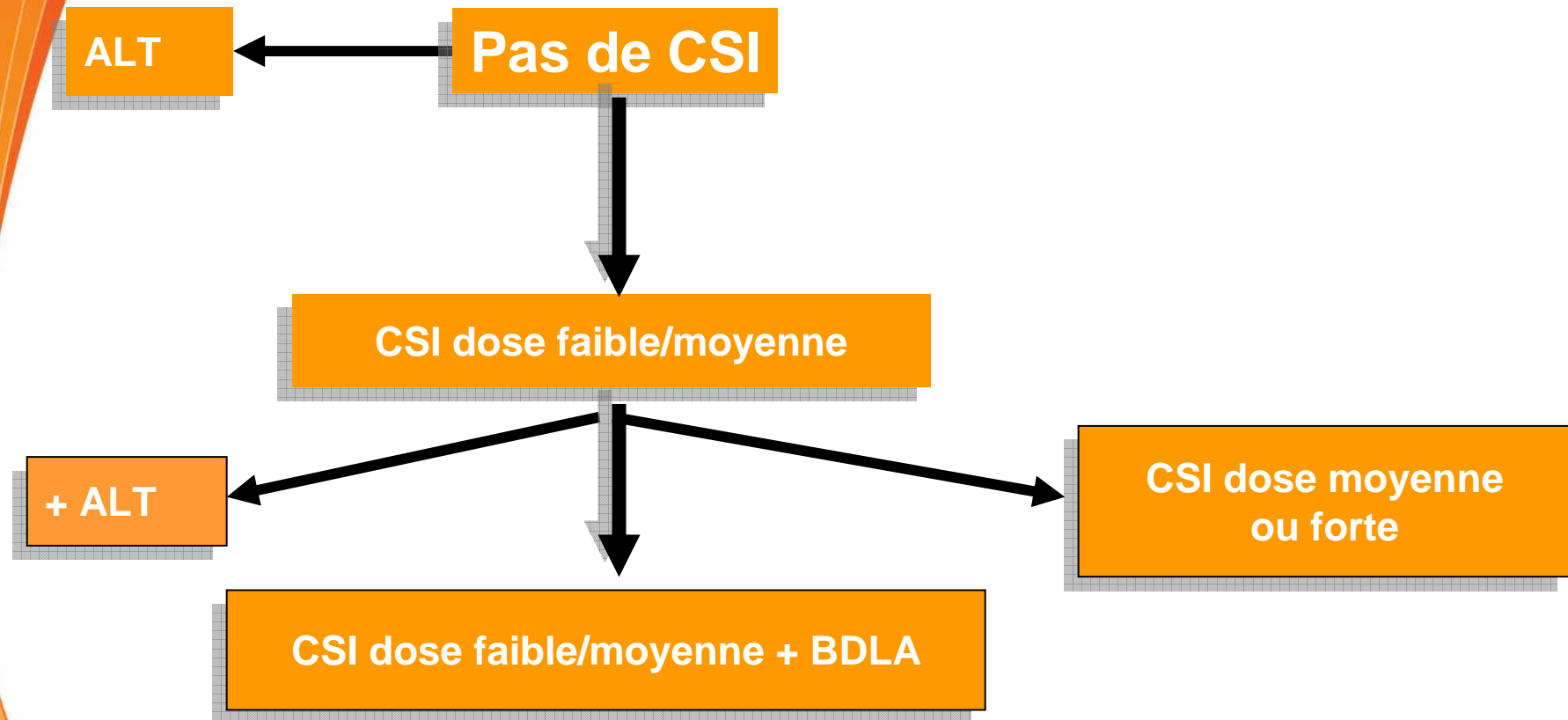


Adaptation du traitement en cas de non contrôle



Step up Therapy for Children with Uncontrolled Asthma Receiving Inhaled Corticosteroids

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED 1912 VOL. 362 NO. 11
MARCH 18, 2010
Step-up Therapy for Children with Uncontrolled Asthma Receiving Inhaled Corticosteroids
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ABSTRACT

BACKGROUND
For children who have uncontrolled asthma despite the use of low-dose inhaled corticosteroids (ICS), evidence to guide step-up therapy is lacking.

