495. Treating childhood asthma

P4815
Transparency in evidence-based pediatric asthma guidelines: GRADE and the other considerations
Nicole Boluyt1, Bart Rottier2, Elianne Vrijlandt2, Johan de Jongste3, 1Pediatrics, Emma Children’s Hospital - Academic Medical Center, Amsterdam, Netherlands; 2Pediatrics, Beatrix Children’s Hospital - University Medical Center Groningen, Groningen, Netherlands; 3Pediatrics, Erasmus University Medical Center - Sophia Children’s Hospital, Rotterdam, Netherlands

Introduction: International evidence-based pediatric asthma guidelines are often not used in clinical practice. In step 3 of pediatric asthma management some guidelines make clear choices for LABA were others give alternative options, but without being transparent in why choices are made. To enhance the usefulness of guidelines, the ATS has chosen GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) as the preferred methodology for rating the quality of evidence and strength of recommendations in clinical practice guidelines.

Objective: Our aim was to develop transparent recommendations on step 3 of asthma management in children.

Methods: We used GRADE to assess the quality of evidence and separately reported other considerations. Final recommendations were formulated on both evidence as well as the other considerations in cooperation with the Dutch Society of Pediatric Pulmonologists.

Results: We found 7 RCTs comparing doubling the dose of ICS versus a combination of ICS and LABA and/or versus LTRA in children with symptomatic asthma despite normal ICS dose. According to GRADE, the quality of evidence was “moderate”, both treatments were effective and individual response could not be predicted. Other considerations included safety, convenience and costs. We suggest in children with symptomatic asthma despite ICS, to first double the dose of ICS. If not effective, a combination of ICS and LABA can be prescribed. In case of adverse effects or poor inhalation technique a LTRA can be prescribed.

Conclusion: By using the GRADE approach together with other considerations clear recommendations for step 3 in asthma management were made. This approach might improve implementation.

P4816
A systematic review of underlying reasons for barriers to asthma management in ethnic minority children
Deborah Bird1, Gill Perkins2, Lorraine Culley2, Jonathon Gregg3, Mark Johnson2, Narynder Johal1, Logan Manikam4, Melanie McFeeters5, Noelle Robertson7, Joanne Wilson6, Monica Lakhanpaul1, 1Medical and Social Care Education, University of Leicester, Leicester, United Kingdom; 2Health and Life Sciences, De Montfort University, Leicester, United Kingdom; 3Centre for Paediatrics, Barts and the London School of Medicine and Dentistry, London, United Kingdom; 4Paediatrics, North Staffordshire NHS Trust, Stoke on Trent, United Kingdom; 5Paediatrics, University Hospitals Leicester NHS Trust, Leicester, United Kingdom; 6Community Child Health, Leicester City Primary Care Trust, Leicester, United Kingdom; 7Clinical Psychology, University of Leicester, Leicester, United Kingdom

Background: Barriers to asthma management are an often cited explanation for poorer outcomes suffered by children from ethnic minorities. Empirical data explaining why and how barriers arise seem poorly articulated.

Methods: Systematic database and internet resources were searched for studies with a primary focus on barriers and facilitators in asthma in ethnic minority children aged 0-18 years. 47 eligible papers were identified, reviewed and data extracted by 2 independent reviewers. A systematic thematic narrative analysis was undertaken.

Results: Minority ethnic groups appear to share common barriers to asthma management. However underlying explanations differ between groups The analysis produced 6 categories of barriers: Knowledge and attitudes, treatment strategies, external influences, intrinsic factors, physician related factors and service related issues. Important gaps and methodological limitations in the literature were also identified including: variations in data quality; inadequate or absent considerations of the concept of ethnicity; variable definitions of asthma; reliance on closed-ended questionnaires which limit the breadth and depth of exploration of underlying explanations.

Conclusion: Further exploration of underlying explanations using open-ended qualitative techniques are required to elucidate ethnic variations in the mechanisms by which barriers to asthma management occur. When developing intervention strategies, practitioners and researchers should recognise that apparently similar barriers may have different explanation in different ethnic groups and tailor strategies accordingly.

Funding: This project is funded by Asthma UK. Study ID 10/037.
Aim: Parents of young children are frequently worried about the potential measurement for 3 months. In these 21 patients, median adherence was 81% [range (35%) were using ICS regularly, 21 of whom consented to electronic adherence 24 (29%) patients used ICS for non-specific respiratory symptoms such as cough 30 patients (36%) used ICS intermittently during symptomatic episodes, were willing to provide information about current ICS use and symptoms of their 106 children (mean age 4.3 yrs) had had an ICS prescription over the Wouter Quak, Ted Klok, Paul Brand.

