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Title: Sputum fluid endotoxin is associated with the FEV_1 response to oral steroids in non-smokers with asthma

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Body: Background Asthma patients who smoke have a reduced sensitivity to corticosteroids. The mechanisms for this are not well understood. Increased bacterial endotoxin has been found in BAL fluid of non-smokers with steroid-resistant asthma and cigarette smoke is a rich source of endotoxin. We compared sputum endotoxin concentration in smokers and non-smokers with asthma, with the FEV_1 response to oral corticosteroids. Methods Sputum was induced from 31 non-smokers and 22 smokers with asthma. Endotoxin was quantified by ELISA (LAL-QCL®, Lonza Biologics plc), and cytokines by luminex (InVitrogen). Spirometry and exhaled nitric oxide measurements were recorded. The response to oral dexamethasone was the change in FEV_1 compared with baseline. Results Non-smokers had improved FEV_1 after steroids; p=0.015, but smokers were refractory; p=0.591. The steroid response decreased with increasing sputum endotoxin in non-smokers; r= -0.422, p=0.032, but not in smokers; r= -0.126, p=0.585. The steroid response increased with pre-steroid FeNO in non-smokers; r=0.479, p=0.015, but not in smokers; r=0.310, p=0.226. The endotoxin and IL-1RA concentrations correlated in non-smokers; r=0.633, p<0.001, but not in smokers; r=0.359, p=0.120. Conclusions Higher endotoxin in sputum fluid was associated with an impaired FEV_1 improvement after steroids only in non-smokers; and was associated with decreased FeNO and increased sputum IL-1RA. We suggest that smoking establishes a chronic refractory state to both steroids and to endotoxin. Identifying intracellular signalling pathways common to both may help understand and potentially reverse these processes.