METHODS
We randomly assigned 165 children (6 to 17 years of age), who had uncontrolled asthma while receiving 100 µg of fluticasone twice daily, to receive each of three blinded step-up therapies in random order for 16 weeks: 250 µg of fluticasone twice daily (ICS step-up), 100 µg of fluticasone plus 50 µg of a long-acting beta₂-agonist twice daily (LABA step-up), or 100 µg of fluticasone twice daily plus 5 or 10 mg of a leukotriene-receptor antagonist daily (LTRA step-up). We used a triple-blind, crossover design and a composite of three outcomes (asthma control days, and the forced expiratory volume in 1 second) to determine whether the frequency of a differential response to the step-up regimens was more than 25%.

RESULTS
A differential response occurred in 161 of 165 patients who were evaluated ($P < 0.001$). The response to LABA step-up therapy was most likely to be the best response, as compared with responses to LTRA step-up (relative probability, 1.6; 95% confidence interval [CI], 1.1 to 2.3; $P = 0.004$) and ICS step-up (relative probability, 1.2; 95% CI, 1.2 to 2.4; $P = 0.002$). Higher scores on the Asthma Control Test before randomization (indicating better control at baseline) predicted a better response to LABA step-up ($P = 0.009$). White race predicted a better response to LABA step-up, whereas black patients were less likely to have a best response to LTRA step-up ($P = 0.005$).

CONCLUSIONS
Nearly all the children had a differential response to each step-up therapy. LABA step-up was significantly more likely to provide the best response than either ICS or LTRA step-up. However, many children had a best response to ICS or LTRA step-up therapy, highlighting the need to regularly monitor and appropriately adjust each child's asthma therapy. (ClinicalTrials.gov number, NCT00935304)

N ENGL J MED 362:975-85
DOI: 10.1056/NEJMoa0902778
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Lemanske RF et al.
N Engl J Med
2010;362:975-85

Etude BADGER

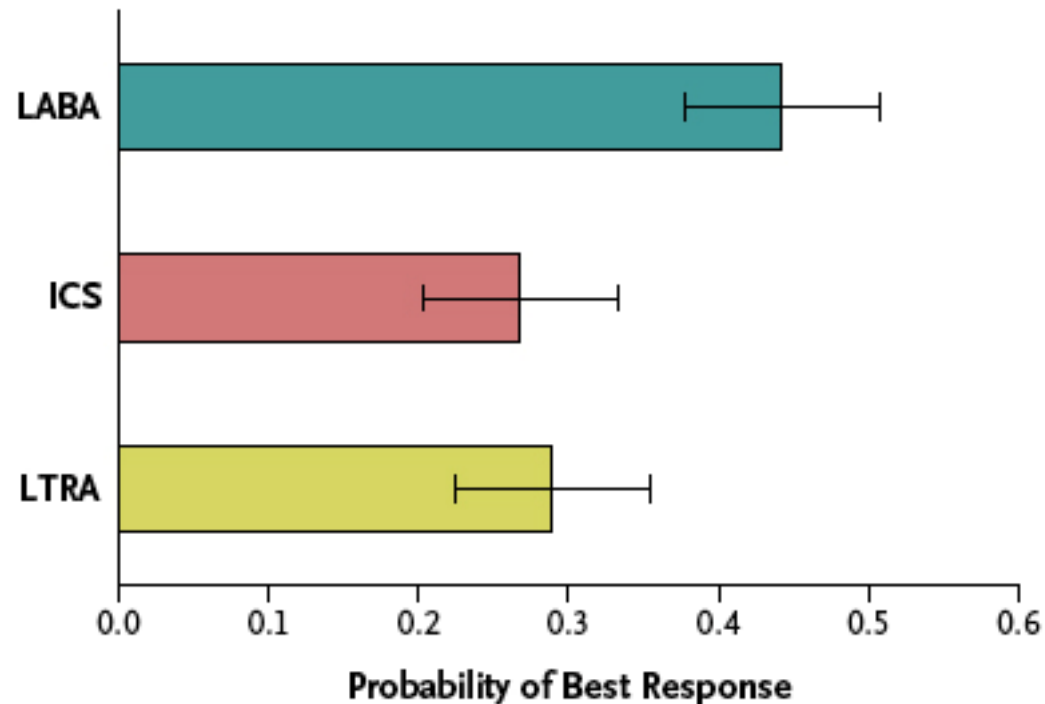
Best Add-on Therapy Giving Effective Responses

