



Family Physician Airways Group of Canada

In this issue:

- 3 Advair in COPD — results from trial of ICS and LABA study group (TRISTAN)
- 4 Steroids in COPD, what is their role?
- 6 Steroids in COPD? New emerging evidence to support their use
- 7 Impact of inhaled corticosteroid (ICS) therapy on bone mineral density (BMD)
- 8 The Role of the Family Physician in the management of COPD
- 11 Use of FEF
- 11 SPIRIVA, A new anticholinergic bronchodilator for COPD
- 13 Update on new medications: Ketek (telithromycin)

Report from the Chair

We have a new look. We have created a partnership with a number of pharmaceutical companies to allow us money for research, educational forums, representation for Family Physicians nationally and internationally and this newsletter. GSK has provided us their production facilities to create this new look journal and to help us with its dissemination. I am excited about its new look and I look forward to your feedback.

Dissemination, that brings up a very topical issue for me now. The Dissemination and subsequent Implementation of guidelines. More guidelines, just what the Family Physician wanted!

The Canadian COPD guidelines were released this spring in a special supplement in the Canadian Respiratory Journal (May 2003, Volume 10, Supplement A). They are also accessible at the website: www.pulsus.com/resp

As I give talks across Canada, I ask whether participants have heard of these guidelines, and unfortunately most have not. We have thus not yet disseminated the information yet as most of you obviously do not read the Canadian Respiratory Journal. There will be many methods of dissemination (such as this newsletter!) and these will definitely get into your hands.

We learned from the Asthma guidelines, amongst others, that dissemination does not mean implementation, or in the vernacular, the horse can be led to water but not made to drink. How do we get the primary care physician/caregiver to utilize the most up to date information? This is the difficulty, and has not yet been resolved. We will have CME programs. The pharmaceutical companies will bring us CMEs and updates along with visits with the pharmaceutical representatives. We will have mailings and published journal articles describing the guidelines. But how to make us drink?

The government could tie our funding to successful treatment; this is currently being done a little in British Columbia and has been done in the United Kingdom for a while. In Australia, physicians are paid for educating their asthmatics in a 3+ Asthma program (paid for three counseling visits). None of us really wants big brother looking over our shoulders especially when we are talking about our livelihood. But what if we were given incentives for doing good things, like immunizing our patients with COPD etc...

We may also want to go to the public and increase the public's expectations for quality of life and have the pressure come upward. Of course, the system has limitations and we are not always the limiting factor. There are not enough of us, and the number of Family Physicians entering

practice falls every year. Do any of you know where the closest Pulmonary Rehabilitation centre is? There is nowhere near enough of these units to deal with our patients with COPD either.

We have put together some new and some reviewed old articles on COPD in this newsletter, trying to keep it to mostly one theme. I hope that this may be a resource for you in the future for your patients with COPD. Please give me feedback on how you liked it at FOR4KIDS@sympatico.ca

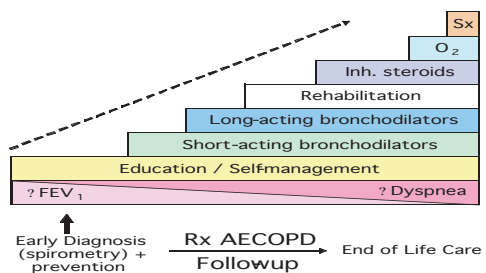
And to let you know what is coming, there have been other groups meeting also. These will result in a Pediatric Asthma Guideline being released this winter as well as an update of the Adult Asthma Guidelines. I look forward to sharing these highlights with you.

ALAN KAPLAN, CHAIR, FPAGC

ADVAIR in COPD – results from trial of ICS and LABA study group (TRISTAN)

The recent CTS Guidelines for the management of COPD outline the pharmacological approach for the management of this chronic and disabling respiratory illness. The main message with respect to the use of drugs is to maximize bronchodilation with a combination of bronchodilators. Only after this is achieved should consideration be given to the addition of inhaled corticosteroids. This is illustrated by the stepwise approach diagram.

Management of COPD (Ideal)



Long acting B2s (LABAs) have been shown to improve lung function and health status and decrease symptoms in patients with COPD. Inhaled corticosteroids (ICS) have been proven to decrease the frequency of exacerbations and reduce the rate of decline in health status. The TRISTAN study was designed to investigate the possible benefit of a combined LABA/ICS (Advair 500).

TRISTAN was a randomized, double blind, placebo controlled trial done in

25 countries including Canada. There were 1465 outpatients with COPD entered into the study. Inclusion criteria were a pre bronchodilator FEV₁ of 25-70 % predicated, an improvement in FEV₁ < 10% post bronchodilator (salbutamol 400 ug), and a FEV₁/FVC ratio of < 70%. In other words all patients met the CST guidelines for diagnosing COPD as partially reversible obstruction. All patients also had a smoking history of at least 10 pack years, chronic bronchitis, 1 AECOPD per year in the previous 3 years, and at least 1 AECOPD in the year before entry into the trial. Exclusion criteria were any other respiratory illness, regular oxygen therapy, or the use of systemic steroids, high dose ICS or antibiotics in the 4 weeks prior to entry into the trial.

There were 4 treatment arms to which patients were randomized; salmeterol 50 ug bid, fluticasone 500 ug bid, the combination of salmeterol 50 ug and fluticasone 500 ug bid, or placebo bid. All were in identical delivery devices.

The primary endpoint was the FEV₁ after 1 year treatment as measured at least 4 hours after any short acting bronchodilator and 12 hours after any study medications. Secondary endpoints were other lung function measurements, use of rescue medication, respiratory symptoms, AECOPD, health status (St. Georges Resp Questionnaire) and adverse events.

There were no significant differences between the patients in each of the 4 study groups. The mean age of the patients was 63 with 83% men and 51% smokers. The mean pre bronchodilator FEV₁ was 45% predicated. Patients were allowed to continue their regular respiratory medication including anticholinergics and theophylline.

