



Interasma since 1954

Final Programme



WCA 2012

XXI WORLD CONGRESS of ASTHMA

Québec City Convention Centre

August 18-21, 2012

Québec City,
Canada

www.wca-2012.com

Organized by:  Interasma Global Asthma Association



PROGRAMME AT A GLANCE

SATURDAY, 18 AUGUST, 2012				SUNDAY, 19 AUGUST, 2012			
REGISTRATION				EXHIBITIONS			
	Room A	Room B	Room C	Room A	Room B	Room C	
8:00							
8:30							
9:00				Keynote Lecture Epidemiology of asthma: Why is asthma prevalence still rising?			
9:15				Break			
9:30				Break-Out Session Asthma pathophysiology I	Break-Out Session The Genetics of asthma	Break-Out Session Asthma, rhinitis and sinusitis guidelines	
11:00				Break			
11:15				Break-Out Session Asthma pathophysiology II	Break-Out Session Biomarkers and asthma	Break-Out Session Pediatric asthma	
12:00							
12:30							
13:00				Advances in the Treatment of Asthma and Allergic Rhinitis - Where are we today? Non-accredited Sponsored Symposium	Symposium: EAC	Oral Presentations Clinical Management	
13:30	Joint meeting of the Société de Pneumologie de langue française, du Réseau en santé respiratoire du FRQS et de l'Association des Pneumologues de la province de Québec	Society Symposium: ACAAI	Oral Presentations Allergy A	Keynote Lecture Frederic E. Hargreave Memorial Lecture			
14:00			Oral Presentations Asthma A				
14:15							
14:30				Break-Out Session Pharmacologic treatment of asthma I	Break-Out Session Asthma exacerbations in adults	Society Symposium: CTS	
15:00				Break			
15:30				PRO - CON Debate Are LABA detrimental to asthma? Are dust-mite exposure preventative measures useful?	Symposium: WAO	Oral Presentations Allergy B	
15:45				Oral Presentations Asthma C	Society Symposium: KAAACI	Oral Presentations Asthma B	
16:00							
16:30	Joint Symposium of the Canadian Network for Respiratory Care and the Réseau québécois de l'asthme et de la MPOC	National Society Symposium: CSACI	Oral Presentations Pediatrics A				
17:00							
17:15							
17:30							
18:00							
18:15							
18:30	Official Opening Opening Lecture The future of learning and health care improvement (How to improve knowledge translation into current care)						
19:00	Welcome Reception						
20:00							

L'ASTHME DANS SES MOTS ...

Bernard Pigearias

Vice-président de la Société de Pneumologie de Langue Française

Asthme, curieux mot qui semble afficher une origine très hellénisante.

Asthme, curieux mot qui peut évoquer une phonétique très arabisante.

Qu'est-ce un asthme ?

Qu'est-ce un asthmatique ?

Maladie d'une fonction vitale,

Maladie d'une vie entière à très haut risque pour certains que l'on saura identifier.

Mesurer la fonction pour définir le pathologique,

Appréhender la clinique pour assurer la maîtrise de cette pathologie du souffle coupé...

Mais le poumon commence au bout du nez : « l'organe respiratoire » est un.

Sa pathologie est commune, son traitement sera global, uniciste.

Organe en relation directe avec l'environnement dont il va extraire cet oxygène pour répondre aux besoins du vivant, il va en subir les agressions physiques, chimiques.

Et il réagira, parfois trop : cette autre réaction littéralement cette allergie (allos/ergein autre travail) utile dans un premier temps pour protéger de ce qui n'est pas soi, va devenir délétère dans sa « sur-réaction ».

Ceci concernera la vie de l'asthmatique au quotidien, son quotidien privé comme son quotidien professionnel.

... un voyage dans l'histoire de la médecine et de la littérature où se croisent Maïmonide, Proust, Laënnec, Zola ...

... un voyage sémantique en centre de la maladie humaine la plus humaine des maladies de l'homme, celle où cet humus

respirant, l'homme, perd son souffle pour le recouvrer avec l'aide de son médecin.

