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Children's Research Center CRC

Pediatric pulmonology

Asthma bei Kindern

PD Dr. med. Alexander Moeller
Leiter Kinderpneumologie
Universitätskinderkliniken Zürich

*The hospital of the
Eleonore Foundation*

1. Frühkindliches Wheezing: was gibt's neues zur Diagnose



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2

Preschool wheeze: structure or asthmatic inflammation?

Structure:
Traction exerted on the airway wall by the elastic components of the surrounding alveoli

Inflammation:
T_H2 cell driven eosinophilic inflammation and innate lymphoid cell driven non-atopic inflammation

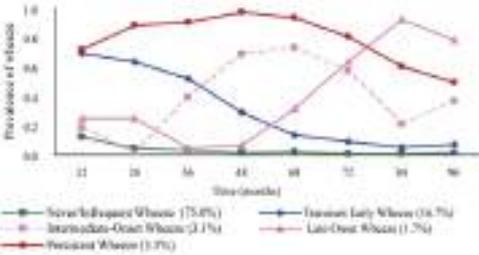


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Frey U. SWM 2001; 131:400
Lambrecht BN. Nature Immunology 2015; 16, 45-56

Der Asthma-Weg: Wheeze Phänotypen

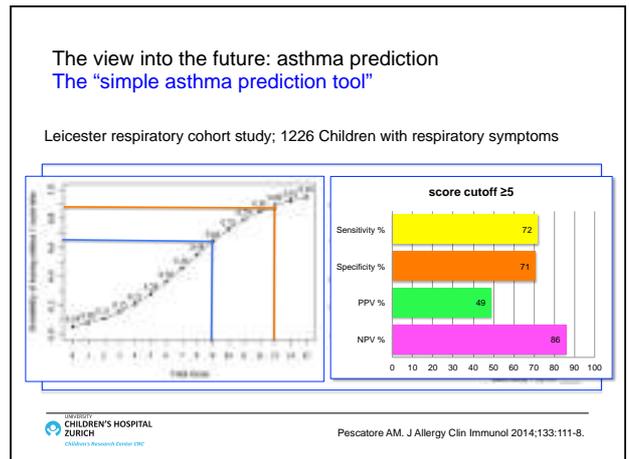
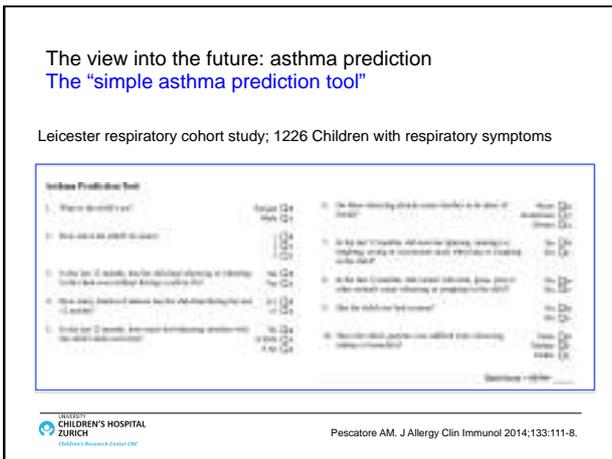
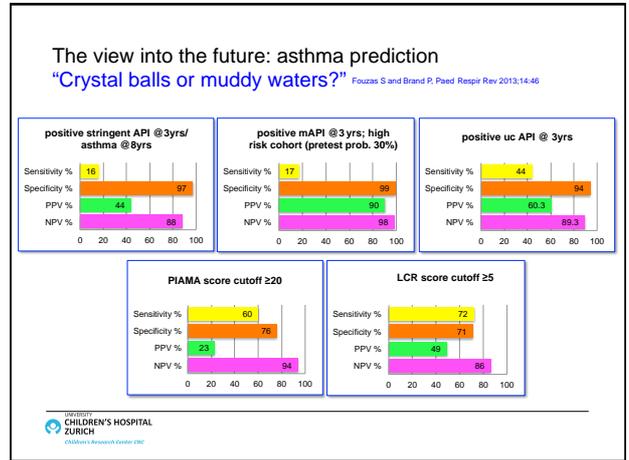
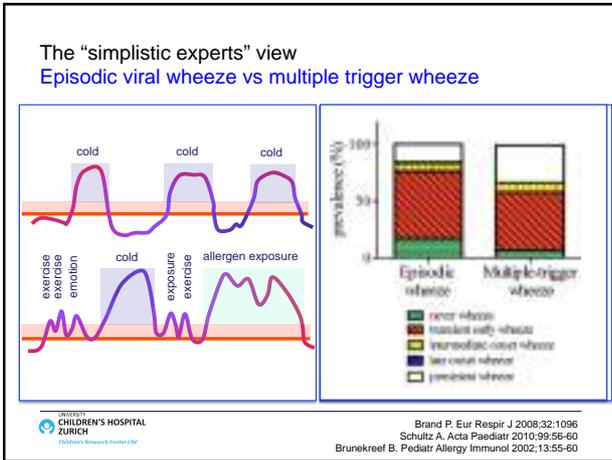
Prevention and Incidence of Asthma and Mite Allergy (PIAMA)



Alter (months)	Never-to-frequent Wheeze (75.0%)	Transient Early Wheeze (16.7%)	Intermittent-Onset Wheeze (3.7%)	Late-Onset Wheeze (1.7%)	Persistent Wheeze (1.9%)
12	0.75	0.17	0.04	0.02	0.01
24	0.70	0.18	0.04	0.02	0.01
36	0.65	0.19	0.04	0.02	0.01
48	0.60	0.20	0.04	0.02	0.01
60	0.55	0.21	0.04	0.02	0.01
72	0.50	0.22	0.04	0.02	0.01
84	0.45	0.23	0.04	0.02	0.01
96	0.40	0.24	0.04	0.02	0.01

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Savenije OW. J Allergy Clin Immunol 2011; online first



Diagnostisches Mosaik

- Häufigkeit und Schweregrad der obstruktiven Episoden
- Assoziation zu Virusinfekten
- Zeichen der bronchialen Hyperreagibilität
- Atopie (Modifizierter Asthma-predictive Index)*

<i>Major Kriterien</i>	<i>Minor Kriterien</i>
Elterliches Asthma	Wheezing ohne Erkältung
Atopische Dermatitis	Eosinophile >4%
Aeroallergen Sensibilisierung	Milch/Ei/Erdnuss Sensibilisierung
- Nachweis der variablen Atemwegsobstruktion
- Nachweis der Atemwegsentzündung
- Therapieversuch

