

Canadian Respiratory Review Panel
Respiratory (Asthma/COPD) Guidelines for Family Practice ('orange book')
2011 UP-DATE

The Respiratory Guidelines are regularly updated to incorporate the results of the latest literature and research. This summary includes all recent Canadian and international guidelines that have been published since the latest version of the guidelines. **Based on this review of the literature, the overall recommendations outlined in the 2007 Respiratory Guidelines for Family Practice are unchanged.**

New Drugs

Guidelines pg. 38/39

Daxas® (roflumilast), a once-a-day oral tablet. First in a new class of treatment, roflumilast inhibits phosphodiesterase 4 (PDE4) which targets underlying COPD-specific inflammation and is the first oral anti-inflammatory treatment specifically developed for severe COPD. In Canada, it is indicated, as add-on therapy to bronchodilator treatment, for the maintenance treatment of severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis (i.e. patients with a history of chronic cough and sputum) in adult patients with a history of frequent exacerbations.

Drug Monograph Changes

Guidelines pg. 15 Ciclesonide (Alvesco®)

Pre-October 2007:

Ciclesonide was only indicated for prophylactic management of asthma in adults 18 years of age and older.

Product Monograph Revision January 23rd, 2009:

Ciclesonide is indicated for prophylactic management of steroid-responsive bronchial asthma in adults, adolescents and children ≥ 6 years of age.

Usual Daily Dosage

Adults and children >12 years: Low to moderate dose: 100-400ug once daily

High dose: up to 400ug twice daily or 800ug once daily

Children 6-11 years: 100-200ug once daily

Berotec® (fenoterol): has been discontinued since 2007

Intal® (sodium cromoglycate): inhaler and spincaps are discontinued, generic nebulas available

ASTHMA

1. CTS 2010 Asthma Update (Lougheed 2010). (Guideline pg.13- NO CHANGE)

No significant changes. Emphasis on 'Management Continuum' approach to therapy that reinforces on-going adjustment of therapy to achieve and maintain control. Highlights importance of environmental control, education, written action plan and availability of a fast-acting bronchodilator on demand. Inhaled corticosteroids (ICS) remain the mainstay of treatment. The lowest dose of ICS required to maintain good asthma control should be used. When the patient's asthma is well controlled a reduction in the dose of ICS should be attempted in order to identify the lowest possible dose required to maintain control. Such an attempt at dose reduction should be carried out on a regular basis.

2. CTS 2010 Asthma Update (Lougheed 2010). (Guideline pg.19- Under discharge treatment)

Acute exacerbations, oral prednisone dosage for adults ranges from 40 to 60 mg daily for 7-14 days (previous was 30 to 60mg daily).

3. Asthma control or severity? (Guideline pg.13- NO CHANGE; CLARIFICATION ONLY)

Guidelines in the past suggested that asthma should be classified by severity and the asthma therapy should be based on the patient's severity of disease. Some updated guidelines do not recommend the classification

of asthma severity as the basis for treatment decisions but, instead, the importance of asthma control is emphasized (Becker 2005; GINA 2010, 2009; Pedersen 2009). As the Canadian 2007 family practice guideline suggests, asthma severity is difficult to assess and may be best determined after asthma is controlled by determining the level of treatment required to sustain acceptable control. In contrast, in the US, the NAEPP (National Heart, Lung, and Blood Institute and National Asthma Education and Prevention Program) 2007 classifies asthma severity in patients who are not already on long-term control medications in three age groups (0-4 years, 5-11 years and ≥ 12 years) in order to initiate therapy. If the patient is on long-term control medications then therapy should be adjusted based on the level of asthma control.

