



# PULMONARY Insights

HIGHLIGHTS FROM ATS  
INTERNATIONAL CONFERENCE, 2019

American Thoracic Society 2019  
International Conference,  
May 17-22, 2019 - Dallas, TX

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PHARMACEUTICALS

In Sinusitis, Otitis Media, LRTI, SSTI & UTI

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References:

1. Thorax 2011; 66:ii1ei23.doi:10.1136/thoraxjnl-2011-200598.
2. Journal of Antimicrobial Chemotherapy (2004) 53, suppl. S1, i3-i20.

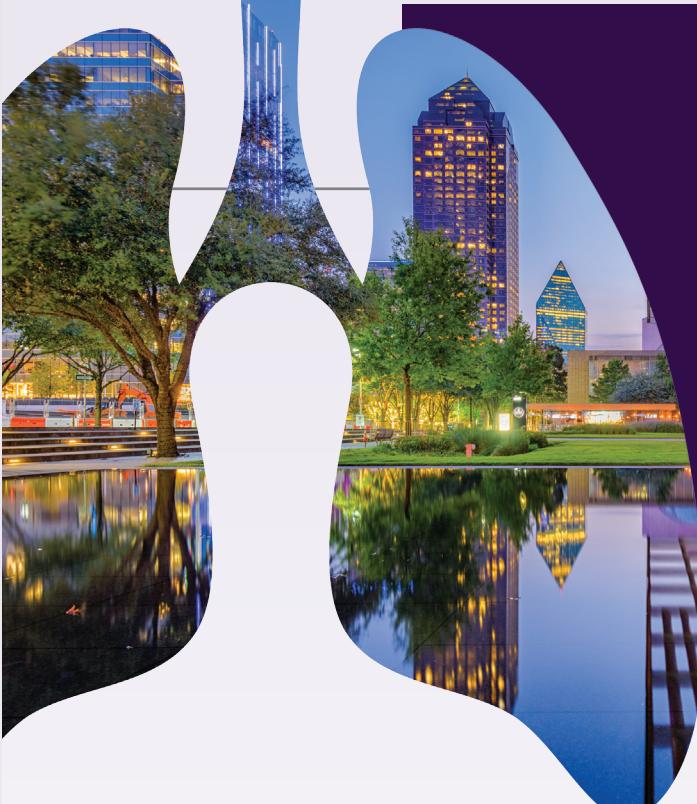
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**Abbreviated Prescribing Information:** **Active Ingredient:** Ibiclav Tablet: Each film-coated tablet contains amoxicillin trihydrate equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg of clavulanic acid; DS for suspension: each 5 ml of the reconstituted suspension contains Amoxicillin Trihydrate IP equivalent to Amoxicillin 400 mg, Potassium Clavulanate Diluted equivalent to Clavulanic acid 57 mg; **Indications:** URTI: sinusitis, otitis media, recurrent tonsillitis; LRTI: AECB, bronchopneumonia; GU infections: cystitis, urethritis, pyelonephritis; SSTIs; **Dosage and Administration:** Adults and children < 40 kg: Once 500 mg/125 mg dose taken TDS; Children < 40 kg: 20mg/5mg/kg/day to 60mg/15mg/kg/day given in three divided doses; **Contraindications:** Hypersensitivity to the active substances, to any of the excipients; History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent; History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid; **Warnings & Precautions:** Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents; Convulsions may occur in patients with impaired renal function or in those receiving high doses; Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected; Concomitant use of allopurinol; feverish generalised erythema; renal impairment; Antibiotic-associated colitis; prolongation of prothrombin time, lymphatic leukaemia, phenylketonuria; **Drug Interactions:** Can occur with oral anticoagulants, methotrexate, probenecid, mycophenolate mofetil, alcohol, oral contraceptives; **Pregnancy and Lactation:** Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. Both substances are excreted into breast milk. It should only be used during pregnancy & breast-feeding after benefit/risk assessment by the physician in charge. **Adverse Reactions:** Mucocutaneous candidosis, overgrowth of non-susceptible organisms, reversible leucopenia (including neutropenia), thrombocytopenia, reversible agranulocytosis, haemolytic anaemia, prolongation of bleeding time and prothrombin time, angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis, dizziness, headache, reversible hyperactivity, convulsions, aseptic meningitis, diarrhoea, nausea, vomiting, indigestion, antibiotic-associated colitis, black hairy tongue, hepatobiliary disorders, rises in AST and/or ALT, cholestatic jaundice, skin rash, pruritis, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalised exanthemous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), interstitial nephritis, crystalluria. Date of Last Review: 31st July 2019; Full Prescribing Information available on request from: Indiabulls Pharmaceuticals Limited, Indiabulls Finance Center, Tower-1, 14th Floor, Senapati Bapat Marg, Elphinstone (W) Mumbai-400013 tel No. 91 22 62498612

