INCIDENCE OF TUBERCULOSIS AMONG PATIENTS OF BRONCHIAL ASTHMA RECEIVING TREATMENT WITH METERED DOSE CORTICOSTEROID BY INHALATION

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ABSTRACT

BACKGROUND
The aim of this study was to evaluate the incidence and pattern of tuberculosis in bronchial asthma patients receiving inhalational corticosteroid therapy by MDI.

MATERIALS AND METHODS
Eighty-four patients taking MDI steroid for bronchial asthma and seventy-eight patients suffering from similar disease but not receiving MDI steroids were followed up for twenty months to study the incidence and pattern of tuberculosis.

RESULTS
Five patients (5.5%) receiving MDI steroid developed tuberculosis as against none among the control (p<0.05). Out of five patients, who developed tuberculosis, two developed sputum smear positive pulmonary disease, one had sputum smear negative disease and two had extra pulmonary tuberculosis in form of pleural effusion and gland tuberculosis one each. All patients were treated with standard antituberculous therapy using RNTCP guidelines and all patients recovered from the disease.

CONCLUSION
Inhalational corticosteroid in the form of MDI causes a significant risk of incidence of tuberculosis.

KEYWORDS
MDI- Metered Dose Inhaler, RNTCP- Revised National Tuberculosis Control Program, TB- Tuberculosis, AFB- Acid Fast Bacilli, FNAC- Fine Needle Aspiration Cytology, CBNAAT- Cartridge Based Nucleic Acid Amplification Test, OCS- Oral Cortico-Stereoids, GINA- Global Initiative for Asthma.

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BACKGROUND
Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium tuberculosis (MTB).⁰⁻¹³ Tuberculosis generally affects the lungs, but can also affect other parts of the body. Most infections do not have symptoms, in which case it is known as Latent tuberculosis. About 10% of latent infections progress to active disease which, if left untreated, kills about half of those infected. The classic symptoms of active TB are a chronic cough with blood-containing sputum, fever, night sweats, and weight loss. The historical term "consumption" came about due to the weight loss.¹³ Infection of other organs can cause a wide range of symptoms.¹⁴ Tuberculosis is spread through the air by droplet nuclei when people who have active TB in their lungs cough, spit, speak, or sneeze. Tiny droplets dry rapidly and may remain suspended in air for hours and may reach the terminal air passages when inhaled by a bystander. The risk of developing disease unlike acquiring infection depends largely on endogenous factors such as individual's innate immunological and non-immunological defenses and the level at which the individual's cell mediated immunity is working.¹⁵ People with latent TB do not spread the disease. Active infection occurs more often in people with HIV/AIDS and in those who smoke. Diagnosis of active TB is based on chest X-rays, as well as microscopic examination and culture of body fluids. Diagnosis of latent TB relies on the tuberculin skin test (TST) or blood tests.

Tuberculosis is a serious public health problem in India causing immense morbidity, mortality and distress to individuals' families and community. About 40% of patients are infected with tubercle bacilli in India the vast majority of who have latent TB rather than TB disease. India accounts for one fourth of the global TB burden. In 2015 an estimated 2.8 million cases occurred and 4.5 lakh people died of TB.¹

