

Airway Acidification and Gastroesophageal Reflux

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Current Allergy and Asthma Reports 2008, 8:79–84

Current Medicine Group LLC ISSN 1529-7322

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Although challenging to study, researchers recently recognized the relevance of airway pH to the pathophysiology of several respiratory diseases, ranging from asthma and cystic fibrosis to pneumonia. The airway epithelium is extraordinarily sensitive to acid. Gastroesophageal reflux can and does cause respiratory symptoms, through both neurally mediated pathways and direct aspiration. Direct aspiration has a variety of immunologic, biochemical, and physiologic effects that aggravate asthma and other respiratory diseases, yet strategies to diagnose and treat gastroesophageal reflux-related respiratory symptoms remain imprecise.

Introduction

Gastroesophageal reflux is one of three broad pathways by which the airways can become acidified [1,2]. The other mechanisms include airway exposure to inhaled acidic aerosols (eg, acid fog) or reactive acidifying gases (eg, chlorine) and disorders of acid- and base-producing mechanisms in the airway epithelial surface itself [1–9]. This third pathway is termed “intrinsic airway acidification” and perhaps serves as an innate immune response to dispose of acid-sensitive invading microbes such as mucoid *Pseudomonas*, rhinovirus, and tuberculosis [1,10•,11•,12]. Airway pH homeostatic processes are only beginning to be investigated, but deviations from pH homeostasis are known to be associated with respiratory diseases including acute asthma, cystic fibrosis, chronic obstructive pulmonary disease (COPD), and bronchopulmonary dysplasia (Table 1) [1,2,11•,13,14•,15•].

Airway Sensitivity to Acid

The airway epithelium is intolerant of acidification [1,2]. Unlike the esophagus—which can readily tolerate acid

contact times of 5% or more and has no problem swallowing acidic drinks [16]—even brief, mild acid insults to the airway activate potent cough and bronchoconstrictive responses and substantially enhance mucus production [1,2,17–19]. Although rapid vagal-mediated airway responses have been associated with isolated esophageal acidification (ie, an airway response to esophageal acid in the absence of aspiration) in some animal studies, the effect of direct airway acidification through aspiration is dramatically greater and dominates the airway pathophysiology of acidic reflux [1,2]. Diseases characterized by intrinsic airway acidification (eg, acute asthma), present with symptoms similar to those occurring after acidic gas inhalation [3], which are also similar to symptoms of patients who have respiratory complications of gastroesophageal reflux disease [4]. Airway acidification may be a central unifying feature of these diverse disease processes.

Difficulty of Measuring Airway pH

Why has such an intuitively important aspect of respiratory pathology received so little attention until recently? In part, the answer lies in the difficulty in obtaining reliable data regarding airway pH. Several factors underlie this difficulty:

1. Passing a pH probe endoscopically into the lung in healthy subjects is highly invasive.
2. Passing a pH probe endoscopically into the lung of patients with active respiratory disease, particularly those with an acute exacerbation of asthma, may worsen bronchospasm.
3. Airway lining fluid is spread out over the tennis court-sized expanse of the lung epithelial surface. Obtaining a sample from this thin layer of fluid without altering its composition is notoriously difficult.
4. The pH of airway lining fluid is unlikely to be anatomically homogenous [1,20•], any more than inflammation is homogenous in any one patient's lung. A scattered few pH measurements in the proximal four divisions of the bronchial tree using a wire pH probe are unlikely to report accurately the conditions of the entire airways/lung.

Table 1. Lung diseases associated with abnormal pH

Study	Disease
Balmes et al. [6], Kodric et al. [7], Honma et al. [8], Hunt et al. [9], Kostikas et al. [13], Herve et al. [16], Jack et al. [17], Boyle et al. [18], Shin et al. [20•], Avidan et al. [29]	Asthma
Kostikas et al. [13]	Chronic obstructive pulmonary disease
Yoon et al. [11•]	Cystic fibrosis
Carraro et al. [10•], Walsh et al. [14•], Hunt et al. [24]	Viral respiratory infection
Gaston et al. [12]	Tuberculosis
Hunt et al. [26•]	Chronic cough
Paget-Brown et al. [15•]	Bronchopulmonary dysplasia

5. Unlike the kidney, which is diagnostically biopsied whenever it is inflamed, lung physicians have been reluctant to biopsy the diseased lung (eg, in asthma); therefore, this potential source of information about pH regulatory enzymes in health and disease is not as routinely available.