Background: Asthma control can be defined in various ways. Objectives: To investigate the association between current and long-term asthma control. Methods: We included 418 children using ICS participating in the PACMAN-cohort study. Current asthma control (last week) was defined using the ACQ. Long-term asthma control (last year) was based on GINA guidelines. This was analysed for the four different seasons separately. Not well-controlled asthma was defined as: >3 of the following items present in a specific season: day-time or night-time symptoms, limitations in activities and rescue medication use. Secondly, this first definition was adjusted for the frequency of symptoms during a season. When asthma control was present in ≥3 seasons we qualified this as long-term asthma control (control during the past year). Current and long-term asthma control were compared to investigate agreement.

Results: Long-term uncontrolled asthma rates were highest in winter (51%) and lowest in summer (33%) (p < 0.05). 42% of the patients did not have long-term asthma control during the past year. Overall agreement between current and long-term asthma control was 67% and kappa statistics (≤0.39) indicated “poor agreement”.

Conclusion: The congruence between current and long-term asthma control is poor in our cohort of asthma children using ICS. There existed significant seasonal differences. In observational studies assessing asthma control, it is therefore important to calculate long-term asthma control (instead of using current asthma control as indicator) or to stratify at least for seasonal variation.

P4818 Poor adherence to inhaled corticosteroids in childhood asthma: Don’t blame (only) the patient

Ted Klok1, Adrian Kaptein2, Eric Duiverman1, Paul Brand1, Princess Amalia Children’s Clinic, Isala Klinieken, Zwolle, Netherlands; 1Unit of Psychology, Leiden University Medical Centre, Leiden, Netherlands; 2Beatrix Children’s Hospital, University Medical Centre Groningen, Groningen, Netherlands

Introduction: In population studies, the adherence to inhaled corticosteroids (ICS) treatment in asthma is usually poor. We previously showed high adherence to ICS in our paediatric asthma clinic, and this was related to parental influence and medication beliefs. The aim of the present study was to measure adherence and its determinants in children with asthma in primary care.

Methods: Children aged 2-6 yrs, who received a prescription for (ICS) by their general practitioner in the past year and who were still using ICS at the time of inclusion were followed for 3 months, during which adherence to ICS therapy was measured electronically by Smartinhaler®.

Results: 106 children (mean age 4.3 yrs) had an ICS prescription over the past year. 45 children were reached by telephone, 82 of whom were willing to provide information about current ICS use and symptoms of their child. 30 patients (36%) used ICS intermittently during symptomatic episodes, 24 (29%) patients used ICS for non-specific respiratory symptoms such as cough, or for intermittent symptoms such as an isolated wheeze episode. 28 children (35%) were using ICS regularly, 21 of whom consented to electronic adherence measurement for 3 months. In these 21 patients, median adherence was 81% [range 34-97%] of prescribed dosages.

Conclusion: The low adherence to ICS in population studies of children with asthma may be partly explained by inappropriate prescription of ICS to children with intermittent episodes of wheeze, and non-specific respiratory symptoms such as cough. High adherence to ICS treatment was found in those patients who received ICS therapy in accordance with international asthma guidelines.

P4819 Lack of behavioural problems in preschool children using inhaled corticosteroids with high adherence

Wouter Quak, Ted Klok, Paul Brand. Princess Amalia Children’s Clinic, Isala Klinieken, Zwolle, Netherlands

Background: Parents of young children are frequently worried about the potential side effects of asthma treatment on their child’s behaviour. Aim: To examine whether preschool children using inhaled corticosteroids (ICS) for asthma are more likely to have more behavioural problems compared with healthy reference group.

Methods: We included 81 children 2-5 years of age with persistent asthma symptoms who were using ICS. During 3 months follow-up, adherence to ICS treatment was recorded by an electronic logging device (Smartinhaler®). The parents completed the Child Behaviour Checklist (CBCL) to assess behavioural problems; results were compared to published reference groups of healthy children. Results: The median (interquartile range) adherence to ICS was 92 (78-97%). There were no significant differences in CBCL scores (total, uncorrecting, externalizing problems) between children on ICS and healthy children (all p values > 0.2). Children with asthma were significantly more likely to have somatic complaints (p=0.001) and significantly less likely to have anxiety/depressive symptoms (p=0.1) than the reference group.