- 182 enfants, âgés de 6 à 17 ans
- Asthme non contrôlé avec 100 mcg \times 2/j de fluticasone
- Randomisation pendant 3 périodes de 12 semaines
 - soit 250 mcg \times 2/j de fluticasone,
 - soit l'addition de salmeterol 50mcg \times 2/j,
 - soit l'addition d'un ALTR, le montelukast 5 ou 10 mg/j.
- Un score composite : survenue d'exacerbation nécessitant une CS orale, nombre de jours avec contrôle et VEMS.
- Egalement
 - Toutes les 4 semaines
 - Questionnaire de contrôle (ACT)
 - Mesure du NO exhalé (eNO)
 - Tous les trimestres
 - Test à la métacholine
 - Réversibilité
 - Questionnaire de qualité de vie.

Etude BADGER

- Un traitement était considéré comme meilleur si
 - Pendant la période, la consommation de CS per os < 180 mg,
 - **ou** si le nombre annualisé de jours contrôlés > de 31 jours
 - **ou** si le VEMS à la fin de la période était $\geq 5\%$.
- Résultats
 - Amélioration significative chez 98 % des enfants
 - L'adhérence (comptage des comprimés et le nombre de bouffées d'aérosol doseur) > 80%.
 - C'est l'addition d'un LABA qui avait la probabilité de meilleure réponse par rapport à l'addition d'un ALTR (RR 1,6 ; $p=0,004$) , ou au doublement de la dose de CSI (RR 1,7 ; $p=0,002$).