Sputum pH has been studied to a certain extent, and there are several reports of sputum acidification occurring in association with respiratory disease [7,11•,21].

Recent Data Regarding Airway Acidification in Disease

The issue of airway pH has received more attention in the past decade because the difficulties of measuring it have been partially overcome by means of exhaled breath condensate (EBC) sampling. Collection of EBC during tidal breathing is a harmless process that can be performed even in patients with profound lung disease [12,13,22]. EBC consists of aerosolized particles or droplets of airway lining fluid that serve as seeds for substantial vapor-phase water condensation, with the water then trapping water-soluble gases, some of which are acids and bases. Acids tend to be volatile when protonated (and uncharged), therefore evaporating from the airway lining fluid more readily if the pH of the airway is acidic. Some of the exhaled acid is retrapped in EBC, altering its pH. This pH can be measured easily; if lower than normal, it serves as a qualitative—and to some extent quantitative—indicator that the airway at some level is acidic [1,9,22,23•].

The EBC assay most commonly employed involves gas standardization, which uses a nonreactive, CO₂-free gas to remove CO₂ from the EBC [9,23•]. CO₂ is a gaseous precursor of acid and is no more volatile from a low-pH source fluid than from a neutral-pH source. When CO₂ is lost from EBC, it causes the pH to drift up *ex vivo* by shifting the H₂CO₃ equilibrium: when it has been removed, pH of EBC is remarkably reproducible [5]. EBC pH assays have been used to identify airway acidification in patients with acute asthma, cystic fibrosis, COPD, acute respiratory distress syndrome, viral respiratory infections,

tuberculosis, and other lung diseases [9,13,14•,24]. EBC pH has been used as the primary, but not sole, indicator that the pH of the airway lining fluid may be substantially acidic in these conditions. Of note, airway acidification in these and other conditions has now been confirmed by more direct but complicated measurements [7].

Association between Airway Acidification and Gastroesophageal Reflux

As noted above, EBC pH assays can be affected by both gastric acid reflux [1,25,26•] and intrinsic pathways. In airways isolated from gastric acid exposure by cuffed endotracheal tubes, EBC acidification clearly occurs with primary respiratory diseases, and pH changes gradually under these conditions [1,14•], not suddenly as has been observed with transient episodes of acid reflux. However, in spontaneously breathing patients providing oral EBC samples, it can still be unclear which low-pH EBC values are caused by acid reflux. This is resolved using multiple collections of EBC from each patient. The pattern of EBC acidification during multiple EBC samples from one patient appears to differentiate between intrinsic airway acidification and reflux/aspiration. Specifically, a cough that is temporally associated (within 15 minutes) with EBC acidification is highly likely to respond to gastric acid suppression therapy [26•].

Gastroesophageal reflux has been associated unequivocally with respiratory symptoms [4,27–30], and there is substantial evidence that acid reflux events most commonly precede the respiratory symptoms [29]. Indeed, although most practicing lung specialists are convinced of the importance of acid reflux to asthma symptoms, they are confused about why the clinical efficacy data for proton pump inhibitors have not been clearly demonstrated [4,30] and remain insufficient for the US Food and Drug Administration to allow these agents to be marketed for respiratory disease. Practitioners are also frustrated by the absence of an objective test to diagnose gastroesophageal reflux-associated respiratory symptoms in their patients [31]. Proton pump inhibition may not be proven effective as

therapy for gastroesophageal reflux-associated respiratory symptoms in some trials due to flawed subject enrollment strategies and a failure to appreciate the heterogeneity of underlying asthma symptoms. Patients selected almost always have respiratory symptoms and symptomatic or pH-probe–documented esophageal acid reflux disease [4,31,32]. This is likely the wrong patient group to be studying, because the real issue is airway acid, not esophageal acid. Data support three primary characteristics of gastroesophageal reflux symptoms associated with asthma symptoms: the patient 1) regurgitates, 2) has proximal reflux, and 3) associates his/her respiratory symptoms with reflux events [33,34]. At least the first two of these risk factors are unequivocally proximal esophageal/pharyngeal acid exposures, likely associated with microaspiration and airway acidification. Therefore, when studying the links between acid reflux and respiratory disease, the appropriate study group is patients who have airway acidification associated with gastroesophageal reflux, a group now easily identifiable with EBC pH testing.