Conclusions: Maintenance treatment with ICS, taken daily as prescribed, is not associated with an increased risk of behavioural problems in preschool children.
P4823
Long-term treatment with fluticasone propionate/formoterol fumarate (FLUT/FORM) combination therapy is well-tolerated and provides sustained effectiveness in paediatric patients with asthma
Tammy McIver1, Andrzej Emeryk2, Rabih Klink3, Birgit Schwab4, European Medical Science, Mundipharma Research Ltd., Cambridge, United Kingdom; 2Department of Paediatric Lung Diseases and Rheumatology, Medical University, Lublin, Poland; 3Cabinet de Pédiatrie et de Pneumo Allergologie Pédagogiques, Private Practice, Laon, France; 4European Medical Operations, Mundipharma Research GmbH & Co. KG, Limburg (Lahn), Germany
Background: A new asthma therapy combining FLUT/FORM in a single aerosol inhaler (platform®) has been shown to be well-tolerated and effective in adolescents and adults over a 9 month period. This study examined the long-term safety and efficacy of FLUT/FORM in paediatric patients.
Methods: Patients aged 4-12yrs (N = 208) with mild/moderate persistent asthma received FLUT/FORM 100/50g b.i.d. in a 24-week, open-label, multicentre extension study. In the core study, patients had received 12 weeks of treatment with FLUT/FORM (100/10g b.i.d.) or fluticasone propionate/salmeterol xinafoate (FLUT/FORM b.i.d.). Efficacy was evaluated on the basis of adverse events (AEs), laboratory parameters, height and weight. The main efficacy endpoint was the change in mean pre-dose FEV1 values during the extension study (from Day 84 to Day 252).
Results: The overall rate of AEs during the extension study (43.8%; n=208) was comparable to the core study treatment groups (FLUT/FORM: 44.2%, n=104; FLUT/SAL: 43.3%, n=104). The majority of AEs were mild, not considered study treatment related and did not result in withdrawal. Mean and median plasma cortisol values remained stable during the extension study, with no evidence of effects on normal growth (mean increases in weight and height were 2.1kg and 2cm respectively). Mean pre-dose FEV1 increased by 105ml from 1.85l at the start of extension phase.
Conclusion: Long-term fluticasone/formoterol combination therapy has a good safety and tolerability profile and provides sustained effectiveness in paediatric patients with mild/moderate persistent asthma.

P4824
Salivary cortisol for assessment of hypothalamic-pituitary-adrenal (HPA) axis function evaluation in asthmatic children with inhaled corticosteroids (ICS)
Lemonia Tsartsilis1, Marios Papadopoulos1, Evagelia Lagona2, George Chrousis2, Kostas Pistits1, 1Pediatric Pulmonology, Penteli Children’s Hospital, Athens, Greece; 2First Pediatric Department, Aegia Sofia Children’s Hospital, Athens, Greece
Background: Aims: Sampling for salivary cortisol (SC) determination is a pain free procedure and thus useful in the pediatric age group. Our aim was to compare Low Dose ACTH Stimulation Test (LDST) salivary test with the classical blood test as well as the diurnal variation in salivary cortisol concentration for the assessment of HPA axis activity of asthmatic children on ICS.
Methods: LDST was performed in 62 asthmatic children (43 males, median age 7.9 yrs) before and after 3 months treatment with ICS. During the test, samples for SC were obtained simultaneously with serum samples (at 0-30-60 min). Patients sampled their own saliva between 09:00 and 21:00 hours (every three hours) for a whole day before and after treatment.
Results: A significant positive correlation was found between salivary and serum cortisol levels at 0′ 30′ and 60′ after ACTH administration (R:0.818, p<0.001). Circadian rhythm cortisol parameters: cortisol awakening response, mean level and range of diurnal changes, correlated with serum cortisol at 60′ (R:0.308, p<0.05; R:0.316 p<0.022; R:0.318, p=0.026) and SC at 0′ (R:0.398, p=0.003; R:0.401, p=0.002; R:0.402, p=0.002; R:0.385, p=0.003; R:0.404, p=0.003) and 60′ (R:0.303, p=0.041; R:0.368, p=0.009).
Conclusion: The salivary low dose ACTH test yields results that parallel the response of serum cortisol to ACTH and may provide an alternative to the blood test for HPA axis function evaluation. Diurnal SC variation may offer a dynamic evaluation over a day with none intervention.