PHÉNOTYPES ET BIOMARQUEURS DE L'ASTHME : OPPORTUNITÉS THÉRAPEUTIQUES

Louis-Philippe Boulet, MD, FRCPC, FCCP

Institut universitaire de cardiologie et de pneumologie de Québec, Québec, Canada

En 2007, Flood-Page et coll. (1) ont publié dans l'*AJRCCM* une étude sur le mépolizumab, un anti-monoclonal anti-interleukine-5 afin de déterminer si l'administration de ce médicament pouvait être bénéfique en ajout aux corticostéroïdes inhalés dans l'asthme. Cette étude tout comme une étude subséquente de Kips (2), n'ont pas démontré d'effets bénéfiques de cette médication. Toutefois, une étude publiée dans le *New England Journal of Medicine* en 2009 par Nair et coll. (3) a bien démontré que cette médication pouvait réduire de façon significative les exacerbations de l'asthme dans une sous-population de patients avec asthme sévère. La principale différence entre ces différentes études était que dans le cas des études négatives, peu de patients avaient une éosinophilie bronchique alors que dans la dernière, ces patients avaient >3% d'éosinophiles dans l'expectoration induite à au moins 3 occasions, confirmant leur phénotype d'asthme éosinophilique. Ces études démontrent que si on ne tient pas compte du phénotype (ou endotype) de l'asthme, lors d'études portant sur certains médicaments ciblant un mécanisme précis, on peut conclure à tort que ce médicament n'est pas utile. Dans le cas ci-haut, l'éosinophilie de l'expectoration induite est donc un marqueur de réponse positive au traitement avec les anti-IL5.

Le traitement de l'asthme selon les guides de pratique

Les guides de pratique nationaux et internationaux récents suggèrent des algorithmes de traitement de l'asthme, principalement fondés sur l'utilisation des corticostéroïdes comme principale médication anti-inflammatoire, à laquelle nous pouvons ajouter d'autres médications en association, telles les bronchodilatateurs β_2 adrénergiques à longue durée d'action, ou dans certain cas, les antagonistes des leucotriènes (4). Cependant, il a déjà été démontré que la réponse aux différentes médications utilisées pour traiter de l'asthme peut varier d'un sujet à l'autre (5). Ceci est particulièrement vrai pour l'asthme sévère, condition où différents mécanismes peuvent jouer un rôle.

Phénotypes de l'asthme

Au cours de la dernière décade, plusieurs publications ont paru pour déterminer la nature des différents phénotypes asthmatiques. On peut définir un « phénotype » comme un groupe de caractéristiques observables chez un individu ou dans une population, résultant de l'interaction entre leur génotype et de l'environnement. L'avantage de caractériser ces différents types d'asthme est non seulement de favoriser la compréhension des mécanismes impliqués, mais également de voir si les traitements peuvent mieux ciblés.

Par le passé, l'asthme a été souvent décrit comme étant d'origine allergique ou non allergique, de multiples caractéristiques les distinguant (6). Plus récemment, tel que revu par Wenzel (7), de nombreuses sous-catégories d'asthme ont été définies selon leur phénotype clinique ou physiologique ou encore selon les facteurs déclenchants responsables et enfin selon le type d'inflammation bronchique présent (Table 1). D'autres études de cohortes ont également caractérisé certains sous-groupes d'asthmatiques qui présentaient des caractéristiques communes selon les symptômes et l'inflammation bronchique sous-jacente (8,9). Enfin, on peut également distinguer les phénotypes de l'asthme selon les co-morbidités associées, telles la rhinite qu'elle soit allergique, non allergique ou polypoïde, la rhinosinusite chronique, l'obésité, le tabagisme ou encore la maladie pulmonaire obstructive chronique associée ou encore différentes complications de l'asthme (ex : ABPA) (10).

Du phénotype à l'endotype

Non seulement l'analyse du phénotype de l'asthme peut suggérer des modifications à la thérapie, mais on tente maintenant également de définir également les « endotypes » de l'asthme qu'on peut définir comme étant les caractéristiques cliniques associées à certains mécanismes physiopathologiques particuliers chez certains types d'asthme. À titre d'exemple dans l'asthme d'apparition précoce et d'origine allergique, les biomarqueurs tel l'oxyde nitrique de l'air expiré et les IgE spécifiques, de même que la périostine peuvent être élevés alors que dans l'asthme persistant éosinophilique on retrouve bien sûr de grandes quantités éosinophiles dans l'expectoration induite (11). On peut retrouver l'éosinophilie aussi dans l'asthme associé à l'aspergillose broncho-pulmonaire allergique, mais dans ce cas on retrouve également des anticorps de types IgE et IgG spécifiques à l'aspergillus. Dans différents types d'asthme tels celui chez l'obèse ou de la personne âgée, il n'y a pas encore eu de biomarqueur clairement identifié cependant.

Pourquoi rechercher des biomarqueurs?