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## **Assessment of potential risk factors of pulmonary fibrosis: A population based study**

*Shojaee A, Kaminski N, Siner JM, Aryan Y, Yan X, et al.*

The occurrence as well as mortality of pulmonary fibrosis (PF) is rising, particularly in the aging population. However, in most of the patients with PF, the risk factors are unknown. A two-stepped population-based study was conducted to investigate the potential risk factors of PF. Information was collected from all-payer Healthcare Costs Utilization Project administrative dataset ( $n=19,194,187$ ). For risk factors identification, Causal Inference Using Composition of Transactions (CICT) method was applied. Evaluation of risk factors suggested by CICT was done using Cox regression (CPH) and non-parametric maximum likelihood estimator (NPMLE) with age as the time scale. Case and control cohorts were recognized and the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9CM) was used for identification of exposure to viral pneumonia and bacterial pneumonia. Categorization of results of post inflammatory PF and idiopathic PF (IPF) was done using a modified version of Esposito et-al algorithm. The CPH models were adjusted for gender, smoking, asthma, chronic obstructive pulmonary disease (COPD), sarcoidosis, rheumatoid arthritis, scleroderma, asbestosis, and bronchiectasis confounders. The two exposures (viral and bacterial pneumonia), and the two outcomes (PF, IPF) were analyzed using entire cohorts and separately on subset cohorts matched on all covariates using the coarsened exact matching algorithm. Results of the study revealed the following:

- A strong causal association was predicted by CICT between viral pneumonia and PF
  - The total patients included in the retrospective cohorts were 11,456,220
  - Out of these, 69048 had PF, 4153 had IPF, 118707 had viral pneumonia, and 151668 had bacterial pneumonia
  - Adjusted hazard ratio for PF (1.68) and IPF (1.8) was increased for viral pneumonia exposure in the entire cohort, and for PF (1.47) and IPF (1.23) in the matched cohorts
  - HR for bacterial pneumonia exposure were - PF=1.11 and IPF=1.09 in the entire cohort, and PF=1.05 and IPF=0.86 in the matched cohorts
  - The median time to diagnosis of PF was found to be nine years earlier in patients with viral pneumonia in comparison to those without, as shown by NPMLE analysis.
- In conclusion, viral pneumonia is an independent risk factor for PF. Bacterial pneumonia, on the other hand, has an insignificant and small effect concerning the risk of fibrosis.

## **Obstructive sleep apnea event duration and arousal index: Effect of pregnancy**

*Stanchina M, Walia P, Bublitz M, Miller M, Bourjeily G.*

Obstructive sleep apnea (OSA) has been associated with poor outcomes in pregnant women. Progesterone levels have been reported to be on a lower side during pregnancy in women with



**The occurrence as well as mortality of pulmonary fibrosis is rising, particularly in the aging population**

OSA as compared to those without OSA; suggesting a potential protective effect; however, the underlying mechanism is not understood. A study was done to evaluate the differences in ventilator stability by assessing differences in arousal index and duration of obstructive events in pregnant patients and in matched (in terms of age/sex/weight/AHI) non-pregnant controls. Full in-laboratory polysomnograms [as per standard American Academy of Sleep Medicine (AASM) protocol] of patients with mean gestational age of 26 weeks and controls suspected of OSA were studied. Scoring of hypopneas (4% desaturation) and apneas was done in accordance with AASM guidelines. Analysis of apneas and hypopneas from non-rapid eye movement (NREM) sleep was done. Comparison of apnea/hypopnea associated arousals between groups was done using Chi square test; while t-tests were used to compare event durations and  $\text{SaO}_2$  nadir between groups, with level of significance at  $p<0.05$ . Results of the study were as follows:

- Total 50 women were included in the study (25 pregnant, matching 1:1)
- Both the groups had a similar mean age and the body mass index (BMI) was  $44.1\pm6.9$  and  $44.0\pm7.3 \text{ kg/m}^2$ , in pregnant vs. non pregnant women, respectively
- Out of total sleep time, REM sleep constituted a median of 14% (pregnant) versus 10% (non pregnant) of sleep time
- Median apnea/hypopnea index was 1.3 and 3.1 events per hour in pregnant and non-pregnant patients, respectively
- The duration of obstructive events was significantly lower in the pregnant group (16.8 vs. 20.9)
- No difference was found in the prevalence of events associated with arousals, or in nadir oxygen saturation or percent of time spent below 90% oxygen saturation, between the two groups.