Microliter quantities of stomach acid entering the airway are sufficient to cause a log order greater increase in respiratory resistance than milliliters of acid placed in the esophagus, reflecting the extreme sensitivity of the airway to acid insult compared with the esophagus [18,35,36]. Indeed, such data have suggested that esophageal pH-monitoring techniques for acid reflux simply may not be sensitive enough to detect the tiny amounts of aspirated acid that may cause airway acidification and respiratory dysfunction [37]. In this regard, whereas standard gastroesophageal pH probe indices consider acid contact times of less than 5% to be normal, airway acid contact times of 0.1% are likely to be of clinical importance.

Another study suggesting the importance of direct airway acidification in gastroesophageal reflux disease–induced respiratory symptoms arises from data collected using EBC pH assays. In one study, multiple EBC samples were collected in patients with chronic cough. Those patients in whom relief was achieved with proton pump inhibitors had EBC acidification temporally associated with their cough episodes. In contrast, the proton pump inhibitor nonresponders did not have EBC acidification [25]. For patients without airway acidification, acid reflux is unlikely to be the cause; however, the differential diagnosis for their cough is still broad, and certainly, non-acid volume reflux remains possible.

Although some reflexes may help protect the airway during large-volume reflux that distends the esophagus [38], the normal neurally coordinated rapid and complete glottic closure that occurs to protect the airway during swallowing is not active; thus, acid aspiration during reflux events is common. Backup protective mechanisms involving acid-sensitive nerves trigger cough in an effort to protect the airway [2]. However, by the time the acid-sensitive reflexes are activated, some acid insult has already occurred to the airway epithelium.

Overall, consensus is building that in most patients, the presence of acid reflux to the level of the pharynx, often with aspiration and resultant airway acidification—regardless of esophageal disease—leads to most of the acid reflux–induced respiratory symptoms of gastroesophageal reflux. It is also appreciated that this mechanism may confound diagnosis and treatment of most major respiratory disease complexes.

High-dose twice-daily proton pump inhibition is now commonly used for suspected acid-reflux cough [39]. It is likely that this higher dosing is necessary to raise the pH of gastric refluxate sufficiently, so that it is less damaging to the highly acid-sensitive airway. Proton pump inhibition most commonly is prescribed to individual respiratory disease patients without objective diagnosis that acid is causing their symptoms. This is not optimal, given the expense of the medications and the increased risk for community-acquired pneumonia, ventilator-associated pneumonia, and osteoporosis associated with their use [40,41].

Airway Acidity and Respiratory Symptoms

Based on in vitro data, airway proton pumps have been calculated to acidify the airway lining fluid at a rate of 0.17 pH units per minute in response to an insult consisting of dust from a swine containment facility [42]. This effect was confirmed in EBC pH measurements performed after in vivo challenges with the same organic material in humans [43]. Indeed, treatment with systemic corticosteroids to shut down the inflammatory response results in normalization of EBC pH in human patients admitted to the hospital with asthma [22].

Intrinsic production of acid in the airway may serve in a host defense capacity, in part directly to kill microorganisms. In this sense, airway acidification may serve the same role as gastric acidification. Indeed, it recently was shown in vitro that T helper (Th) 1 cytokines, through activation of nitric oxide synthase, can acidify epithelial cells; moreover, this work confirmed that acidification can help prevent airway epithelial rhinovirus replication [10•]. Airway acidity will trigger protective acid receptors and result in cough, which may also assist in host defense by clearing organisms. The response to an airway acid insult can be expected to vary among patients. This may result from differential expression or activation of acid receptors in the airway (including vanilloid receptor-channels) [19,44]. Indeed, in patients with chronic cough of multiple etiologies, these acid receptors are upregulated. This new finding may help explain why some patients have a particularly low respiratory tolerance for airway acid in the context of acid-saturated mucus in asthma [45].