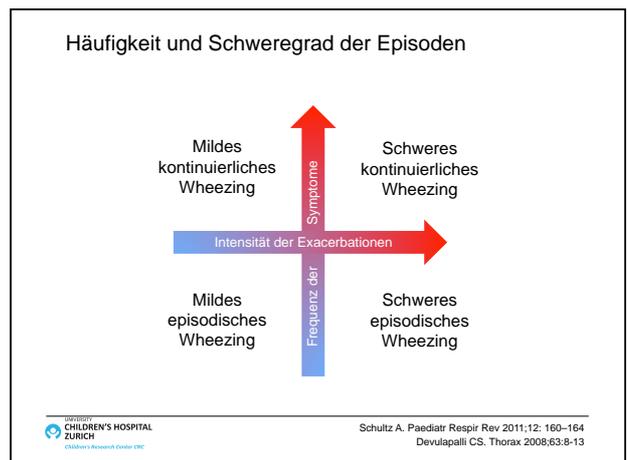
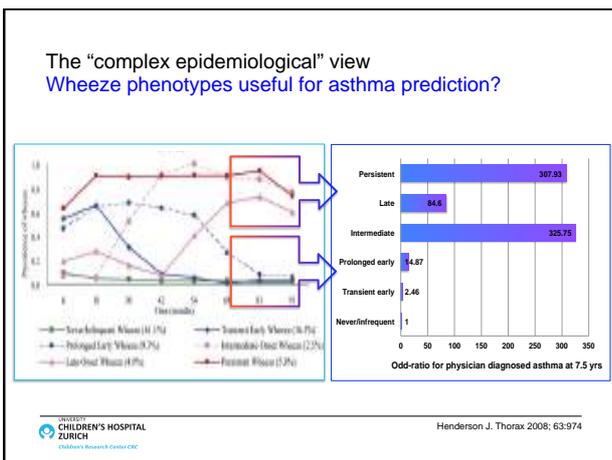
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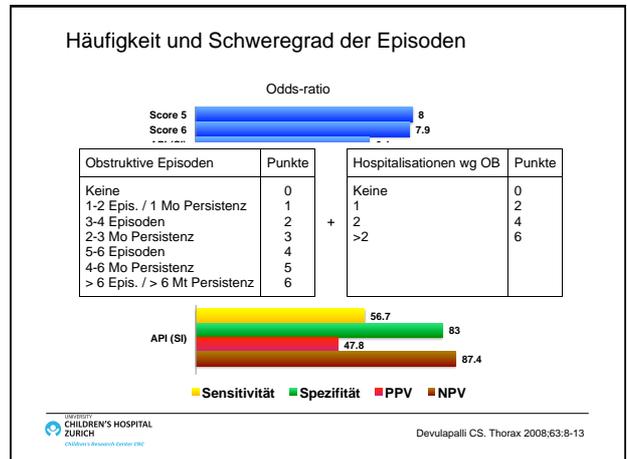
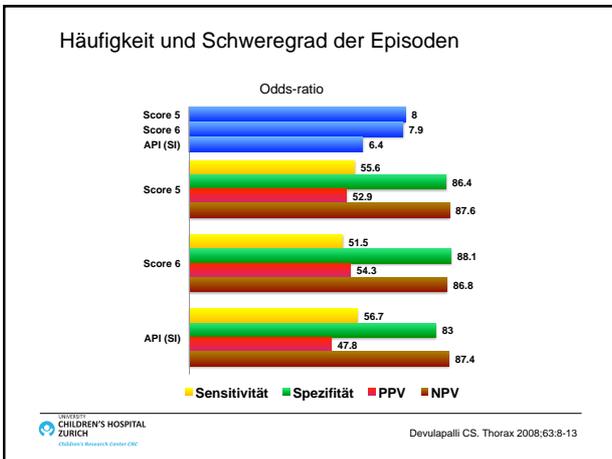
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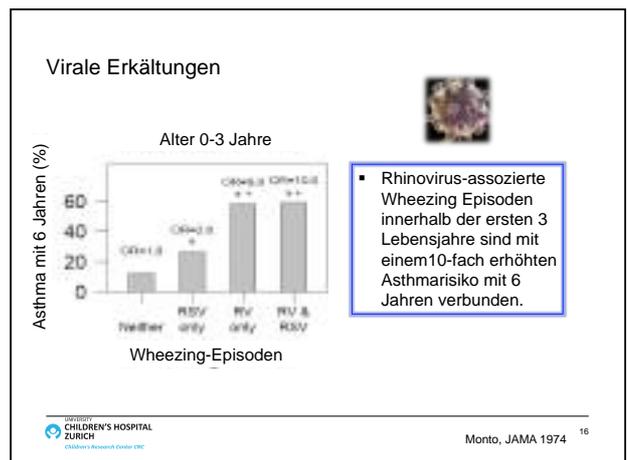




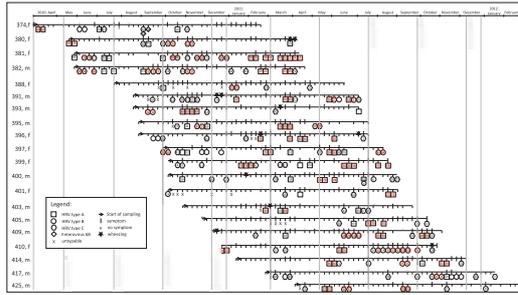
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Are Biomarkers of help to predict asthma?
Virus tests.....but



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Müller LPediatr Infect Dis J. 2015;:34(8):907-9

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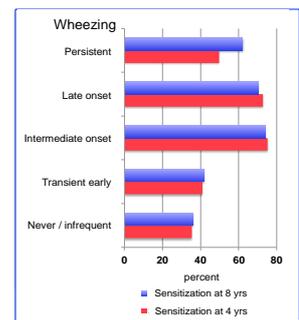
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Are Biomarkers of help to predict asthma?
Total and specific IgE

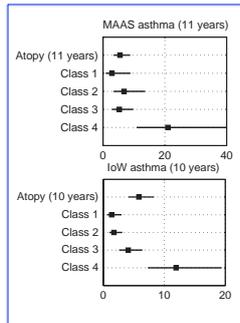
- Early, severe and persistent sensitization to common aero-allergens are independent risk factors for childhood asthma¹
- Sensitization associated with wheezing-phenotypes²
- Sensitization to perennial allergens at 3 years associated with loss of lung function at school age, aggravated by persistent exposure³



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¹Sly PD. Lancet 2008;372:1100-6
²Savenije OW. J Allergy Clin Immunol 2011 Jun;127:1505-12
³Illi S. Lancet 2006;368:763

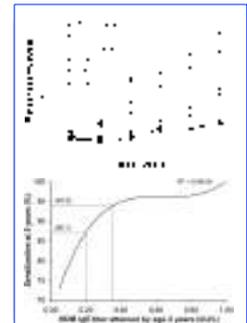
Are Biomarkers of help to predict asthma?
Total and specific IgE

- Manchester Asthma and Allergy Study (MAAS); n= 1028; Isle of Wight birth cohort study; n=1226
 - Machine learning approach to independently cluster children into different classes of atopic sensitization
- 0 few or no positive atopy tests
 - 1 sensitivity to grass pollens and late-onset sensitivity to peanut
 - 2 sensitivity to mite
 - 3 sensitivity to mite and grass pollens, late-onset sensitivity to pets
 - 4 sensitivity to a wide variety of allergens, including mite, pollens, cat and dog



