Common Disorders of the Ear, Nose, and Throat

A Clinical Update

By Joan Lewis, MD Otorhinolaryngologist

Introduction

Disorders of the ear, nose, and throat (ENT) are the cause of many patient visits to a primary care physician. Some of the common ENT disorders include acute and recurrent otitis media (OM); acute, chronic, and recurrent tonsillitis; and allergic and recurrent rhinitis and chronic rhinosinusitis (CRS). However, the common cold remains one of the most frequent upper respiratory tract infections (URIs). Approximately half of the cases of colds in children can be attributed to a wide variety of up to 200 different viruses that are seasonally active, such as rhinoviruses in the early fall, spring, and summer. Other viruses that might cause URIs include coronavirus, parainfluenza virus, adenovirus, enterovirus, and respiratory syncytial virus.1 The subsequent development of recurrent sinusitis2,3 and OM4 commonly has been related to viral URIs that last longer than a week. A child can be expected to have 6 to 10 colds annually, whereas adolescents may have only 2 to 4 colds per year. In developing countries, URIs tend to be more severe, such as pneumonia and influenza, with a higher risk of complications. Therefore, URIs can be a leading cause of death for children younger than 5 years.5

An increased understanding of the pharmacoeconomic incidence, relevance of antibiotic resistance, physi-

4

cian involvement, and anatomical and physiological features of each of the common ENT disorders will improve clinical outcomes. An integrative medical approach that uses complementary and alternative therapies, such as antihomotoxic medications, in addition to mainstream medical therapies is a therapeutic strategy that shows much promise in reducing the current disease burden and preventing further recurrences.

Pharmacoeconomic Incidence

The annual cost of time lost from school for adolescents and from work for adults, because of URIs, is substantial and is estimated to be as high as \$15 billion in direct treatment costs by practitioners, with more than half of that amount being for ambulatory care centers in hospitals. The indirect cost wages from URIs is estimated at \$9 billion.⁶ The over-the-counter cough and cold remedy market was identified as being the "most competitive category in North America," with sinusitis showing the most potential growth. Figures extrapolated from a survey of 4000 US residents suggested that a total economic burden of \$40 billion, including income lost from time off for these occurrences, was related to noninfluenza viral URIs alone.

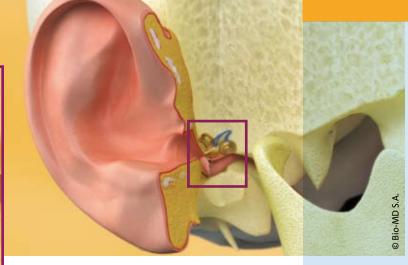
Antibiotic Resistance

In 2007, prudent antibiotic use was not correlated with appropriate knowledge of microbial resistance8; thus, the reduction of unnecessary antibiotics as treatment options for the virally associated common cold was identified in 2008 as a public health priority.9 Recent public opinion polls show an increased understanding of the relationship between the development of resistant bacterial strains and inappropriate antibiotic use and also report a significantly higher level of trust in physicians who did not prescribe antibiotics for the common cold.¹⁰ However, 45% of respondents in the United States in 2008 and 41% of a population in Belgium in 2001 still did not understand the lack of efficacy of antibiotics in treating viral illnesses.¹¹ These data suggest that there is still a considerable opportunity to better educate patients and health care providers.

Environmental Impact

In the pediatric population, the close proximity of children in day-care centers contributes to the transmission of respiratory tract disease.¹² Childhood exposure to common environmental pollutants, such as firsthand or secondhand smoke, and common household allergens, such as aerosolized cleaning products, in persons with a genetic predisposition might be associated with later





development of asthma and allergic conditions through inappropriate sensitization.¹³ Furthermore, asthmatic children have URIs more frequently than their nonasthmatic classmates. The polycyclic aromatic hydrocarbons present in diesel exhaust particles have recently been shown to stimulate the release of interleukin (IL) 4, IL-8, and histamine from basophil cells,¹⁴ suggesting that other common environmental pollutants also can play a role in the development of asthma and allergic rhinitis.