The predisposing factors for tuberculosis are corticosteroid therapy, immunosuppressive and anticancer therapy, and co-infection with HIV, presence of diabetes mellitus, renal transplant, gastrojejunosotmy patients and not the least in alcoholic persons.²
Bronchial asthma is one of the diseases recognized as a distinct entity since long, but it has come to the center stage as a public health problem only in the last 3-4 decades. It is a serious global health problem. People of all ages in countries throughout the world are affected by this chronic airway disorder that when uncontrolled, can place severe limits on daily life and is sometimes fatal. Prevalence of asthma has increased dramatically and is now recognized as a major cause of disability, medical expense and preventable deaths. Bronchial asthma is a heterogeneous disease characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and intensity, together with expiratory airflow limitation. There are many factors influencing the development and expression of asthma e.g. host factors like genes predisposing to atopy, airways hyper responsiveness, environmental factors like allergens, infections, occupational sensitizers, tobacco smoke, air pollutions and diet etc. The different allergens by a set of immunological reactions superimposed by neurological actions cause release of inflammatory cells and mediators of inflammation causing bronchial hyper responsiveness, mucus hyper secretion and paroxysmal attacks of bronchoconstriction manifesting as wheeze, cough, chest tightness and dyspnoea. Bronchial asthma and tuberculosis (TB) are two of the very common diseases seen in developing countries. Patients with bronchial asthma often require life-long therapy with steroids. Whether use of steroids in an asthmatic causes flare up of tuberculous lesions has been a long continuing debate. More than 30% of the Indian population is subclinically infected with Mycobacterium tuberculosis. Corticosteroids have been shown to affect the lymphocytes, and thereby, affecting inflammatory and immunologically mediated processes. Corticosteroids impair antibody production and cell-mediated immunity, leading to blunting of the patient’s response to infection. Hence, this study was undertaken to estimate the incidence of pulmonary and extra pulmonary tuberculosis among patients with bronchial asthma treated with inhalational corticosteroids. Anti-inflammatory drugs like oral and inhalational corticosteroids in form of MDI play a major role in abating an acute attack of asthma as well as they are useful in management of chronic asthma. Corticosteroid used in MDI in our part in equivalent doses are beclomethasone dipropionate (100 - 200 mcg/day in two divided doses), Budesonide (200-400 mcg/day as a single or in two divided doses), fluticasone propionate (100-250 mcg/day in two divided doses) in the low doses and (500-800 mcg/day in two divided doses), (1000-1600 mcg/day in two divided doses) and (600-1000 mcg/day in two divided doses) at the high doses respectively (GINA’s asthma guidelines). They are usually combined with long acting beta 2 agonists like formoterol, salmeterol etc. ICS have local anti-inflammatory effects and are useful in management of bronchial asthma. MDI in bronchial asthma might facilitate infection with mycobacterium tuberculosis in the form of either reinfection or reactivation.

There has been significant no. of reports of association between use of inhaled corticosteroids and risk of tuberculosis from both abroad and India. So we thought it prudent to study its incidence in our region and evaluate the possible role of corticosteroids in causing tuberculosis in patients with bronchial asthma necessitating use of MDI therapy.

MATERIALS AND METHODS
This hospital-based, cross-sectional study was conducted at Patna Medical College and Hospital, Patna, Bihar in the period between 2014 and 2017 on the patients of bronchial asthma attending Medical and Chest and TB OPD. One hundred patients suffering from bronchial asthma and taking MDI corticosteroid therapy were enrolled in the study group. Diagnosis of bronchial asthma was made after eliciting detailed medical history, symptoms, physical examination and measurement of pulmonary functions as outlined by GINA 2006. For diagnosis of tuberculosis too, after taking detailed history, clinical examinations including relevant examination and investigations especially sputum examination for AFB and where possible CBNAAT test for mycobacterium tuberculosis were done. Anti-tuberculosis therapy (DOTS regimen as per government RNTCP programme) was started after diagnosis of tuberculosis. An equal number of age and sex matched patients suffering from bronchial asthma but not taking MDI corticosteroids constituted control group. Patients of both groups were followed for twenty months. Patients with preexisting tuberculosis or giving past history of intake of antituberculous therapy (ATT) were excluded from study.

All patients in study and control groups were followed for twenty months at four monthly intervals. On each follow up visit, response to MDI corticosteroids therapy and development of fresh symptoms such as fever, cough, expectoration, haemoptysis, loss of weight, loss of appetite and breathlessness were recorded. Chest roentgenogram was done at each visit for assessment of emergence of fresh pulmonary infections and for evaluation of previous shadows. All suspects developing fresh respiratory symptoms and infiltrates in X-rays were subjected to sputum examination for acid fast bacilli (AFB) using Ziehl-Nelson stain on two consecutive days. Additional tests such as pleural fluid analysis, pleural biopsy, fine needle aspiration cytology and/or biopsy of enlarged nodes, bronchoalveolar lavage (BAL) and CT scan of chest were also done for confirmation of tuberculosis when and where required. All subjects confirmed or strongly suspected to have developed tuberculosis were started on antituberculosis chemotherapy using RNTCP regimen as per WHO guidelines.