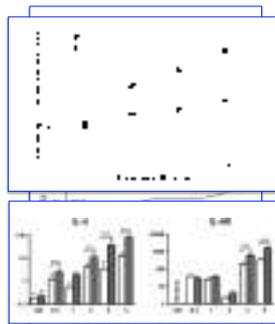
Are Biomarkers of help to predict asthma?
Total and specific IgE

- 198 Children with positive family history for atopy
- Identification of biomarkers at 2 yrs predictive for persistent atopy and wheeze at 5 yrs
- Blood 0.5, 1, 2, 3, 4, 5 years
- Sensitization to HDM at 2yrs associated with sensitization at 5yrs
- HDM IgE titers at 2yrs predictive for wheeze at 5yrs
- HDM specific cytokine responses

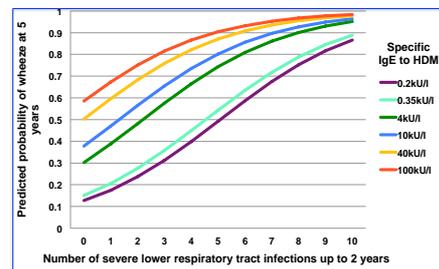


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Are Biomarkers of help to predict asthma?
Virus tests and IgE



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Nachweis der reversiblen Atemwegsobstruktion hochspezifisch

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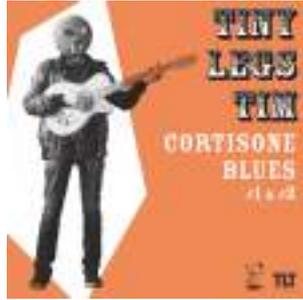
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2. Therapie frühkindliches Asthma: back to ICS?



Therapie: Vorschulkind Behandlungsplan

Virale obstruktive Bronchitiden

„Ad hoc“ im Infekt
 - Montelukast 4mg bei ersten Zeichen des Luftwegsinfekts
 - 5-7 Tage

Präventiv
 - Montelukast 4mg 1xtgl
 - ((ICS tiefdosiert))
 - Reduktion virale Infekte ?

Frühkindliches Asthma

„Ad hoc“ im Infekt
 - Hochdosierte ICS (Stufe 4)
 - 7 Tage

Präventiv
 - Kleinkinder Asthma-Stufenbehandlungsplan
 - Adaptierte ICS, alternativ Montelukast

1. Frühkindliches Wheezing: was gibt's neues

REVIEW
PRESCHOOL WHEEZING

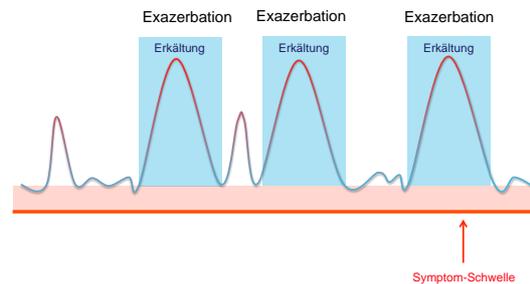
Classification and pharmacological treatment of preschool wheezing: changes since 2008

Paul L.P. Brand^{1,2}, Daan Caudri¹, Ernst Eber¹, Erol A. Gallard¹, Luis Garcia-Marcos¹, Gunilla Hedlin¹, John Henderson¹, Claudia E. Kuehni¹, Peter J.F.M. Merkus¹, Soren Pedersen¹, Arunas Valiulis¹, Goran Wennergren¹ and Andrew Bush^{1*}

TABLE 1 Distinction between temporal patterns of preschool wheeze and recommendations for controller therapy, as issued in the European Respiratory Society 2008 Task Force report [8]

Phenotype	Temporal pattern	Proposed first choice of controller therapy
Episodic viral wheeze	Wheezing during discrete time periods, often in association with clinical evidence of a viral cold, with absence of wheeze between episodes	Montelukast
Multiple-trigger wheeze	Wheezing that shows discrete associations (as with episodic viral wheeze) but also symptoms between episodes	Inhaled corticosteroids

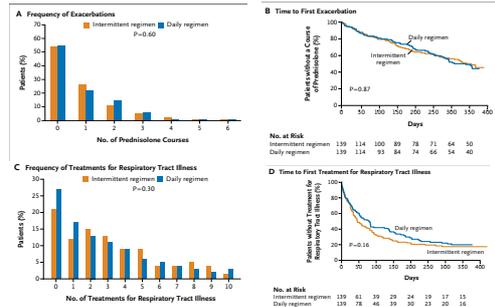
Therapie frühkindliches Asthma: Rationale für intermittierende Therapie



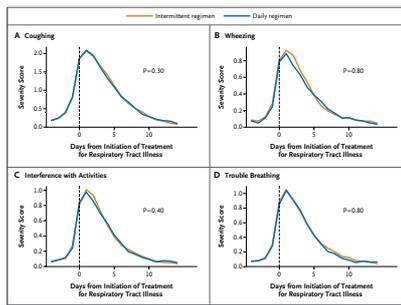
Therapie frühkindliches Asthma:
Rationale für intermittierende Therapie

Run-in: 2 Weeks	Treatment Phase: 52 Weeks		
Placebo once nightly and albuterol as needed	Randomized Treatment Group	Nightly Except during Respiratory Tract Illnesses	During Respiratory Tract Illnesses Only for 7 Days
	Daily	Budesonide (0.5 mg)	Placebo in a.m. Budesonide (0.5 mg) in p.m.
	Intermittent	Placebo	Budesonide (1.0 mg) in a.m. Budesonide (1.0 mg) in p.m.

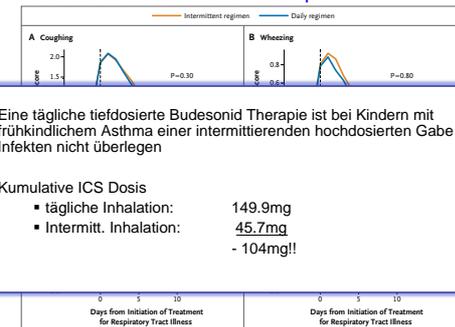
Therapie frühkindliches Asthma:
Rationale für intermittierende Therapie



Therapie frühkindliches Asthma:
Rationale für intermittierende Therapie



Therapie frühkindliches Asthma:
Rationale für intermittierende Therapie



- Eine tägliche tiefdosierte Budesonid Therapie ist bei Kindern mit frühkindlichem Asthma einer intermittierenden hochdosierten Gabe während Infekten nicht überlegen
- Kumulative ICS Dosis
 - tägliche Inhalation: 149.9mg
 - Intermitt. Inhalation: 45.7mg - 104mg!!

Therapie: Vorschulkind

FIGURE 3
Meta-analyses of strategies for preventing severe exacerbations in preschoolers with recurrent wheeze.

IV. Daily ICS versus Daily Montelukast



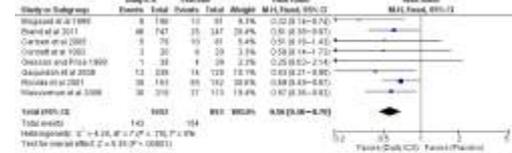
IV. Intermittent ICS versus Intermittent Montelukast



Therapie: Vorschulkind

FIGURE 5
Meta-analyses of strategies for preventing severe exacerbations in preschoolers with persistent asthma (subgroup analysis).

