

European Respiratory Society Annual Congress 2013

Abstract Number: 359

Publication Number: P1126

Abstract Group: 7.2. Paediatric Asthma and Allergy

Keyword 1: Asthma - management **Keyword 2:** Children **Keyword 3:** Comorbidities

Title: Causes of problematic asthma in children: Retrospective cohort study

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Body: A considerable minority of children remain symptomatic despite inhaled corticosteroid (ICS) treatment ("problematic asthma"). This has two major causes: not getting the basics right (e.g. adherence, inhaler technique, comorbidities) or true therapy-resistant asthma (ongoing problematic symptoms despite getting the basics right and step 3 treatment). The aim of this study was to investigate the underlying causes of problematic asthma in children referred from primary care to a hospital-based secondary care asthma clinic. We retrospectively reviewed the medical records of all 142 children (age 5-18 year) referred to specialist care at the Princess Amalia Children's Clinic (Zwolle, the Netherlands) by general practitioners because of problematic asthma between 2006 and 2011. Causes of problematic asthma were classified as: comorbidity ("asthma plus"), wrong diagnosis ("not asthma at all"), incorrect inhaler technique, ongoing exposure to environmental triggers, poor adherence to treatment, and true therapy-resistant asthma. In 138 children (97.2%) an underlying cause for problematic asthma was found: poor adherence (n=53, 37.3%), persistent exposure to environmental triggers (n=40, 28.2%), comorbidities (n=28, 19.7%), incorrect inhaler technique (n=11, 7.7%) or incorrect diagnosis (n=6, 4.2%). Only 4 children (2.8%) fulfilled the criteria for true therapy-resistant asthma. An underlying cause in the basics of asthma management can be found in nearly all children with problematic asthma referred to a hospital-based asthma clinic. True therapy-resistant asthma appears to be very rare in children.