Pre bronchodilator FEV₁ at 12 months was improved significantly more for the

combination group (10% increase) compared to the salmeterol only group (2 % increase), the fluticasone only group (3 % increase) and the placebo group (3% decrease). This improvement was seen at 2 weeks into the trial and maintained for the entire year. A similar trend was noted for other measurements of lung function. Smoking did not influence this finding. The acute exacerbation rate was decreased in all treatment groups by a significant amount compared to the placebo group. It was decreased the most in the combination group but the difference between treatment groups did not reach statistical significance (combination 25%, salmeterol 20% and fluticasone 19%). This effect was noted most in patients with more severe disease (ie FEV₁ < 50%) where a 30% reduction in exacerbations was seen with combination therapy. Combination therapy also showed improvement in symptoms compared to the medications alone or placebo. This was seen for dyspnea scores, use of relievers, night time awakenings, and cough. Only the combination group showed an improvement in health status scores that was statistically significant at 1 year. There was no difference in adverse events between the 4 study groups except for oral candida which was seen more in the combination and fluticasone only groups. All other side effects as well as ECG changes and am cortisol levels were not significantly different between the groups.

Comments:

The TRISTAN study is important in many ways. It is a large study. It is a long study. It compares 3 treatment groups to placebo. It allowed the use of regular medication for the treatment of COPD to continue. Entry criteria were strict and met Canadian guidelines for the

diagnosis of COPD. Patients enrolled did not have asthma or other respiratory illnesses. The patients in the study for the most part had moderate to severe disease by Canadian standards. Given the slow progression of COPD this is often the stage that many patients are diagnosed. This is likely to be the case until CTS guidelines for screening are more widely implemented. The primary endpoint of the study was significantly improved in the combination group compared to the other 2 active treatment groups and placebo. The clinical significance of this is yet to be widely accepted or understood. However the increase in pre bronchodilator FEV₁ seen with Advair is similar to that seen with tiotropium (Spiriva) in clinical trials. Further, there were significant improvements in symptoms and health status scores which presently are treatment goals for the management of COPD as reversal of the disease process is not yet possible. All therapies decreased the rate of acute exacerbations of COPD with a trend to the combination treatment being the most effective and it being the most effective in the most severe patients (ie FEV₁ < 50%). This is consistent with CTS guidelines.

The limitations of the trial include the fact that it is not helpful for management of very severe COPD as these patients were excluded. Mild patients were also excluded but present guidelines would not recommend the use of ICS for them.

Current CTS guidelines suggest maximal bronchodilator therapy with the use of both a LAB2 and long acting anticholinergic (and even theophylline) before the use of ICS for the maintenance treatment of COPD. The TRISTAN study suggests that once maximal bronchodilation has been attempted and a patient remains symptomatic or continues to experience AECOPD that rather than adding an ICS as the next step, the LAB2 could be discontinued and a combination therapy started. Careful clinical follow up watching for symptomatic improvement and with spirometry to see improvement in FEV₁ is important. Theoretically there is a synergistic action between LAB2 and ICS when they are given in a combined device. This is largely accepted in asthma and may be at play in COPD as well. Also the cost of the combination device compared to the cost of the drugs individually may also be of benefit.

Hopefully this approach will help our patients with COPD meet current treatment goals of symptom control, prevention of exacerbations, and improvement of lung function and health status.

JOHN REA MD CCFP(EM), FCFP

Comment:

Dr. Rea has done a great job reviewing this exciting study. It gives us a comfort range in where to add a combination product in patients with COPD. Just as in asthma, the combination medicines are more than the sum of the parts! This has not changed the paradigm of care as illustrated in the article. We are still adding inhaled steroids to patients with moderate to severe COPD and with frequent exacerbations.

It would be interesting to see how the patients with the most severe COPD, and thus excluded from this study, would have done. I think we all suspect that this group would get the most benefit. I guess that study has to be done next!

ALAN KAPLAN MD CCFP(EM)

Steroids in COPD, what is their role?

Steroids have their place in the management of COPD, but not for everyone. There are a lot of misconceptions regarding the utility of steroids, especially inhaled steroids in the maintenance phase of patients with COPD. I will break this up into two articles. The management of acute exacerbations of COPD is very different, with different goals, than the treatment of stable COPD.

I. Steroids in Acute Exacerbations of COPD.

a) Systemic steroids in Acute Exacerbations of COPD.

Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, et al. Effects of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. N Engl J Med 1999; 340(25):1941-47

This study randomized patients admitted to hospital with AECB and randomized them to receiving steroids for either two or eight weeks or placebo. Treatment failure, which was defined as death, intubation and mechanical ventilation, readmission for COPD, or change in therapy, was significantly lower in the steroid treatment group. The eight week course was no better than the two week course.

Other studies have shown that oral steroids will do the same thing. Steroids were given once daily at a dose of 30 mg. per day for two weeks. These patients again showed shortened hospital stays and increased FEV₁¹. Shorter three day courses were not as effective as 10 day courses for COPD².

Systemic steroids are problematic for the patients and this must be kept in mind. The risk of hyperglycemia is not trivial. Davies study¹ showed that 20% of the steroid treated patients developed hyperglycemia. There have been concerns of dose related increased incidences of weakness, cataracts, candidiasis, and skin bruising. The specter of avascular necrosis is present. Concerns re osteoporosis abound.

I would consider using systemic steroids in all patients with AECB if they have moderate to severe COPD. A 10-14 day

course is necessary, and use the minimal dose required; doses over 30 mg need not be used in non-hospitalized patients.

b) Inhaled Steroids in Acute Exacerbations of COPD

We just do not have the data to support the use of inhaled steroids for AECB. One trial³ of almost 200 patients randomized into nebulized budesonide, oral prednisolone and placebo. Other than similar improvements in FEV₁ at 72 hours, there was not the same benefits to the ICS group as the systemic steroids group. More research is needed into this area.

II. Steroids in Stable COPD

a) Systemic steroids in stable COPD

There is no supportive data for the routine use of systemic steroids in patients with COPD of any severity. Adverse effects potentially obviate any benefits in long term use, unless the benefits were extraordinary. Most of those patients who are on low dose oral steroids can be weaned off slowly with safety. Ensure nutritional and emotional support as the systemic steroids often give a (false) sense of well being.