I. Daily ICS versus Placebo

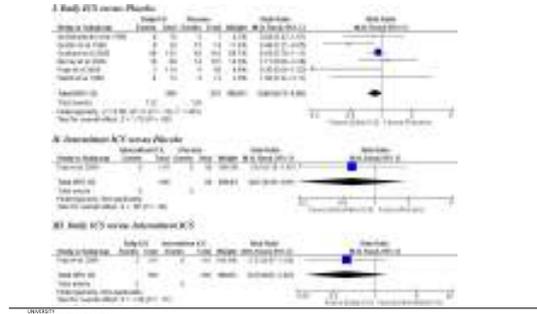


II. Daily ICS versus Daily Montelukast



Therapie: Vorschulkind

FIGURE 6
Meta-analyses of strategies for preventing severe exacerbations in preschoolers with unclear or mixed wheezing phenotypes (subgroup analysis). Mantel-Haenszel.



Therapie: Vorschulkind

Therapie	Events, Total	RR	95% CI	NNT
Täglich ICS vs Placebo*	15/3278	0.7	0.61-0.79	9
Persistent Asthma				
Täglich ICS vs Placebo	8/2505	0.56	0.46-0.70	11
Täglich ICS vs Montelukast	1/202	0.59	0.38-0.92	
Intermitt.A. / viral wheeze+				
Intermitt.A. / viral wheeze+	5/422	0.65	0.51-0.81	6

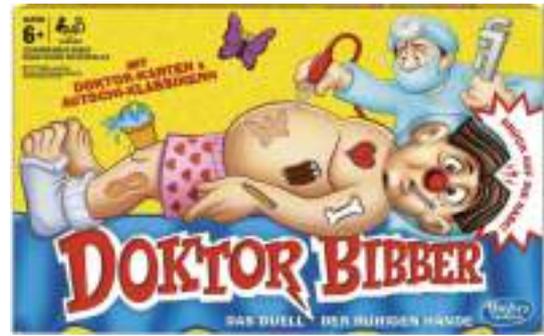
Therapie: Vorschulkind

Therapie		RR	95% CI	NNT
Täglich ICS vs Placebo*	15/3278	0.7	0.61-0.79	9

LIMITATIONS: More studies are needed that directly compare these strategies.
CONCLUSIONS: There is strong evidence to support daily ICS for preventing exacerbations in preschool children with recurrent wheeze, specifically in children with persistent asthma. For preschool children with intermittent asthma or viral-triggered wheezing, there is strong evidence to support intermittent ICS for preventing exacerbations.

Intermitt.A. / viral wheeze+	5/422	0.65	0.51-0.81	6
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Asthma Diagnose: ein Kinderspiel?



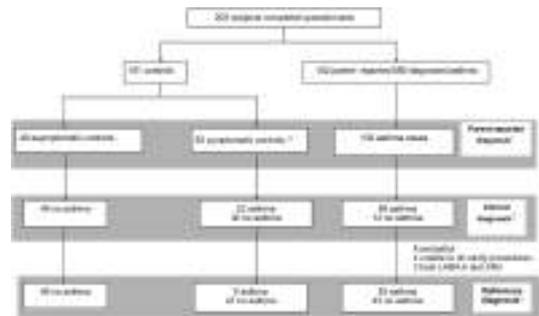
Schulalter. Stimmt die Diagnose?



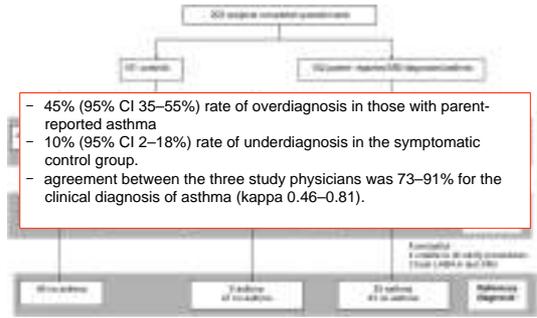
Misdiagnosis of Asthma in Schoolchildren

C.L. Yang,^{1,2} E. Simons,^{3,4} R.G. Foty,³ P. Subbarao,^{1,2,4} T. To,^{3,4} and S.D. Dell^{1,2,3,4*}

Schulalter. Stimmt die Diagnose?



Schulalter. Stimmt die Diagnose?



- 45% (95% CI 35–55%) rate of overdiagnosis in those with parent-reported asthma
- 10% (95% CI 2–18%) rate of underdiagnosis in the symptomatic control group.
- agreement between the three study physicians was 73–91% for the clinical diagnosis of asthma (kappa 0.46–0.81).

Schulalter. Stimmt die Diagnose?

Research
Ingrid Looijmans-van den Akker, Karen van Luijn and Theo Verheij

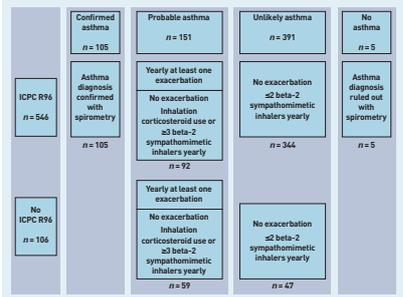
Overdiagnosis of asthma in children in primary care:
a retrospective analysis

Schulalter. Stimmt die Diagnose?

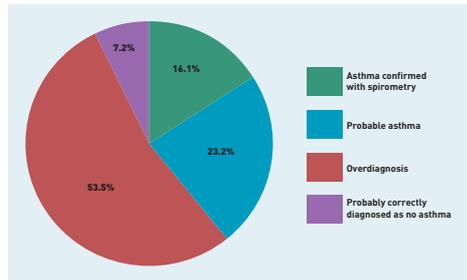
Table 1. Characteristics of children in study group (n = 652)

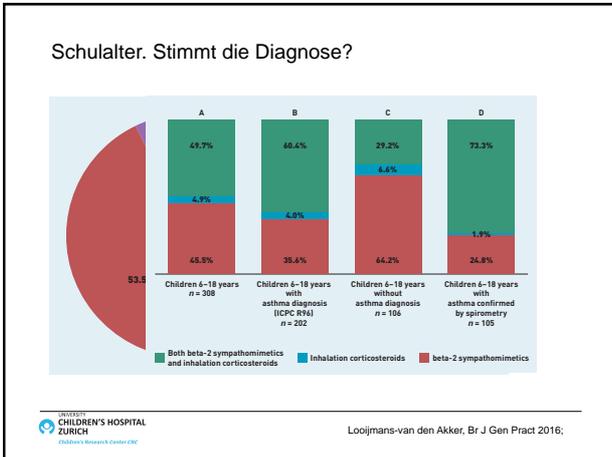
Parameter	n (%)
Mean age, years	10.7 ± 3.2 (range 6–17)
Sex	
Male	387 (59.4)
Female	265 (40.6)
Diagnosis of asthma (ICPC R96)	546 (83.7)
Medication use	308 (47.2)
Mean exacerbations in 2012, n ± SD	0.2 ± 0.4

ICPC = International Classification of Primary Care; SD = standard deviation.