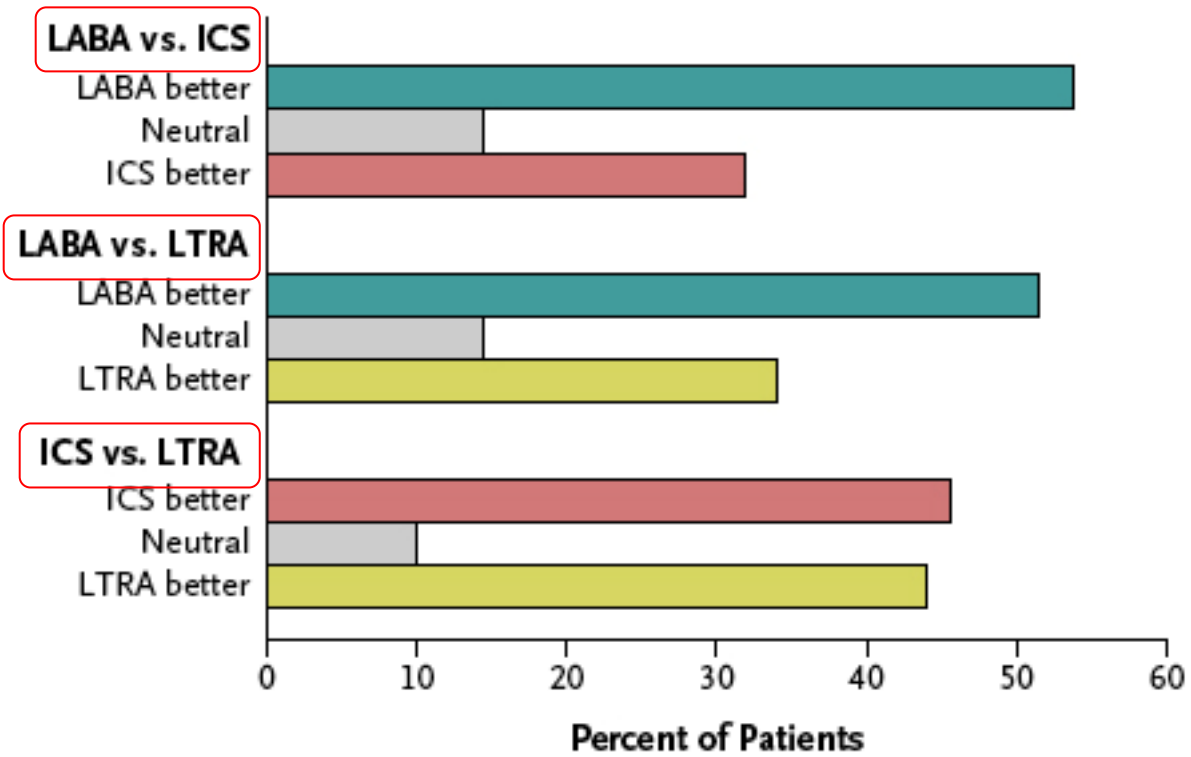
Probabilité de meilleure réponse



La probabilité que les LABA apportent le meilleur contrôle était de environ 45% et un peu moins de 30% pour le doublement des CSI ou l'addition d'un ALTR

Lemanske, NEJM, 2010

Comparaison par paire des options thérapeutiques



Etude BADGER

- Seul le score de l'ACT était prédictif d'une meilleure réponse aux LABA ($p=0,009$).
- Les enfants de race blanche étaient les plus susceptibles d'une meilleure réponse aux LABA
- les enfants de race noire la moins bonne réponse aux ALTR ($p=0,005$).
- En revanche non prédictifs de la réponse à une des 3 stratégies.
 - le seuil de positivité à la métacholine, le eNO,
 - le sexe,
 - une sensibilisation perannuelle,
 - le VEMS de base, la réversibilité,
 - le nombre de jours contrôlés, le nombre d'exacerbations récente

Etude BADGER

- Ces résultats montrent que
 - si l'addition des LABA apporte la meilleure réponse,
 - de nombreux enfants sont plus améliorés par l'une ou l'autre des 2 autres stratégies
- Nécessité de réévaluer régulièrement le contrôle de l'asthme pour optimiser la stratégie thérapeutique.
- Il n'y a pas lieu de changer les recommandations proposées récemment

AA et Apnées Obstructives du sommeil

- Etude multicentrique
- Comparaison résultats polysomnographies avant et après AA pour apnées obstructives du sommeil
- 8 centres
- 578 enfants $6,9 \pm 3,8$ ans
- 50 % obèses
- 30 % asthmatiques
- 40 % rhinite allergique
- Polysomnographie post AA faite au minimum 40 j après l'AA