3. LABA and corticosteroid use (Guideline pg. 14 NO CHANGE; CLARIFICATION ONLY)

Most updated guidelines recommend increasing inhaled corticosteroid (ICS) doses in all children with asthma not controlled on low-dose ICS before adding a LABA. NAEPP differs slightly in that it recommends that in patients aged 5-11 years equal weight is given to increasing the ICS dose or including add-on therapy to low-dose ICS. In patients ≥ 12 years GINA (2008) and NICE (2008) recommend adding LABA to low-dose ICS over increasing the ICS dose, whereas NHLBI guidelines give equal weight to these choices. The BTS/SIGN guidelines contain a good practice point: when using a high dose of ICS (e.g., ≥ 800 mcg/day of beclomethasone dipropionate or equivalent) and in the event of a severe intercurrent illness which might place the child in clinical adrenal insufficiency, steroid replacement should be part of the management plan. Specialist consultation advised.

4. Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma (Guideline Pg. 16)

In evaluating alternative treatment options for poorly controlled asthma by inhaled glucocorticoid use, a 3-way double-blind, triple-dummy crossover trial was performed on 210 patients (Peters 2010). The addition of tiotropium bromide was compared to doubling the glucocorticoid and to the addition of LABA salmeterol. The use of tiotropium was superior to double-dose glucocorticoid in terms of morning and evening expiratory flow, proportion of asthma control days, the FEV₁ in 1 second before bronchodilation and daily symptom scores. Tiotropium was also noninferior to the addition of salmeterol for all outcomes and increased prebronchodilator FEV₁ more than salmeterol. When added to an inhaled glucocorticoid, tiotropium improved symptoms and lung function in patients with uncontrolled asthma; its effects appeared to be equivalent to those with the addition of salmeterol.

Tiotropium could be a potential new drug to utilize in the management of asthma, but still requires further study in comparing itself to other LABAs, LTRAs and combination products used in asthma before a recommendation can be made.

COPD**1. COPD Classification by symptoms and Airflow Obstruction (Guideline pg. 29: Table 4).**

COPD is classified by airflow obstruction into mild, moderate and severe categories in the CTS 2008 update. The “At Risk” category, present in the previous edition, is no longer included because there is incomplete evidence that the individuals who meet the “At Risk” category necessarily progress on to the “Mild” stage. (CTS, 2008; GOLD, 2008).

Classification of COPD by Severity of Airflow Obstruction. (Guideline pg. 29. Table 5).

	Respiratory Guidelines for Family Practice (MUMS) 2007	Canadian Thoracic Society (CTS) 2008
Airflow Obstruction	Post-Bronchodilator Spirometry (FEV₁)	
Mild	FEV ₁ = 60-79% predicted FEV ₁ /FVC<0.7	FEV ₁ >80% predicted FEV ₁ /FVC<0.7
Moderate	FEV ₁ 40-59% predicted FEV ₁ /FVC<0.7	FEV ₁ 50-80% predicted FEV ₁ /FVC<0.7
Severe	FEV ₁ <40% predicted FEV ₁ /FVC<0.7	FEV ₁ 30-50% predicted FEV ₁ /FVC<0.7
Very Severe	N/A	FEV ₁ <30% predicted

2. Review of New COPD Literature since 2007

Study	Important Outcomes and Comments
UPLIFT, 2008	<ul style="list-style-type: none"> - Tiotropium 18mcg once daily vs. placebo in mod-severe COPD x 4 years - No difference in rate of decline in lung function (FEV₁, FVC) - Tiotropium associated with statistically significant reduction in time to first exacerbation (median 16.7 months in tiotropium group vs. 12.5 months, placebo group) but no difference in number of exacerbations - No statistically significant differences between groups in the risk of MI (RR 0.73, 95%CI 0.53 to 1.00) or stroke (RR 0.95, 95%CI 0.70 to 1.29). - High drop out rate in both the tiotropium (36.2%) and placebo (44.6%) groups, mainly due to adverse events.
Singh, 2008 Tiotropium	<ul style="list-style-type: none"> - Meta-analysis of 17 trials suggests that inhaled anticholinergics increased risk of MI, CV death vs. placebo, 1.8% vs. 1.2% - Results were driven mainly by one ipratropium study - Many of the studies were short duration (6wks-6mos), therefore ability to detect cardiovascular outcomes is limited
Singh, 2008 (ICS - inhaled corticosteroids)	<ul style="list-style-type: none"> - Meta-analysis of 18 trials suggests that ICS >24 weeks in severe COPD patients are associated with increased risk of pneumonia vs. control (7.4% vs. 4.7%) - ICS was not associated with increased overall mortality (6% mortality in both groups) - No consistent definition or reporting of pneumonia in each of the trials included - Studies included may not be able to detect true mortality effect