Schulalter. Stimmt die Diagnose?

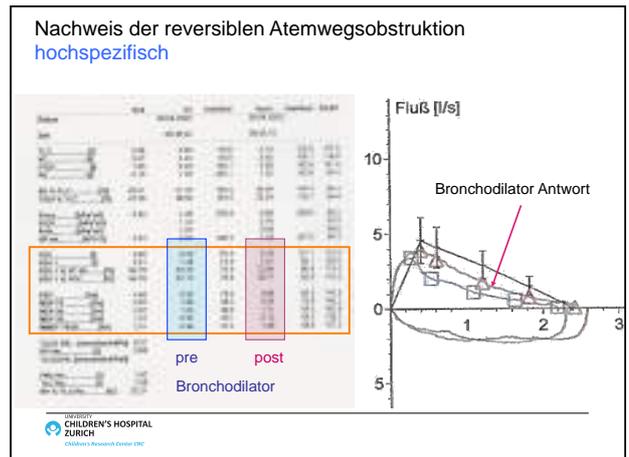




Anamnese

- Anfallsartige/nächtliche Atemnot und/oder Brustenge und/oder Husten
- pfeifende Atemgeräusche („Giemen“)
- Belastungssymptome
- Intensität/Variabilität
- Therapie-Ansprechen

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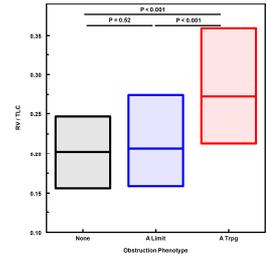


Zeichen der bronchialen Hyperreagibilität

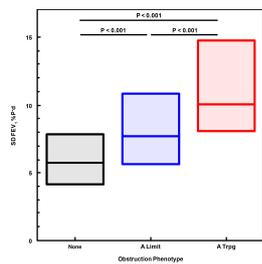


Obstruktion als Prädiktor für Asthma-Schweregrad

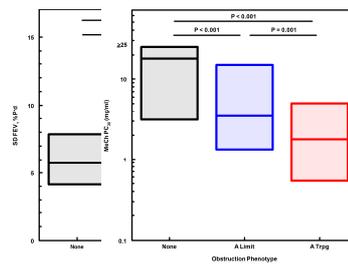
- Airflow limitation was defined as a $Z\text{-FEV}_1/\text{FVC} < -1.64$
- Air-trapping was defined as $Z\text{-FVC} < -1.64$ or a change in the FVC with bronchodilation of $\geq 10\%$ predicted

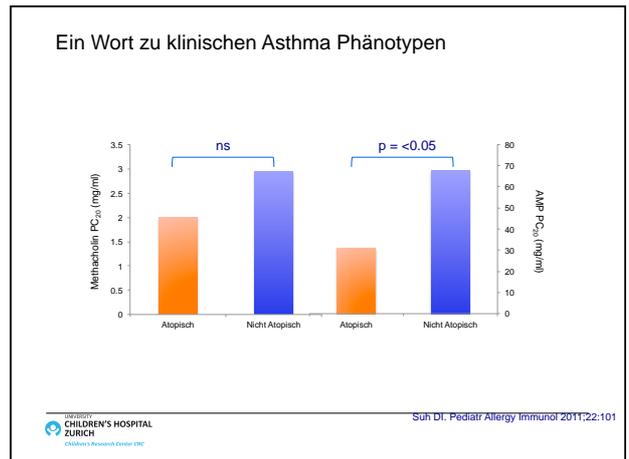
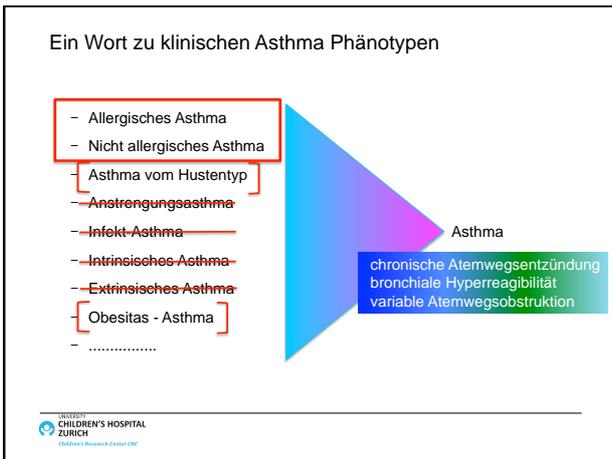
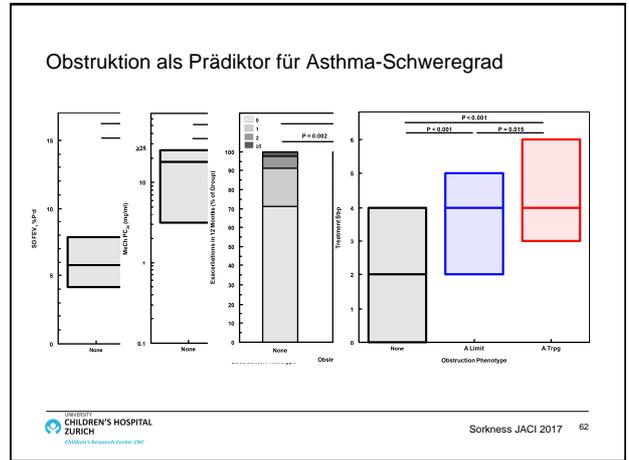
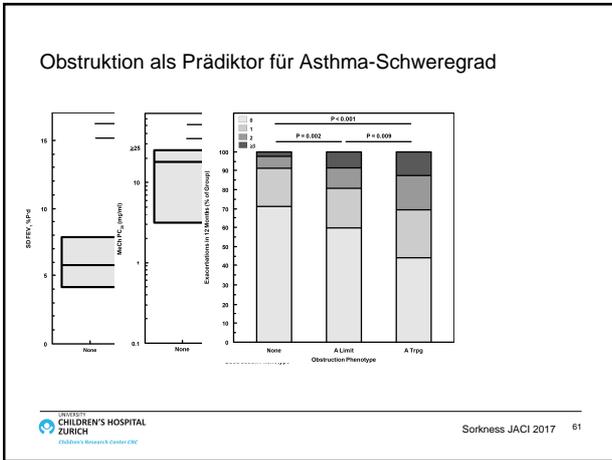