There may well be a role for oral steroids in identifying the 20% of patients with stable COPD who are steroid responders. A steroid trial of 30 mg per day for two weeks in a stable, non-smoking, bronchodilated individual will separate the patients with an FEV₁ increase of 20% (positive) vs. all others (negative). If positive, the dose of steroid should be tapered to the lowest dose maintaining the level of FEV₁. The GOLD guidelines suggest that a steroid trial be done with three months of equivalent of 500 ug Fluticasone twice daily to observe a 20% increase in FEV₁ in the same type of individuals. This has the advantage of safety, but the disadvantage of longer time to the diagnosis and increased cost.

b) Inhaled steroids in stable COPD

Here is the tough one! There seems to be a lot of pressure to prescribe inhaled steroids to patients with COPD. We feel that on average, 20% of patients with COPD are steroid responders and will have reversibility in their lung function with improvement. Then why are 70% or so of our patients on inhaled steroids? Inhaled steroids cause oral candidiasis, bruising, the potential for decreased bone mineral density and possibly increased risk of cataracts.

Many studies, Renkena et al 1996, Weir et al, 1999, EUROSCOP 1999, Copenhagen 1999, Lung Health Study 2000, and ISOLDE 2000, have looked at this issue. Only ISOLDE with Fluticasone 500 ug BID in patients with moderate to severe ($FEV_1 < 50\%$) COPD showed any benefit. At that, it did not show benefit to lung function or mortality, although there was fewer exacerbations, decreased length of hospitalization and a slower decline in quality of life. Criticisms of the study include that it did not separate smokers and non-smokers, nor did it identify those with reversibility prior to therapy.

c) *Combination with LABAs*

Trials are currently underway to assess the potential for benefit from the combination agents. TRISTAN⁴ is one such trial wherein the combination product of salmeterol and fluticasone was compared to each of its individual parts separately and found to be better. In Asthma we see the beneficial effect of the single molecule in terms of compliance and rapidity of onset compared with the two agents separately. Please see Dr. Rea's review of this study in this newsletter.

Summary:

After all that, what to do?

COPD is increasing and disabling. We have known therapies that bronchodilate. New long-acting anticholinergic bronchodilators are beneficial. (see Spiriva). New therapies such as phosphodiesterase inhibitors are emerging. The role of steroids continues to be controversial. In our efforts to help our patients we must remember the dictum of "do no harm".

This author's recommendations are the following.

- AECB in patients with anything other than the mildest COPD should be accompanied by 1-2 weeks of systemic steroids in the lowest effective dose.
- Patients with stable COPD, once maximally bronchodilated and not smoking should be offered a steroid trial if there symptoms continue to be symptomatic. If positive, their dose of steroids should be maintained at the dose that keeps their lung function improved. If negative, there

does seem to be a 100-150 ml single time improvement in patients with moderate to severe COPD and the ISOLDE trial shows that there may be decreased exacerbations in these patients placed on high dose ICS. The very real issues of adverse effects and cost must counterbalance the benefits to these patients. It should therefore not yet be routine to use ICS in non-steroid responders. Also, response to systemic steroids during an acute attack does NOT predict a successful steroid trial. Combination agents may well change this paradigm, and we await the results of the analyses of TRISTAN and other landmark trials⁵.

- Another place that I have seen in practice inhaled steroids work is not studied anywhere in the literature that I have found. This is NOT evidence based. There have been a few patients with borderline oxygenation at rest that have responded to systemic and subsequent inhaled steroids with an increased diffusion capacity and increased oxygen saturation. We have that grey area where we feel Oxygen would be beneficial (eg. Accompanying Coronary Artery Disease) but the patient does not meet the criteria. Try it there and let me know how it worked for you!! (Called an n=1 trial!).

References:

1. Davies L, Angus RM, Calverley PM, Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive lung disease: a prospective randomized control trial. *Lancet* 1999; 354(9177):456-60
2. Sayiner A, Aytemur ZA, Cirit M, Unsal I. Systemic glucocorticoids in severe exacerbations of COPD. *Chest* 2001; 119(3): 726-30
3. Maltais F, Ostinelli J, Bourbeau J, Tonnel AB, Jacquemet N, Haddon J, et al. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Am J Respir Care Med* 2002; 165(5):698-703
4. Calverley PMA, Pauwels RA, Vestbo J, Jones PW, et al. Salmeterol, Fluticasone propionate combination for one year provides greater clinical benefits than its individual components in COPD. *Am J Resp Crit Care Med* 2002; 165(8) suppl: A226
5. Szafranski W, et al. *Eur Respir J* 2003;21:74

Steroids in COPD? New emerging evidence to support their use

Van der Valk P, et al. Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* November 15, 2002;166:1358-63

I wrote quite a detailed dissertation on the benefits of inhaled steroids in COPD a couple of newsletters ago. The authors here looked at it from the other direction, ie., what happens to patients with COPD if you stop their inhaled steroids?

This was a randomized, double-blind, placebo controlled trial to assess the effect of discontinuation of high

dosage inhaled fluticasone on quality of life and exacerbations in patients with moderate to severe COPD.

506 patients with COPD were eligible, 269 were randomized, and 263 completed the four month run in period where they received 500ug of inhaled Fluticasone propionate BID. 85% were men, 73% were former smokers and 83% had been on inhaled steroids prior to the study.

Outcomes measured were time to first and second exacerbations, recurrent exacerbations and quality of life. An exacerbation was defined as worsening of respiratory symptoms which required 10 day treatment with an antibiotic or oral corticosteroid.

The placebo group experienced an exacerbation 34.6 days sooner than the FP group. Rapid recurrent exacerbations occurred in 21.5% of the placebo group vs. 4.9% of the FP group. A statistically significant difference was noted between the placebo and FP treated groups in

measurements of quality of life.

The authors concluded that cessation of ICS in patients with moderate to severe COPD decreased health related quality of life, decreased the time to first and second exacerbations, and increased the risk of recurrent exacerbations.

