Can Reactive Airways Dysfunction Syndrome (RADS) Be Iatrogenic?

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Reactive airways dysfunction syndrome (RADS) is an asthma-like illness that develops after a single high-level exposure to a pulmonary irritant. Two different cases are reviewed, in which the exposure circumstances were not sufficient to result in adverse health effects yet resulted in persistent respiratory symptoms and a clinical diagnosis of RADS. Potential explanations for an erroneous diagnosis of RADS included an incomplete exposure assessment, medication adverse effects that can contribute to respiratory symptoms, and alternative explanations for respiratory symptoms or test findings. In particular, the empirical use of bronchodilator medications without a clear indication appeared to contribute to continued respiratory symptoms. Without a clear understanding of the patient's exposure, a RADS diagnosis should be carefully considered. The possibility of an iatrogenic sequence of events in which medication adverse effects facilitate respiratory symptoms and a mistaken RADS diagnosis should be considered, particularly in patients who have a poorly defined exposure history. *Key words: reactive airways dysfunction syndrome; RADS; albuterol; bronchodilator; gastroesophageal reflux; hydrogen sulfide; hydrochloric acid; iatrogenic.* [Respir Care 2011;56(8):1188–1194. © 2011 Daedalus Enterprises]

Introduction

Reactive airways dysfunction syndrome (RADS), also termed acute irritant-induced asthma, is an asthma-like illness that develops after a single high-level exposure to a pulmonary irritant.[1-3] RADS cases originally described by Brooks, and subsequent reports, typically involved intense high-level exposure to a pulmonary irritant, which resulted in acute respiratory symptoms of a severity generally requiring immediate medical attention and hospitalization. Those reported after lower exposures involved extended exposure to the irritant. Often the exposure occurred in a confined space, an environment with limited ventilation, or in circumstances in which the individual was not able to immediately escape the exposure. The criteria described by Brooks et al include:

- Documented absence of preceding respiratory complaints
- Symptoms onset after one specific exposure incident or accident
- The gas, smoke, fume, or vapor was in a very high concentration and had irritant qualities
- Symptoms onset within 24 hours of exposure, and symptoms persist for at least 3 months
- Requires immediate medical assistance
- Symptoms mimic asthma: cough, wheezing, and dyspnea predominate
- Pulmonary function tests (PFTs) may show air-flow obstruction
- Methacholine challenge test positive at levels in the range of asthma (ie, < 8 mg/mL)
- Other types of pulmonary diseases ruled out

The validity of RADS diagnoses has been controversial. The diagnosis is frequently complicated by difficulty in quantifying the chemical exposure, the absence of pre-exposure baseline PFT data, and inability to fully exclude

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other potential causes of respiratory symptoms, such as smoking, allergies, infections, other exposures, or other health conditions. In a review of published RADS cases, Shakeri et al reported that in 59 reviewed articles, only 63 (11%) of 570 cases met Brooks's criteria, and the others had insufficient data.[4]

Review of cases in litigation has indicated that some physicians have made a RADS diagnosis without a clear understanding of the chemical involved, the extent of exposure, and/or the known association, if any, between the chemical in question and RADS. Several errors may then ensue: respiratory treatments are started empirically; diagnostic studies can be misinterpreted; and alternative explanations for the reported symptoms are not fully considered. One or more of these factors then leads to an erroneous diagnosis of a chronic respiratory condition, with attendant disability.

Using 2 illustrative litigated cases that have been resolved, potential sources of error associated with a RADS diagnosis and the potential complications associated with treatment were reviewed. The author, as an occupational medicine physician, was retained to address the validity of the RADS diagnosis by evaluating the exposure circumstances, the toxicology of the involved chemicals, and potential alternative causes. In both cases, the physicians who made the RADS diagnosis were the original primary care physician and pulmonologist, who made the diagnosis prior to litigation. The 2 cases, which were selected from a series of several unrelated cases with similar findings, occurred in different areas of the United States, had different treating physicians, and had different exposures, but resulted in a similar progression of post-exposure events. Specific details of the cases and identifying information have been omitted to preserve confidentiality, while still permitting a discussion of key findings.