To conclude, the duration of apnea is shorter in pregnant women than controls indicating a possibly altered arousal threshold associated with pregnancy.



As compared to non-pregnant women, the duration of apnea is shorter in pregnant women, indicating a possibly altered arousal threshold associated with pregnancy

## Cardiac fibrosis in pneumococcal pneumonia: Assessing the association

Babu BL, Hinojosa CA, Restrepo C, Reyes LF, Takahashi M, et al.

Community-acquired pneumonia (CAP) is amongst the most frequent causes of infectious deaths globally. *Streptococcus pneumoniae* (Spn) is the most common bacterial pathogen causing CAP. A major complication identified in CAP patients is the development of cardiovascular events (CVEs). Recently, deposition of cardiac collagen has been reported following antibiotic treatment. In this context, a study was carried out to assess whether collagen myocardium deposition results in fibrosis and further CVEs. The measurement was done using cardiac magnetic resonance imaging (cMRI). Two translational science projects were designed:

- i) Experimental design of a murine model ( $n=8$ ) with intratracheal inoculation of Spn (TIGR4-dose of  $10^5$  CFU) managed with intraperitoneal ampicillin 30h post-



Community-acquired pneumonia is amongst the most frequent causes of infectious deaths globally

inoculation (80mg/kg q12 hours x 4 days) vs. a control ( $n=3$ , no infection, but managed with ampicillin). At day 7 post infection, a post mortem MRI (10mmol/kg <gadolinium) for small experimental models was done. Cardiac myocardium fibrosis was the primary outcome.

ii) cMRI (gadolinium) was performed in three groups of patients - (1)Acute survivors at 7-14 days post-Spn CAP; (2) Convalescent survivors evaluated at 15-365 days post-Spn CAP; and (3) Control group. Cardiac myocardium fibrosis was the primary outcome.

Results divulged the following:

- At 7 days post-Spn inoculation, cardiac fibrosis was found in cMRI of 60% of the experimental models, with changes located in the ventricular walls and apex vs. no cardiac fibrosis in the control group
- The presence of cardiac fibrosis in Spn treated group was also corroborated by results of histopathology and collagen staining
- In the human study, eight patients were enrolled – 3 acute survivors, 1 convalescent survivor, and 4 in the control group
- Evidence of cardiac fibrosis was not found in cMRI of any of these patients.

In conclusion, presence of cardiac fibrosis in the experimental models while the absence of it in the human survivors of pneumococcal CAP, indicate the need for further research to assess whether patients are developing cardiac fibrosis that may lead to long-term CVEs.

## **Increased risk of hospital admission as well as exacerbations following use of lithium in patients with chronic obstructive pulmonary disease**



Lithium therapy used for the management of psychiatric illnesses may be associated with increased risk of hospital admission and exacerbations in patients with COPD

*Shojaee A, Gomez JL, Perez MF.*

Chronic obstructive pulmonary disease is a common chronic respiratory disease associated with significant mortality. Exacerbations associated with the condition result in frequent hospitalizations; furthermore, they expedite the process of irreversible pulmonary function loss. A study was conducted to evaluate new risk factors for COPD exacerbations.

Patients in the age group of 30-85 years having  $\geq 2$  inpatient or emergency department visits were recruited in the study as cases and controls. Possible risk factors were determined with the help of CICT method which were subsequently validated by NPMLE and Cox proportional hazard models. Exposure to risk factors and COPD with and without exacerbations was primarily evaluated. Age was used as the time scale and Cox models were tested unadjusted and adjusted for gender, smoking, asthma, delirium, episodic mood disorder, psychosis, and organic neurological disorder. Results divulged the following:

- A total of 7,907,516 patients were included out of which 2,986 patients received lithium therapy, 302,068 patients had COPD exacerbation and 51,233 patients were without exacerbation
- Lithium therapy was found to be associated with hospital admission as determined by CICT (CICT coefficient: 0.68, range 0-1; 1 indicating a strong probability of causality, 0, indicating a random relationship)
- Adjusted multivariate COX models revealed an increased hazard ratio (HR) for COPD [2.31 (CI: 1.87- 2.85)] and COPD exacerbation [2.39 (CI: 2.08-2.75)] following exposure to lithium therapy in the entire study cohort
- Likewise, lithium therapy was associated with increased HRs for COPD [1.28 (CI: 0.88-1.68)] and COPD exacerbation [1.44 (CI: 1.36-1.63)] in the matched cohorts
- NPMLE analysis revealed that time to COPD exacerbation-associated admission was 15 years earlier in patients exposed to lithium therapy.