On peut penser que la recherche de biomarqueurs pourra aider au traitement de l'asthme en permettant : 1. Mieux définir les populations qui pourront bénéficier le plus d'un médicament particulier (pharmacogénétique); 2. Trouver de nouveaux traitements et comment mieux les administrer (pharmacocinétique); 3. Prédire l'évolution de la maladie (justification de traitements prolongés ou plus intenses) (diagnostic et pronostic); 4. Monitorer les effets d'un traitement (pharmacodynamique); 5. Prédire le devenir clinique (cible reflétant la maladie); 6. Monitorer les effets secondaires (biomarqueurs de sûreté); 7. Identifier les nouvelles voies biologiques impliquées dans la pathologie de la maladie (12).

Pour l'asthme, de très nombreux médiateurs, cytokines et divers mécanismes sont impliqués et particulièrement dans l'asthme sévère certains de ces mécanismes peuvent être prédominants. Dans le cas de l'asthme allergique en particulier, différents mécanismes associés à la stabilisation des mastocytes ou à l'antagonisme de mécanismes associés à la SYK-kinase, les c-Kit et le plus connu bien sûr, celui des IgE pour lequel l'omalizumab a été développé sont des cibles qui ont été déjà mentionnées. Pour l'omalizumab, pour l'instant les patients atopiques avec taux d'IgE élevés semblent la population cible pour ce type de médication, mais encore ici, il est difficile de prédire qui répondra de façon plus marquée au traitement (13).

Traitement selon le phénotype inflammatoire de l'asthme

Présentement avec le développement des mesures non invasives de l'inflammation bronchique telle l'expectoration induite et le NO de l'air expiré, il est possible de mieux définir les phénotypes inflammatoires de l'asthme. À cet effet, on y distingue l'asthme de type éosinophilique habituellement associé à des facteurs environnementaux tels la sensibilisation aux allergènes ou certains agents sensibilisants au travail, l'asthme neutrophilique, qui peut faire suite à des infections virales ou bactériennes ou tabagismes, ou des polluants atmosphériques, de même qu'en association avec l'obésité ou chez les athlètes. Dans l'asthme paucigranulocytopenique, on retrouve peu d'inflammation.

Les études récentes ont bien démontré que l'asthme éosinophilique répondait mieux au traitement corticostéroïdien alors que l'asthme paucigranulocytopenique ou neutrophilique y répondent moins (14). De plus, tel que démontré

également par Green et coll. (15) et Jarayam et coll. (16), un suivi du traitement de l'asthme modéré à sévère par l'expectoration induite visant à maintenir l'éosinophilie de l'expectoration induite des taux normaux ou quasi normaux peut permettre de réduire les exacerbations de l'asthme, particulièrement celles d'origine éosinophilique (16). Il a été également démontré que les stratégies basées sur l'analyse de l'expectoration induite peuvent améliorer la fonction pulmonaire, diminuer les exacerbations de patients avec MPOC et possiblement réduire le remodelage bronchique. Pour ce qui est du NO expiré, cette mesure pourrait également être utile, mais semble moins bonne pour prédire la réponse au traitement que l'éosinophilie de l'expectoration induite.

Autres phénotypes/endotypes de l'asthme et leur influence sur le traitement

Certaines études sur l'asthme sévère ont suggéré que le facteur de nécrose tumorale α (TNF- α) pourrait possiblement prédire la réponse au traitement chez certains patients présentant une augmentation de l'expression de cette cytokine au niveau bronchique (17). Malheureusement, les études subséquentes n'ont pas démontré d'utilité de ce biomarqueur. Plus récemment, Corren et coll. (18) ont suggéré que la périostine pourrait être un marqueur de réponse à un anticorps monoclonal, le librikizumab (anti-interleukine-13). Des études sont donc à faire sur ce type de médiateur et d'autres biomarqueurs similaires afin de déterminer s'ils pourraient être utiles dans le traitement de certains sous-types d'asthme sévère.

Nouvelle méthode de mesure de composante de l'air expiré

Quoi que jusqu'à maintenant les études sur la mesure des médiateurs et cytokines dans le condensat de l'air expiré ont été considérées peu utiles dans le suivi de l'asthme, de nouvelles méthodes telles l'olfactométrie semblent prometteuses (19). Pour l'instant, ces méthodes requièrent un matériel peu disponible et une analyse fort complexe des différents composés volatils organiques de l'air expiré. Une meilleure connaissance de la valeur de ces techniques et le développement de méthodes plus simples et moins coûteuses pourront certainement être utiles (19,20). À cet effet, des initiatives d'envergure telles U-BIOPRED en Europe sont en cours actuellement afin d'identifier de possibles biomarqueurs sur divers matériels biologiques afin d'aider au phénotypage et à la prédiction de l'efficacité thérapeutique des médicaments (20). Il ne faut pas oublier qu'il est possible qu'une association des marqueurs puisse être plus efficace qu'un marqueur seul pour caractériser les phénotypes et la réponse au traitement.

