatic patients.

What is unknown?

- There are only few studies which address the impact of ICS use on the risk of pneumonia in asthmatics, but the results are inconsistent.
- These studies are based only on adult subjects and the results for children with asthma are unavailable to date.

Aim

- To determine the association of ICS use with pneumonia risk in asthmatic children.
- We hypothesized that ICS use in asthmatic pediatric patients does not pose an increased risk of pneumonia

Methods

Study setting and population

- Children born in Olmsted county between1997 to 2016 (n=37,451) were identified from the Rochester Epidemiology Project using ICD-9/10 and CPT codes related to birth.

Methods

Study design, subjects and variables

- Study design: A population-based nested case-control study
- Study subjects: Asthmatic children (<18 years) were identified using ICD9/10 codes from electronic medical records of patients born at Mayo Clinic from 1997-2016 and followed until 12/31/2017
  - Exclusion criteria :1) no research authorization for using medical record for research, 2) insufficient medical record to determine asthma status, 3) non-Olmsted County residency as of one year prior to index date, or 4) the presence of any chronic conditions which make ascertainment of asthma difficult
- Identification of Cases (pneumonia) and matched Controls
  - Cases: Pneumonia cases (confirmed by ICD-9/10 codes) after at least 3 months of asthma diagnosis (asthma index date) were included.
  - Controls: identified by matching to age, gender, asthma index date to Cases (1:1 matching).
  - Manual chart review for random 20 patients (10%) was done which confirmed accuracy of ICD codes for pneumonia (100%) for a physician diagnosis of pneumonia.
- Exposure: ICS prescribed at least 90 days or longer prior to pneumonia
  - All prescriptions for ICSs, alone or in combination, dispensed between the asthma index date and pneumonia diagnosis were identified.
  - 5 groups of ICS identified- Fluticasone, Beclomethasone, Ciclesonide, Budesonide, and Mometasone.
  - ICS dose was defined and analyzed for each age group as per NAEPP guidelines (0-4 years, 5-11 years and >=12 years) into low, medium and high dose depending on total mcg/mg use each day.

Data Analysis

- Matched analysis via conditional logistic regression was used, with pneumonia status as the target endpoint in the model and asthma status as the primary explanatory variable.
- Association between ICS use and pneumonia was estimated by conditional logistic regression in terms of type of ICS use, dose of ICS and combination of type and dose of ICS.
- SAS software package, version 9.4M5 (SAS Institute, Cary, NC).
- Based on the study by McKeever et al, the minimum number of cases (1:1 matching) to obtain 80% of power to detect the difference is 185 subjects. Our study had adequate power for analysis of ICS and pneumonia association (216 cases).

Table 1. Baseline Characteristics

Variables	Cases (n=216)	Controls (n=216)	Total (N=432)	P-Value
Gender				1.000[1]
Female	83 (38%)	83 (38%)	166 (38%)	
Age at asthma diagnosis				0.933[2]
Mean (SD)	3.79 (2.93)	3.81 (2.90)	3.798 (2.91)	
Average number of clinic visits per year				< 0.001[2]
Mean (SD)	9.785 (6.76)	7.533 (3.91)	8.659 (5.63)	
Average influenza vaccine over follow up				0.037[2]
Mean (SD)	0.742 (0.33)	0.674 (0.35)	0.708 (0.34)	
Influenza vaccine status				0.221[1]
Up-to-date	150 (69.4%)	138 (63.9%)	288 (66.7%)	
Pneumonia vaccine up to date				0.856[1]
Up-to-date	199 (92.1%)	138 (63.9%)	288 (66.7%)	
Asthma severity				0.079[3]
Intermittent	66 (31%)	91 (42%)	157 (36%)	
Mild persistent	92 (43%)	82 (38%)	174 (40%)	
Moderate persistent	44 (20%)	33 (15%)	77 (18%)	
Severe persistent	14 (7%)	10 (5%)	24 (6%)	
OCS use within 1 year				<0.001[1]
Yes	105 (49%)	65 (30%)	170 (40%)	
Houses index score				0.681[3]
1	69 (33%)	59 (28%)	128 (30%)	
2	51 (24%)	50 (24%)	101 (24%)	
3	43 (20%)	51 (24%)	94 (22%)	
4	48 (23%)	50 (24%)	98 (23%)	