Immunologic Effects of Airway Acidification

Extracellular acidosis triggers maturation of human dendritic cells and production of interleukin (IL)-12 to

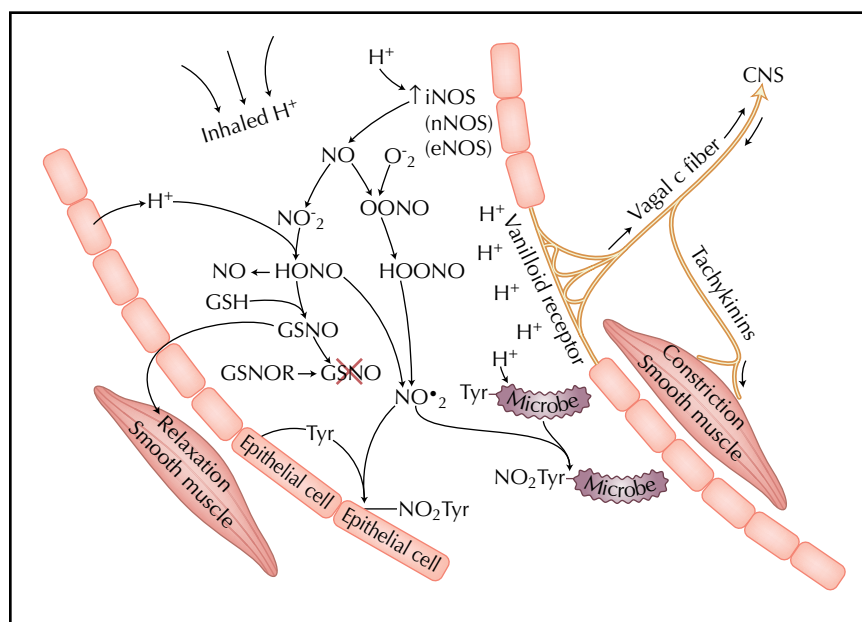


Figure 1. Schematic of interactions among acids, nitrogen oxides, and tachykinins in the airway. Acid (H^+) increases nitric oxide (NO) output from nitric oxide synthase enzymes (NOS). H^+ can be inhaled, aspirated, or excreted by cells. In the airway, H^+ can enhance oxidant activity and trigger acid-sensitive nerves (some of which are vanilloid receptors), which in turn release inflammatory and smooth muscle active tachykinins. Nitrite (NO_2^-)—a storage pool for NO activity—is protonated to nitrous acid (HONO), which serves as a precursor to the endogenous bronchodilator S-nitrosoglutathione (GSNO) or decomposes back to NO. GSNO can be catabolized by GSNO reductase (GSNO reductase), which is upregulated in asthma. NO can be oxidized to peroxynitrite (OONO) and NO_2^- , which, particularly when protonated to peroxynitrous acid (HOONO) and HONO, are capable of nitrating tyrosine residues (NO_2 -Tyr) of foreign and self proteins, in an immunologically relevant process. (Adapted from Hunt [50].)

stimulate interferon (IFN)- γ production [46•]. Further, eosinophils and neutrophils are activated and survive longer at low pH, and migrate down pH gradients toward the acidic areas [47,48]. Neurogenic inflammatory pathways (with tachykinins dominating) are activated by low pH [1] (Fig. 1). Particularly low pH causes necrosis and degranulation of leukocytes and injury to the airway epithelium. Finally, low pH itself has antimicrobial effects in the airway, protecting the epithelium from viruses such as rhinovirus and bacteria such as mucoid *Pseudomonas aeruginosa* [1,10•,11•,12].

Biochemical Effects of Airway Acidification

Nearly every enzyme in the airway is pH sensitive. Therefore, a decrease in airway pH causes a broad range of biochemical effects [1,9]. Oxidative stress, for example, is uniformly enhanced under acidic conditions (just as acid leads to iron rusting). For example, hypochlorous and hypobromous acids have pKa near neutral and are free-radical donors when protonated. Further, biologically important nitrogen oxides (including nitrite and peroxynitrite), have increased toxicities in an environment of low pH. For example, peroxynitrous (pKa ~ 6.9) and nitrous acids (pKa ~ 3.6) are free-radical donors when protonated. Moreover, mucus viscosity increases substantially at low pH [45], with conversion from the easy-flowing sol phase mucus to a mucus-plugging, thicker gel phase. These are examples of the range of biochemical effects of acidic effects of low pH in the airway [1,9].