Conclusion

L'asthme est de plus en plus considéré comme étant un ensemble de pathologies avec différentes présentations cliniques et également différents mécanismes. La recherche sur les biomarqueurs pourra possiblement faire progresser le diagnostic, l'établissement de phénotypes/endotypes et l'ajustement thérapeutique de maladies comme l'asthme, la MPOC et possiblement d'autres maladies respiratoires. Les relations restent à établir entre ces différents marqueurs-cibles et les différentes entités.

Tableau 1. PHÉNOTYPES DE L'ASTHME

Phénotypes cliniques ou physiologiques, définis en fonction

- De la sévérité
- Du nombre d'exacerbations
- De l'atteinte fonctionnelle
- De la résistance au traitement
- De l'âge de début

Phénotypes liés à des facteurs déclenchants

- Aspirine, AINS
- Allergènes environnementaux
- Allergènes ou irritants professionnels
- Menstruations
- Effort

Phénotypes inflammatoires

- Inflammation à éosinophiles
- Inflammation à neutrophiles
- Inflammation peu granulocytaire

Adapté de la référence 7.

BIBLIOGRAPHIE

1. Flood-Page P, Swenson C, Faiferman I, Matthews J, Williams M, Brannick L, et coll. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007;176:1062-71.
2. Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HA, Postma DS, et coll. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. *Am J Respir Crit Care Med* 2003;167:1655-9.
3. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, Hargreave FE, et coll. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985-93.

4. Lougheed MD, Lemiere C, Ducharme FM, Liciskai C, Dell SD, Rowe BH, et coll. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. *Can Respir J* 2012;19:127-64.
5. Szeffler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, et coll. Significant variability in response to inhaled corticosteroids for persistent asthma. Asthma Clinical Research Network of the National Heart Lung, and Blood Institute. *J Allergy Clin Immunol.* 2002;109:410-8.
6. Barnes PJ. Intrinsic asthma: not so different from allergic asthma but driven by superantigens? *Clin Exp Allergy.* 2009;39:1145-51.
7. Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet* 2006;368:804-13.
8. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et coll. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med.* 2008;178:218-24.
9. Jarjour NN, Erzurum SC, Bleecker ER, Calhoun WJ, Castro M, Comhair SA, et coll. Severe asthma: lessons learned from the National Heart, Lung, and Blood Institute Severe Asthma Research Program. *Am J Respir Crit Care Med.* 2012;185:356-62.
10. Boulet LP. Influence of comorbid conditions on asthma. *Eur Respir J.* 2009;33:897-906.
11. Wenzel S. Severe asthma: from characteristics to phenotypes to endotypes. *Clin Exp Allergy* 2012;42:650-8.
12. Cazzola M, Novelli G. Biomarkers in COPD. *Pulm Pharmacol Ther* 2010;23:493-500.
13. Holgate S, Buhl R, Bousquet J, Smith N, Panahloo Z, Jimenez P. The use of omalizumab in the treatment of severe allergic asthma: A clinical experience update. *Respir Med* 2009;103:1098-113.
14. Pavord ID, Sterk PJ, Hargreave FE, Kips JC, Inman MD, Louis R, Pizzichini MM, Bel EH, Pin I, Grootendorst DC, Parameswaran K, Djukanović R. Clinical applications of assessment of airway inflammation using induced sputum. *Eur Respir J Suppl* 2002;37:40s-43s.
15. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, Wardlaw AJ, Pavord ID. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715-21.
16. Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemièrè C, Pizzichini E, et coll. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. *Eur Respir J* 2006;27:483-94.
17. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, et coll. Evidence of a role of tumor necrosis factor alpha in refractory asthma. *N Engl J Med.* 2006 Feb 16;354(7):697-708.
18. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et coll. Lebrikizumab treatment in adults with asthma. *N Engl J Med.* 2011;365:1088-98.
19. Fens N, Zwinderman AH, van der Schee MP, de Nijs SB, Dijkers E, Roldaan AC, et coll. Exhaled breath profiling enables discrimination of chronic obstructive pulmonary disease and asthma. *Am J Respir Crit Care Med.* 2009;180:1076-82.
20. Auffray C, Adcock IM, Chung KF, Djukanovic R, Pison C, Sterk PJ. An integrative systems biology approach to understanding pulmonary diseases. *Chest* 2010;137:1410-6.