Comparison between two groups was carried out using student t-test for continuous variables and X² test for categorical variables. Statistical significance was tested at a level of p<0.05. In addition, multivariate logistic regression analysis was carried out to identify risk factor(s) responsible for development of tuberculosis.
RESULTS
Out of the two hundred subjects (100 cases and 100 controls), the age and sex distribution are summarized in table 1. During study period 16 cases and 22 controls did not come for regular follow up and were subsequently excluded from analysis.

The dose of MDI ranged from 200 mcg to 800 mcg/day and the duration of treatment varied from two months to twenty months. Most of our patients were using beclometasone dipropionate or budesonide alone or a combination of ICS with long acting beta 2 agonist as formoterol and budesonide or as salmeterol and fluticasone. Five (5.9%) out of the 84 cases developed tuberculosis as against none of the controls (p<0.05). Of these 5 patients three developed pulmonary tuberculosis (two were sputum smear positive and one had clinicoradiological evidence), one developed pleural effusion and another one developed cervical lymphadenopathy demonstrating caseating granuloma in FNAC. All patients who developed tuberculosis were treated successfully with RNTCP regimen according to WHO guideline.

Multiple logistic analysis was done to evaluate risk factors like age, sex, underlying disease, maximum dose of inhaled corticosteroid, duration of treatment and additional supportive therapy. The incidence of tuberculosis did not show significant association with any of this variable.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases Mean Age ± SD</th>
<th>Controls Mean Age ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>46.2±14.0</td>
<td>36.8±16.6</td>
</tr>
<tr>
<td>Male</td>
<td>38 (45.25%)</td>
<td>46 (58.97%)</td>
</tr>
<tr>
<td>Female</td>
<td>46 (54.76%)</td>
<td>32 (45.02%)</td>
</tr>
</tbody>
</table>

**Table 1. Patient Characteristics in the Study Population**

**Table 2. Details of Five Patients Who Developed Tuberculosis During the Study Period**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.)</td>
<td>50</td>
<td>44</td>
<td>48</td>
<td>28</td>
<td>35</td>
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<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Max. daily dose</td>
<td>400mcg</td>
<td>200mcg</td>
<td>400mcg</td>
<td>800mcg</td>
<td>600mcg</td>
</tr>
<tr>
<td>Duration in months</td>
<td>8</td>
<td>20</td>
<td>12</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Site of Tuberculosis</td>
<td>Pulmonary</td>
<td>Pulmonary</td>
<td>Pleural effusion</td>
<td>Cervical gland</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>Sputum smear for acid fast bacilli</td>
<td>Positive</td>
<td>Negative</td>
<td>--</td>
<td>--</td>
<td>Positive</td>
</tr>
<tr>
<td>Outcome</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
</tr>
</tbody>
</table>

DISCUSSION
Asthma is a worldwide problem with an estimated 300 million affected individuals5,10 and its prevalence is increasing especially among children in many countries. Despite a number of published reports on the prevalence of asthma in different populations lack of a precise and universally accepted definition of asthma makes it difficult to compare the reported prevalence from different parts of the world. Health-care expenditure on asthma is also very high, up to 1% to 2% of total health-care expenditures. In the early days of corticosteroid therapy, concerns were often expressed about reactivation of latent TB and the development of TB in tuberculin-positive individuals with no evidence of clinical disease. Whenever a patient on corticosteroids developed overt TB, the two events tended to be regarded as causally related. The view that asthma and pulmonary TB are mutually exclusive is widespread globally. A long continuing debate has been whether steroids result in flare up of tuberculous lesions. The role of steroid therapy in an asthmatic precipitating TB is controversial. Many studies conducted worldwide showed definite association between corticosteroid therapy and development of overt TB.11,12 In 1972, Lieberman et al12 observed no reactivation of TB among 50 asthmatic patients in a study of complications of corticosteroid treatment and found that the difference was not statistically significant. P N Agrawal et al14 in their study of seventy-seven patients receiving oral corticosteroids found significant increase in the incidence of tuberculosis in them. Over the years, several studies have been carried out to determine the influence of corticosteroid therapy in development of tuberculosis but very few studies are with inhalational corticosteroid therapy.

