

P130 PREVALENCE AND CLINICAL OUTCOMES OF FUNGAL SENSITIVE ASTHMA IN A SEVERE ASTHMA POPULATION

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10.1136/thoraxjnl-2016-209333.273

Introduction It has been proposed that severe asthma patients with fungal sensitisation might endure worse clinical outcomes than non-sensitised patients. However, the extent of fungal sensitisation and its influence on the disease severity remain unconfirmed. This study explores the prevalence of severe asthma with fungal sensitisation (SAFS) and its clinical effect.

Methods Consecutive patients referred to a severe asthma centre has been put through systematic assessment protocol to establish their asthma diagnosis, severity, and clinical outcome measures that includes lung function, biomarkers, exacerbations and hospital admissions frequency. Total and specific serum immunoglobulin E (IgE) and skin prick testing to 27 allergens including 5 fungal allergens were undertaken.

Results A total of 263 patients with a mean age of 45.5 yrs (SD \pm 14.6), 72% females, mean age at onset of asthma 21.52 years (range 0.0–69 years), mean pre FEV1% predicted 69.8 (SD \pm 24.5) and FEV1/FVC ratio of 66.1 (SD \pm 15.3) were considered for the analysis. Allergic characterisation demonstrated atopic status in 182/256 (71.1%), positive sensitisation to alternaria 27/256 (10.5%), aspergillus 57/256 (22.3%), candida 24/256 (9.4%), cladosporium 24/256 (9.4%), penicillium 16/256 (6.2%), meeting SAFS criteria 93/254 (36.4%), and allergic bronchopulmonary aspergillosis (ABPA) 18/247 (7.3%). The SAFS group had higher total IgE than non SAFS group: mean total IgE 974.5 ng/l vs 330.1. However, we observed no statistically different outcomes for the SAFS versus non SAFS groups, ACQ 3.17 vs 3.515, AQLQ 4.0 vs 3.52, FeNO 36.4 ppb vs 32.9, peripheral blood eosinophils (PBE) 385 cells/ μ l vs 361, annual hospital admissions 1.28 vs 0.97 and annual OCS burst therapy of 5.7 vs 5.9. In contrast the ABPA versus non ABPA cohort had higher PBE 585 cells/ μ l vs 364, total IgE 2882ng/L vs 326, lower% predFEV1 60.2L vs 71 L, and ever ITU admissions 0.9 vs 0.46.

Conclusion Fungal sensitisation is relatively common in severe asthma but it did not seem to influence overall clinical outcomes. ABPA is less common with worse outcomes.

P131 OUTDOOR FUNGAL SPORE LEVELS, LUNG FUNCTION AND SYMPTOMS IN PATIENTS WITH ASTHMA AND ASPERGILLUS SENSITISATION

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10.1136/thoraxjnl-2016-209333.274

Background IgE sensitisation to *Aspergillus fumigatus* is seen in a significant proportion of patients with refractory asthma. The EVITA3 study recently showed that three months' treatment with voriconazole did not improve asthma-related outcomes in this patient group. It is not known whether daily variations in outdoor fungal spore levels are associated with concomitant fluctuations in symptoms and lung function in patients with *Aspergillus*-associated asthma.

Methods Participants in the EVITA3 study kept daily diaries of peak expiratory flow (PEF) and asthma symptoms during their follow-up period. These diary records were retrospectively analysed together with contemporaneous fungal spore levels

measured locally, in those patients (n = 36) who consented to the secondary use of their clinical and research data. Participants also underwent skin-prick tests for *Aspergillus*, *Alternaria*, *Cladosporium*, *Penicillium* and *Botrytis*. For each participant, cross-correlation was used to investigate the relationship between PEF and local spore counts of *Aspergillus/Penicillium*, *Alternaria*, *Cladosporium*, *Botrytis*, *Sporobolomyces*, *Tilletiopsis*, and *Didymella*. Group-level relationships were investigated using linear mixed models for PEF and generalised estimating equations for daily symptom scores, with participants stratified by skin prick test status. The analyses were performed with the exposure and outcome measured on the same day (lag 0), and with the exposure lagged by 1 day with respect to the outcome (lag 1).

Results The analysis cohort comprised 20 men and 16 women with a mean (standard deviation) age of 60 (8) years. No significant or consistent relationships were observed between fungal spore counts and either PEF or self-reported symptom scores, regardless of skin prick test status and lag time between exposure and outcome. In a linear mixed model, the effect size of total fungal spore count on morning PEF was negligible (-0.000011 , $p = 0.343$ for lag 0; -0.000002 , $p = 0.847$ for lag 1).

Conclusion In this retrospective analysis we found no evidence of a significant link between fungal spore counts and either PEF or symptoms in patients with *Aspergillus*-associated asthma. Further research is required to confirm this result in a prospective study and to identify whether aeroallergen levels relate to other important asthma outcomes such as exacerbations.

P132 FACTORS ASSOCIATED WITH NEAR-FATAL ASTHMA REQUIRING EXTRACORPOREAL MEMBRANE OXYGENATION

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10.1136/thoraxjnl-2016-209333.275

Introduction Until recently the ceiling of management for life-threatening asthma exacerbation involved intubation and mechanical ventilation. In many cases these measures were inadequate given the degree of airflow obstruction. The emergence of extracorporeal membrane oxygenation (ECMO) has offered a management strategy for these otherwise fatal events, however there is a dearth of published data regarding ECMO use in asthma. We sought to investigate factors associated with the requirement for and success of using ECMO in near-fatal asthma.

Methods Patients requiring mechanical ventilation (MV) and/or ECMO for acute asthma at our tertiary centre between 2011–2015 were retrospectively identified from an electronic database.