PHARMACOGENETICS AND PEDIATRIC ASTHMA

Dr Sophie Laberge

Research Center, CHU Sainte-Justine, Department of Pediatrics, University of Montreal, Canada

Current treatment guidelines recommend the use of inhaled corticosteroids as the first-line long-term controller asthma medication in children. Inhaled short acting β_2 -agonists (SABA) are the preferred reliever for acute asthma attack whereas long-acting β_2 -agonists (LABA) can be used in combination with inhaled corticosteroid therapy to provide long-term asthma control. Although most asthmatic patients derive some benefit from these drugs, there is heterogeneity of therapeutic responses to each of these agents even in patients with an apparently identical clinical phenotype. Although the basis of this variable drug treatment response is not known with certainty, it is clear this is in large part genetically determined (1). This is not surprising given that asthma arises from a complex series of interactions between key genetic and environmental factors. Multiple pharmacogenetic studies have focused on the role of genetic variants in the response to β_2 -agonists, since SABA are used by virtually all patients as rescue bronchodilator. Moreover, regular treatment with β_2 -agonists may be associated with tachyphylaxis due to receptor desensitization raising concerns about the potential long-term adverse effects of SABA and LABA in some individuals. LABA were shown to be associated with an increased risk of asthma exacerbation in a subset of asthmatic patients. Pharmacogenetic studies of asthma therapy may help to identifying these at-risk individuals. Here, we review some of the published data on the genetic determinants underlying the response to β_2 -agonists in particular in asthmatic children. We also present the results of our own studies on the role of two novel candidate genes, *PDE4D* and *RGS5*, on the acute response to salbutamol in children with asthma.

The β 2-adrenergic receptor is a G protein-coupled receptor (GPCR) the activation of which leads to an increase in the levels of adenylyl cyclase, an enzyme that catalyses the conversion of ATP to cyclic AMP. Cyclic AMP in turns binds to protein kinase A, which activates a downstream cascade of target proteins resulting in airway smooth muscle relaxation. A number of polymorphisms in coding and regulatory regions of *ADRB2* gene have been described (2). The Arg16Gly attracted particular attention because it was shown *in vitro* to affect agonist-promoted receptor down-regulation. Initial studies demonstrated that homozygous Arg 16 individuals were more likely to show a positive response to single salbutamol use but experienced deleterious effects to the drug when used on a regular basis (3). Further studies failed to show consistent association between this genetic variant and response to both SABA and LABA. Some *ADRB2* haplotypes but not individual polymorphisms have been associated with response to SABA suggesting that haplotype analysis are required for a more comprehensive analysis of the *ADRB2* gene in bronchodilator response (2, 4). In conclusion, although *ADRB2* is the most studied gene in asthma pharmacogenetics, no clear conclusion as to its functional effects has been reached. Other genetic variants in genes involved pathways independent of the β 2-adrenergic receptor pathway have been found to be associated with β 2-agonist response, in particular in children, including *ARG1* and *GSNOR* genes (5, 6).

We recently investigated the role of genetic variants in *PDE4D* gene as potential predictive factors on the response to a single dose of salbutamol in children with asthma (7). This gene encodes for the predominant phosphodiesterase isoform expressed in airway smooth muscle (ASM) cells. Phosphodiesterase enzymes regulate the cAMP turnover in ASM cells degrading cAMP generated following β 2-adrenergic receptor activation providing thus a pivotal acute feedback mechanism. Genome-wide association study identified *PDE4D* as a highly plausible candidate gene for asthma susceptibility (8). We assessed the bronchodilator response (% change in baseline FEV1) after administration of salbutamol in asthmatic children with airway obstruction. FEV1 % change adjusted for baseline FEV1 values was significantly different between genotypes of rs1544791 G/A polymorphism and -1345 C/T (rs1504982) promotor variation. The association remained significant with inclusion of age, sex, atopy, and controller therapy into multivariate model. Our work identified new genetic variants implicated on modulation of asthma treatment, one of them (rs1544791) previously associated with asthma phenotype.

We next focused our investigation on the impact of genetic variants of the *RGS5* gene on the response to salbutamol in a similar cohort of asthmatic children. Recent studies support a role for *RGS5* in regulating the bronchomotor tone in asthma. In addition, tolerance to β 2-agonist treatment has been associated with altered lung tissue expression of regulator of G protein signalling 5 (*RGS5*) (9). The most well-known function of regulators of G proteins signaling is to inhibit signaling output from G protein-coupled receptor activation. Airway smooth muscle contraction and relaxation are mainly mediated by Ca²⁺-dependent pathways following agonist-G- proteins coupled receptor activation. In human ASM cells, *RGS5* protein is the dominant RGS molecule expressed. Our work identified new genetic variants in *RGS5* gene that influence the bronchodilator response to a single dose of salbutamol in asthmatic children (unpublished results). Additive effect on the treatment outcome was also seen with specific polymorphism of the *PDE4D* gene suggesting gene-gene interaction on response to salbutamol.