P4825
The oral corticosteroid sparing effect of omalizumab in patients with severe chronic asthma: Is there a difference when you become 12 years old?
Samantha Moss, Michael Mckeane, David Spencer. Respiratory Pneumologists, Great North Childrens Hospital, Newcastle upon Tyne, United Kingdom
Omalizumab is licensed for treatment of severe persistent allergic asthma over the age of 6 years. In England and Wales, the National Institute of Clinical Excellence recommends omalizumab as a possible treatment for young people over the age of 12, but not for children age 6 – 12.
We describe a population of children with severe asthma who have undergone a 16 week open label therapeutic trial of omalizumab.
The dose of oral corticosteroids at the start & end of the trial was documented. Some children completed modified quality of life and asthma symptom control questionnaires before and after the trial.
To date 15 children (13 boys) age 3-11 years, and 19 children (12 boys) age 11-16 years have completed a therapeutic trial in our centre. The baseline IgE was comparable between groups. We were able to reduce the daily corticosteroid dose in 13 children < 12 years (median pre 20, post 10 mg p<0.01) and in 16 children >12 years (median pre 10, post 5 mg, p<0.01).There was a significant increase pre- to post- trial in documented quality of life, using AQLQ (<12 n=8, >12 n=16), and asthma control (<12 n=8, >12 n=15) in all 21 patient in each group.
In conclusion, the use of omalizumab in children with severe asthma may result in a clinically significant decrease in the use of oral corticosteroids and an improvement in quality of life and a reduction in asthma symptoms. In our practice omalizumab was as effective in children <12 years of age as in the older age group. A placebo-controlled randomised control trial of omalizumab using steroid sparing as primary outcome in a paediatric population is urgently required.

P4826
Safety and efficacy of omalizumab in children with allergic asthma
Judith Pitts1, Shahid Sheikh2, Karen McCoy3, 1Division of Pulmonary Medicine/Department of Pediatrics, Nationwide Children’s Hospital, Columbus, OH, United States; 2Division of Pulmonary Medicine/Department of Pediatrics, Ohio State University College of Medicine/Nationwide Children’s Hospital, Columbus, OH, United States
Background: Omalizumab (Xolair) is a humanized monoclonal antibody used in the treatment of adults and children over 12 years with moderate to severe allergic asthma. Pediatric studies are few.
Objective: A retrospective chart review of pediatric patients who received oma-
liumab in the past 10 years for asthma at Nationwide Children’s Hospital, Columbus, Ohio.
Results: We had 13 patients, M/F 7:6, median age 13 years (range 9-17), median duration of therapy 36 months (range 1 to 59 months). 9 African American and 4 Caucasian, duration of asthma 15 years (8 to 16). Eight are still on therapy. All patients had severe persistent asthma. Twelve patients were receiving combi-
nation therapy (ICS and LABA). Only 4 patients claimed compliance with their asthma controller therapy. Five had family history of asthma, 6 had smoking exposure. Median Ige before starting omalizumab was 249 (range 78 to 2619).
Mean BMI was 25.7 and 46% of the patients were above the 100 percentile for BMI. Comparing between one year before and during omalizumab, mean hospital admission/patient/year decreased from 1.7±2.4 to 0.5±1.4 (p<0.05). There was also a trend towards improvement in ED visits from 2.3±3.2 to 1.7±3. Mean FEV1 during one year before omalizumab therapy, at initiation of therapy and during therapy was 91±18, 94±17, and 93±11 and was not statistically different.
Two of 13 patients were taken off omalizumab because of serious side effects, one with anaphylaxis and second with dilated cardiomyopathy. Anaphylaxis was noted on first dose and cardiomyopathy was diagnosed in 5th year on therapy.
Conclusion: Omalizumab is add-on therapy for some patients with allergic asthma. Adverse reactions in children are limiting factor.

P4827
Effect of leukotriene receptor antagonist on expression and variation of TGF-beta in T lymphocyte for mild persistent asthma in children
Wenfang Dong, Xiaojian Zhou, Jianguo Hong.
Wenfang Dong, Xiaojian Zhou, Jianguo Hong Pediatrics, Shanghai First People’s Hospital, Shanghai Jiaotong University, Shanghai, China
Objective: To investigate the role of TGF-β1 and action of montelukast (MT) in the pathogenesis of asthma in children.