Obstruktion als Prädiktor für Asthma-Schweregrad



Obstruktion als Prädiktor für Asthma-Schweregrad

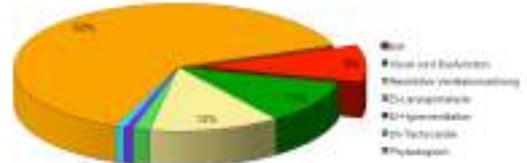




Ein Wort zu klinischen Asthma Phänotypen



Ein Wort zu klinischen Asthma Phänotypen



3. Nützt das Encasing?

ORIGINAL ARTICLE

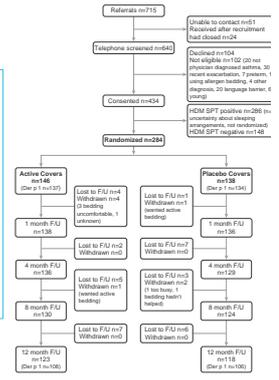
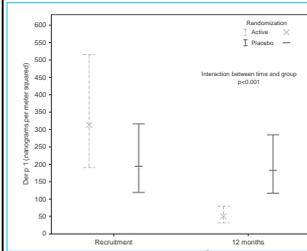
Preventing Severe Asthma Exacerbations in Children
A Randomized Trial of Mite-Impermeable Bedcovers

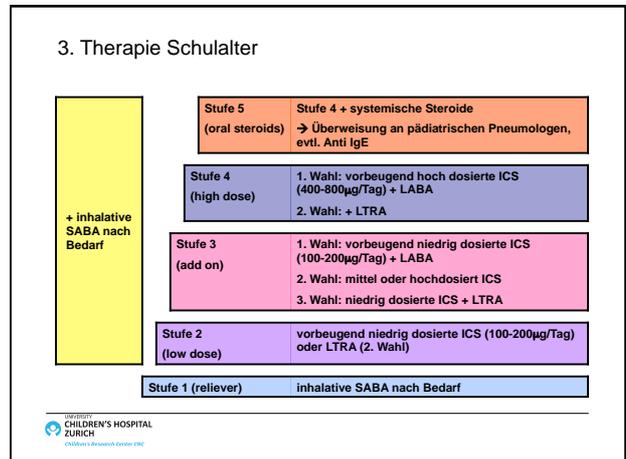
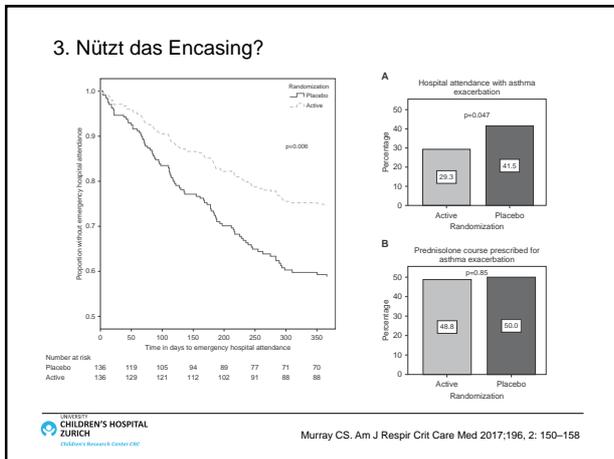
Claire S. Murray^{1,2,3}, Philip Foden^{1,2}, Helen Sumner¹, Elizabeth Shepley^{1,2,4}, Adnan Custovic⁵, and Angela Simpson^{1,2}

¹Division of Infection, Immunity and Respiratory Medicine, Manchester Academic Health Sciences Centre, University of Manchester, Manchester, United Kingdom; ²University Hospital of South Manchester, Manchester, United Kingdom; ³Royal Manchester Children's Hospital, Central Manchester University Hospitals National Health Service Foundation Trust, Manchester, United Kingdom; ⁴National Institute for Health Research South Manchester Respiratory and Allergy Clinical Research Facility, University Hospital of South Manchester, United Kingdom; and ⁵Department of Paediatrics, Imperial College London, London, United Kingdom

ORCID ID: 0000-0003-2733-6666 (A.S.).

3. Nützt das Encasing?





3. Sind LABA sicher?

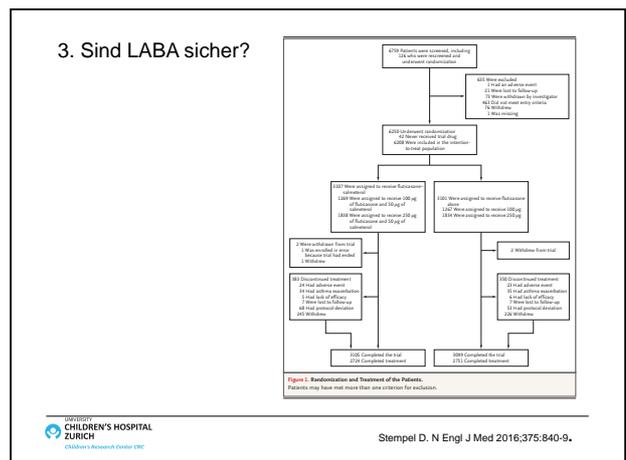
THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma

David A. Stempel, M.D., Stanley J. Szefler, M.D., Søren Pedersen, Dr.Med., Robert S. Zeiger, M.D., Ph.D., Anne M. Yeakey, M.D., Laurie A. Lee, M.D., Andrew H. Liu, M.D., Herman Mitchell, Ph.D., Kenneth M. Kral, M.S., Ibrahim H. Rappiou, Ph.D., Barbara A. Prillaman, M.S., M.A., Kathleen S. Buaron, B.S.N., Suyong Yun Kirby, Ph.D., and Steven J. Pascoe, M.B., B.S., for the VESTRI Investigators*

Children's Hospital ZÜRICH
Stempel D. N Engl J Med 2016;375:840-9.



3. Sind LABA sicher?

Table 2. Composite Safety End Points and Hospitalizations, According to Age, Race, and Sex, in the Intention-to-Treat Population.

Safety End Point	Fluticasone-Salmeterol (N=3107)	Fluticasone Alone (N=3101)
Composite safety end point — no. (%)	27 (0.9)	21 (0.7)
Asthma-related death	0	0
Asthma-related intubation	0	0
Asthma-related hospitalization	27 (0.9)	21 (0.7)
Total no. of asthma-related hospitalizations*	28	22
Patients hospitalized — no./total no. (%)		
According to age		
4-6 yr	11/1096 (1.0)	10/1114 (0.9)
7-11 yr	16/2011 (0.8)	11/1987 (0.6)
According to race		
White	11/1998 (0.6)	13/2032 (0.6)
Black	6/539 (1.1)	3/511 (0.6)
Other	10/570 (1.8)	5/558 (0.9)
According to sex		
Female	12/1187 (1.0)	4/1227 (0.3)
Male	15/1920 (0.8)	17/1874 (0.9)

* One patient in each treatment group was not withdrawn from the trial after the first hospitalization and was hospitalized a second time.