Physician Involvement

Most persons with ENT disorders visit their health care practitioners early in the disease process because the associated signs and symptoms are readily apparent to both the patient and practitioner and frequently affect activities of daily living. The high visibility of the nasal and oral area and the high risk of symptoms interfering with activities of daily living may precipitate an early practitioner visit. The mechanical and physical appearances of structures (eg, teeth, palate, gingiva, and tongue) indicate a variety of physiological states and can be used diagnostically with a minimal investment of time. For example, fasciculations of the tongue might indicate neural disorders; glossy tongue is associated with nutritional deficiencies, such as a deficiency in vitamin B₁₂. Dental caries or loss correlates with impaired immune systems, smoking or tobacco use or exposure,¹⁵ and poor nutritional status. Xerostomias are linked to poor hygiene, and temporomandibular joint disorders can be attributed to trauma or articular disorders.¹⁶

Relevant Anatomical and Physiological Features

Lymphatic tissue in the Waldeyer ring is designed to protect the body from pathogens and toxins encountered in this vulnerable area; therefore, it is strategically placed to protect critical respiratory and digestive functions. It is the first protective barrier encountered by orally ingested and inhaled toxins, viruses, and bacteria. An interaction with the body's lymphatic tissues provokes a reaction that includes copious nasal discharge, sneezing, coughing, and mucosal egorgement as a mechanism to remove the offending substance. The resultant reaction, with its associated signs and symptoms, is diagnosed as the common cold or rhinitis. Further progression to include fever and exhaustion, and the presence of clusters of similar infections in the community and a documented influenza virus infection, would lead to a diagnosis of the flu.

Treatment for these uncomfortable reactions is largely symptomatic. Over-the-counter remedies for these conditions are common and constitute one of the highest sources of pharmaceutical sales for all persons seeking symptom relief.¹⁰ According to a recent survey in both the United States and Belgium, antibiotics are still widely prescribed despite evidence that challenges their usefulness. Therefore, there is still an increase in bacterial resistance and a subsequent increase in pathology.¹¹

Pathological Conditions

A short review of the relevant pathological features of each of the common ENT disorders is included to provide further insight into potential therapeutic strategies.

Otitis Media

Acute OM: Acute OM is the most frequent ailment encountered by pediatricians.17 Persistent middle ear effusion from a failure of the mucus and microbial and immune system debris in the middle ear to drain via the Eustachian tube to the pharynx is associated with recurrent OM.18 Implicated factors include functional obstruction of the Eustachian tube, anatomical differences in the infant's Eustachian tube, and a more horizontal position when bottle feeding an infant in a supine position, favoring a retrograde flow of milk. Furthermore, passive smoke environments impairing normal ciliary movement that sweeps away debris and immune system disorders associated with increased mucus produc-



tion are thought to be predisposing factors.¹⁹ An allergic etiology, such as to cow's milk and other food allergens, has been implicated²⁰ but is controversial.^{21,22} Other associated factors include frequent attendance at day-care centers and low socio-economic status.²²

Recurrent OM: Preexisting antibiotic treatment is associated with an increased rate of recurrent OM in young children,²³ inferring support for the hygiene hypothesis (in which the interruption of a normal inflammatory response to infections [Thelper {Th} 1] during childhood leads to an imbalance in Th1/Th2 cell regulation, predisposing a child toward allergy). Novel otopathogens can be cultured in those with recurrent OM after a month-long course of antibiotics for acute OM. This evidence would seem to support the occurrence of microbial-resistant pathogens yet fails to exclude the hygiene hypothesis²⁴ as a contributing factor. This evidence also might suggest that there may be unique infectious causes between the 2 diseases. Long-term morbidity, with recurrent OM occurring before the age of 3 years, might affect the child's subsequent decreased comprehension when reading.25

Bioregulatory treatment: For acute OM, use the basic/symptomatic ap-

proach as follows: Prescribe Belladonna-Homaccord (8-10 drops 2 times per day) and Traumeel (8-10 drops or 1 ampoule warmed up and poured into the appropriate ear 2 times per day). If resolution does not occur within a reasonable time, individualize the therapy as follows:

- With a confirmed bacterial etiology and a marked inflammatory reaction and serious infection, prescribe Echinacea compositum. For acute conditions, prescribe 1 tablet every 30 to 60 minutes to a maximum of 12 tablets per day. For chronic conditions, prescribe 1 tablet dissolved in the mouth 3 times per day. If injection therapies are within the practitioner's regulatory framework, prescribe 1 ampoule intramuscularly (IM), subcutaneously (SC), intradermally (ID), or intravenously (IV) 1 to 3 times per week. N.B. Avoid the use of Echinacea compositum in patients with a known hypersensitivity reaction to botanicals in the Compositae family.
- With a confirmed viral etiology, prescribe Engystol (in general, 1 tablet 3 times per day or 1 ampoule per day). If the situation is acute, prescribe 1 ampoule per day IM, SC, ID, or IV.
- With marked restlessness, possible fever, and agitation, prescribe Viburcol suppositories. For acute disorders in adults, insert 1 sup-

pository into the anus 2 to 3 times per day. Use only half of 1 suppository in infants and children up to the age of 6 months, up to a total of 1 suppository per day.