Poster Discussion
Room D201-202 - 08:30-10:30

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Room D201-202 - 08:30-10:30
Methods: A single-blind, placebo-controlled trial was conducted in 60 mild persistent asthmatic children (5-14 years). Patients were randomly assigned to receive 5mg MT or placebo for 12 weeks. 30 healthy children (5-14 years) were as control. Clinical and pulmonary function were assessed before and after treatment. The mRNA expression of TGF-β1 in PBMC cells, subtypes of Foxp3+CD4+ T cells and TGF-β1 in plasma were measured.

Result: After treatment, symptoms were improved with significant increase in pulmonary function in asthmatic, MT superior to placebo (p<0.05). The mRNA expression of TGF-β1 and TGF-β2 level in asthmatic were lower than that in control (0.31±0.07 vs 0.60±0.2. p<0.05 and 0.45±0.13 vs 0.32±0.04, p<0.05, respectively). Total Foxp3+CD4+ cell and CD4+RA Foxp3,β were higher in asthmatic (3.8%±1.3% vs 6.05±1.8%, p=0.007 and 4.69%±1.05% vs 3.27%±1.03%, p=0.011, respectively). CD4+RA Foxp3,β was lower (0.75%±0.13% vs 0.93%±0.26%, p=0.021). After treatment, CD4+RA Foxp3,β was increased in MT compared to placebo group (1.16%±0.22% vs 0.89%±0.22%, p=0.01). TGF-β1 levels had no correlation with those levels of pulmonary function.

Conclusion: The expression of TGF-β1 was low in asthmatic children. Insufficient secretion of TGF-β1 and the defect in activating Foxp3+CD4+ Treg cells might play an important role in pathogenesis of asthma. Up-regulation of expression of TGF-β1 and induction of expression of CD4+RA Foxp3,β in Foxp3+CD4+ Treg cells by MT may be one of the mechanisms by which airway inflammation is inhibited in asthma.

P4829 Did inappropriate delivery systems hamper therapeutic efficacy of di-sodium-cromo-glycate (DSCG)? Time for a reappraisal

Manfred Keller, Oliver Denk, Albert Bucholzki, Martin Knoch. Aerosol Research Institute, PARI Pharma GmbH, Graefelfing, Germany

Chymase-positive cells located in distal airways play a crucial role in asthma (Balzar 2005 & 2010). A review on inhaled DSCG by Keller & Schierholz (2011) provided evidence that poor efficacy of DSCG is most probably linked with sub-therapeutic lung doses. The hygroscopic nature of DSCG causes particle growth under simulated conditions was used to measure delivered dose from ProAir HFA pMDIs (108 µg albuterol sulphate/actuation, Teva Specialty Pharmaceuticals LLC). Three brands of VHC-facemask systems were tested: preproduction Op-tiChamber Diamond (Diamond) VHCs with preproduction LiteTouch facemasks (Philips Respironics), AeroChamber Plus Z Stat (Z Stat) VHCs with ComfortSeal facemasks (Monaghan Medical Corp.), and Vortex VHCs with Spinner Duck facemasks (PARi GmbH). A face replica of a four-year-old child, with a replaceable aerosol filter in the "mouth", was connected to a breathing simulator (ASL 5000; IngMar Medical Ltd) to simulate a pediatric breathing pattern (Vt=155 mL, f=25 bpm I:E=2:3). Each VHC-facemask system was naturally positioned against the face replica with a constant applied force supplied by a mass of 1.9 kg. Albuterol sulfate was quantified using HPLC after 1, 2, 4 and 8 "breaths" following pMDI actuation.

The delivered dose using the Diamond-LiteTouch system, after 1 breath, was significantly higher than the delivered dose using the Z Stat-ComfortSeal or the Vortex-Spinner Duck system after 8 breaths (p<0.01).

Table 1. Mean dose recovered on filter (% of dose)

<table>
<thead>
<tr>
<th>Total number of breaths</th>
<th>Diamond-LiteTouch system</th>
<th>Z Stat-ComfortSeal system</th>
<th>Vortex-Spinner Duck system</th>
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<tbody>
<tr>
<td>1</td>
<td>49</td>
<td>39</td>
<td>4.9</td>
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<tr>
<td>2</td>
<td>65</td>
<td>26</td>
<td>1.4</td>
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<tr>
<td>4</td>
<td>65</td>
<td>33</td>
<td>5.8</td>
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<tr>
<td>8</td>
<td>63</td>
<td>34</td>
<td>9.3</td>
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