Case Report 1

A 54-year-old male barge fuel tank inspector reported an exposure to hydrogen sulfide during his work. He noted a characteristic rotten-egg smell and symptoms of a runny nose, sore throat, and tightness in his chest, while he was examining tanks. There was no loss of consciousness or other symptoms suggestive of a high-level exposure. His history was notable for gastroesophageal reflux and occasional use of proton-pump inhibitors. He had quit smoking several years prior, but had smoked about half a pack per day for 20 years, and still smoked an occasional cigar. There was no history of asthma or other respiratory conditions.

During the incident he was wearing a personal hydrogen sulfide monitor, which provided continuous monitoring and documentation of hydrogen sulfide exposure near his breathing zone and which confirmed the degree of exposure. The monitor data showed 10 hydrogen sulfide exposures that were above the alarm level of 10 parts per million (ppm), and ranged as high as 45 ppm during 2 consecutive days. However, all the exposures were less than one minute. The peak measured exposure of 45 ppm was for 12 seconds. He had been trained to remove himself immediately from the source of exposure if his monitor alarmed, which explains the short duration of the exposures.

After the exposure he went on a previously planned vacation for several days, and then returned to work. Approximately 2 weeks after the incident, he saw his primary care physician, complaining of a productive cough, nasal discharge, and subjective fever and chills. His lungs were clear, but he had coughing on deep inspiration. His PFT, despite coughing during the test, showed that forced vital capacity and FEV_1 were both $> 80\%$ of predicted, with minimal change from a pre-employment PFT. A chest radiograph was negative. He was started on an albuterol inhaler and an antibiotic for a diagnosis of pneumonitis and bronchitis. He was seen one week later with a continued unrelenting cough and referred to a pulmonologist for further evaluation. His pulmonologist noted a history of "sulfa fume" exposure and symptoms of rhinorrhea and congestion prior to the exposure incident. He was diagnosed with RADS secondary to sulfa fumes and recommended not to return to work. His treatment included additional antibiotics, a prednisone dose-pack, and albuterol home nebulizer treatments 4 times a day. A fluticasone-salmeterol inhaler was later added. Four months later he was found to have continued unrelenting cough triggered by various fumes, had not returned to work, and was still using the nebulizer 4 times a day.

Case Report 2

A 50-year-old male reported exposure to hydrochloric acid fumes while staying at a roadside motel. The incident was caused by a tanker truck parked overnight at the motel, which began leaking hydrochloric acid during the night. The motel was immediately evacuated when a whitish cloud around the leaking truck was identified. He was asleep in his room when firemen knocked on the door to wake him and advise him to leave. He exited the room and walked to a staging area away from the leaking tanker truck. Although he reported not smelling anything unusual in the room or when he went outside, he requested to be seen in the emergency room, due to concern about possible exposure. His medical history was notable for a 15-year smoking history of 0.5–1.5 packs per day. He had no history of asthma or other respiratory conditions.

At the emergency room on the day of the incident, he had no complaints or objective findings of eye irritation and no respiratory symptoms such as shortness of breath,

coughing, wheezing, or respiratory distress. He was able to converse easily with no hoarseness. His lungs were clear, oxygen saturation was normal on room air, and a chest radiograph was normal. His treatment included an intramuscular injection of dexamethasone and acetaminophen for a headache. He was discharged within 2 hours, and returned to the motel, where he was interviewed by the local news channel. There was no evidence of eye irritation, skin burns, respiratory distress, coughing, or hoarseness during the interview.

No air monitoring data were collected during the incident. However, no one else who was in the motel nor any of the response personnel experienced health effects that required medical evaluation. This included the truck driver, who was also staying at the motel, in a room closer to the leaking truck, and inspected the leaking valve on the truck that morning without wearing respiratory protection.