The study findings helped conclude that lithium therapy used for the management of psychiatric illnesses may be associated with increased risk of hospital admission and exacerbations in patients with COPD.

## Impact of insulin resistance on deterioration of lung function in patients with asthma

*Peters MC, Schiebler M, Bleeker ER, et al.*

Obesity is one of the comorbidities commonly associated with severe asthma. Obesity-associated metabolic dysfunction may deteriorate lung function in patients with asthma. Hyperinsulinemia and insulin resistance are other manifestations often present in obese individuals. However, it remains elusive whether insulin resistance has an impact on the lung function in patients with asthma. Thus, a study was conducted to evaluate if insulin resistance accelerates loss of lung function in asthmatic individuals.

A total of 306 adults with asthma recruited in the Severe Asthma Research Program-3 (SARP-3) were evaluated for fasting blood glucose and insulin levels. Based on the results of Homeostatic Model of Insulin Resistance Index (HOMA-IR), patients were categorized into normal, elevated insulin (EI), and insulin-resistant (IR) groups. Relationship between HOMA-IR measures and clinical parameters including decline in lung function over 3 years duration was determined using linear regression models. Results were as follows:

- Proportion of patients in the EI and IR groups were 23% and 25%, respectively
- Elevated BMI along with reduced pre- and post-bronchodilator values of FEV1% predicted and FVC% predicted were reported in patients in the EI and IR groups as compared to those with normal insulin levels ( $p<0.001$ )
- Statistically significant association between insulin resistance and deteriorations in lung parameters ( $p<0.001$ ) was reported even after adjusting for BMI, age, blood eosinophil counts and oral corticosteroid use



**Insulin resistance is associated with deteriorated lung function in patients with asthma**

- Number of exacerbation events were reported to be significantly higher in the IR group as compared to those with normal insulin levels ( $p=0.02$ )
- Likewise, rate of decline in FEV1% predicted values over a period of 3 years was significantly higher in the IR group than patients having normal insulin levels ( $p=0.005$ ).

Findings of the study substantiated that insulin resistance is associated with deteriorated lung function in patients with asthma.

## Blood eosinophil count: Potential biomarker of oral corticosteroid therapy success in chronic obstructive pulmonary disease

*Kerkhof M, Chaudhry I, Kocks J, et al.*

Patients with COPD having blood eosinophils 2% or more have been shown to achieve better outcomes with oral corticosteroid (OCS) therapy as compared to those having blood eosinophils less than 2%. Kerkhof and colleagues conducted a large, real-life, population-based historical cohort study to determine the association between blood eosinophil count (BEC) and success of OCS therapy (with or without antibiotics).



**Blood eosinophil count  $\geq 150$  cells/ $\mu\text{L}$  measured at the time of exacerbation may indicate success of oral corticosteroid therapy in patients with chronic obstructive pulmonary disease**

The investigators used the combined UK electronic medical records from the Optimum Patient Care Research Database and the Clinical Practice Research Datalink (CPRD) to select patients with COPD who had BEC measured on the day of a COPD exacerbation and had not received OCS or antibiotic treatment in the 2 weeks before the exacerbation. COPD exacerbation was defined as a prescription for acute OCS with or without antibiotics. In a subpopulation of patients from CPRD with Hospital Episode Statistics (HES) available, hospital admission for COPD exacerbation was also evaluated as an outcome. High BEC and low BEC cut-off points were 250 cells/ $\mu\text{L}$  (primary outcome) and 150 cells/ $\mu\text{L}$  (sensitivity analysis), respectively. Count-response relationship was evaluated by comparing associations for incremental categories of BEC with the reference category of BEC  $\geq 50$  cells/ $\mu\text{L}$  and  $< 150$  cells/ $\mu\text{L}$ , as a sensitivity analysis. The results divulged the following:

- A total of 7,152 patients with OCS prescribed for a COPD exacerbation (2,773 with HES) were included in the study
- Patients with elevated BEC ( $\geq 250$  cells/ $\mu\text{L}$ ) (35%) were found to have a significantly lower risk of hospitalization as compared to patients with BEC  $< 250$  cells/ $\mu\text{L}$
- No significant difference was found in overall risk of treatment failure between the two groups ( $p=0.074$ )
- Likewise, compared to patients with BEC  $< 150$  cells/ $\mu\text{L}$ , those with BEC  $\geq 150$  cells/ $\mu\text{L}$  (64%) had a significantly lower risk of hospitalization and overall treatment failure
- No count-response relationship was observed for incremental BEC categories  $> 150$  cells/ $\mu\text{L}$

- The greatest risk of treatment failure was observed among patients with BEC <50 cells/ $\mu$ L.

