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Title: Exhaled nitric oxide in children with severe asthma

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Body: Introduction: Exhaled nitric oxide (FE_{NO}) is a biomarker of eosinophilic airway inflammation, but the relationship between FE_{NO} and asthma severity is uncertain. We compared FE_{NO} normalized against reference values ($\%FE_{NO}$) in children with Problematic severe (PA) and controlled (CA) asthma and investigated whether increased $\%FE_{NO}$ is associated with morbidity, irrespective of predefined severity classification. Methods: Children with PA had recurrent symptoms despite treatment with ≥800 µg Budesonide, those with CA had few symptoms with 100-400 µg. The protocol included Asthma control test, spirometry (%), methacholine provocation (dose response slope), FE_{NO} (p.p.b.), computerized tomography (CT) of the lungs (PA only) and blood sampling for eosinophils ($10^9 \times L^{-1}$) and IgE (kU/L). The difference between measured and expected FE_{NO} ($Ln(FE_{NO}) = 0.0112 \times$ height (cm) + 0.641) were given in percentages ($\%FE_{NO}$). Results: Children with PA (n=57, age 13y) had a trend towards higher levels of FE_{NO} and $\%FE_{NO}$ compared to children with CA (n=39, age 14y): 22 (10-40) vs. 17 (9-26), p=0.13 and 210% (101-367) vs. 139% (85-216), p=0.07, respectively. When analysing all children (n=96), those with $\%FE_{NO}$>200 had reduced asthma control (18.5 (17-20) vs. 20.4 (19-22), p=0.04) and FEV1/FVC (77 (74-81) vs. 83 (81-86), p=0.004) and increased bronchial hyperresponsiveness (54 (5-67) vs. 2 (0.4-36), p=0.001), bronchial wall thickening on CT (25 (21-29) vs. 17 (14-19), p=0.004), eosinophils (0.5 (0.4-0.6) vs. 0.3 (0.2-0.3), p<0.001) and IgE (539 (253-1525) vs. 140 (43-425), p<0.001) compared to those with $\%FE_{NO}$<200. Conclusion: Children with high levels of $\%FE_{NO}$ have increased morbidity which is partly independent of predefined severity classification.