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Epithelial-Associated Inflammatory Pathways Underlie Residual Asthma Exacerbations in Urban Children Treated with Mepolizumab Therapy

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681 Persistent sex and race disparities in anaphylaxis mortality in the US, 1999 to 2020: an analysis of the CDC Multiple Cause of Death database

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RATIONALE: To compare trends of anaphylaxis-related mortality in the US by sex and race.

METHODS: We extracted the age-standardized anaphylaxis-related mortality rate (ASMR) between 1999 and 2020 from US CDC Multiple Cause of Death database according to ICD10. We report ASMR per 1million by sex as male and female, and race as Black/African American (BAA) and White/Caucasian (WC). We used Joinpoint regression to analyze trends as estimated Annual Percentage Changes (EAPC)

RESULTS: There were 5208 anaphylaxis-related deaths from 1999 to 2020. Men had higher ASMRs than women in all years except 2008, where the rates were equal. BAA had higher mortality rates compared with WC in 19 years of the 22 years. Joinpoint demonstrated a single trend in women with EAPC +0.8 (95% Confidence Interval -0.2, +1.9; p=0.1). The EAPC for men was +1.1 (95% CI 0.4, 1.7; p=0.003). WC EAPC demonstrated a biphasic pattern with inflection at 2004: EAPC 1999 through 2004 was -5.8 (95% CI -10.4, -1.0; p=0.02) and 2004 through 2020 was +2.1 (95% CI 1.3, 3.0; p<0.001). For BAA, the EAPC between 1999 and 2020 was +0.9 (95% CI -0.5, 2.3; p=0.2).

CONCLUSIONS: Men have persistently greater anaphylaxis-related mortality than women. While BAA have proportionally greater mortality than WC, there is a recent significant increasing trend in WC. This highlights an urgent need to address rising mortality from anaphylaxis in these populations.

682 sCD14 and Intestinal Fatty Acid Binding Protein are Elevated in the Serum of Patients with Idiopathic Anaphylaxis.

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RATIONALE: Intestinal epithelial integrity compromise has been identified in gastrointestinal (GI), atopic, and autoimmune diseases. Episodes of idiopathic anaphylaxis (IA) are often accompanied by GI manifestations. We therefore sought to determine whether surrogate markers of GI permeability were aberrant in this patient population.

METHODS: Serum levels of zonulin, intestinal fatty acid binding protein (I-FABP), and soluble CD14 (sCD14) measured in 54 patients with IA were compared to levels in healthy controls (HCs); and correlated with clinical and laboratory parameters.

RESULTS: I-FABP was elevated in sera of patients with IA compared to HCs (median 1410.0 pg/mL vs 479.0 pg/mL respectively, $p < 0.001$). sCD14 was also elevated compared to HCs (median 2017.0 ng/mL and 1189.0 ng/mL respectively, $p < 0.001$), whereas zonulin was comparable between patients with IA and HCs (median 49.6 ng/mL vs 52.4 ng/mL respectively, $p = 0.40$). I-FABP was elevated in patients with IA who experienced vomiting and/or diarrhea compared to patients with IA who did not ($p = 0.0091$).

CONCLUSIONS: I-FABP and sCD14 are elevated in the serum of patients with IA. Elevations in these biomarkers of IA provides evidence that increased gastrointestinal permeability, as is observed in other allergic conditions such as food allergy, is a common finding in those with IA and offers possible insight into the pathogenesis of this disease.

683 Epithelial-Associated Inflammatory Pathways Underlie Residual Asthma Exacerbations in Urban Children Treated with Mepolizumab Therapy

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RATIONALE: Identification of airway inflammatory pathways in asthma has proven essential to understanding mechanisms of disease and has led to effective personalized treatment with biologic therapies. However, relatively little is known about patterns of airway inflammation at the time of respiratory illnesses and how such patterns relate to responsiveness to biologic therapies.

METHODS: The MUPPITS-1 (n=106) and MUPPITS-2 (n=290) studies investigated asthma exacerbations in urban children with exacerbation-prone asthma and ≥150/microliter blood eosinophils. Children in both studies received guidelines-based asthma care; in MUPPITS-2, participants were additionally randomized (1:1) to placebo or mepolizumab. Nasal lavage samples were collected during respiratory illnesses for RNA-sequencing and analyzed by modular analysis to assess genome-wide expression patterns associated with exacerbation illnesses.

RESULTS: Among 284 illnesses, exacerbations that occurred in the absence of mepolizumab therapy showed significantly higher upregulation of eosinophil associated inflammatory pathways (fold change values [FC]=1.27-1.43, p-values<0.05), including a Type-2 inflammation module composed of eosinophil, mast cell, and IL-13 response genes. In contrast, exacerbations that occurred while on mepolizumab therapy showed significantly higher upregulation of several epithelial inflammatory pathways (FC=1.36-1.64, p-values<0.05) including TGF-β/Smad3 signaling, extracellular matrix production, and epidermal growth factor receptor signaling.

CONCLUSIONS: These results indicate that novel inflammatory pathways, likely originating from the airway epithelium and distinct from Type-2 or eosinophilic inflammation, drive residual exacerbations that occur in children treated with mepolizumab therapy added to guideline-based care. These findings identify likely mechanisms of persistent disease expression in these children despite significant depletion of eosinophils and can identify novel treatment targets for future studies.

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