He was not seen again by a health provider until a month after the incident. At that time he was noted to have difficulty breathing, with wheezing and coughing, for 3 days. He had been using his son's albuterol inhaler up to 6 times per day for an undetermined period. He was subsequently diagnosed with RADS secondary to the hydrochloric acid exposure, and was started on a course of antibiotics, tapering steroids, and bronchodilators, including home nebulizer treatments. He was using an albuterol inhaler up to 5 times per day several months after the incident. A fluticasone-salmeterol inhaler was later added to his treatment regimen. A history of "severe" gastroesophageal reflux since the incident was identified as contributing to his respiratory symptoms and was attributed to the hydrochloric acid exposure by his physician. A PFT obtained 6 months after the incident showed a mild obstructive or mixed pattern, with normal diffusion capacity, and no response to bronchodilators. There were no prior PFTs for comparison. Approximately one year after the incident, a methacholine challenge test was obtained and interpreted as positive at a dose of 6 mg/mL. At that time he had not returned to work and was noted to have continued heartburn, hoarseness, nocturnal cough, and shortness of breath. His physician concluded that all his symptoms were related to a hydrochloric acid inhalational injury, and that RADS was confirmed by the methacholine challenge test.

Analysis of the RADS Diagnoses

Review of these 2 cases indicated that they fit several of the criteria for a RADS diagnosis (Table 1). However, the fundamental criterion for making a RADS diagnosis is that exposure to a high level of a respiratory irritant occurred. In these 2 cases this criterion was not met and thereby does not support a RADS diagnosis.

Table 1. Analysis of the 2 Cases Reviewed Per the RADS Criteria

RADS Criteria	Case 1 (hydrogen sulfide)	Case 2 (hydrochloric acid)
Absence of preceding respiratory complaints	Yes	Yes
Onset after a single exposure incident	Yes	Yes
Chemical has irritant qualities	Yes	Yes
Exposure to high concentration	No	No
Onset of symptoms within 24 h	No	No
Required immediate medical assistance	No	No
Symptoms mimic asthma	Yes	Yes
Pulmonary function tests show obstruction	No	Yes
Positive methacholine challenge test	Not done	Yes
Other explanations ruled out	No	No

RADS = reactive airways dysfunction syndrome

Discussion

The term "iatrogenic" is defined as "an unfavorable response to therapy, induced by the therapeutic effort itself."[5] In the described cases, the exposure clearly was not consistent with the development of persistent respiratory effects, based on personal air monitoring, exposure circumstances, and clinical presentation. However, in both cases the respiratory status appeared to substantially worsen after the exposure and did not improve with treatment. The physicians' reasoning in diagnosing RADS appeared to be based mainly on the temporal relationship of the exposure. Causal opinions based on such reasoning may be termed *post hoc*, *ergo propter hoc* (ie, after this, therefore because of this). Reasoning that one event preceded another event is not sufficient for establishing a causal association; additional investigation is required to determine whether there is a true causal relationship. Regardless, incorrect RADS diagnoses led to unnecessary treatment and reported disability.

It is unknown whether these cases are representative of a tendency to misdiagnose or overdiagnose RADS. Because such cases typically involve an unforeseen environmental exposure, they are frequently the subject of litigation claims that further skew analysis. While the possibility of permanent airway injury from inhalation of irritant gases should not be discounted, these and other reviewed cases have demonstrated RADS diagnoses that were highly questionable, based on the exposure history. The literature contains numerous RADS case reports in which there was limited exposure assessment and raises the question of whether other explanations were fully considered. Potential errors in diagnosing RADS and the sequelae that can result from an erroneous RADS diagnosis are described on the next page.