[1]Pearson's Chi-squared test [2]Linear Model ANOVA [3]Trend test for ordinal variables
HOUSES: HOUsing-based SocioEconomic Status index

Results

- Our birth cohort included 1544 asthmatic children with 36% intermittent and 64 % persistent asthma. 216 children had at least one pneumonia event during the follow-up period (1997-2017).
- Poorly controlled asthma status (OCS use in prior year) posed the highest risk of pneumonia [2.6 (1.64-4.12), p=<0.001] followed by asthma severity.
- ICS use was not associated with risk of pneumonia in both univariate [1.29 (0.86-1.92), p=0.22] and multivariate analysis [1.09 (0.25-4.66), p=0.91].
- Fluticasone was the most used ICS (30.1%) followed by Budesonide (4.2 %). Different types of ICS were not associated with the risk of pneumonia.
- After adjusting for poorly controlled asthma status, higher ICS doses was associated with greater protective effects [1.1 (0.67-1.78) low, 0.99 (0.49-1.99) medium, 0.55 (0.13-2.36) high dose.

Table 2. Association between type and dose of ICS use and risk of pneumonia

Variables	Cases (n=216)	Controls (n=216)	Total (N=432)	P-Value
ICS use				0.233[1]
Yes	87 (40%)	75 (35%)	162 (38%)	
Type of ICS				
Beclomethasone	4 (2%)	2 (1%)	6 (1%)	
Budesonide	11 (5%)	7 (3.2%)	18 (4%)	
Fluticasone	68 (32%)	62 (29%)	130 (30%)	
Mometasone	4 (2%)	4 (2%)	8 (2%)	
Dose of ICS				
Dose of ICS				0.669[3]
Low	58 (27%)	48 (22%)	106 (25%)	
Medium	25 (12%)	23 (11%)	48 (11%)	
High	4 (2%)	4 (2%)	8 (2%)	

Table 3. Multivariate Analysis combining type of ICS and dose with risk of pneumonia after adjusting for positive confounders

Type of ICS	Univariate OR (95% CI)	Adjusted OR (for asthma severity)	Adjusted OR (for OCS use)
ICS use (Yes)	1.29 (0.86-1.92, p=0.22)	0.89 (0.53-1.51, p=0.67)	1.02 (0.66-1.57, p=0.92)
Beclomethasone	2.28 (0.41-12.78, p=0.35)	1.45 (0.24-8.65, p=0.68)	2.26 (0.4-12.66, p=0.36)
Budesonide	2.05 (0.67-6.27, p=0.21)	1.26 (0.37-4.21, p=0.71)	1.96 (0.61-6.29, p=0.26)
Fluticasone	1.20 (0.78-1.85, p=0.41)	0.85 (0.49-1.47, p=0.56)	0.89 (0.56-1.43, p=0.64)
Mometasone	1.07 (0.27-4.33, p=0.92)	0.82 (0.19-3.48, p=0.79)	1.09 (0.25-4.66, p=0.91)
Dose of ICS			
Low	1.34 (0.84-2.11, p=0.22)	1.15 (0.61-2.17,p=0.67)	1.1 (0.67-1.78, p=0.71)
Medium	1.24 (0.64-2.39, p=0.53)	0.57 (0.23-1.41, p=0.22)	0.99 (0.49-1.99, p=0.98)
High	1.04 (0.26-4.16, p=0.96)	0.41 (0.07-2.55, p=0.34)	0.55 (0.13-2.36, p=0.42)