Comment:

Forty percent of the study patients experienced no down side from discontinuing the ICS. I think we still must attempt to tease out which patients with COPD are the ones which benefit from steroids. These also were patients from a pulmonary clinic, thus perhaps not really mirroring what we see in primary care. In the meantime, I will continue using inhaled steroids in patients with COPD who have severe disease, recurrent exacerbations, or are steroid responders. The studies on combination therapies may also have some input on the utilization of inhaled steroids in patients with COPD.

Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: a meta-analysis

E R Sutherland, H Allmers, N T Ayas, A J Venn, R J Martin

Background: Chronic obstructive pulmonary disease (COPD) is a syndrome of chronic progressive airflow limitation which occurs as a result of chronic inflammation of the airways and lung parenchyma. However, the role of inhaled corticosteroids in the treatment of COPD is controversial. We hypothesised that

inhaled corticosteroids reduce the progression of airflow limitation in COPD.

Methods: A comprehensive literature search was conducted and data were analysed using random effects methodology. The effect of inhaled steroids on annual change in forced expiratory volume in 1 second (FEV₁) was determined for all trials, for trials with high dose treatment regimens, and for trials in subjects with moderate to severe airflow limitation.

Results: Data from eight controlled clinical trials of >2 years were included (n = 3715 subjects). Meta-analysis of all study data revealed that inhaled corticos-

teroids reduce the rate of FEV₁ decline by 7.7 ml/year (95% confidence interval (CI) 1.3 to 14.2, p = 0.02). Meta-analysis of studies with high dose regimens revealed a greater effect of 9.9 ml/year (95% CI 2.3 to 17.5, p = 0.01) compared with the meta-analysis of all studies.

Conclusions: Inhaled corticosteroid treatment for >2 years slows the rate of lung function decline in COPD. The effect observed with high dose regimens is greater than that with all regimens combined. These data suggest a potential role for inhaled corticosteroids in modifying the long term natural history of COPD.

Impact of inhaled corticosteroid (ICS) therapy on bone mineral density (BMD)

Author: Halpern MT Schmier JK Van Kerkhove MD Watkins M Kalberg CJ

Citation: CHEST 2003;124(4 SUPPL.):87S. Conference Info: American College of Chest Physicians, Chest 2003. Orlando, FL, USA, 25 OCT 2003 to 30 OCT 2003

Abstract: Purpose: ICS are a common therapy for both asthma and COPD. While use of systemic corticosteroids can decrease BMD, the impact of long-term ICS use on BMD is uncertain.

Methods: A meta-analysis evaluating the impact of ICS therapy on BMD was performed. We searched MEDLINE and EMBASE databases and consulted with experts to identify published and unpublished literature reporting BMD among adult asthma and COPD patients using ICS and non-ICS using controls. Studies selected for review included at least one-year of follow-up. Two independent reviewers evaluated studies; data from those meeting specified inclusion criteria were abstracted. Random-effects meta-analysis was performed for all outcomes present in at least four included studies.

Results: A total of 266 studies were identified and reviewed; 14 (5.3%) met specified inclusion criteria for the meta-analysis. Sufficient data were available to perform meta-analysis on BMD measures for ICS-using patients; only one measure (lumbar BMD) was available among non-ICS using controls. Using current NAEPP defini-

tions, the majority of studies (12 of 14) included patients receiving moderate to high doses of ICS. Mean changes in lumbar BMD were not significantly different from baseline or from controls (-0.02%) for patients with asthma (+0.13%) and COPD (-0.42%) following 1 to 4 years of treatment. Among ICS users, changes from baseline in femoral neck and major trochanter BMD (-0.17% and +1.46%, respectively) were not statistically significant. Non-significant changes from baseline in lumbar BMD of -0.20%, -0.39%, and -0.73% were observed with fluticasone, budesonide, and beclomethasone, respectively.

Conclusions: Long-term use of ICS in patients with asthma or COPD was not associated with significant changes in BMD. Clinical implications: Treatment with ICS at standard doses in patients with asthma or COPD does not have a clinically meaningful effect on BMD.

The Role of the Family Physician in the management of COPD

With the release of new Canadian COPD Guidelines, I thought it prudent to analyze the role for Family Physicians in the office management of this common disease. Its prevalence is increasing and Family Physicians have the ability to intervene in this disease to prevent morbidity and effectively manage their care. The guidelines can be found in their entirety at: http://www.pulsus.com/Respir/10_SA/supp_A_master.pdf

COPD is currently the fifth commonest cause of death and is rising; it will rise to third by 2020¹. (Figure 1) It is a common cause of disability and lost years of productivity. The largest cost in COPD is in hospital admissions and emergency care.

Definition

COPD is a respiratory disorder largely caused by smoking, which is characterized by progressive, partially reversible airway obstruction, systemic manifestations, and increasing frequency and severity of exacerbations.

Percent Change in Death Rates

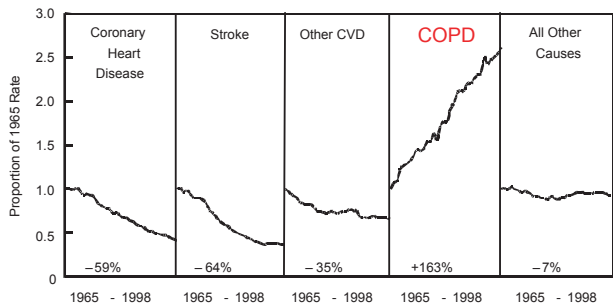


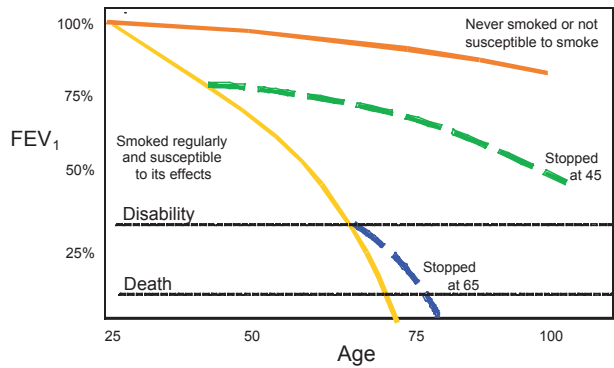
Figure 1

Screening

Family physicians are in a prime position to identify and diagnose COPD. Cigarettes of course mostly cause it and screening smokers has been proven to be effective. Screening of the population has proven to be effective and cost effective. One active screening program cost \$564 per detected case. Contrast that to other screening programs like breast cancer screening which can cost from \$5700 to \$23,400 per detected case². If one can identify the smokers who are at highest risk of COPD, those who are losing lung function at an advanced rate (thought to be roughly 20% of smokers) and get them to stop

smoking, the economic impact will be huge. Smoking cessation at any age will benefit your patient (Figure 2). You will also save many years of morbidity and quality of life years lost, in addition to decreasing mortality later. You can't just wait until symptoms develop, as this may well occur later in the disease as patients often become accustomed to their symptoms.