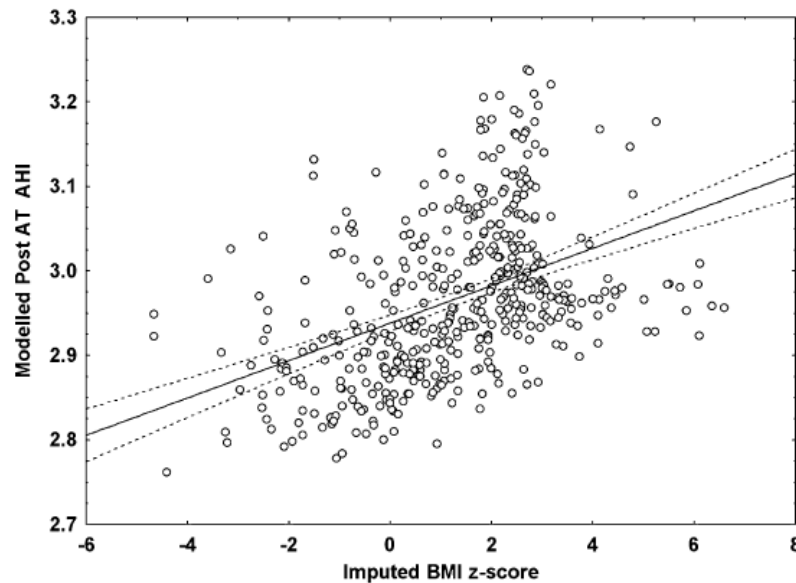
Résultats

Variable	Preadenotonsillectomy	Postadenotonsillectomy	P Value
Sleep efficiency, % (n = 397)	83.8 ± 11.2	85.5 ± 11	<0.001
Sleep onset latency, min (n = 393)	29.8 ± 38.3	27.4 ± 33.9	= 0.264
Number of awakenings, no. (n = 300)	12.9 ± 11	10.6 ± 8.2	<0.001
Wake after sleep onset, % of TST (n = 397)	13.4 ± 37.7	9.2 ± 11	= 0.113
REM onset latency, min (n = 371)	157.6 ± 97	155.7 ± 80.5	= 0.719
Stage 1 sleep, % of TST (n = 394)	6.8 ± 8	5.6 ± 5.2	= 0.002
Stage 2 sleep, % of TST (n = 394)	43.3 ± 12.5	45.8 ± 27.3	= 0.075
Stage 3 sleep, % of TST (n = 394)	7.8 ± 7.2	8.5 ± 11.2	= 0.151
Stage 4 sleep, % of TST (n = 394)	20.5 ± 9.9	21.5 ± 11.7	= 0.134
Stage REM sleep, % of TST (n = 507)	16.6 ± 7.4	16.8 ± 7.1	= 0.380
Total no. of obstructive hypopneas (n = 408)	90.7 ± 100.3	25.5 ± 38.8	<0.001
Total no. of obstructive apneas (n = 408)	37.9 ± 69.2	5.8 ± 20	<0.001
Apnea-hypopnea index, events/h TST (n = 578)	18.2 ± 21.4	4.1 ± 6.4	<0.001
Obstructive apnea index, events/h TST (n = 476)	6 ± 10.3	1.3 ± 4.4	<0.001
Total apnea index, events/h TST (n = 420)	6.7 ± 10.7	1.6 ± 3.3	<0.001
Respiratory arousal index, events/h TST (n = 173)	7.7 ± 8.1	2.4 ± 3	<0.001
Total arousal index, events/h TST (n = 285)	14.8 ± 16.2	9.8 ± 6	<0.001
Oxygen saturation nadir, % (n = 493)	80.2 ± 13.1	86.2 ± 8.3	<0.001

Seulement 27% des enfants ont un index AH < 1 /h

Facteurs influençant l'IAH post AA

■ Age (>7 ans)	$p < 0,001$
■ BMI	$p < 0,001$
■ Asthme	$p = 0,017$
■ IAH pre AA (c/ non obèse)	$p = 0,04$
■ Rhinite	0,5
■ Age	0,1
■ Ethnie	0,8



Histoire naturelle et facteurs prédictifs de progression des apnées obstructives du sommeil de l'enfant

Sleep-disordered breathing

Natural history and predictors for progression of mild childhood obstructive sleep apnoea

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See Editorial, p 4
 Additional data are published online only at <http://thorax.bmj.com/content/65/27/3>

ABSTRACT
Aims: The natural history of mild childhood obstructive sleep apnoea (OSA) was examined and factors associated with disease progression were identified.
Methods: Subjects were recruited from an epidemiological study which examined the prevalence of OSA in Chinese children aged 6–13 years. The first 50 consecutive children identified with mild OSA (apnoea-hypopnoea index 1–5) were invited for a repeat assessment 2 years after the diagnosis.
Results: 40 children participated in the follow-up study, 13 of whom (33%) the OSA was found to have worsened. Compared with those in whom OSA had not worsened, the worsened group had a greater increase in waist circumference, a higher prevalence of large tonsils (occupying >50% of the airway) at both baseline and follow-up, and a higher prevalence of habitual snoring at both baseline and follow-up. The presence of large tonsils had a positive predictive value of 53% and a negative predictive value of 65% for worsening OSA over a 2-year period. Multivariate linear regression analysis showed that the change in obstructive apnoea index was associated with age at baseline ($\beta = -0.02$) ($p = 0.026$), gender (male = 1; $\beta = 0.01$) ($p = 0.001$), presence of large tonsils at baseline ($\beta = 4.69$) ($p < 0.001$), change in waist circumference ($\beta = 0.09$) ($p = 0.002$) and persistently large tonsils ($\beta = 5.69$) ($p < 0.001$) over the 2-year period.
Conclusions: Mild OSA in the majority of children does not resolve spontaneously. Subjects with tonsillar hypertrophy, especially boys, should be closely monitored to allow early detection of worsening OSA. Weight control should be stressed in the management of childhood OSA.