Table 2. Chemicals and Exposures in the 2 Cases Reviewed

	Case 1 (hydrogen sulfide)	Case 2 (hydrochloric acid)
Chemical description	Colorless gas	Colorless fuming gas
Sources	Sewer gas, hot springs, swamps, cigarette smoke, vehicle exhaust, intestinal gas, human breath	Stomach acid, consumer products such as toilet bowl cleaner and muriatic acid used in cleaning masonry
Odor	Rotten eggs	Pungent
Odor threshold	< 1 ppm	< 1 ppm
Health effects	5–50 ppm: Mild eye irritation > 150 ppm: Olfactory paralysis 250 ppm: Pulmonary edema ≥ 700 ppm: Unconsciousness	5–10 ppm: Immediately irritating 10–50 ppm: Maximum tolerable concentration
OSHA PEL*	20 ppm (ceiling) 50 ppm (peak)	5 ppm (ceiling)
Exposure level	5–45 ppm	Probably < 1 ppm No odor detected
Duration of exposure	Seconds	Unknown: sleeping during reported exposure period

* For hydrogen sulfide, the Occupational Safety and Health Administration Permissible Exposure Limit (OSHA PEL) for hydrogen sulfide is 20 ppm (ceiling), with the exception that if no other measurable exposure occurs during an 8-hour work shift, the exposure may exceed 20 ppm but not more than 50 ppm (peak) for a single time period of up to 10 min. For hydrochloric acid, exposures should not exceed 5 ppm during an 8-hour shift. (Adapted from References 6 and 7.)

Diagnosis Based on Incomplete Exposure Assessment

As demonstrated in the above-described cases, the physician may conclude that an individual has RADS without a clear understanding of the exposure. The diagnosis may be based mainly on the patient's self-reported exposure description, with limited attempts to determine the severity of the exposure or the potential for the exposure to cause adverse health effects. While patient history is the first step in obtaining a valid diagnosis and cannot be ignored, a more evidence-based approach is necessary when evaluating these types of cases. In the absence of air monitoring data, other indicators of exposure can be assessed, such as the severity of mucous membrane irritation or occurrence of symptoms in other individuals similarly exposed.

The potential for a specific chemical to cause RADS can also be assessed by examining its toxicology profile, dose-response relationship, and whether there are any reports of the chemical causing RADS. Table 2 shows relevant toxicology information for hydrogen sulfide and hydrochloric acid. In Case 1, personal air monitoring data demonstrated that the exposures were brief and below the occupational exposure guideline levels. Such levels are not known to cause irreversible respiratory effects. Although no air monitoring data were available for Case 2, the lack of substantial exposure was evident from the fact that he did not detect the pungent smell of hydrochloric acid, was asleep at the time the exposure supposedly occurred and was not awakened by irritant effects, had no relevant objective findings when he was seen at the emergency room, and was able to return to the scene of the incident within hours of the exposure with no obvious evidence of irritant effects.

Despite the widespread presence of hydrogen sulfide in the environment, a review of the literature identified only one case report of RADS possibly attributed to hydrogen sulfide.[8] That case involved an exposure in a poorly ventilated swine confinement building. The described exposure was not comparable to that of Case 1, given that the hydrogen sulfide level was apparently high enough to cause death in nearby animals. Similarly, there have been few reports of RADS secondary to hydrochloric acid, and in the cases in which persistent respiratory effects were reported, the affected individuals had substantial and immediate irritant effects.[9-13]

In the present 2 cases, which eventually went into litigation, there ultimately was a wealth of additional information regarding the exposure to determine the plausibility of a RADS diagnosis. This included depositions from involved individuals, air testing data, air modeling, interviews with coworkers or bystanders, and emergency responder reports. As in these cases, it is unlikely that a physician will obtain the full story on an exposure incident from the initial patient history alone. However, without a more clear understanding of the involved chemical and

reported exposure, a diagnosis of RADS should be carefully considered. Missing data should be identified by the treating physician, with an attempt to verify the exposure. This may require a call to the patient's employer to obtain additional information regarding the exposure, a site visit to get a better understanding of the exposure circumstances, review of the medical and toxicology literature regarding the chemical, and/or consultation with a toxicologist to determine the potential health effects of the exposure. Based on the exposure circumstances and initial presenting symptoms alone, it would have been difficult to substantiate a diagnosis of RADS in these 2 cases, regardless of the identity of the involved chemicals.

