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ANALYSIS OF RISK OF PNEUMONIA IN OBSTRUCTIVE LUNG DISEASE AMONG LOCAL POPULATION OF PAKISTAN

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Abstract:

Introduction: *Inhaled corticosteroids (ICS) are widely used in high doses in the management of obstructive lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). Current asthma treatment guidelines recommend stepping up the ICS dose if lack of control persists.* ***Objectives of the study:*** *The main objective of the study is to analyze the risk of pneumonia in obstructive lung disease among local population of Pakistan.* ***Methodology of the study:*** *This study was conducted at Services Institute of medical sciences, Lahore in March 2018. This study was done with the permission of ethical committee. For this purpose we select 50 patients of pneumonia for further analysis. The patients of both gender were selected for this study. Diagnosis of pneumonia: (i) unconfirmed i.e. all unique patients with codes for pneumonia and, (ii) confirmed by chest radiograph or resulting in hospitalization within one month of pneumonia diagnosis.* ***Result:*** *Significant differences were observed between patients who received extra-fine versus fine-particle COPD in the demographics and baseline characteristics, as shown in Table 1. The COPD treatments prescribed to patients before and at step-up are shown in S1 Table in the supporting information.* ***Conclusion:*** *In conclusion, the COPD exacerbation rate was higher among the patients who had a history of pneumonia or a high rate of COPD exacerbation in the preceding period of 1 year.*

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INTRODUCTION:

Inhaled corticosteroids (ICS) are widely used in high doses in the management of obstructive lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). Current asthma treatment guidelines recommend stepping up the ICS dose if lack of control persists. Alternatively, the combination of low-dose ICS with long-acting β2-agonist (LABA) has been shown to achieve better asthma control, sparing patients higher doses of ICS [1]. In patients with COPD, low-dose ICS/LABA combination has been shown to reduce exacerbations, improve quality of life and lung function, through an underlying complementary anti-inflammatory cellular action. However there continues to be significant concern regarding inappropriate prescribing of high-dose ICS in patients with obstructive lung diseases, with untoward consequences for patients [2].

The first laboratory based observational study was conducted in Rawalpindi between 2002 and 2003. The study demonstrates a low diagnostic yield for isolated pathogens 88 out of 510 specimens (17.25%). Most commonly identified pathogen was Haemophilus influenzae (HI) with a strikingly high relative frequency (64 out of 88) among isolates [3]. However, this yield is reported in a majority of paediatric population (41 out of 64) with 33 being less than five years of age. These figures therefore will not be in any way reflective of adult CAP status.
The most comprehensive study was The Active Study. This study was conducted as a part of an international survey that included nine countries from all over the world. This contribution from Pakistan comprised of 200 samples. SP and HI were almost equally identified in CAP cases (90 and 87 respectively)[4]. Macrolide showed poor sensitivity against SP with 28% being resistant to erythromycin and clarithromycin. Resistance to levofloxacin was detected in 3% of SP tested in this study. All were sensitive to beta lactams. Fluoroquinolones and cephalosporins were found to be consistently active against HI tested in this study. Although beta lactamase producing HI is an emerging problem all over the world the results of this study suggest that beta lactamase producing strains of HI are less prevalent in Pakistan as all the isolates were sensitive to beta lactams, macrolides and cephalosporins with a very low level resistance to ampicillin (3%) [4].

Indeed, regular use of ICS has been linked to several systemic effects, including a higher risk of pneumonia, where it is thought that ICS exert an anti-inflammatory and immunosuppressive effect that could affect the pathogenesis of pneumonia [3]. Most randomized controlled trials (RCTs), observational studies and meta-analysis, in patients with COPD suggest an increased risk of pneumonia with a dose-response relationship between ICS and pneumonia, although there is some evidence suggesting to the contrary [4]. This association is not as clear-cut in asthmatics; ICS are associated with a decreased risk of pneumonia based on RCTs, but observational studies suggest a higher risk of pneumonia[5]. Importantly though, all the published literature has assessed the risk of pneumonia only for conventional fine-particle ICS and not for extra-fine particle ICS in patients with obstructive lung disease.

Theoretical background

Despite the fact that free vaccination is available in Pakistan, pneumonia is killing around 92,000 children annually under-five years of age, health experts said Tuesday during a press briefing to mark upcoming World Pneumonia Day on November 12. According to the World Health Organisation (WHO) estimates, pneumonia accounts for 16 percent of the total child deaths making it the leading killer of children less than 5 years of age globally. Pneumonia is a form acute respiratory infection that affects lungs. When an individual has pneumonia, the alveoli (small sacs in lungs which fill with air when a healthy person breathes) are filled with pus and fluid, which makes breathing painful and limits oxygen intake. It is to be noted that vaccines are considered second only to clean drinking water in reducing infectious diseases, he added. Pneumonia is caused by a number of infectious agents, including viruses, bacteria and fungi. The most common causes of pneumonia amongst children include streptococcus pneumoniae and haemophilus influenzae type b (Hib) [6].

Objectives of the study

The main objective of the study is to analyze the risk of pneumonia in obstructive lung disease among local population of Pakistan.

METHODOLOGY OF THE STUDY:

This study was conducted at Services Institute of medical sciences, Lahore in March 2018. This study was done with the permission of ethical committee. For this purpose we select 50 patients of pneumonia for further analysis. The patients of both gender were selected for this study. Diagnosis of pneumonia: (i) unconfirmed i.e. all unique patients with codes for pneumonia and, (ii) confirmed by chest radiograph or resulting in hospitalization within one month of pneumonia diagnosis.