If there are still signs and symptoms after a reasonable time using the basic/symptomatic approach (even with appropriate individualized therapies), the patient may not have the ability to self-regulate and the correct etiology may not have been identified and addressed. Furthermore, if the condition is recurrent, it can also be assumed that the patient has lost the ability to self-regulate. In both these situations, the regulation/3-pillar approach (detoxification and drainage, immunomodulation, and cell and organ support) would be most appropriate.²⁶ During periods of flare-ups, the basic/symptomatic approach should be used, as previously described. During latent phases, Mucosa compositum (and, if necessary, Coenzyme compositum and Ubichinon compositum) should be used as cellular and organ support, Traumeel as an immunomodulator, and the Detox-Kit* for basic detoxification and drainage.

Persistent middle ear effusion can lead to hearing deficits and speech delay; therefore, for unresolving cases, it might be necessary to refer patients to the appropriate health care professional for a myringotomy.

6

* The Detox-Kit consists of Lymphomyosot, Nux vomica-Homaccord, and Berberis-Homaccord.

Tonsillitis

Acute tonsillitis: Tonsils, part of the Waldever ring of lymphatic tissue in the oropharynx and nasopharynx, are considered to be the site of antigen presentation, resulting in the mounting of an appropriate B-cell response. Acute tonsillitis commonly presents as erythematous and swollen tonsils accompanied by stertorous breathing in children. Hypertrophied tonsils are a common cause of sleep disorders in children and can be associated with resultant daytime inattentiveness during classes.²⁷ In cases in which the diagnosis is unclear, a microbiological evaluation is needed and positive throat culture or rapid antigen detection tests are required to exclude the diagnosis of streptococcal pharyngitis, which requires appropriate antibiotic treatment to avoid cardiovascular and/or renal complications.²⁸ The presence of tonsils is considered to play a significant role in the maturation of natural killer lymphocytes, one of the first lines of the body's defense foreign substances,29 against suggesting that a tonsillectomy should be considered as a therapy of last resort.

Chronic tonsillitis: Acute tonsillitis can have either a viral or a bacterial etiology. However, chronic tonsillitis is generally restricted to bacteria and is considered to be more prevalent in adults than in children. Chronic tonsillitis can be associated with crypts containing pus that form in the tonsils. Surgical excision of tonsillar tissue is controversial for chronic tonsillitis, in part because of the subsequent impact on pharyngitis postoperatively, despite the lack of a visible recurrent tonsillar infection.30 Changes in oral flora noted after tonsillectomy indicate that the

chronically infected tonsil may serve as a nidus, harboring anaerobic bacteria, and that surgical removal may help restore normal oral flora colonization.31 The presence and ratio of matrix metalloproteinases to inhibitors of metalloproteinase activity suggest that these substances may be a factor in the progression of tonsillar disease states.32 Common emergent complications of chronic tonsillitis include a peritonsillar abscess (also termed quinsy) when the crypts fail to drain appropriately. This is identified by drooling, a distinctive "thrust forward" head position, a "hot potato" voice, and a visible asymmetrical mass in the area of the affected pharyngeal tonsil. Treatment for this condition requires the oral extraction of purulent bacterial material and is associated with an immediate decrease in symptoms.