Effects of Smoking and Stopping Smoking on FEV₁



Fletcher, 1997

Figure 2

Diagnosis

The diagnosis of COPD is made through spirometry, which shows chronic airflow obstruction. This is also, of course, how you screen your patient population. Rick Hodder in Ottawa has developed the thirty second COPD test as a tool to make you think of COPD in your patients. See Figure 6.

Post-bronchodilator FEV₁/FVC <0.7 and FEV₁ <80% predicted are both required for the diagnosis of COPD.

The goals^{3,4} of management of COPD are as follows:

- To prevent disease progression (smoking cessation).
- To alleviate breathlessness and other respiratory symptoms.
- To improve exercise tolerance.
- To prevent and treat exacerbations.
- To improve health status.
- To reduce mortality.

Prevent disease progression

Smoking cessation is the only intervention that has been proven to delay or halt COPD progression. This needs to be dealt with by multifactorial interventions by physicians, government and patient groups. In the day to day office practice that we have, I find the Prochaska model of readiness to change very useful. In it you identify people who are in different levels of readiness. Precontemplative, contemplative, preparation, action, and maintenance are the levels. I would suggest that

you suggest smoking cessation to those who are not ready to change and keep your energies fresh for those who are more prepared to change.

Assessment of severity

Severity of COPD can be decided based on a symptom scale and/or by measurement of lung function. (Figure 4) Figure 3 shows the MRC dyspnea scale which gives a severity based on the patient's symptoms. This is a user friendly method for the Family Physician. Previous guidelines made decisions based on the spirometric measurements of lung function.

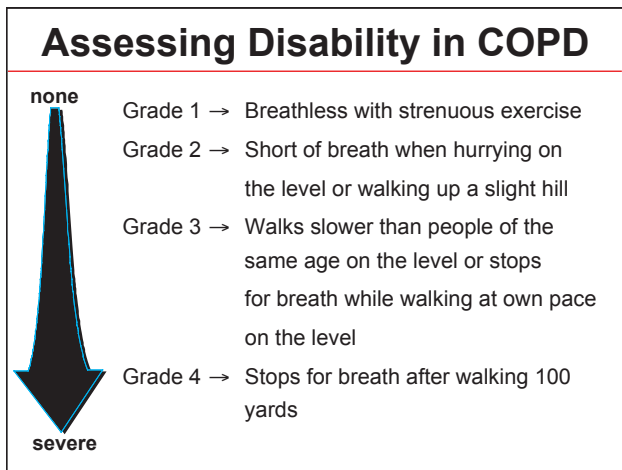


Figure 3

COPD Classification by Symptoms / Disability*

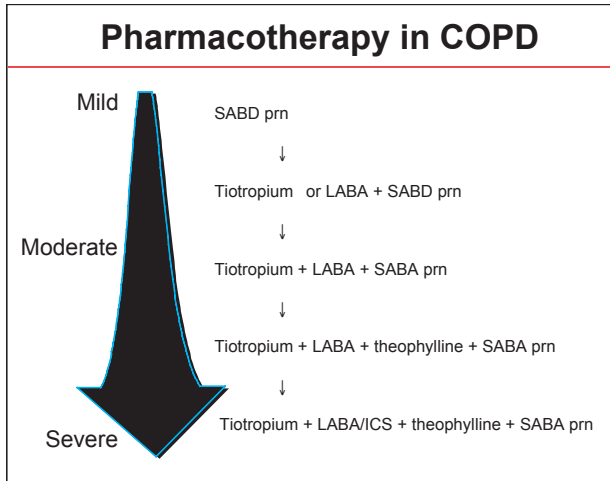
COPD Stage	Symptoms
At Risk <i>(does not "yet" fulfill the diagnosis of COPD)</i>	Asymptomatic smoker, ex-smoker or chronic cough/sputum, but post-bronchodilator FEV ₁ / FEV > 70% and / or FEV ₁ > 80% predicted
Mild	Shortness of breath from COPD †with strenuous exercise or when hurrying on the level or walking up a slight hill (MRC 1-2)
Moderate	Shortness of breath from COPD †causing the patient to walk slower than people of the same age on the level or stop after walking about 100 meters (or after a few minutes) on the level (MRC 3-4)
Severe	Shortness of breath from COPD †resulting in the patient too breathless to leave the house, or breathless after dressing/undressing (MRC 5) or the presence of chronic respiratory failure or clinical signs of right heart failure

Can Respir J Vol 10 Suppl A May/June 2003, pg. 15A

Figure 4

Pharmacologic therapy

The therapy depends on the symptoms and the disease severity. Bronchodilators are begun with Short acting bronchodilators (SABD) prn and once they are being used regularly, long acting bronchodilators should be added. Tiotropium (long acting anti-cholinergic) and Long Acting Beta₂-Agonists (LABA) such as Salmeterol or Formoterol and are your current choices.



Can Respir J Vol 10 Suppl I A May/June 2003, pg. 15A

Figure 5

Inhaled corticosteroids(ICS) are indicated if patients are steroid responders or have poor lung function and have frequent exacerbations. To be defined as a steroid responder, one must test for it. A patient who is not smoking and optimally bronchodilated with continued symptoms are challenged with two weeks of 30 mg per day of Prednisone or three months of Fluticasone or equivalent at 500 ug BID. If the repeat FEV₁ shows a 20% improvement with at least 180 cc, you have defined a responder.