INSPIRE, 2007	<ul style="list-style-type: none"> - Salmeterol/fluticasone 50/500mcg (Advair®) vs. tiotropium (Spiriva®) 18mcg daily x 2 years in moderate-severe COPD patients showed no difference in exacerbation rates between the two groups (~60% in each group had at least one exacerbation) - Higher all-cause mortality rate in tiotropium group (6% vs. 3%), but TIO group may have had greater disease severity. - Advair® associated with higher reported rates of pneumonia (8 % vs 4%)
TORCH, 2007	<ul style="list-style-type: none"> - Salmeterol/fluticasone (Advair®) 50/500mcg vs. salmeterol 50mcg vs. fluticasone 500mcg vs. placebo daily in moderate-severe COPD patients (FEV1<60%) x 3 years - All-cause mortality: combination 12.6%, salmeterol 13.5%, fluticasone 16%, placebo 15.2% (not statistically significant) - Combo therapy decreased exacerbations vs. placebo (0.67 per year vs. 0.92) [significant] - Statistically significant increase in pneumonia with preparations containing fluticasone vs. placebo: combination 19.6%, fluticasone 18.3%, salmeterol 13.3%, placebo 12.3% - Demonstrated the potential negative effects on mortality with starting with an ICS immediately in the first step of COPD treatment

3. Clinical Controversy: Increased cardiovascular disease risk in COPD patients using anticholinergics agents.

Background:

In March 2008, the FDA announced a safety alert regarding the use of tiotropium and possible increase in stroke. An unpublished pooled safety analysis of 29 placebo-controlled studies performed by Boehringer Ingelheim estimated that the risk of stroke was 8 patients per 1000 patients treated for one year with tiotropium (Spiriva®) and 6 patients per 1000 patients treated for one year with placebo. (FDA tiotropium safety information, 2008).

Since this safety alert was announced, there has been conflicting data regarding the cardiovascular safety of tiotropium. The meta-analysis by Singh, 2008 suggests that anticholinergic use is associated with an increase in cardiovascular disease; however this analysis did not include the long term UPLIFT study which does not suggest increased stroke or MI risk with long-term tiotropium use.

Clinical summary and bottom line:

The additional trial data published since 2007 does not change the COPD treatment guidelines on pg 38.

Inhaled corticosteroids should be reserved for moderate-severe COPD. TORCH demonstrated the negative effects on mortality with starting with an ICS immediately in the first step of COPD treatment

Long-acting anticholinergics (i.e. tiotropium) are for symptomatic treatment only. Tiotropium improves lung function and decreases hospitalization rates, but do not affect the rate of lung function decline (UPLIFT, 2008)

The potential increase in cardiovascular disease with anticholinergic use is controversial, but the estimated absolute increase is small (0.6%).

Inhaled corticosteroids increase the risk of pneumonia by about 4%.

4. Treatment of Acute Exacerbations of Chronic Bronchitis (AECB) and Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) (Guideline pg. 43/44 CHANGES TO TREATMENT TABLE AND RISK STRATIFICATION).

Quinolones are no longer recommended in low-risk (simple) cases. For complete up-date see pages 26/27 of *Anti-infective Guidelines for Community-acquired Infections* 2010.