Physiologic Effects of Low pH

Ciliary beating is inhibited at mildly low (< 6.5) pH values [49]. Further, mucus production/glandular secretion

is enhanced at low pH though neurogenic mechanisms. Bronchospasm and cough are triggered by acidity. Finally, surfactant dysfunction occurs at low pH.

Conclusions

Several lines of evidence now make it clear that airway pH is relevant to normal airway function and to disease. Evidence from many groups demonstrates that humans with asthma exhale more volatile acids than healthy controls. The explanation for the increased exhalation of acids lies in the increased volatility of many acids from source fluid with low pH. Airway lining fluid pH is usually mildly alkaline, but can become acidic by means of biochemical regulatory mechanisms in the lung itself and by mechanisms involving reflux and aspiration of gastric acids. Acid airway insults adversely affect airway biochemistry and cell biology. Perhaps for this reason, the airway has sensory mechanisms that identify acidity and reflexes leading to cough and bronchospasm. These mechanisms protect the airway by expelling the acid itself and microbes, but they also can cause troublesome or unnecessary symptoms. Simple, non-invasive, exhaled breath pH monitoring may become useful in defining which asthma symptoms are caused by acid and which are not and in providing prognostic information about asthma exacerbations and recovery. However, once airway acidification is recognized, appropriate therapy will require knowing the cause of the airway acidification. Specific differentiation of acid reflux from primary lower airway acidity is therefore an important goal.