Discussion

- Our study involving asthmatic children did not show any relation to type of ICS for risk of pneumonia. The association in fact became protective with higher dose of ICS after adjusted for poorly controlled asthma status.
- Our study results are consistent with the study findings reported by O'Byrne et al. (investigated among adults and children) where they assessed clinical trials involving budesonide (26 trials). Overall, they did not find increased risk of pneumonia with higher dose of Budesonide and Fluticasone however; pneumonia was not their primary outcome event and results were based on pooling various study cohorts.
- This also points towards a protective effect of ICS on asthmatic children for pneumonia prevention. Study done by Doull showed significant decrease in lower respiratory tract infection before and after therapy with ICS (30% to 15% ICS) in a randomized controlled trial done in school age children.
- McKeever et al. conducted a nested case-control study using The Health Improvement Network database and found ICS use (only Fluticasone) to be associated with an increased risk of pneumonia and lower respiratory tract infection in adults.
- However, recently the same group (McKeever) performed a randomized trial among adult patients quadrupling ICS dose to abort asthma exacerbation. This intervention resulted in a lower rate of asthma exacerbation but did not cause significant difference in the incidence of pneumonia.
- Qian et al. used Quebec health insurance database and performed a quasi- cohort study among young patients (12-35 years). They found an increased risk of pneumonia associated with current ICS use with incremental dose relation.
- The reason for varied effects in adult vs. children patients could be different dose adjustments of ICS ,confounding factors like comorbid conditions in adults. Also, asthma pathophysiology (Th2 for pediatric asthma vs. Th2 or Th1 mixed for adult asthma). The studies also did not adjust for important confounding factors as reported in our study.
- The biological mechanism explaining the association of ICS and pneumonia risk is still not clear. Mouse models and in vitro studies of human bronchial epithelial cells have demonstrated that ICSs reduce bacterial invasion, whereas, can reactivate chronic infection by atypical bacteria.
- Genome wide association studies have discovered genes (GLLCCI1, FBXL7, T gene, ALLC, CMTR1) that may play role in ICS response in asthma. However, pneumonia risk association with the genes have not been studies yet.
- However, increased risk pneumonia can occur with severe or poorly controlled asthma, due to the disease entity itself and Th2-high induced suppression of innate immunity. Therefore, high-dose ICS associated with more severe or poorly controlled asthma is likely to be a confounder in relation to the risk of pneumonia.

Strengths and Limitations

- **Strengths:** First population-based study design that used rigorous approaches for ascertaining ICS use and pneumonia incidence through a longitudinal data using Mayo Birth Cohort focusing on pediatric population and pediatric dose based ICS use. Adequate power for study. The study has also attempted to control for major confounders like asthma severity, OCS use, socioeconomic status and vaccination status .
- **Limitations:** We were not fully disentangle asthma severity or control status as confounder. Also, compliance with ICS use or assess device type was not assessed. Asthma and pneumonia diagnosis were based on ICD codes raising the possibility of misclassified diagnoses. However, to address this concern, we did perform a manual chart review for 20 random cases (10%).

Conclusions

- ICS use in asthmatic children is not associated with the risk of pneumonia regardless of type and dose. The results should reassure parents of asthmatic children who are concerned about ICS safety.
- As our study had relatively small sample size, findings need to be replicated with a larger study.

References

- McKeever T, Harrison TW, Hubbard R, Shaw D. Inhaled Corticosteroids and the Risk of Pneumonia in People With Asthma. Chest. 2013;144(6):1788-1794.
- Qian CJ, Coulombe J, Suissa S, Ernst P. Pneumonia risk in asthma patients using inhaled corticosteroids: a quasi-cohort study: Inhaled corticosteroids and risk of pneumonia in patients with asthma. Br J Clin Pharmacol. 2017;83(9):2077-2086.
- O'Byrne PM, Pedersen S, Carlsson L-G, et al. Risks of Pneumonia in Patients with Asthma Taking Inhaled Corticosteroids. Am J Respir Crit Care Med. 2011;183(5):589-595.
- McKeever T. Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations. N Engl J Med. 2018;378(10):902-910.
- Doull IJ, Effect of inhaled corticosteroids on episodes of wheezing associated with viral infection in school age children. BMJ. 997;315(7112):858-862

Acknowledgement

National Institute of Health (NIH)-funded R01 grant (R01 HL126667), NIH R21 (R21 AI142702), NIH T32 (GM08685).

We thank Ms. Kelly Okeson for her administrative assistance.