Secondary outcomes:

1. Exacerbation of asthma or COPD: An asthma *exacerbation* was defined as a course of oral corticosteroids (OCS), hospital admission, or emergency department attendance for asthma during the outcome year. For patients with COPD, exacerbations were defined as an acute course of OCS, antibiotics for a lower respiratory tract infection, or a recorded hospitalization for COPD.
2. An acute respiratory event was defined as an occurrence of any of asthma or COPD related hospital admission, or emergency department attendance or acute use of OCS or antibiotics prescribed with lower respiratory consultation (consisting of the following: i) Lower respiratory read codes (including Asthma, COPD and LRTI Read codes); ii) Asthma/COPD review codes excluding any monitoring letter codes; iii) Lung function and/or asthma monitoring; iv) Any additional respiratory examinations, referrals, chest x-rays or events).

Exclusion criteria

Patients with any other chronic respiratory disease, at any time were excluded from the study.

Statistical analyses

Baseline characteristics of unmatched and matched patients prescribed either fine- or extra-fine particle ICS are described using summary statistics and compared using χ^2 or Mann-Whitney *U* tests as appropriate.

RESULTS:

Significant differences were observed between patients who received extra-fine versus fine-particle COPD in the demographics and baseline characteristics, as shown in Table 1. The COPD treatments prescribed to patients before and at step-up are shown in S1 Table in the supporting information.

Table 01: Baseline and clinical characteristics of pneumonia patients with obstructive lung diseases

Demographic and clinical baseline characteristics		**COPD**		**P-value[a]**
		Patients (n = 50)		
		Fine-particle	**Extra-fine particle**	
Demographics				
Sex, female		9046 (61)	4871 (59)	0.004
Age		44 (17)	44 (18)	0.018
Baseline weight BMI (kg/m^2), mean (SD)		28 (7)	29 (7)	0.001
Smoking[b]	Non-smokers	8679 (59)	4873 (59)	0.024
	Current smokers	3474 (24)	1904 (23)	
	Ex-smokers	2476 (17)	1392 (17)	
Respiratory diagnosis	None	174 (1.2)	114 (1.4)	NA
	Asthma/ no COPD	11516 (77.9)	7171 (87.2)	
	COPD/ no asthma	197 (1.3)	93 (1.1)	
	Asthma and COPD	2901 (19.6)	847 (10.3)	
Comorbidities and Therapy				
Rhinitis diagnosis and/or therapy[c]		6175 (42)	2754 (34)	<0.001
GERD diagnosis and/or drugs[d]		3827 (26)	2115 (26)	0.784
Ischaemic heart disease diagnosis[e]		1084 (7)	433 (5)	<0.001
Coding for pneumonia[f]		73 (0.5)	22 (0.3)	0.010
Confirmed coding for pneumonia[g]		25 (0.2)	12 (0.1)	0.674
Baseline characteristics				
Acute oral corticosteroid courses[h]	0	8542 (58)	6008 (73)	<0.001
	1	3103 (21)	1420 (17)	
	2+	3143 (21)	797 (10)	
Antibiotics prescribed with lower respiratory consultation[i]	0	9027 (61)	5440 (66)	<0.001
	1	3060 (21)	1667 (20)	
	2+	2701 (18)	118 (14)	

Patients stepping-up their ICS therapy to extra-fine particle ICS were significantly less likely to be coded for pneumonia compared to those stepping-up to fine-particle ICS, having adjusted for confounders (table 2).

Table 2: Pneumonia diagnosis by treatment group.

Pneumonia diagnosis	**By treatment group**		**Total**	**P-value[a]**
	Fine-particle	**Extra-fine particle**		
Yes, n (%)	73 (0.5)	22 (0.3)	95 (0.4)	0.011
No, n (%)	14715 (99.5)	8203 (99.7)	22918 (99.6)	
Total, n (%)	14788 (100)	8225 (100)	23013 (100)	
Odds ratio adjusted for baseline confounders[b]	1.00	0.60 (0.37, 0.97)		

DISCUSSION:

The pathophysiological mechanisms that contribute to an increased susceptibility to pneumonia in patients treated with ICS are unclear. In murine models, ICS have been shown to significantly increase alveolar macrophage efferocytosis (uptake of apoptotic cells by alveolar macrophages), thereby reducing their ability to combat microbes[7], including *Streptococcus pneumoniae*, the most common cause of community acquired pneumonia in patients with COPD [8]. A recent study in a cohort of children with persistent asthma taking daily ICS showed nearly four times greater oropharyngeal colonization with *Streptococcus pneumoniae* compared to children not receiving ICS, which may increase the risk of having pneumococcal respiratory infections. Several studies have demonstrated an intra-class difference between both mono-component ICS and fixed combinations of ICS/LABA with regard to the risk of pneumonia and pneumonia related events in COPD patients [9,10]. The risk of patients with COPD developing serious pneumonia is particularly elevated and dose related with fluticasone use and much lower with budesonide. Although there have been no studies directly comparing the effects of fluticasone and budesonide on host defence, differences are likely related to their contrasting pharmacokinetic and pharmacodynamic properties. To prevent any confounding by differences between FP and budesonide, we therefore excluded patients using budesonide in our current analyses [11].

In summary, we have shown important findings relevant to prescribing clinicians in the day-to-day management of patients with obstructive lung disease, where an increased risk of pneumonia and higher rates of adverse respiratory events are more likely with fine-particle COPD compared to extra-fine particle COPD [12].

CONCLUSION:

In conclusion, the COPD exacerbation rate was higher among the patients who had a history of pneumonia or a high rate of COPD exacerbation in the preceding period of 1 year.

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