In summary, studies have identified several genetic variants in genes involved in β 2-adrenergic receptor signalling pathways and in other pathways, that may influence the response to β 2-agonists.

1. Drazen JM et al. heterogeneity of therapeutic responses in asthma. *Br Med Bull* 2000;56:1054-1070.
2. Hawkins Ga et al. Sequence, haplotype, and association analysis of *ADRB2* in a multi-ethnic case-control study. *Am J Resp Crit Care Med* 2006;174:1101-9.
3. Tse SM et al. The pharmacogenetics and pharmacogenomics of asthma therapy. *The Pharm J* 2011;11:383-392.
4. Drysdale CM et al. Complex promotor and coding region beta2-adrenergic receptor haplotypes alter receptor expression and predict *in vivo* responsiveness. *Proc natl Acad Sci USA* 2000;97:10483-10488.
5. Litonjua AA et al. *ARG1* is a novel bronchodilator response gene: screening and replication in four asthma cohorts. *Am J Respir Crit Care Med* 2008;178:688-694.
6. Moore PE et al. Genetic variants of *GSNOR* and *ADRB2* influence response to albuterol in African-American children with sever asthma. *Ped Pulm* 2009;44:649-654.
7. Labuda M et al. Phosphodiesterase type 4D gene polymorphism : association with the response to short-acting bronchodilators in paediatric asthma patients. *Mediator of Inflammation* 2011;id 301695
8. Himes BE et al. Genome-wide association analysis identifies *PDE4D* as an asthma-susceptibility gene. *Am J Hum Gen* 2009; 84:581-593.
9. Yang Z et al. B-agonist associated reduction in *RGS5* expression promotes airway smooth muscle hyperresponsiveness. *J Biol Chem* 2011;286:11444-55.

PROMOTING ASTHMA SELF-MANAGEMENT: NOT WITHOUT A PLAN

Francine M. Ducharme

Most children with asthma have poor disease control, partly attributable to suboptimal adherence of physicians to guidelines and of patients to medical recommendations. The challenge is to introduce children to guided self-management, that is, asthma education, medical review and the provision of a written action plan.

Written action plan as add-on to management education. There is clear evidence that comprehensive guided self-management improves health outcomes over usual care.¹ However, the independent contribution of a written plan to the overall effect remained to be documented.²

Written action plan as a unique self-management tool. When comparing guided self-management with and without an action plan, that addition of a plan reduced acute care visits, absenteeism, nocturnal awakenings, and symptoms.³ Moreover, a Cochrane review concluded that symptom-based plans were superior to peak flow-based plans in children to prevent acute care visits and achieved children's preference.⁴

Incorporating written action plan in clinical practice. Yet, delivery of action plans remains low in part due to the limited time and competing demands during typical medical visits. We develop a written self-management plan based on available scientific evidence and expert opinions that was clear and perceived relevant by children, adolescents, and their parents.⁵ Available in French and English, the plans are divided in three control zones identified by symptoms (optional peak flow values) and symbolised by traffic lights. By incorporating the prescription and chart copies in the triplicate format, they were designed to facilitate dispensing by physicians in both the clinic and acute care settings.

Written action plan in the ED setting Whether providing written action plan is useful when concurrent asthma education and medical review is at best limited, was unclear. In a randomized controlled trial, the provision of the triplicate written action plan significantly increased patient adherence to inhaled and oral corticosteroids and asthma control. Interestingly, it also improved physicians' recommendation for maintenance fluticasone and medical follow-up, supporting its independent value in the acute-care setting.⁶

The best way to achieve guided self-management remains a multifaceted approach. Yet, when other elements of guided self-management cannot be provided concurrently, a written action plan with prescription may be one of the simplest and cheapest effective means to improve guidelines implementation by physicians, patients' self-management and asthma control.