The Isolde⁶ trial showed that people with moderate to severe COPD who used Fluticasone at 500 ug BID had decreased number and severity of exacerbations.

Thus consider adding inhaled steroids to the daily treatment of patients with moderate to severe disease and recurrent exacerbations, even if they are not 'steroid responders'.

Non-pharmacologic therapy

Nutritional support of those who are undernourished, pulmonary rehabilitation and exercise training are other key factors in improving outcomes.

Patients who are undernourished have a much poor prognosis with COPD. They have decreased muscle mass and thus cannot clear secretions as well and do more poorly with exacerbations. In essence they are working so hard to breathe that they become malnourished. Nutritional supplementation with sufficient protein intake is important.

Pulmonary rehabilitation formally has been shown to

- improve and maintain skeletal and respiratory muscles
- increase exertional endurance
- lessen dyspnea
- aid in clearance of secretions
- decrease hospitalization during exacerbations
- encourage patients to stay active mentally and physically

Even if you do not have a formal program in your area, exercise and muscle training have these benefits.

Surgical treatments for severe disease have been used with some success. These include lung transplants and lung reduction surgery. The principle of this is simply that large bullae may not allow the rest of the lung to properly expand and function. Thus removing the bulla will improve the function of the rest of the lung.

Oxygen:

The only drug that has shown to decrease mortality in COPD is Oxygen. Long Term Oxygen therapy:

- Level IA support for domiciliary oxygen (≥ 15 hrs/day to achieve $\text{SaO}_2 \geq 90\%$) in:
 - stable COPD patients with severe hypoxemia ($\text{PaO}_2 \leq 55$ mmHg), or
 - when the $\text{PaO}_2 \leq 60$ mmHg plus ankle oedema, cor pulmonale or hematocrit $\geq 56\%$

Prevention and treatment of exacerbations:

I have mentioned the role of ICS in potentially decreasing exacerbations. There is good data for Tiotropium also in decreasing exacerbations. Influenza and Pneumococcal vaccination are key strategies for prevention.

Once they occur, this is not the population to be stingy with antibiotics in. If they have increased sputum, sputum purulence and fever with increased shortness of breath, they likely have a bacterial etiology. Your choice of antibiotics will depend on severity of illness, co-morbidities and antibiotic exposure. Increase the bronchodilator, assess oxygenation and treat with systemic steroids for a short course as well in all but the mildest exacerbation.

The Thirty Second COPD Test

- ✓ Do you smoke currently, or have you smoked cigarettes?
- ✓ Do you cough regularly?
- ✓ Do you bring up mucous regularly?
- ✓ Do even simple chores make you breathless?
- ✓ Do you get frequent colds that persist longer than those of other people you know?

Figure 6

Conclusion:

Suspect COPD, screen for it with spirometry and make the diagnosis. Early diagnosis can markedly change your patient's prognosis, quality of life and outcome. Step up your efforts for smoking cessation with the identified patient. Ensure adequate immunization, nutrition and rehabilitation. Medication can help and the treatment regimens are much better with our long acting bronchodilators. Family physicians

are the cornerstone of the Canadian health care system; we can make the difference for these patients.

References:

1. Murray CJL, Lopez AD. Alternate projections of mortality and disability by cause 1990-2020: Global burden of disease study *Lancet* 1997;349:1498-1504
2. Van den BoomG, van Schank CP, Rutten-vanMolen MPMH et al. Active Detection of chronic obstructive pulmonary disease and asthma in the general population. Results and economic consequences of the DIMCA program *Am J Resp Crit Care Med* 1998;158:1730-8
3. Pauwels RA, Buist AS, Calverley PMA et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung/disease (GOLD) Workshop summary. *Am J Resp Crit Care Med* 2001;163:1256-76
4. O'Donnell D, Aarons S, Bourbeau J, et al Canadian Thoracic Society recommendations for management of Chronic obstructive pulmonary disease- 2003. *Can Respir J* 2003;10(Suppl A):11A-33A
5. Fletcher CM, Elmes PC, Wood CH. The significance of respiratory symptoms and diagnosis of chronic bronchitis in a working population. *Br Med J* 1959; 1:257-266.
6. Burge PS, Calverley PMA, Jones PW, et al. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297-1303

About the author:

Alan Kaplan MD CCFP(EM) is a Family Physician and Emergency Physician in Richmond Hill, Ontario. He is the current chair of the Family Physician Airway Group of Canada (FPAGC). The FPAGC is a Family Physician group of currently about 800 Family Physicians across Canada. Our mandate is to improve asthma and other airway diseases across Canada by assisting in educational endeavors for Family Doctors. We have done this through the creation of two Mainpro C workshops, one on Asthma and one on Spirometry, which have been run across Canada. We have a relationship with the College of Family Physicians of Canada. We have representation to many organizations including CNAC (Canadian Network for Asthma Care), The Canadian COPD Coalition, The National Asthma Control Task Force of Canada, the Ontario Steering Committee on Asthma Management, the Canadian Consensus Asthma Guidelines Committee, the Canadian COPD guidelines group, the Asthma Society, the International Primary Care Respiratory Group, and others. You can find the FPAGC website at <http://www.fpagc.com>

Use of FEF₂₅₋₇₅

After having done countless workshops and lectures on spirometry, a recurrent question that arises is the use of the FEF₂₅₋₇₅. This reading is felt to be the least effort dependent portion of the expiratory maneuver. Obstruction seems to begin in the small airways in COPD. The FEF₂₅₋₇₅ is seen as the value which represents the condition of the small

airways and many be a better predictor of hypoxemia than the FEV₁.

A Turkish paper, 'Spirometric predictors for the exclusion of severe hypoxemia in COPD' (Can Respir J 2001;8(4);245-249) looked into the need of for arterial blood gases in patients with severe COPD. The objective was to investigate the correlation between severe hypoxemia and multiple spirometric parameters in patients with COPD and FEV₁ 50% of predicted or greater. Patients with Hb less than 100 or with cardiovascular disease were excluded.