Potential Treatment Errors and Consequences

Review of these and other suspected RADS cases has found that patients often are empirically started on a treatment regimen of inhaled steroids and bronchodilators to address respiratory complaints. The present 2 cases showed little improvement and were arguably worse after such treatment. This sequence of events may be secondary to the medications rather than to the initial exposure.

The National Heart Lung and Blood Institute asthma management guidelines state that regularly scheduled, daily, ongoing use of short-acting bronchodilators such as albuterol is not recommended and can have deleterious respiratory effects.[14] Long-term use of β_2 agonists is associated with tachyphylaxis to the bronchodilating effect, reduced baseline FEV_1 (possibly secondary to decreased airway caliber and rebound bronchoconstriction), increased bronchial hyper-responsiveness, and increased bronchial sensitivity to allergens.[15-19] Such effects have been reported to occur at relatively low doses, within only a week of use.[20,21]

In the present 2 cases, albuterol inhaler use began within one month of the reported exposures. The indication for albuterol use was questionable, and there was evidence that it was used excessively. In addition, regular home nebulizer treatments, up to 4 times a day with albuterol, were later added, potentially increasing the deleterious effects on lung function. There was no evidence in either case of severe bronchoconstriction at any time following the exposure incident that resulted in an emergency department visit, hospitalization, or substantially decreased respiratory function as measured by a PFT or peak flow meter.

The use of inhaled corticosteroids also is a consideration for complaints of persistent cough. In a survey of adult asthma patients using inhaled steroids, persistent cough, hoarseness, and throat irritation were observed much more frequently than anticipated.[22] It was speculated that a residue from the inhaled substance may contribute to irritation of the pharyngolaryngeal mucosa. Both the present cases were later started on a fluticasone-salmeterol inhaler, within a few months after presentation, which might have been a further source of β_2 agonist adverse effects, in addition to the irritant effects of the preparation itself.

Another potential explanation for this sequence of events is the induction or exacerbation of preexisting gastroesophageal reflux. Reflux is often associated with asthma and is one of the most common causes of chronic cough.[23] Patients with asthma who have documented gastroesophageal reflux have greater airway responsiveness, which tends to increase as gastroesophageal reflux worsens.[24] Gastroesophageal reflux is also associated with greater bronchial reactivity in individuals without asthma.[25] It is theorized that the association of gastroesophageal reflux and asthma may be secondary to chronic microaspiration of stomach acids into the airways, with resulting inflammation of the airways and, in effect, an intrinsic cause of RADS.

In addition to the direct adverse respiratory effects described above, asthma medications can increase the symptoms of gastroesophageal reflux. Inhaled bronchodilators may increase the risk of gastroesophageal reflux, due to a dose-dependent relaxation of the lower esophageal sphincter, which facilitates upward movement of stomach acids.[26] A proposed mechanism is that much of the "inhaled" dose is swallowed, which relaxes smooth muscle in the digestive tract.[27] Oral corticosteroids may increase gastroesophageal reflux and associated symptoms due to increased esophageal acid contact time. Patients may note the onset or worsening of gastroesophageal reflux after beginning oral corticosteroids.[28]

As demonstrated in the present 2 cases, bronchodilator medication use without a clear indication is a potential, albeit unproven, explanation for increased gastroesophageal reflux and associated respiratory symptoms. Both of the present cases had a history of gastroesophageal reflux and/or increased gastroesophageal reflux symptoms following exposure-related treatment. Unfortunately, neither patient underwent evaluation to determine the relative severity of their gastroesophageal reflux or the adequacy of treatment.

Diagnostic Errors

The primary test to confirm RADS is the methacholine challenge test, performed to demonstrate the presence of airway hyperreactivity. However, the methacholine challenge test has poor positive predictive value, as there are numerous conditions associated with a positive test.[25]

In Case 1 a RADS diagnosis, surprisingly, was made without any attempt to confirm airway hyper-reactivity. In Case 2, RADS was diagnosed based on a methacholine challenge test that showed borderline hyper-reactivity at 6 mg/mL.[29] In addition, a history of concurrent smoking and severe gastroesophageal reflux in Case 2 are important

confounders that are associated with a higher rate of positive methacholine challenge test results. Thus, the positive methacholine challenge test in Case 2 does not reliably confirm a diagnosis of RADS and must be considered in the context of other information.