References

1. Coffman JM, Cabana MD, Halpin HA, Yelin EH. Effects of asthma education on children's use of acute care services: a meta-analysis. *Pediatrics* 2008;121 (3):575-86.
2. Lefebvre F, Piper M, Weiss K, Mark D, Clark N, Aronson N. Do written action plans improve patient outcomes in asthma? An evidence-based analysis. *J Fam Pract* 2002;51 (10):842-8.
3. Agrawal SK, Singh M, Mathew JL, Malhi P. Efficacy of an individualized written home-management plan in the control of moderate persistent asthma: a randomized, controlled trial. *Acta Paediatr* 2005;94 (12):1742-6.
4. Zemek R, Bhogal SK, Ducharme FM. Systematic review of randomized controlled trials examining written action plans in children: What is the plan? *Arch Pediatr Adolesc Med* 2008;162 (2):157-63.
5. Ducharme FM, Noya F, McGillivray D, Resendes S, Ducharme-Benard S, Zemek R, et al. Two for one: a self-management plan coupled with a prescription sheet for children with asthma. *Can Respir J* 2008;15 (7):347-54.
6. Ducharme FM, Zemek RL, Chalut D, McGillivray D, Noya FJ, Resendes S, et al. Written action plan in pediatric emergency room improves asthma prescribing, adherence, and control. *Am J Respir Crit Care Med* 2011;183 (2):195-203.

HOW TO IMPROVE TREATMENT ADHERENCE IN ASTHMA

Lyne Guénette

Introduction

Developing new drugs is a very long and expensive process to produce what we can expect to be fairly safe and effective drugs. However, when a drug is marketed, its acceptability, how prescribers and patients will use it and its effectiveness in real-life settings is relatively unknown. Will patients adhere to the treatment? Is non-adherence to recommendations a major concern in conditions such as asthma? And finally, what can be done to improve adherence?

At Laval University's Chair on Adherence to Treatments we work on such research questions and they are what will be discussed here.

Medication adherence

Medication adherence is becoming the term replacing the outmoded and somewhat paternalistic *compliance*. Adherence implies a more collaborative approach and is often defined as the "extent to which patient's behaviour coincides with medical or health advice" (Sackett *et al.*, 1977). A new taxonomy describing and defining adherence to medications (Vrijens *et al.*, 2012) distinguishes three concepts: 1) treatment initiation, or the filling of the first prescription; 2) treatment persistence, which pertains to consistency of use over time; 3) treatment implementation or execution, which refers to following the regimen and dosage exactly.

The magnitude of the problem in asthma

In asthma, as in other conditions, treatment initiation is the least studied of all adherence concepts. One study revealed that 8% of patients never filled their inhaled corticosteroids (ICS) prescription (Williams *et al.*, 2007).

Persistence with treatment is the second most studied concept in asthma. One study reported that persistence fell to 10% and 5% after 12 months for combination (ICS + long-acting B2-agonists) and concurrent new users of ICS and long-acting B2-agonists (ICS/LABA in the same inhaler), respectively (Marceau *et al.*, 2006). In another study, cumulative rate of persistence at 12 months was 1.5% for new users of ICS and 27.1% for previous users, while for new and previous users of ICS + LABA, rates were 6% and 44% respectively (Latry *et al.*, 2008).

Treatment implementation is often based upon medication availability measured using prescription claims in administrative health databases. In the last study mentioned, this proportion was 84% for new users of ICS and 66% for previous users (Latry *et al.*, 2008). Over a one-year period, the proportions of days covered was 53% and 19% respectively, taking and not taking, the number of allowable refills into account (Blais *et al.*, 2011).

Intervention study: an example

Our team developed an integrated-care intervention based on a theoretical model and evaluated its impact using a quasi-experimental design. We recruited 349 participants diagnosed with asthma and aged 12 to 45 years from 42 pharmacies in the province of Quebec. Inclusion criteria were use of a short-acting beta-2 agonist more than three times a week, or a corticosteroid (inhaled or oral) regardless of frequency. The intervention was offered over a 12-month period to 108 participants enrolled in one region, while remaining participants received usual care. We interviewed participants at study entrance and again after 12 months, concerning several factors that potentially contribute to improved use of asthma drugs and better health outcomes. We also administered both the Asthma Control Questionnaire (Juniper *et al.*, 1999b) and Mini-Asthma Quality-of-Life Questionnaire (Juniper *et al.*, 1999a). To test the impact of the intervention we measured differences in these factors between exposed and non-exposed participants before and after the intervention.

Population description

Many participants perceived their asthma as very mild or mild (47.3%) (Jobin *et al.*, 2011). A majority (67.3%) expressed negative beliefs concerning asthma (63.3%) and 29.2% had asthma-related low self-confidence. Extent of knowledge varied with 28.9%, 37.5%, 54.2% and 61.9% demonstrating poor knowledge about asthma pathophysiology, symptoms, triggers and drugs respectively.