The study found that one in five patients with COPD and an FEV₁ of 50% or greater was hypoxemic (PaO₂ less than 60 mmHg). FEV₁, FEV₁/FVC, PEF parameters all failed to predict or exclude severe hypoxemia. The negative predictive value of the FEF₂₅₋₇₅ being greater than 50% of predicted value was 92%. Therefore it would be reasonable to withhold ABG analysis in the clinical analysis of patients with FEV₁ equal or greater than 50% and FEF₂₅₋₇₅ of greater than 50%.

SPIRIVA, A new anticholinergic bronchodilator for COPD

From GOLD guidelines to the upcoming new Canadian COPD Guidelines the first treatment after smoking cessation for COPD is bronchodilators. Vagally mediated bronchoconstriction is thought to be the major reversible component of airway obstruction in these patients. Bronchodilators, with anticholinergics and β_2 -Agonists, alone or in combination, are recommended in all stages of COPD treatment.

Muscarinic receptors in the airways control a significant amount of smooth muscle function in human airways. There have been three types of muscarinic receptors identified. M1 receptors facilitate cholinergic neurotransmission through the parasympathetic ganglia. M2 receptors are located on the postganglionic

cholinergic nerves and provide negative feedback modulation of acetylcholine release. Therefore, inhibition of M2 receptors results in increased release of acetylcholine and bronchoconstriction. M3 receptors are located on bronchial smooth muscle and mucous glands. They mediate the airway smooth muscle contractile response and mucus secretion which occurs as a response to acetylcholine.

Tiotropium bromide is the newest member of the quaternary ammonium class of the anticholinergic bronchodilators, which dilate bronchial smooth muscle through antagonism of muscarinic receptors located in the airway smooth muscle. It binds equally to the M1, M2, and M3 receptors, but dissociates much more slowly from the M1 and M3 receptors than from the M2 receptors. Therefore, the negative feedback from the M2 receptor is decreased which allows a long duration of action and therefore once daily administration in patients with COPD.

Twenty percent of an orally inhaled dose of tiotropium is deposited in the lung. It is rapidly absorbed into the systemic circulation, with peak plasma levels at 5 minutes declining to low

levels in less than one hour. There was no evidence of drug accumulation once steady state was achieved. Seven percent of the delivered dose is excreted unchanged in the urine. At steady state, the mean plasma elimination half life was 5 to 6 days. 18ug has been decided to be the optimal dose. Inspiratory flow rates necessary for the HandiHaler device of 15 L/min are sufficient for lung deposition. This is possible even in patients with severe COPD (FEV₁ 65% to <27% of predicted¹)

Lung function as measured by trough FEV₁, trough FVC, and am and pm PFR. These were all improved by Tiotropium vs. placebo in one year studies^{2,3}.

Lung function as measured by trough FEV₁ and FVC, am/pm PFR, and FEV₁ at one year were improved in all severities of COPD compared with Ipratropium⁴.

Lung function measured by trough FEV₁, FVC, and PFR showed an improved response with tiotropium to Salmeterol 50ug BID in a placebo controlled six month strategy⁵.

Health related quality of life, COPD exacerbations and dyspnea were also superior^{2,3,5}.

Dyspnea, measured by the TDI (Transition Dyspnea Index) was

improved vs. placebo, Ipratropium, and Salmeterol^{2,3,5}.

Similarly, time to first exacerbation was lengthened, the number of exacerbations were reduced, there were fewer hospitalizations for COPD, and fewer days spent in hospital due to exacerbations vs. Placebo³. There were reduced incidence of COPD exacerbations, the number of COPD exacerbations, time to first exacerbation and time to first exacerbation vs. Ipratropium². There was a tendency for fewer exacerbations with COPD in the tiotropium vs. Salmeterol⁵. Tiotropium patients took fewer rescue Salbutamol in all the trials (both groups reduced vs. Salmeterol).

Tiotropium may cause reduced salivation; therefore the commonest side effect is that of dry mouth. It is generally of mild intensity and resolves with continued treatment and did not necessitate treatment cessation².

Tiotropium is delivered once daily, morning or evening but at the same time every day, via dry powder by the HandiHaler. A capsule, which must be kept in its sealed pouch until just

before use, is punctured in the device and the dry powder is inhaled. The capsule should not be swallowed. The capsules should be stored in a cool dry place, and not be frozen or heated.

In summary, Tiotropium is a long acting anticholinergic bronchodilator that is administered once daily by dry powder inhalation for the treatment of COPD. Studies show improvement in lung function and decreased exacerbations of COPD. There has been no evidence of tachyphylaxis and the studies hint that disease progression, as measured by FEV₁ at one year, will be blunted in patients receiving tiotropium. There will be benefit to our patients with this product, but also to the health care system with reduced exacerbations. We do not know yet if this medication will modify the natural course of COPD after one year (ie. slow down the progressive decline in lung function in COPD). We also will see if combining tiotropium with long acting B2s will further improve the situation.

ALAN KAPLAN MD CCFP(EM)

References:

1. Chodosh S, Flanders J, Serby CW, et al. Effective use of HandiHaler dry powder inhalation system over a range of COPD disease severity. *Am J Respir Crit Care Med* 1999;159 Suppl: A524
2. Vincken W, van NoordJA, Greefhorst APM, et al. Improved health outcomes in patients with COPD during one years treatment with tiotropium. *Eur Respir J* 2002 Feb 19(2):200-16
3. Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in COPD. *Eur Respir J* 2002 Feb; 19(2): 217-24
4. Vincken WG, Vermiere P, Menjoge SS, et al. Maintenance of bronchodilatation following tiotropium in patients with mild moderate and severe COPD in one year clinical trials. *Eur Resp J Suppl* 2001 Sept; 18 Suppl. 33: 331s (abstract P2202) Donohue JF, van Noord JA, Bateman ED, et al. A 6 month comparison study comparing lung function and
5. Health status changes in COPD patients treated with tiotropium or salmeterol. *Chest*. In press.

Update on new medications: Ketek (telithromycin)

Company: Aventis

Class: Ketolide

Ketolides included in the class of macrolide-lincosamide streptogram.

Mechanism:

inhibits bacterial protein synthesis by binding to TWO sites on the 50S Ribosomal Subunit.