Alternative Explanations

In addition to possible medication adverse effects and gastroesophageal reflux, these 2 cases had other confounders that raise questions as to the validity of a RADS diagnosis. In Case 1 there was clear evidence of a respiratory infection at the time of the exposure. Case 2 presented a month after the reported exposure with a 3-day history of cough suggestive of a respiratory infection. Despite those findings, their treating physicians generally discounted the possibility of a respiratory infection, rather than a poorly documented chemical exposure, as the basis for their initial respiratory complaints.

Both patients were smokers. Cigarette smoke is composed of thousands of chemicals and is a respiratory irritant. Because one of the characteristics of RADS is increased sensitivity to airway irritants, it would seem unlikely that an individual with true RADS would be able to tolerate continued smoking or be around others who smoke. The reliability of a RADS diagnosis in a current smoker must be seriously questioned. In the present cases the tolerance for smoking was largely ignored.

Other common conditions that may not be fully considered by the physician and may be associated with increased airway reactivity, include chronic sinusitis, allergic rhinitis, obstructive sleep apnea, and autoimmune diseases. Because these conditions may be associated with a positive methacholine challenge test, their presence may also affect the reliability of a RADS diagnosis.

A diagnosis of RADS requires substantial exposure to a chemical irritant. In the 2 described cases the reported exposure was exceedingly unlikely to have resulted in permanent respiratory symptoms, and suggests alternative etiologies for their continued respiratory symptoms. Although the exact cause of post-exposure symptoms in these 2 individuals is unknown, their use of inhaled medications is one possible explanation. Admittedly, the latter inference is the same type of *post hoc*, *ergo propter hoc* reasoning that lead to the original RADS diagnosis. However, an important distinction is that the medications were being used regularly at a dose and frequency not recommended for the control of asthma and that excessive use of these medications has known adverse respiratory effects. Taken together, these facts strongly suggest a potential causal relationship that could have been further explored by the treating physicians. Due to the litigation environment, one must also consider the possibility of symptom embellishment. Despite these limitations, the fact remains that an erroneous RADS diagnosis resulted in avoidable and arguably iatrogenic outcomes, including an unfounded determination of disability and unnecessary medication use.

Prior to diagnosing and instituting treatment for RADS, the treating physicians should ensure that they understand the reported exposure and whether its association with RADS is plausible. This is particularly true with patients who appear to have had a minimal exposure and required minimal treatment immediately after the exposure incident. The possibility of an iatrogenic sequence of events, in which adverse medication effects facilitate respiratory symptoms and a mistaken RADS diagnosis, should be considered, particularly in a patient with a poorly defined exposure history.