References

- 1) Anti-infective Review Panel. Anti-infective Guidelines for Community-acquired Infections 2010. Toronto: MUMS Guidelines Clearinghouse. 2010.
- 2) Becker A, Lemiere C, Berube D, et al. Summary of recommendations from the Canadian Asthma Consensus guidelines, 2003. *CMAJ*. 2005;173(6 Suppl):S3-11.
- 3) Becker A, Berube D, Chad Z, et al. Canadian Pediatric Asthma Consensus guidelines, 2003 (updated to December 2004): introduction. *CMAJ*. 2005;173(6 Suppl):S12-4.
- 4) Bousquet J, Clark TJ, Hurd S. et al. GINA guidelines on asthma and beyond. *Allergy*. 2007;62(2):102-12.
- 5) BTS/SIGN (British Thoracic Society, Scottish Intercollegiate Guidelines Network); Management of asthma. A national clinical guideline: London; 2007. Available at: <http://www.brit-thoracic.org.uk/>
- 6) Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356(8):775-89.
- 7) Calverley PM, Rabe KF, Goehring UM et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009;372:685-94.
- 8) Fabbri LM, Calverley PMA, Izquierdo-Alonso JL et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. *Lancet* 2009; 374: 695–703.
- 9) FDA MedWatch Safety Information and Adverse Event Reporting Program, Tiotropium. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/> Accessed October 9th, 2009.
- 10) GINA (Global Initiative for Asthma). Global strategy for asthma management and prevention. 2008. Available at: <http://www.ginasthma.com/>
- 11) GINA (Global Initiative for Asthma). Asthma Management and Prevention in Children 5 years and younger. 2009 Available at: <http://www.ginasthma.com/>
- 12) GOLD (Global Initiative for Chronic Obstructive Lung Disease). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2010. Available at: <http://www.goldcopd.com/>
- 13) Hanania NA *et al.* Efficacy of Roflumilast in Patients Receiving Concomitant Treatments for Chronic Obstructive Pulmonary Disease Over 12 Months. *Am J Respir Crit Care Med* 2010;181: A4435
- 14) ICSI (Institute for Clinical Systems Improvement). *Health care guideline: diagnosis and management of asthma*. 2008; Available at: www.icsi.org
- 15) Loughheed MD, Lemiere C, Dell S, et al. Canadian Thoracic Society Asthma Management Continuum - 2010 Consensus Summary for children 6 years and over and adults. *Can Respir J* 2010; 17 (1).
- 16) NAEPP (National Heart, Lung, and Blood Institute and National Asthma Education and Prevention Program). Expert panel report 3: guidelines for the diagnosis and management of asthma. 2007. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf>
- 17) NICE (National Institute for Clinical Excellence). Corticosteroids for the treatment of chronic asthma in adults and children aged 12 years and over. NICE technology appraisal guidance 138. 2008. Available at: <http://www.nice.org.uk/>
- 18) O'Donnell DE, Hernandez P, Kaplan A, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update. *Can Respir J*. 2008;15 Suppl A:1A-8A
- 19) O'Donnell DE, Aaron S, Bourbeau J. et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. *Can Respir J*. 2007;14 Suppl B:5B-32B.
- 20) Pedersen S. From asthma severity to control: a shift in clinical practice. *Prim Care Resp J*. 2009;18: in press. E-published Oct. 2009.
- 21) Peters SP, Kunselman SJ, Icitovic N et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *NEJM* 2010; 363; 1715-26.
- 22) Prener BM. Role of long-acting beta2-adrenergic agonists in asthma management based on updated asthma guidelines. *Curr Opin Pulm Med*. 2008;14(1):57-63.
- 23) Singh S, Amin AV, Loke YK. Long-term Use of Inhaled Corticosteroids and the Risk of Pneumonia in Chronic Obstructive Pulmonary Disease. *Arch Intern Med* 2009;169:219-229.
- 24) Singh S, Loke YK, Furberg CD. Inhaled Anticholinergics and Risk of Major Adverse Cardiovascular Events in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis. *JAMA* 2008;300:1439-50.
- 25) Tashkin DP, Celli B, Senn S et al. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2008;359: 1543-54.
- 26) Wedzicha JA, Caverley PM, Seemungal TA et al. The Prevention of Chronic Obstructive Pulmonary Disease Exacerbations by Salmeterol/Fluticasone Propionate or Tiotropium Bromide. *Am J Respir Crit Care Med* 2008;177:19-26.