Childhood obstructive sleep apnoea (OSA) can lead to a number of important short- and long-term complications including hypertension, ventricular dysfunction, insulin resistance and neurocognitive deficits. The natural history of OSA in children with weight gain and obesity are predictors of worsening of OSA.^{1–4} In contrast, coexisting adenotonsillar hypertrophy and obesity suggest that the weight gain and obesity are not predictors of worsening of OSA.⁵ In contrast, coexisting adenotonsillar hypertrophy and obesity suggest that the weight gain and obesity are not predictors of worsening of OSA.⁵ In contrast, coexisting adenotonsillar hypertrophy and obesity suggest that the weight gain and obesity are not predictors of worsening of OSA.⁵

Early studies were mostly based on subjective data from parent-reported questionnaires.^{6–8} In a study of 14 children with habitual snoring at 1.5 years of age, no longer did so 2 years later.⁹ Uchritz *et al* performed a 1-year follow-up study which also reported similar results.¹⁰ In addition, the investigators found that low maternal education, household smoking and low snoring at baseline were predictors of persistent snoring in children.¹⁰ Two other studies in

children suggested that more children with primary snoring did not progress to OSA over a course of several years.^{11,12} To our knowledge, there is only one study that has examined the natural history of children with mild OSA.¹³ In that study, 13 of seven children studied with mild OSA at the initial survey had significant disease progression. However, the investigators could not determine predictors for worsening of OSA and the small sample size and lack of a control group. Understanding factors that are associated with disease worsening would allow a more scientific approach for future patient care. A scientific nature of the condition would mandate planning of potentially influencing treatment planning in an early stage. We aimed in this study to examine the natural history of mild childhood OSA and to investigate important risk factors that may influence disease progression.

SUBJECTS AND STUDY DESIGN
 This was a prospective longitudinal follow-up study, an extension of our Childhood OSA Prevalence (COP) study which was initiated in 2005 with the aim of evaluating the prevalence of OSA in Hong Kong Chinese children aged 6–15 years.¹⁴ The COP study was a community-based study in which children in two districts in OSA were randomly selected from 13 primary schools in two districts in the territory. It was a two-phase study involving an OSA questionnaire screening followed by overnight polysomnography (PSG) confirmation and adenotonsillar size assessment by a paediatric otolaryngologist. Subjects identified as having mild OSA (obstructive apnoea-hypopnoea index (OAHI) 1–5) and confirmed not to have received any treatment for their condition in the follow-up study. They completed the same OSA questionnaire and underwent the same set of investigations as previously.

Questionnaire
 A validated sleep questionnaire based on parental reporting information and other OSA-related following information:
 ▶ Snoring frequency and other OSA-related symptoms rated on a 5-point rating scale (0 = none, 1 = rarely (0–1 nights per month), 2 = sometimes (1–2 nights per week), 3 = often (1–2 nights per week), 4 = frequently (>2 nights per week), 5 = habitual snoring was defined as snoring frequency

Li et al, Thorax. 2010;65:27-3

Histoire naturelle et facteurs prédictifs

- 45 enfants de 6-13 ans
- IAH « léger » compris entre 1 et 5 /h
- 2^{de} polysomnographie 2 ans après
- Aggravation chez 29%
- Facteurs associés à l'aggravation
 - Jeune âge
 - Grandes amygdales (persistance de l'hypertrophie : 53%)
 - Sexe mâle
 - Augmentation du périmètre abdominal entre les 2 (mais pas le BMI en z-score)
- Mauvaise corrélation entre progression vers un SAOS polysomnographique et symptômes cliniques

Conclusions

- Chirurgie AA efficace sur polysomnographie
- Mais seulement 27% ont un enregistrement normal
- Identifier ceux à risque d'AOS résiduel
 - > 7 ans
 - Obèses
 - Non obèse avec IAH pré AA élevé
- Près d'un tiers des SAOS « légers » d'aggravent
 - Nécessité d'une « surveillance armée » chez garçon, jeune, hypertrophie amygdales persistante et probablement les plus gros
 - Etude prospective (Childhood AdenoTonsillectomy Study) en cours pour évaluer la morbidité chez enfant avec IAH $\leq 2/h$

A lire aussi...

Diagnostic Testing of Patients Suspected of Primary Ciliary Dyskinesia

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Rationale: Electron microscopy (EM) of ciliated epithelium is widely used to diagnose primary ciliary dyskinesia (PCD). Ciliary beat frequency (CBF) has been used to screen samples to determine whether EM is indicated. Beat pattern analysis has been advocated as an additional diagnostic test. Neither has been subject to formal review.