Recurrent tonsillitis: In children, recurrent tonsillitis is considered a more accurate term than chronic tonsillitis. A difference from the chronic tonsillitis of adulthood is a higher percentage of antigen in the acute stages compared with a higher percentage of antigen in the chronic stages of tonsillitis in adults.³⁴ If a peritonsillar abscess is associated with chronic tonsillitis, tonsillectomy may be the first-line treatment.³⁵ Antigen presentation and B-cell activity and response are preserved in children with recurrent disease,³⁶ indicating the maintenance of normal physiological function of the lymphoid tissue despite an infectious appearance. These data provide support for a decision to leave the tonsils surgically intact. If possible, it is important to avoid a tonsillectomy because, as previously mentioned, the natural killer lymphocytes undergo normal maturation within tonsils, contributing to the ultimate

development of a normal immune response.²⁹

Bioregulatory treatment: For acute tonsillitis, use the basic/symptomatic approach as follows: Prescribe Angin-Heel[†] (in acute situations, prescribe an initial massive dose of 1 tablet every 15 minutes for a maximum of 2 hours or, in general, 1 tablet 3 times per day), Vinceel (spray once 1-3 times per day), and Mercurius-Heel (1 tablet 3 times per day). If resolution does not occur within a reasonable time, individualize the therapy as follows:

- With a confirmed bacterial etiology and a marked inflammatory reaction, prescribe Echinacea compositum. For acute conditions, prescribe 1 tablet every 30 to 60 minutes to a maximum of 12 tablets per day. For chronic conditions, prescribe 1 tablet to be dissolved in the mouth 3 times per day. If injection therapies are within the regulatory framework, prescribe 1 ampoule IM, SC, ID, or IV 1 to 3 times per week. N.B. Avoid the use of Echinacea compositum in patients with a known hypersensitivity reaction to botanicals in the Compositae family.
- With a confirmed viral etiology, prescribe Engystol (in general, 1 tablet 3 times per day or 1 ampoule per day). If the situation is acute, prescribe 1 ampoule per day IM, SC, ID, or IV.
- For chronic dysregulation of the lymphatic system, prescribe Barijodeel (1 tablet to be dissolved in the mouth 3 times per day).

If there are still signs and symptoms after a reasonable time using the basic/symptomatic approach (even with appropriate individualized therapies), the patient may not have the ability to self-regulate and the

⁺ Marketed as Belladonna compositum in the United States.

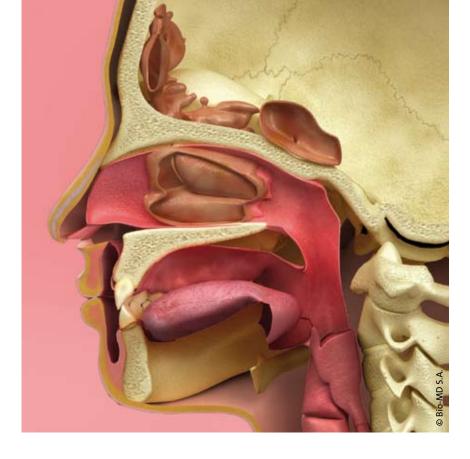
correct etiology may not have been identified and addressed. Furthermore, if the condition is chronic or recurrent, it can also be assumed that the patient has lost the ability to self-regulate. In both these situations, the regulation/3-pillar approach (detoxification and drainage, immunomodulation, and cell and organ support) would be most appropriate.26 During periods of acute flare-ups, the basic/symptomatic approach should be used, as previously described. During latent phases and for chronic tonsillitis, the Detox-Kit should be used for basic detoxification and drainage, with prolonged use of Lymphomyosot if resolution of symptoms does not occur within a reasonable time. Traumeel or Tonsilla compositum can be used for immunomodulation, and Mucosa compositum (and Coenzyme compositum and Ubichinon compositum) can be used for cellular and organ support.

The tonsils form an important part of the innate immune system; therefore, a tonsillectomy should only be considered as a treatment of last resort.

Rhinitis

8

Allergic rhinitis: The diagnosis of allergic rhinitis is based on the presence of copious clear rhinorrhea associated with exposure to a known allergen, usually in the spring and summer. Symptoms are more likely to be associated with bronchial hyperresponsiveness, wheezing, and conjunctivitis in children with exposure to furry pets in addition to pollen rather than pollen alone.37 Resultant nasal stuffiness and sleep deprivation have been treated successfully with leukotriene receptor antagonists, such as montelukast and topical nasal steroids; adverse effects were not enumerated in this study.³⁸ The decreased frequency of allergic



rhinitis in children who are exposed to the childhood diseases of their siblings before they are aged 2 years (ie, before their immune systems have fully developed) and an observed increased frequency of allergic rhinitis after tonsillectomies support the hygiene hypothesis.³⁹ A persistent imbalance between T-regulatory and Th2 cells may be associated with the development and expression of allergic asthma, providing a promising option for using natural health products or pharmaceutical agents that target T cells for treatment other than the mainstay of inhaled steroids.40 Allergic rhinitis is a costly disease because of the many physician visits, the high cost of prescription medications, related comorbidities, and lost productivity because of absenteeism and presenteeism (ie, poor performance on the job when ill). The conventional symptomatic treatment protocols include antihistamines and steroids.