REFERENCES

1. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. Chest 1985;88(3):376–384.
2. Brooks SM. Irritants, sensitisers and asthma symposium: reactive airways syndromes. J Occup Health Safety, Aust NZ 1992;8(3):215–220.
3. Brooks SM. Occupational and environmental asthma. In: Rom WN, editor. Environmental & occupational medicine. Philadelphia: Lippincott-Raven; 1998:481–524.
4. Shakeri MS, Dick FD, Ayres JG. Which agents cause reactive airways dysfunction syndrome (RADS)? A systematic review. Occup Med (Lond) 2008;58(3):205–211.
5. Stedman TL. Stedman's illustrated medical dictionary. Baltimore: Lippincott, Williams & Wilkins; 1982.
6. Beauchamp RO, Bus JS, Popp JA, Boreiko CJ, Andjelkovich DA. A critical review of the literature on hydrogen sulfide toxicity. Crit Rev Toxicol 1984;13(1):25–97.
7. American Industrial Hygiene Association. The AIHA 1998 emergency response planning guidelines and workplace environmental exposure level guides handbook.
8. Cormier Y, Coll B, Laviolette M, Boulet LP. Reactive airways dysfunction syndrome (RADS) following exposure to toxic gases of a swine confinement building. Eur Respir J 1996;9(5):1090–1091.
9. Boulet LP. Increases in airway responsiveness following acute exposure to respiratory irritants. Reactive airway dysfunction syndrome or occupational asthma? Chest 1988;94(3):476–481.
10. Boyce SH, Simpson KA. Hydrochloric acid inhalation: who needs admission? J Accid Emerg Med 1996;13(6):422–424.
11. Finnegan MJ, Hodson ME. Prolonged hypoxaemia following inhalation of hydrogen chloride vapour. Thorax 1989;44(3):238–239.
12. Promisloff RA, Lenchner GS, Phan A, Cichelli AV. Reactive airway dysfunction syndrome in three police officers following a roadside chemical spill. Chest 1990;98(4):928–929.
13. Tarlo SM, Broder I. Irritant-induced occupational asthma. Chest 1989; 96(2):297–300.
14. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma: summary report 2007. J Allergy Clin Immunol 2007;120(5 Suppl):S94–S138. Erratum in: J Allergy Clin Immunol 2008;121(6): 1330.
15. Wraight JM, Hancox RJ, Herbison GP, Cowan JO, Flannery EM, Taylor DR. Bronchodilator tolerance: the impact of increasing bronchoconstriction. Eur Respir J 2003;21(5):810–815.
16. Wraight JM, Smith AD, Cowan JO, Flannery EM, Herbison GP, Taylor DR. Adverse effects of short-acting beta-agonists: potential

impact when anti-inflammatory therapy is inadequate. Respirology 2004;9(2):215–221.
17. Taylor DR, Sears MR, Herbison GP, Flannery EM, Print CG, Lake DC, et al. Regular inhaled beta agonist in asthma: effects on exacerbations and lung function. Thorax 1993;48(2):134–138.
18. Cockcroft DW, Bhagat R, Kalra S, Swystun VA. Inhaled beta 2-agonists and allergen induced airway responses. J Allergy Clin Immunol 1995;96(6 Pt 1):1013–1014.
19. Bhagat R, Swystun VA, Cockcroft DW. Salbutamol-induced increased airway responsiveness to allergen and reduced protection versus methacholine: dose response. J Allergy Clin Immunol 1996; 97(1 Pt 1):47–52.
20. Wahedna I, Wong CS, Wisniewski AF, Pavord ID, Tattersfield AE. Asthma control during and after cessation of regular beta2 agonist treatment. Am Rev Respir Dis 1993;148(3):707–712.
21. Inman MD, O'Byrne PM. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. Am J Respir Crit Care Med 1996;153(1):65–69.
22. Bhalla RK, Jones AS, Roland NJ. Prevalence of pharyngeal and laryngeal complications in adult asthmatics using inhaled corticosteroids. J Laryngology Oncology 2008;122(10):1078–1083.
23. Irwin RS. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. Chest 2006;129(1 Suppl):80S–94S.
24. Stein MR. Possible mechanisms of influence of esophageal acid on airway hyperresponsiveness. Am J Med 2003;115(Suppl 3A):55S–59S.
25. Hewitt DJ. Interpretation of the "positive" methacholine challenge. Am J Ind Med 2008;51(10):769–781.
26. Crowell MD, Zayat EN, Lacy BE, Schettler-Duncan A, Liu MC. The effects of an inhaled beta(2)-adrenergic agonist on lower esophageal function: a dose-response study. Chest 2001;120(4):1184–1189.
27. Lacy BE, Mathis C, DesBiens J, Liu MC. The effects of nebulized albuterol on esophageal function in asthmatic patients. Dig Dis Sci 2008;53(10):2627–2633.
28. Lazenby JP, Guzzo MR, Harding SM, Patterson PE, Johnson LF, Bradley LA. Oral corticosteroids increase esophageal acid contact times in patients with stable asthma. Chest 2002;121(2):625–634.
29. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing, 1999. Am J Respir Crit Care Med 2000;161(1):309–329.