Objectives: To determine the ability of CBF and beat pattern analysis to predict EM-diagnosed PCD. Methods: CBF calculation and beat pattern analysis, using high-speed video microscopy, and EM were performed on nasal tissue from 371 patients consecutively referred to the Leicester Royal Infirmary for diagnostic assessment for PCD. With EM as the "gold standard," receiver operating characteristic (ROC) curves were constructed and diagnostic assessment for PCD, with EM as the "gold standard," sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values were calculated for CBF less than 11 Hz, ciliary beat frequency greater than or equal to 2, at least 90% of ciliated edges beating dykinetically, and an immotility index equal to or exceeding 10%.

Measurements and Main Results: PCD was excluded in 270 patients and confirmed in 70 by EM. The sensitivity, specificity, PPV, and NPV for CBF less than 11 Hz were 87.1, 77.2, 50.0, and 95.8%, respectively. These values were higher for ciliary dyskinesia scores equal to or exceeding 2 (92.5, 97.6, 91.2, and 98.0%) and when at least 90% of ciliated edges were dykinetic (97.1, 95.3, 84.6, and 99.2%). ROCs confirmed that the ciliary dyskinesia score and percentage of ciliated edges were superior screening indices compared with dykinetic edges were superior screening indices compared with CBF and the immotility index.

Conclusions: The use of CBF alone to screen which biopsies should have EM will result in a significant number of missed diagnoses. Ciliary beat pattern analysis is a more sensitive and specific test for PCD with higher PPV and NPV.

Keywords: cilia; primary ciliary dyskinesia; bronchiectasis; ciliary beat pattern; sinusitis

Efficient clearance of mucus from the upper and lower respiratory tract by coordinated ciliary movement is a major component of host defense. This system relies on coordinated beating of cilia with a normal beat pattern and beat frequency (1, 2). The importance of functioning cilia is highlighted in patients with primary ciliary dyskinesia (PCD), whose cilia are either immotile or beat with an abnormal pattern that fails to

(Received in original form March 26, 2009; accepted in final form November 11, 2009)

Supported by Action Medical Research, Cystic Fibrosis Trust (UK). We are very sad to report the death, in a car accident, of Dr. Wendy Stanward, who was an outstanding pediatrician and researcher.

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Am J Respir Crit Care Med Vol 181, pp 1057-1063, 2010. doi:10.1164/rccm.200903-0493OC

Originally published in *Am J Respir Crit Care Med* on November 12, 2009

Internet address: www.atsjournals.org

AT A GLANCE COMMENTARY

Scientific knowledge on the subject of electron microscopy of ciliated epithelium, is widely used to diagnose primary ciliary dyskinesia. Ciliary beat frequency (CBF) has been used to screen samples to determine whether electron microscopy is indicated and ciliary beat pattern analysis has been advocated as an additional test. Neither test has been subject to formal review.

What This Study Adds to the Field

The use of CBF alone to screen for biopsies requiring further assessment by electron microscopy will result in missed diagnoses.

transport mucus. Many of those affected remain undiagnosed and many are diagnosed only after years of chronic respiratory symptoms. Severe lung disease is not uncommon in older patients (3-6).

The diagnosis of PCD in patients with a typical clinical phenotype relies on a number of tests, most of which have not been subject to formal review. Diagnostic testing has traditionally been based on measurement of ciliary beat frequency (CBF) and electron microscopy (EM) (7). EM is used to detect defects in the ciliary axoneme and is the most widely used diagnostic test for PCD, although a phenotype of PCD with no obvious ultrastructural defect has been described (9). A CBF of less than 11 beats per second (<11 Hz) has been suggested as a cutoff value, with only those with lower beat frequency proceeding to EM (7). It has been shown, using slow motion video analysis, that specific ultrastructural abnormalities of axoneme seen in PCD result in characteristic abnormalities of ciliary beat pattern (10, 11). Beat pattern analysis has been adopted by a number of diagnostic centers as a method of screening biopsies in addition to CBF measurement (5). However, the ability of CBF and ciliary beat pattern analysis to predict an EM diagnosis of PCD has not been determined.