In 1971, a joint statement of American Thoracic Society, National Tuberculosis and Respiratory Disease Association and Communicable Disease Centre,19 commented that there is danger of reactivation of latent tuberculosis or developing re-infection with mycobacterium tuberculosis after therapy with corticosteroid and recommended that patients with healed pulmonary tuberculosis receiving systemic corticosteroids should receive isoniazid prophylaxis.

Am J Respir. Crit. Care Med. 2011,5 also published the study of effects of inhaled corticosteroid and risk of pulmonary tuberculosis and found no association in the presence of simultaneous use of OCS, however the risk was increased in the non-users of OCS. Ni S, Fu Z et al in Journal of Thoracic disease 2014,7 published that corticosteroid inhalation is associated with an increased risk of mycobacterium infections in patients with chronic pulmonary disease.

Corticosteroids, through its immunosuppressive and anti-inflammatory effects on many organ systems, impair antibody formation and cell mediated immunity. ICS reduce inflammatory cell numbers and their activation in the airways. In the airway mucosa they reduce eosinophils, activated T lymphocytes and surface mast cells.5,18 They transiently sequester T-cells, decrease monocyte, lymphocyte, basophil, eosinophil count in peripheral blood, and reduce polymorphonuclear inflammatory response. By
switching off the transcription of multiple activated genes that encode inflammatory proteins they inhibit cytokine production through the effects on lymphocyte and monocyte and additionally block the effects of cytokine on some target cells. Through these actions, corticosteroid predisposes patients to a variety of secondary infections, reactivation of latent tuberculous infection and reinfection with mycobacterium tuberculosis. These effects on cells are more evident if inhaled corticosteroid doses exceed 1000 mcg/day, the therapy is given continuously for longer periods. The prolonged therapy has more profound immunosuppressive activity as compared with intermittent therapy.

In our study, five out of 84 cases (5.55%) on MDI corticosteroid therapy developed tuberculosis. Out of 5 cases 2 were sputum smear positive (40%). The zero incidence of tuberculosis in control group (88 cases) is not surprising in light of estimated risk of tuberculosis of <1%/year in general population. In our study no definite correlation was elicited between the dose of ICS and development of tuberculosis as is evident from table no 2. However, in a retrospective study done by Shu CC. et al, 2010, it was found that high dose ICS (equivalent to >500mcg of Fluticasone, the use of 10 mcg or more oral corticosteroids, and prior pulmonary TB were independent risk factors for the development of active pulmonary tuberculosis.

The duration of MDI corticosteroid therapy before development of tuberculosis in the present study varied from 4 months to 20 months. This suggests that reactivation can occur either shortly after therapy is started, or several months or year later. In all three cases that developed pulmonary tuberculosis in this study, the appearance of fresh symptoms led to the suspicion of tuberculosis. A high index of suspicion is necessary for early detection of tuberculosis in these patients.

The reason for sputum negativity in one patient with pulmonary tuberculosis in this study could be antibiotics therapy (Ciprofloxacin and Amikacin) received by the patient before the diagnosis of tuberculosis. These drugs are second line anti tuberculosis drugs. All the patients 100% in this study responded well to standard short course anti tuberculous chemotherapy under guidelines of RNTCP.

CONCLUSION
There is statistically significant increase in incidence of tuberculosis due to inhalational corticosteroid therapy, especially in areas with high prevalence of tuberculosis such as North Bihar. The disease, however, responds well to standard anti tuberculosis chemotherapy. Duration and dose of inhalational corticosteroid also influences the development of tuberculosis. However, the upper dose limit of ICS which can lead to development of tuberculosis was not established in our study. A longer study, involving a large study population, would be desirable for further verification of these results.

REFERENCES
[17] https://www.nice.org.uk, inhaled corticosteroids dosage- nice