Disclosures

Drs. Hunt and Gaston are founders of, and shareholders in, Respiratory Research, Inc.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Hunt JF, Gaston B, Ricciardolo F: Acid stress in the airway. *J Allerg Clin Immunol* 2004, **84**:731–765.
 2. Ricciardolo FL: Mechanisms of citric acid-induced bronchoconstriction. *Am J Med* 2001, **111**(Suppl 8A):18S–24S.
 3. Bosse GM: Nebulized sodium bicarbonate in the treatment of chlorine gas inhalation. *J Toxicol Clin Toxicol* 1994, **32**:233–241.
 4. Harding SM: Gastroesophageal reflux as an asthma trigger: acid stress. *Chest* 2004, **126**:1398–1399.
 5. Vaughan JL, Ngamtrakulpanit TN, Pajewski R, et al.: Exhaled breath condensate pH is a robust and reproducible assay of airway acidity. *Eur Respir J* 2003, **22**:889–894.
 6. Balmes JR, Fine JM, Christian D, et al.: Acidity potentiates bronchoconstriction induced by hyposmolar aerosols. *Am Rev Respir Dis* 1988, **138**:35–39.
 7. Kodric M, Shah AN, Fabbri LM, Confalonieri M: Airways acidification in asthma studied by means of induced sputum. *Am J Respir Crit Care Med* 2007, **175**:905–910.
 8. Honma S, Tanaka H, Teramoto S, et al.: Effects of naturally-occurring acid fog on inflammatory mediators in airway and pulmonary functions in asthmatic patients. *Respir Med* 2000, **94**:935–942.
 9. Hunt JF, Fang K, Malik R, et al.: Endogenous airway acidification. Implications for asthma pathophysiology. *Am J Respir Crit Care Med* 2000, **161**:694–699.
 10. Carraro S, Doherty J, Zaman K, et al.: S-nitrosothiols regulate cell-surface pH buffering by airway epithelial cells during the human immune response to rhinovirus. *Am J Physiol Lung Cell Mol Physiol* 2006, **290**:L827–L832.
- Th1 responses to rhinoviruses stimulate inducible nitric oxide synthase to make S-nitrosothiols, which inhibit pH buffering enzymes, lowering pH and killing rhinoviruses in the airway epithelium.
11. Yoon SS, Coakley R, Lau GW, et al.: Anaerobic killing of mucoid *Pseudomonas aeruginosa* by acidified nitrite under conditions characteristic of the cystic fibrosis airway. *J Clin Invest* 2006, **116**:436–446.
- In cystic fibrosis, acidic sputum prevents growth of mucoid *Pseudomonas aeruginosa* through nitrite protonation.
12. Gaston B, Adjei A, Amoah AG, et al.: Breath condensate pH and ammonia levels are low in patients with active pulmonary tuberculosis. *Proc Am Thorac Soc* 2005, **2**:A574.
 13. Kostikas K, Papatheodorou G, Ganas K, et al.: pH in expired breath condensate of patients with inflammatory airway diseases. *Am J Respir Crit Care Med* 2002, **165**:1364–1370.
 14. Walsh BK, Mackey DJ, Pajewski T, et al.: Exhaled-breath condensate pH can be safely and continuously monitored in mechanically ventilated patients. *Respir Care* 2006, **51**:1125–1131.
- Breath condensate pH is low in patients with lung disease who are endotracheally intubated, demonstrating conclusively that the low pH is not an effect of oral chemistry.
15. Paget-Brown A, Hunt J, Gaston B: Tracheal fluid pH in human preterm infants. *Eur Respir J* 2007, In press.
- The pH of fluid lining the airway falls with prolonged ventilation in preterm human infants.
16. Herve P, Denjean A, Jian R, et al.: Intraesophageal perfusion of acid increases the bronchomotor response to methacholine and to isocapnic hyperventilation in asthmatic subjects. *Am Rev Respir Dis* 1986, **134**:986–989.
 17. Jack CI, Calverley PM, Donnelly RJ, et al.: Simultaneous tracheal and oesophageal pH measurements in asthmatic patients with gastro-oesophageal reflux. *Thorax* 1995, **50**:201–204.
 18. Boyle JT, Tuchman DN, Altschuler SM, et al.: Mechanisms for the association of gastroesophageal reflux and broncho-spasm. *Am Rev Respir Dis* 1985, **131**:S16–20.
 19. Ricciardolo FLM, Rado V, Fabbri LM, et al.: Bronchoconstriction induced by citric acid inhalation in guinea pigs: role of tachykinins, bradykinin, and nitric oxide. *Am J Respir Crit Care Med* 1999, **159**:557–562.
 20. Shin H-W, Shelley DA, Fitzpatrick A, et al.: Airway nitric oxide is reduced following phosphate buffered saline inhalation in asthma. *J Appl Physiol* 2007, **102**:1028–1033.
- Phosphate buffer inhalation prevents nitrite protonation in certain lung compartments, particularly in asthma, demonstrating that airway pH is low.
21. Karnad DR, Mhaisekar DG, Moralwar KV: Respiratory mucus pH in tracheostomized intensive care unit patients: Effects of colonization and pneumonia. *Crit Care Med* 1990, **18**:699–701.
 22. Hunt J: Exhaled breath condensate: an evolving tool for noninvasive evaluation of lung disease. *J Allergy Clin Immunol* 2002, **110**:28–34.
 23. Horvath I, Hunt J, Barnes PJ, et al.: ATS/ERS Task Force on Exhaled Breath. Condensate Exhaled breath condensate: methodological recommendations and unresolved questions. *Eur Respir J* 2005, **26**:523–548.
- Summary of ATS/ERS task force recommendations.
24. Hunt J, Ngamtrakulpanit L, Vaughan J, et al.: Airway acid-base disturbance in rhinovirus cold. *Eur Respir J* 2003, **22**(Suppl 45):S66S.
 25. Effros RM, Bosbous M, Foss B, et al.: Exhaled breath condensates: a potential novel technique for detecting aspiration. *Am J Med* 2003, **115**:137S–143S.
 26. Hunt J, Yu Y, Burns J, et al.: Identification of acid reflux cough using serial assays of exhaled breath condensate pH. *Cough* 2006, **2**:3–6.
- Breath condensate acidity identifies reflux-related cough.
27. Harding SM: Acid reflux and asthma. *Curr Opin Pulm Med* 2003, **9**:42–45.
 28. Harding SM: Gastroesophageal reflux: a potential asthma trigger. *Immunol Allergy Clin North Am* 2005, **25**:131–148.
 29. Avidan B, Sonnenberg A, Schnell TG, et al.: Temporal associations between coughing or wheezing and acid reflux in asthmatics. *Gut* 2001, **49**:767–772.
 30. Littner MR, Leung FW, Ballard ED, et al.: Effects of 24 weeks of lansoprazole therapy on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult asthmatic patients with acid reflux symptoms. *Chest* 2005, **128**:1128–1135.
 31. Heading RC: Review article: diagnosis and clinical investigation of gastro-oesophageal reflux disease: a European view. *Aliment Pharmacol Ther* 2004, **20**:9–13.
 32. Kiljander TO: The role of proton pump inhibitors in the management of gastroesophageal reflux disease-related asthma and chronic cough. *Am J Med* 2003, **115**:65S–71S.
 33. Harding SM, Richter JE, Guzzo MR, et al.: Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *Am J Med* 1996, **100**:395–405.
 34. Schnatz PF, Castell JA, Castell DO: Pulmonary symptoms associated with gastroesophageal reflux: use of ambulatory pH monitoring to diagnose and to direct therapy. *Am J Gastroenterol* 1996, **91**:1715–1718.
 35. Tuchman DN, Boyle JT, Pack AI, et al.: Comparison of airway responses following tracheal or esophageal acidification in the cat. *Gastroenterology* 1984, **87**:872–881.
 36. Ishikawa T, Sekizawa SI, Sant'Ambrogio FB, et al.: Larynx vs esophagus as reflexogenic sites for acid-induced bronchoconstriction in dogs. *J Appl Physiol* 1999, **86**:1226–1230.
 37. Patterson RN, Johnston BI, MacMahon J, et al.: Oesophageal pH monitoring is of limited value in the diagnosis of "reflux-cough." *Eur Respir J* 2004, **24**:724–727.