Therefore, the primary aim of this article was to determine the sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of CBF measurement and ciliary beat pattern analysis in predicting PCD diagnosed by EM. Our group receives referrals, almost exclusively from pediatric and adult respiratory specialists, for diagnostic testing of patients who are thought to have PCD on clinical and demographic grounds. In this article, we also describe the prevalence of clinical and demographic features among referrals who go on to receive positive and negative EM diagnoses. We have observed that many referrals who do not have EM evidence of PCD exhibit areas of ciliated epithelium with a dykinetic beat pattern. In many of these dykinetic areas, CBF is also low. We therefore report comparative ultrastructural

Am J Respir Crit Care Med 2010; 181: 1057-1063
DOI: 10.1164/rccm.200903-0493OC
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A 20-year experience of electron microscopy in the diagnosis of primary ciliary dyskinesia

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ABSTRACT: Transmission electron microscopy (TEM) analysis of ciliary ultrastructure is classically used for the diagnosis of primary ciliary dyskinesia (PCD). We report our extensive experience of TEM analysis in a large series of patients in order to evaluate its feasibility and results.

TEM analysis performed in 1,149 patients with suspected PCD was retrospectively reviewed. Biopsies (1,450) were obtained from nasal (44%) or bronchial (56%) mucosa in children (66.5%) and adults (33.5%). TEM analysis was feasible in 71.4% of patients and showed a main defect suggestive of PCD in 29.9%. TEM was more feasible in adults than in children, regardless of the biopsy site. Main defects suggestive of PCD were found in 76.5% of patients with sinopulmonary symptoms and in only 0.4% of patients with isolated upper and lower respiratory tract infections. The defect pattern was similar in children and adults, involving dynein arms (81.2%) or central complex (CC) (18.8%). Situs inversus was never observed in PCD patients with CC defect. Kartagener syndrome with normal ciliary ultrastructure was not an exceptional condition (10.2% of PCD).

In conclusion, TEM analysis is feasible in most patients and is particularly useful for PCD diagnosis in cases of sinopulmonary syndrome of unknown origin.

KEYWORDS: Airways, cilia, dynein, Kartagener syndrome, situs inversus, ultrastructure

Cilia, evolutionarily conserved structures, are classified according to their cytoskeleton core called axoneme: primary cilia with sensory function, and motile cilia ensuring fluid transport. Defects in primary cilia have been associated with a growing number of rare genetic diseases (polycystic kidney disease, Bardet-Biedl syndrome and retinitis pigmentosa), whereas motile cilia are involved in the most prominent ciliopathy called primary ciliary dyskinesia (PCD) [1].

PCD is a congenital disorder with an estimated prevalence of 1:15-30,000 live births [2] and is due to impaired mucociliary transport resulting from a lack of ciliary motion leading to chronic respiratory infections. The clinical features of PCD, usually beginning in early childhood, are characterised by bronchiectasis and chronic sinusitis, sometimes associated with situs inversus and male sterility [3]. The axoneme of motile cilia is composed of nine peripheral doublet microtubules with attached inner and outer dynein

arms (DA and ODA, respectively) and radial spokes, surrounding a central complex (CC) consisting of two central microtubules surrounded by the central sheath. PCD is a heterogeneous group of genetic disorders usually transmitted as autosomal recessive traits with various ciliary ultrastructural defects [3]. The absence of pathognomonic clinical and laboratory signs makes PCD difficult to recognise; this disease is of prime importance to recognise this disease in order to start appropriate therapy of respiratory tract infections and minimise lung damage. In this context, the finding by PCD carry most respiratory cilia of patients with PCD that ultrastructural defects has opened up new ways to manage this disease, especially by providing the first objective test of diagnostic value.

Transmission electron microscopy (TEM) analysis of cilia is still a relevant technology now frequently combined with new innovative investigations for the diagnosis of PCD. However, TEM analysis is an arduous and expensive

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Received: March 22, 2009
Accepted after revision: Sept 29, 2009
First published online: Oct 19, 2009

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

VOLUME 36 NUMBER 5

EUROPEAN RESPIRATORY JOURNAL

L'analyse de la fréquence de battement ciliaire est insuffisante, en particulier en cas d'anomalies des micr centraux ou de désorientation ciliaire.
Intérêt de l'analyse fine du battement en vidéo haute fréquence