Recurrent rhinitis: The diagnosis of recurrent rhinitis is based on the frequency of rhinitis experienced

annually, generally referring to more than 12 weeks of symptoms with incomplete resolution. An imbalance in subsets of lymphocytes (Th2 and T-regulatory cells) has been implicated in the development of CRS.41,42 When present with nasal polyps, eosinophilic aggregations indicate an association with a predominant Th2-allergic etiology. In pediatric CRS, the nasal mucosa shows a predominance of macrophages and neutrophils,43 indicating a Th1 predominance. Allergic upper respiratory tract disorders may present with laryngeal dysphonia and may be misdiagnosed as reflux disease.44 T-cell imbalances have been implicated as contributing etiological factors for CRS in children with an increased production of Th17 cells,45 and the receptors that bind nucleotides found in the nasal mucosa of patients with allergic rhinitis are down-regulated.46 In CRS with nasal polyps, the IL-6 level is significantly increased,47 whereas the IL-17 level is decreased, indicating a pathophysiological response. The conventional first-line treatment for this disorder may include the topical

application of steroids to the mucosa for prophylaxis.48,49 Some of the newer steroids for allergic rhinitis show a mechanism of action of binding to the glucocorticoid receptor, resulting in the inhibition of IL-4 and IL-5 levels; these steroids are associated with suppressed overnight cortisol levels and hypothalamic-pituitary-adrenal axis suppression.50 Associated adverse effects include mucosal atrophy, perioral dryness, and rebound⁵¹; the use of long-term steroids can be associated with decreased growth rates. However, these therapies fail to address the significant disturbance of normal immune support physiological mechanisms⁵² and often have poor patient compliance because of their perceived lack of efficacy and the adverse effects encountered.53

Bioregulatory treatment: For acute rhinitis with a suspected microbial cause, use the basic/symptomatic approach as follows: Prescribe Euphorbium compositum (1-2 sprays per nostril 3-5 times per day and 10 drops every 15 minutes for a maximum of 2 hours and then reduce to 10 drops 6 times per day or 1 ampoule per day). In cases of marked rhinitis, add Naso-Heel (8-10 drops 3 times per day). If the etiology has a documented allergic component (especially seasonal allergy), use Luffeel (1-2 sprays into each nostril 3-5 times per day and 1 tablet every 15 minutes for a maximum of 2 hours and then decrease to 1 tablet 3 times per day) instead of Euphorbium compositum. If resolution does not occur within a reasonable time, individualize the therapy as follows:

• With a confirmed bacterial etiology and serious inflammation and septic conditions, prescribe Echinacea compositum. For acute conditions, prescribe 1 tablet every 30 to 60 minutes to a maximum of 12 tablets per day. For chronic conditions, prescribe 1 tablet to be dissolved in the mouth 3 times per day. If injection therapies are within the regulatory framework, prescribe 1 ampoule IM, SC, ID, or IV 1 to 3 times per week. N.B. Avoid the use of Echinacea compositum in patients with a known hypersensitivity reaction to botanicals in the Compositae family.

- With a confirmed viral etiology, prescribe Engystol (in general, 1 tablet 3 times per day or 1 ampoule per day). If the situation is acute, prescribe 1 ampoule per day IM, SC, ID, or IV.
- For chronic discharge from the nasal mucosa, Natrium-Homaccord (in general, 10 drops 3 times per day) should be used.
 N.B. Long-term use of this medication (ie, over periods of longer than a few months) should be supervised by the appropriate health care professional.

If there are still signs and symptoms after a reasonable time using the basic/symptomatic approach (even with appropriate individualized therapies), the patient may not have the ability to self-regulate and the correct etiology may not have been identified and addressed. Furthermore, if the condition is recurrent, it can also be assumed that the patient cannot self-regulate or that there is a persistent etiological factor that has not been adequately addressed. In both these situations, the regulation/3-pillar approach (detoxification and drainage, immunomodulation, and cell and organ support) would be most appropriate.²⁶ During periods of acute flare-ups, the basic/symptomatic approach should be used, as previously described. During the latent phases, the regulation/3-pillar approach is indicated. The Detox-Kit should be used for basic detoxification and drainage, Traumeel or Tonsilla compositum for immunomodulation, and Mucosa compositum (and Coenzyme compositum and Ubichinon compositum) for cellular and organ support. There are many different potential etiologies for rhinitis; therefore, it is important to identify and try to remove or reduce the effects of the initiating causes.