This study suggests that BEC  $\geq$ 150 cells/ $\mu$ L measured at the time of exacerbation may indicate success of OCS therapy. Also, very low BEC (<50 cells/ $\mu$ L) seems to be associated with the greatest risk of treatment failure.

## Potential application of oscillating positive expiratory pressure therapy in chronic obstructive pulmonary disease or chronic bronchitis

*van Es M, Schokker S, Been-Buck S, et al.*

Chronic cough and excessive sputum production, in patients with COPD or chronic bronchitis, are associated with various patient-related outcomes including exacerbations, hospitalizations, lung function decline and increased mortality. This suggests that mucus clearance techniques, such as Oscillating Positive Expiratory Pressure (OPEP) therapy may be effective in patient management. In the present study, van Es and colleagues evaluated the effectiveness of OPEP therapy on respiratory symptoms and cough in patients with COPD or chronic bronchitis.

In this ongoing double-blind controlled trial, the investigators randomized patients with COPD or chronic bronchitis ( $>40$  years) with excess mucus production to the intervention group (OPEP device) or the control group (sham version of the device) and instructed them to use the device 10 minutes twice daily for three months. The primary outcome included respiratory symptoms measured by the Clinical COPD Questionnaire (CCQ) and the secondary outcomes comprised cough symptoms measured by the Leicester Cough Questionnaire (LCQ), and lung function (FEV1 and FEV1/FVC % predicted).

The results divulged the following:

- The investigators included 54 patients till the publication of this study (63% male, age  $69.4 \pm 8.3$  years, pack-years  $33.2 \pm 19.6$ , smoking status (ex-/current/never 71%/23%/6%)
- The preliminary evaluation of available longitudinal data (n=39) demonstrated a statistically significant improvement of the total CCQ from  $2.8 \pm 0.9$  (baseline) to  $2.5 \pm 1.2$  at follow up ( $p=0.04$ )
- Likewise, there was statistically significant improvement in the LCQ score from  $13.8 \pm 13.0$  at baseline to  $15.6 \pm 3.0$  at follow up ( $p<0.001$ )
- No changes in the lung function were observed
- Majority of patients (83%) showed adherence to the device use; 42% were satisfied with the device, 8% of patients were dissatisfied and 50% of patients were neither satisfied nor dissatisfied.

Preliminary findings from this ongoing trial suggest that OPEP therapy may be a practical approach and may be associated with positive effects on respiratory symptoms in COPD and chronic bronchitis in routine clinical practice.



Oscillating Positive Expiratory Pressure therapy may be a practical approach with positive effects on respiratory symptoms in chronic obstructive pulmonary disease and chronic bronchitis in routine clinical practice

## **Clinical and biologic characteristics of patients with asthma-chronic obstructive pulmonary disease overlap in an asthma cohort**



**Patients with asthma-COPD overlap, as compared to those with asthma alone, are more likely to be active smokers, have more second-hand smoke exposure, and demonstrate worse measures of disease control and quality of life**

*Lipkin-Moore Z, Gomez J, Chupp G.*

Asthma-COPD overlap (ACO) is defined as the presence of several features usually associated with asthma and several features usually associated with COPD in an individual. Lipkin-Moore and colleagues conducted a cross-sectional study to determine the clinical and biologic characteristics of patients with ACO in a cohort of patients with airway disease [Asthma and Airways Disease (YCAAD) cohort]. Data from the initial visit were evaluated. ACO was defined using the following criteria: asthma diagnosis, age  $\geq 40$  years, pre-bronchodilator FEV1/FVC  $<0.7$ , and a smoking history of  $\geq 10$  pack-year. Subsequently, patients with ACO were compared to age-matched patients with asthma only. The results divulged the following:

- The study involved a total of 271 patients, of which 14 (5%) were identified as having ACO
- As compared to patients with asthma, the ACO subgroup had:
  - » A higher proportion of active smokers (46% versus 10%)
  - » More years of second-hand smoke exposure (mean 29 versus 13 years)
  - » Increased sputum eosinophils (mean 14% versus 9%)
  - » Lower asthma control test and mini-Asthma Quality of Life Questionnaire scores.

This study suggests that patients with ACO, as compared to those with asthma alone, are more likely to be active smokers, have more second-hand smoke exposure, and demonstrate worse measures of disease control and quality of life. As compared to those with asthma, patients with ACO also have elevated sputum eosinophils but no significantly different other Th2 inflammatory markers.

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