Indications:

treatment of the following organisms in the following conditions; Community acquired pneumonia due to

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Chlamydia pneumoniae*
- *Mycoplasma pneumoniae*

Acute bacterial exacerbations of COPD due to

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella Catarrhalis*

Tonsillitis of pharyngitis due to:

- *Streptococcus pyogenes* (when beta lactams not felt to be appropriate)

¹Approved for patients 18 years and older, except in tonsillitis/pharyngitis when it is down to 13 years old.

Metabolism:

- Rapidly absorbed following oral administration
- 33% undergoes first-pass metabolism and 57% of each dose reaches systemic circulation
- Metabolized by liver (37%), excreted in feces unchanged (7%), or excreted unchanged in the urine (13%).
- Half of the metabolism of this medication is mediated by Cytochrome P450 3A4
- Half life is 10 hours and steady state dosing is reached within 2-3 days of once daily dosing.

Dosing:

Two 400 mg tablets once daily with or without food.

²**Pneumonia:** 10 days

³**AECOPD** 5 days

⁴**Tonsillitis/pharyngitis** 5 days

⁵**Sinusitis** 5 days (Similar outcomes to 10 days of Clavulin or Ceftin) (studies show this but they do not have the official indication yet)

No dosing adjustment needed other than reducing to one tablet daily of patients with severe renal impairment (creatinine clearance <30 ml/min). No need to reduce dose in patients with liver disease.

It is an inhibitor of Cytochrome P450 3A4 and a weak inhibitor of Cytochrome P450 2D6.

Thus it may increase the concentration of drugs metabolized by these routes (like simvastatin) and use of CYP 3A4 inducers like St. Johns Wort, Rifampin, Dilantin and Tegretol can decrease the dose of Ketek and thus lose its therapeutic effect. Do not use with ergot products as it may cause ergot toxicity.

It should be noted that many of these traits are shared with other macrolides.

Side effects:

Most common are diarrhea, nausea, vomiting and loose stools. It can prolong the QTc interval so it should thus be avoided in patients with long QTc intervals or other patients with conditions that are pro-arrhythmic (like low potassium or magnesium) or patients on antiarrhythmics (esp Class 1A or 3). Rare cases of hepatic dysfunction or hepatitis have been reported. Blurred vision is an uncommon side effect.

Cost: \$31.05 per 10 tablet blister card

Comment:

We have a new class of antibiotic for oral administration. Is it just a new macrolide? The data suggests that its mechanism of action, working at two sites, may well allow a **decrease in resistance development**. It has a good spectrum for respiratory tract infections, but will not likely be as effective as quinolones for gram negative infections.

It is used once daily and shorter regimens for AECOPD and tonsillitis are available; this will improve compliance. The concept of rotating antibiotics to prevent resistance is key in primary care. This medication is a new class with real advantages along that line.

Bibliography:

1. George Zhamel The Ketolides, a critical review, *Drugs* 2002; 62(12): 1171-1804
2. Hagberg L et al. Telithromycin in the treatment of community acquired pneumonia: a pooled analysis. *Respir Med* 2003; 97(6): 625-33
3. Zervos MJ et al. Oral telithromycin 800 mg nce daily for five days vs. Cefuroxime axetil 500 mg twice daily for 10 days in adults with AECB. *J Int Med Research* 2003; 31:157-69
4. Quinn J et al. Efficacy and tolerability of 5-day, once daily telithromycin compared with 10-day, twice daily clarithromycin for the treatment of Group A beta-hemolytic streptococcal tonsillitis/pharyngitis : a multicenter, randomized, double blind, parallel-group study. *Clinical therapeutics* 2003; 25(2):422-43
5. Luterman M et al. Efficacy and tolerability of telithromycin 5 ir 10 days vs.amoxil/clavulinic acid for 10 days in acute maxillary sinusitis. *Ear nose and throat Journal* 2003; 82 (8): 576-90

The Committee

Dr. ALAN KAPLAN
(Chairperson)
17 Bedford Park Avenue
Richmond Hill, ON L4C 2N9
(905) 883-1100
e-mail:
FOR4KIDS@sympatico.ca

Dr. ROBERT HAUPTMAN
(Secretary/Treasurer)
62-143 Liberton Drive
St. Albert, AB T8N 6A7
(780) 460-4562

Dr. JOSIAH LOWRY
333 Mary Street
Orillia, ON L3V 3E9

Dr. GORD DYCK
Box 21427
Steinbeach, MB ROA 2T3
(204) 326-6111

Dr. ALAIN COUET
181 Principale, Suite C-12,
Aylmer, PQ J9H 6A6
(819) 685-9110

Dr. JOHN REA
104-348 Muskoka Rd. 3
North Huntsville, ON P1H 1H8
(705) 789-3255

Dr. STEVE COYLE
Charleswood Medical Clinic
3360 Roblin Blvd.,
Winnipeg, MB R3R 0C5
(204) 889-7200

The FPAGC would like to thank GlaxoSmithKline for their financial and technical support in the production of this special COPD edition of our newsletter.

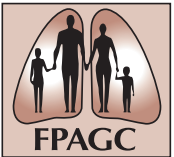


The FPAGC also wishes to thank the following companies for their continued support of our programs:

*Altana
AstraZeneca
Aventis
Boehringer Ingelheim
GlaxoSmithKline
Merck Frosst*

NAME	AFFILIATIONS
ADDRESS	UNIVERSITY:
PHONE (WORK)	HOSPITALS:
PHONE (HOME)	LUNG ASSOCIATION:
FAX	COLLEGE OF FAMILY PHYSICIANS:
SPECIAL INTEREST: (E.G., LECTURING, RESEARCH, WRITING, OTHERS)	OTHER:

MISSION STATEMENT



The Family Physicians Airways Group of Canada is committed to helping those with airway diseases lead a full life. The group is dedicated to helping all family physicians maintain and increase their skill in assisting those with asthma and COPD. The strategy of the Group is to maintain a speaker bank, a data base, and practical tools to help physicians attain in these skills.

The opinions expressed in this newsletter are those of the authors, and not necessarily those of the Family Physicians Airway Group of Canada.