38. Shaker R, Dodds WJ, Ren J, et al.: Esophagoglottal closure reflex: a mechanism of airway protection. *Gastroenterology* 1992, 102:857–861.
 39. Halstead LA: Extraesophageal manifestations of GERD: diagnosis and therapy. *Drugs Today (Barc)* 2005, 41(Suppl B):19–26.
 40. Gregor JC: Acid suppression and pneumonia: a clinical indication for rational prescribing. *JAMA* 2004, 292:2012–2013.
 41. Laheij RJ, Sturkenboom MC, Hassing RJ, et al.: Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004, 292:1955–1960.
 42. Burvall K, Palmberg L, Larsson K: Metabolic activation of A549 human airway epithelial cells by organic dust: a study based on microphysiometry. *Life Sci* 2002, 71:299–309.
 43. Acevedo F: Exhaled breath condensate (EBC): changes in magnesium, pH and conductivity after exposure to swine hours dust or inhaled LPS. *Eur Respir J* 2005, 26:P4669.
 44. Undem BJ, Carr MJ: The role of nerves in asthma. *Curr Allergy Asthma Rep* 2002, 2:159–165.
 45. Holma B: Influence of buffer capacity and pH-dependent rheological properties of respiratory mucus on health effects due to acidic pollution. *Sci Total Environ* 1985, 41:101–123.
 46. Martinez D, Vermeulen M, von Euw E, et al.: Extracellular acidosis triggers the maturation of human dendritic cells and the production of IL-12. *J Immunol* 2007, 179:1950–1959.
- Interesting immunologic effects of pH relevant to asthma.
47. Rabinovich M, DeStefano MJ, Dziezanowski MA: Neutrophil migration under agarose: stimulation by lowered medium pH and osmolality. *J Reticuloendothel Soc* 1980, 27:189–200.
 48. Zigmond SH, Hargrove RL: Orientation of PMN in a pH gradient: acid-induced release of a chemotactic factor. *J Immunol* 1981, 126:478–481.
 49. Luk CK, Dulfano MJ: Effect of pH, viscosity and ionic-strength changes on ciliary beating frequency of human bronchial explants. *Clin Sci* 1983, 64:449–451.
 50. Hunt J: Airway acidification: interactions with nitrogen oxides and airway inflammation. *Curr Allergy Asthma Rep* 2006, 6:47–52.