3. Sind LABA sicher?

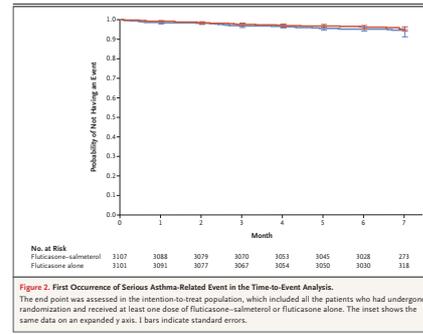
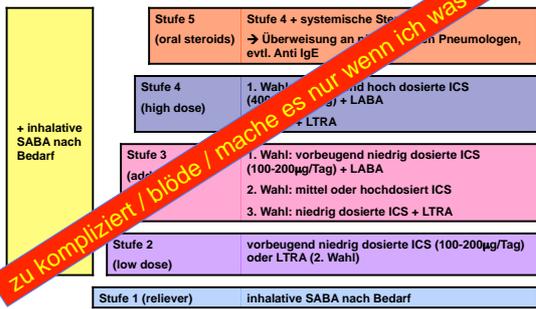
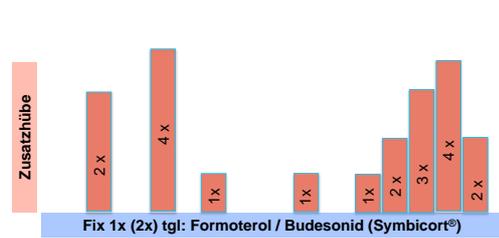


Figure 2. First Occurrence of Serious Asthma-Related Event in the Time-to-Event Analysis.
The end point was assessed in the intention-to-treat population, which included all the patients who had undergone randomization and received at least one dose of fluticasone-salmeterol or fluticasone alone. The inset shows the same data on an expanded y axis. I bars indicate standard errors.

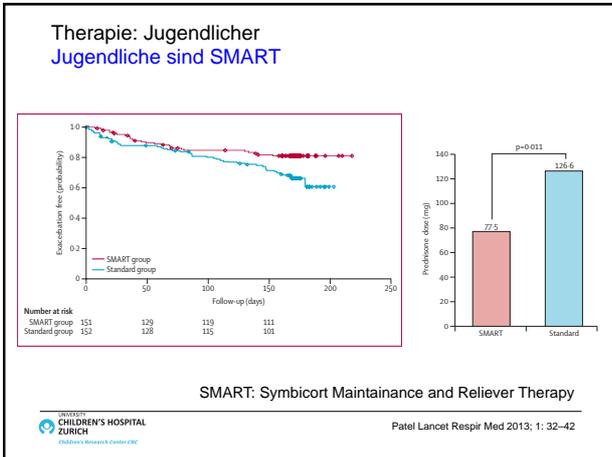
3. Sind LABA sicher?
SMARTE Therapie?



Therapie: Jugendlicher
Jugendliche sind SMART



SMART: Symbicort Maintenance and Reliever Therapy



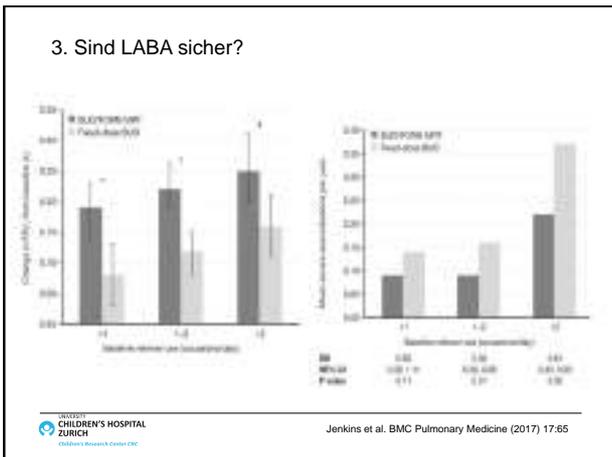
3. Sind LABA sicher?

RESEARCH ARTICLE Open Access

Efficacy of budesonide/formoterol maintenance and reliever therapy compared with higher-dose budesonide as step-up from low-dose inhaled corticosteroid treatment

Christine R. Jenkins^{1*}, Göran Eriksson², Eric D. Bateman³, Helen K. Reddel⁴, Malcolm R. Sears⁵, Magnus Lindberg⁶ and Paul M. O'Byrne⁶

Jenkins et al. BMC Pulmonary Medicine (2017) 17:65



Ist SMART smart?

Im Vergleich zu Fix-Dosis Kombinationen

- Reduktion Exazerbationen (system. Steroide / Hosp / ER Visiten)
- Keine klare Evidenz bezüglich severe adverse events
- Durchschnittliche ICS Dosis (inkl. „Reliever-Dosen“) war immer tiefer

- Die Flexibilität des ICS Gebrauchs mit SMART mit Erhöhung der Dosis nur bei Bedarf bei tiefer Dosis wenn stabil, ist effektiver als die Fix-Dosis-Standard-Therapie

- Keine Studien für Kinder < 12 Jahren.

Kew. Cochrane Database Syst Rev. 2013 Dec 16;(12):CD009019

Fallbeispiel

Marco 12j: Allergisches Asthma bronchiale

- Monosensibilisierung auf Aspergillus fumigatus
- Schlechte Symptomkontrolle trotz ausgebauter Therapie (Stufe 4)
- Arzt über Mutter „unprofessionelle Betreuung“
- Häufige Exacerbationen (bis 10x/Jahr)
- Persistierende fixierte Obstruktion (FEV1 75%)



Fallbeispiel

Jan Nino 14j: Allergisches Asthma bronchiale

- Schlechte Symptomkontrolle
- Allergie auf Gräser (6), Roggen (5), Hausstaubmilbe (5), Hund (3)
- Gesamt IgE 700kU/l
- Exacerbationen in Pollenflugsaison
- „indolent“, „unsportlich“



- Persistierende obstruktive Ventilationsstörung FEV1 79%/77%/70%
- Symbicort 200/6 2-0-2 ohne Effekt
- Prednison 30mg über 14 Tage, Besserung, aber nicht anhaltend



Fallbeispiel

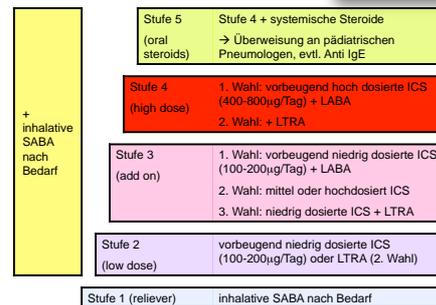
Martina 9j: Persistierendes Asthma mit obstruktiver Ventilationsstörung

- Häufige Exacerbationen: Katzenkontakt und Infekt
- Allerg. Sensibilisierung: Katzen- und Hundepithelien, Pferdehaare, Hausstaubmilben
- Lebt auf dem Land, viele Katzen auch in der Schule und bei allen Verwandten
- Exacerbationen und Anfälle bereits bei indirektem Katzen-Kontakt
 - Führt zur Isolation des Mädchens
 - Verleugnung der Symptome
 - bedrohliche Anfälle und Symptome mit BUD/FORM bis 10x tgl



Problematisches schweres Asthma

Definition



Problematisches schweres Asthma

Definition



Trotz regelmässiger Therapie mit $\geq 800\mu\text{g}$ Budesonide (oder Aequivalent) plus LABA oder Montelukast (oder Theophyllin)