Results Seventy-five patients were identified. 56/75 (75%) received MV and 19/75 (25%) received ECMO. The proportion of females in the ECMO group was significantly greater than in the MV group (68% vs. 29%, $P = 0.002$). Median age in the ECMO group was lower (24 years old vs. 41, $P = 0.003$). There was no statistically significant difference in the smoking history or 30- and 90-day survival between ECMO and MV groups. Bronchoscopy was undertaken in all ECMO and in 28/56 MV patients on admission. Respiratory viruses were identified in significantly more patients requiring ECMO than MV (58% vs. 29%, $P = 0.04$). The proportion of patients with positive bacterial and fungal cultures was not significantly different between groups. In a subgroup analysis there was no difference in

duration of ECMO or MV between patients with and without positive virology.

Conclusion In a single regional intensive care unit we demonstrate that requirement for ECMO due to acute asthma is associated with female gender, younger age and positive virology on admission. To our knowledge, this is the first case series analysing factors relating to ECMO use in asthma in the United Kingdom. It highlights the role of respiratory viruses in near-fatal exacerbations and the need for novel anti-viral approaches to reduce morbidity and mortality. Further research is needed in this population to identify whether differences in underlying inflammatory mechanisms exist that may explain the development of such severe events.

P133 SAFETY AND EFFECTIVENESS OF INFLUENZA VACCINES IN PEOPLE WITH ASTHMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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10.1136/thoraxjnl-2016-209333.276

Introduction and objectives Influenza vaccination is offered annually in the UK to high-risk individuals such as those with asthma as a preventive measure against influenza infection and influenza-related complications. However, the effectiveness and safety of influenza vaccination in people with asthma is not well established.¹

Methods We conducted a systematic review and meta-analysis assessing the overall quality of evidence using the GRADE methodology. Published literature was searched through 13 electronic databases from Jan 1970 to Jan 2016 for clinical trials and epidemiological studies. Unpublished or ongoing literature was searched through references and citations of key publications, and by contacting influenza vaccine manufacturers. The screening for eligible studies, data extraction and quality appraisal was conducted by two reviewers independently. Separate meta-analyses were undertaken for observational and experimental evidence using random-effects models.

Results We identified 35 eligible studies, and four contributed to the meta-analyses. Risk of bias was high for one randomised controlled trial (RCT), unclear for 11 RCTs, and low for eight RCTs. The quality of five non-RCTs, four cohorts, and two case-control studies was strong. Moderate quality was found for one non-RCT, and three cohort studies. In people with asthma, pooled vaccine effectiveness (VE) was 45% (OR: 0.55; 95% CI: 0.44 to 0.69; I² = 0%) for laboratory confirmed influenza. Pooled effectiveness of live vaccines was 81% (RR: 0.19; 95% CI: 0.06 to 0.67; I² = 0%) for influenza infection (confirmed by cell culture or rise in antibody titre) and 72% (RR: 0.28; 95% CI: 0.10 to 0.80; I² = 0%) for influenza-like illness. VE was also observed against asthma attacks. No increased risk of vaccine-induced asthma symptoms and attacks was identified. The quality of the body of evidence was considered very low for all outcomes.

Conclusions Evidence on VE in people with asthma against influenza, asthma exacerbations, and other clinical outcomes is limited and of very low quality. Thus, better quality evidence is required, especially in adults with asthma. Vaccination with inactivated or live vaccines was found to be safe and well tolerated in patients with asthma.

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P134 METHACHOLINE CHALLENGE TO DEMONSTRATE THERAPEUTIC EQUIVALENCE OF TERBUTALINE VIA DIFFERENT TURBUHALER DEVICES IN PATIENTS WITH MILD TO MODERATE ASTHMA: APPRAISAL OF A PHASE III, FOUR-WAY CROSSOVER DESIGN

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10.1136/thoraxjnl-2016-209333.277

Background/objective To demonstrate therapeutic equivalence of terbutaline via two different Turbuhaler® devices by evaluating its protective effect against methacholine-induced bronchoconstriction in patients with stable asthma.

Methods In this double-blind, double-dummy, multicentre, single-dose, 4-way crossover study, patients with stable, mild-to-moderate asthma (FEV1 ≥ 80% predicted normal) were randomised to 0.5 or 1.5 mg terbutaline via either Turbuhaler® M3 or M2 followed by a methacholine challenge test. Primary outcome variable: concentration of methacholine causing a 20% drop in FEV1 (PC20). Patients had to have a PC20 methacholine < 8 mg/mL, reproducible after 2 weeks, and a stable baseline FEV1 at all visits (90–110% of enrolment value).

Results 60 patients were randomised to treatment and completed the study. There was a clear dose–response for both devices. The within-device ratios (1.5 mg: 0.5 mg) were 1.79 and 1.87 for Turbuhaler M3 and M2, respectively (both p < 0.001). The between-devices ratio (M3:M2) was 0.92 (95% CI: 0.75–1.13) for 0.5mg and 0.88 (95% CI 0.72–1.08) for 1.5 mg. Both CIs lie inside the interval (0.67–1.50), which was the pre-specified condition for equivalent effect.

Conclusions Bronchoprotection with PC20 as the outcome measure in a standardised methacholine challenge model proved to be a useful design to show therapeutic equivalence between devices in patients with mild to moderate asthma. This model provides robust reproducible data, involves smaller patient numbers with fewer dropouts resulting in reduced costs versus a conventional efficacy study.

Disease Progression and Burden in Obstructive Lung Disease

P135 TREATMENT OF LUNG DISEASE IN ALPHA-1 ANTITRYPSIN DEFICIENCY: A SYSTEMATIC REVIEW

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10.1136/thoraxjnl-2016-209333.278

Introduction Alpha-1 Antitrypsin Deficiency (AATD) is a rare genetic condition predisposing individuals to COPD. The