A considerable proportion (33.2%) perceived no risk of dying due to asthma if drugs were not taken as directed. Only 14.9% had a written action plan and 1.7% used a peak flow meter daily. Only 12.9%, 33.5% and 20.6% respectively had ever attended an asthma education clinic, had ever had a health professional verify their inhalation technique and had ever obtained written information on asthma from a health professional. Fifty-four percent reported low social support for their asthma. These results highlight important barriers to effectively managing asthma.

Factors associated with optimal use

Using criteria based on the then current Canadian guidelines, we assessed the appropriateness of reported asthma drug use (Jobin *et al.*, 2011). Of the 349 participants, 43 (12.3%) were deemed to be using an appropriate asthma

treatment. Patients with sound knowledge about their drugs, those in good, very good or excellent self-perceived health, those who consulted a specialist during the preceding year and those who stated they were short of drugs due to lack of money, were more likely to use their asthma drugs appropriately. These results reveal a great need for effective interventions to improve appropriate use of asthma medications.

Impact of the intervention

A higher percentage of the intervention group improved their asthma control compared to the 241 control individuals (-0.51 vs. -0.25; $p=0.02$). Moreover, those exposed to the intervention bettered their knowledge about asthma (+23.2% vs. +4.8%; $p=0.01$) and appropriate use of asthma drugs (+4.5% vs. -4.6%; $p=0.01$). As for treatment adherence, the exposed group remained quite stable while the others dropped somewhat. These results show that an asthma integrated-care intervention can improve several factors associated with poor asthma outcomes and asthma control.

Conclusion

Despite improvements in asthma treatment and related practices, asthma control remains suboptimal. Effective interventions targeting factors such as the treatment non-adherence associated with suboptimal control can be developed and implemented to improve the situation. An intervention based on a theoretical model and targeting key problems has proven effective at improving several factors associated with poor asthma outcomes and asthma control.

NITRIC OXIDE MONITORING: DOES IT IMPROVE ASTHMA OUTCOMES?

Myron Zitt, MD

*Clinical Associate Professor, Medicine
State University of New York, Stony Brook*

Optimal control of asthma has yet to be achieved globally, as patient quality of life remains inadequate, mortality rates are unacceptably high and costs of care continue to rise. While prevalence rates are increasing, asthma continues to be under-diagnosed and under-treated. Because of disease heterogeneity, it is difficult to determine the type and dose of medication that will afford individual patients the best risk/benefit ratio and to determine which patients will or will not develop irreversible airflow limitation. Identifying asthma phenotypes should improve asthma outcomes, and recognizing poor patient compliance/ adherence, which negatively impacts asthma control, would be extremely beneficial. While inflammation, is an essential component of asthma, current practice parameters do not include its measurement in the diagnosis or management of disease.

Studies employing surrogate markers of inflammation to orchestrate therapy, including induced sputum for eosinophils and methacholine sensitivity, a measure of airways hyper-reactivity, have revealed improved asthma outcomes. While these studies are less invasive than the direct assessment of inflammation with bronchial biopsy and/or evaluation of BAL washings, they are still time consuming and labor intensive and impractical for routine asthma management.

Inducible nitric oxide synthase (iNOS) is produced predominantly by airway epithelial cells and is up-regulated as part of the inflammatory process resulting in elevated levels of fractional exhaled nitric oxide (FENO) in patients with asthma. As there is a positive correlation between airways hyper-reactivity, sputum eosinophilia and FENO, this surrogate marker of eosinophilic inflammation, has significant potential as an "inflammometer" in the management of asthma. Its measurement is simple, quick, non-invasive, and reproducible and has been standardized for clinical use by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) and approved by the US Food and Drug Administration.

In 2011, the ATS published a clinical practice guideline providing a foundation for clinicians in the interpretation of the measurement of FENO in the context of the diagnosis and management of asthma. This guideline has received the official support of the American College of Allergy Asthma and Immunology (ACAAI) and the American Academy of Allergy Asthma and Immunology (AAAAI).

The 2011 guideline indicates that the measurement of FE_{NO} offers complementary information that is not available solely through the use of traditional clinical tools, including history, physical examination, and pulmonary function measurements. It strongly advocates for the use of FE_{NO} to identify patients who are likely to respond to inhaled corticosteroid (ICS) therapy when FE_{NO} is high, and to recognize patients who are unlikely to respond to ICS therapy when FE_{NO} is low. Specific cut points are suggested to aid in interpreting FE_{NO} values. Additionally, FE_{NO} is a biomarker