- schlechte Symptomkontrolle
- tägliche Asthmasymptome
- rezidivierende schwere Asthma-Exacerbationen ($\geq 2 \times$ OCS/Jahr)
- lebensbedrohlicher Asthma-Anfall („near fatal asthma attack“)
- persistierende obstruktive Ventilationsstörung
- Notwendigkeit von systemischen Steroiden (längerdauernd)

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Children's Research Center CHC

Bush A. Lancet 2008;372:1019e21 85
Chung KF. Eur Respir J 2014;43:343-373

Problematisches schweres Asthma

Typen

- Kein Asthma
 - Falsche Diagnose
- Asthma „plus“
 - Asthma durch Ko-Morbiditäten verschlechtert / exazerbiert
- Ungenügend behandeltes Asthma
 - Reversible Faktoren: Adhärenz / Inhalationstechnik
- Schweres Therapie-refraktäres Asthma
 - trotz adäquater Therapie und Ausschluss reversibler Faktoren

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Bush A. Lancet 2010; 376: 814-25 88

Problematisches schweres Asthma

Typen

- Kein Asthma
- „difficult to treat“ Asthma
- Therapie refraktäres Asthma

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Bush A. Lancet 2010; 376: 814-25 87

Problematisches schweres Asthma

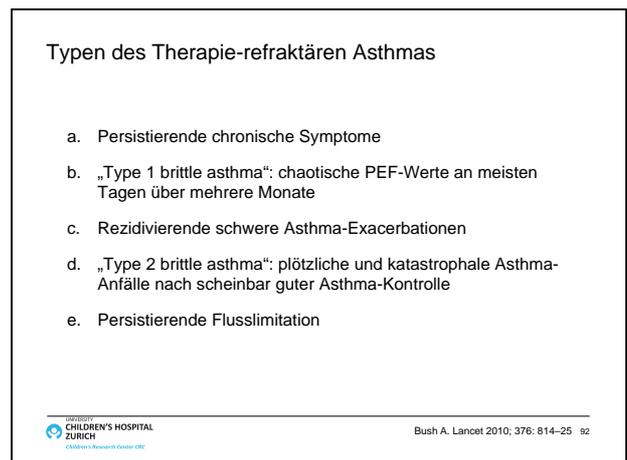
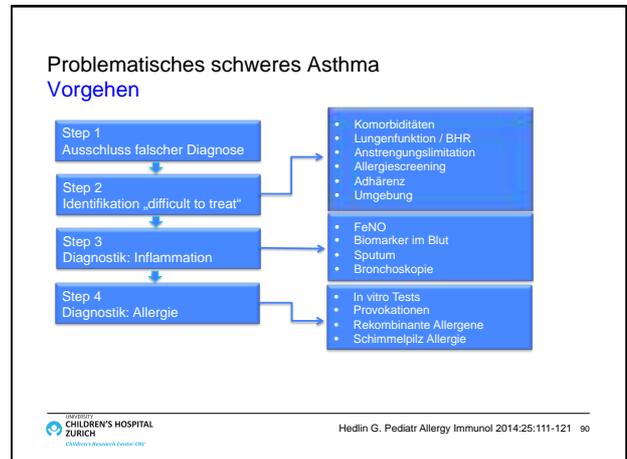
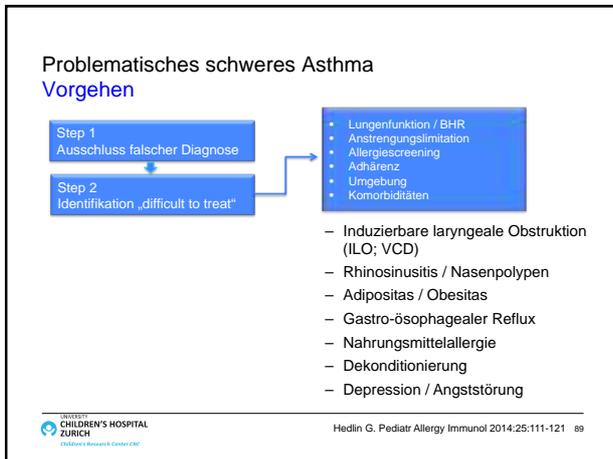
Vorgehen

Step 1
Ausschluss falscher Diagnose

- Dysfunktionelle Atmung
- Induzierbare laryngeale Obstruktion (ILO; VCD)
- Strukturelle Anomalitäten
 - Tracheobronchomalazie, Vaskulärer Ring, Trachealstenose, Bronchogene Zyste, Tumor
- Intrabronchiale Obstruktion (Fremdkörper)
- Cystische Fibrose
- Primäre Ziliäre Dyskinesie / non-CF Bronchiektasie
- Bronchopulmonale Dysplasie
- Bronchiolitis obliterans
- Immundefekt
- Gastro-ösophagealer Reflux; Aspiration

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Children's Research Center CHC

Hedin G. Pediatr Allergy Immunol 2014;25:111-121 88



Problematisches schweres Asthma Vorgehen

Step 1 Ausschluss falscher Diagnose	<ul style="list-style-type: none"> • Komorbiditäten • Lungenfunktion / BHR • Anstrengungslimitation • Allergiescreening • Adhärenz • Umgebung
Step 2 Identifikation „difficult to treat“	
Step 3 Diagnostik: Inflammation	<ul style="list-style-type: none"> • FeNO • Biomarker im Blut • Sputum • Bronchoskopie
Step 4 Diagnostik: Allergie	<ul style="list-style-type: none"> • In vitro Tests • Provokationen • Rekombinante Allergene • Schimmelpilz Allergie
Step 5 Diagnostik: Steroid-Response	<ul style="list-style-type: none"> • Dosis-Steigerung ICS • OCS Trial • i.m. Triamcinolon-Test

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Children's Research Center CRC Hedlin G. *Pediatr Allergy Immunol* 2014;25:111-121 93

Therapie-refraktäres Asthmas Vorgehen

- Steroid-Trial 1-2mg Prednison/Kg/Tag für 10-14 Tage
 - Steroid-Response evaluiert mit:
 - Symptomenscore
 - FeNO
 - Lungenfunktion
- Weitere Therapien:
 - Behandlungsplan
 - SMART Konzept
 - Anti-IgE; Omalizumab (Xolair®)
 - Spezifische Immuntherapie



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Children's Research Center CRC Bush A. *Lancet* 2010; 376: 814-25 94

Konklusionen

Schweres allergisches Asthma: was können wir tun?

- Saubere Diagnostik: ist es überhaupt Asthma?
- Komorbiditäten
- „Get the basics right“: difficult to treat oder Therapie-refraktär?
- Stufe 5 Therapien

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Problematisches schweres Asthma „get the basics right“

- Ist es wirklich Asthma?
- Was sagt die Lungenfunktion?
- Wird die Therapie durchgeführt?
- Ist die Inhalationstechnik korrekt?
- Allergenexposition minimalisiert?
- Rolle der viralen Infekte?
- Gibt es Komorbiditäten?
- Wie steht es mit der Tabackrauchexposition?
- Umweltfaktoren im Spiel?
- Psychosoziale Trigger?



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