Conclusions

The mainstream medical treatment options include surgical removal of tonsils, steroid ablative treatment for symptoms that reflect a normal physiological response to pathogens, antibiotic intervention in cases in which no true disease state can be identified, and a failure to allow the normal homeostatic immune system defense processes to proceed unimpeded. These options do not appear to result in better health outcomes. Recent research seems to support the more restrained approach of watchful waiting through the discomforts of the usual childhood disease states and the use of supportive medical therapies that allow the body to "learn" to selectively neutralize threats to health.

References

- Chonmaitree T, Revai K, Grady JJ, et al. Viral upper respiratory tract infection and otitis media complication in young children. *Clin Infect Dis.* 2008;46(6):815-823.
- Ramadan HH. Pediatric sinusitis: update. J Otolaryngol. 2005;34(suppl 1):S14-S17.
- Alho OP. Viral infections and susceptibility to recurrent sinusitis. *Curr Allergy Asthma Rep.* 2005;5(6):477-481.
- Winther B, Alper CM, Mandel EM, Doyle WJ, Hendley JO. Temporal relationships between colds, upper respiratory viruses detected by polymerase chain reaction, and otitis media in young children followed through a typical cold season. *Pediatrics*. 2007;119(6):1069-1075.
- Denny FW Jr. The clinical impact of human respiratory virus infections. *Am J Respir Crit Care Med.* 1995;152(4, pt 2):S4-S12.

g

- Dixon RE. Economic costs of respiratory tract infections in the United States. Am J Med. 1985;78(6B):45-51.
- Fendrick AM, Monto AS, Nightengale B, Sarnes M. The economic burden of noninfluenza-related viral respiratory tract infection in the United States. *Arch Intern Med.* 2003;163(4):487-494.
- McNulty CA, Boyle P, Nichols T, Clappison P, Davey P. Don't wear me out: the public's knowledge of and attitudes to antibiotic use [published online ahead of print February 16, 2007]. J Antimicrob Chemother. 2007;59(4):727-738. doi:10.1093/jac/ dkl558
- Earnshaw S, Monnet DL, Duncan B, O'Toole J, Ekdahl K, Goossens H. European Antibiotic Awareness Day, 2008: the first Europe-wide public information campaign on prudent antibiotic use: methods and survey of activities in participating countries. *Euro Surveill*. 2009;14(30):19280.
- Andre M, Vernby A, Berg J, Lundborg CS. A survey of public knowledge and awareness related to antibiotic use and resistance in Sweden [published online ahead of print April 1, 2010]. J Antimicrob Chemother. 2010;65(6):1292-1296. doi:10.1093/jac/ dkq104
- Edgar T, Boyd SD, Palame MJ. Sustainability for behaviour change in the fight against antibiotic resistance: a social marketing framework. *J Antimicrob Chemother*. 2009;63(2):230-237.
- Fleming DW, Cochi SL, Hightower AW, Broome CV. Childhood upper respiratory tract infections: to what degree is incidence affected by day-care attendance? *Pediatrics*. 1987;79(1):55-60.
- Arshad SH. Does exposure to indoor allergens contribute to the development of asthma and allergy? *Curr Allergy Asthma Rep.* 2010;10(1):49-55.
- Lubitz S, Schober W, Pusch G, et al. Polycyclic aromatic hydrocarbons from diesel emissions exert proallergic effects in birch pollen allergic individuals through enhanced mediator release from basophils. *Environ Toxicol.* 2010;25(2):188-197.
- Tanaka K, Miyake Y, Sasaki S, et al. Active and passive smoking and tooth loss in Japanese women: baseline data from the Osaka Maternal and Child Health Study. *Ann Epidemiol.* 2005;15(5):358-364.
- McNeill RA. Comparison of the bacteria found in the ear and nasopharynx in acute otitis media. *J Laryngol Otol.* 1962;76:617-622.
- Natal BL, Chao JH. Otitis media. eMedicine Web site. http://emedicine.medscape.com/ article/764006-overview. Updated February 26, 2010. Accessed August 3, 2010.
- Emerick KS, Cunningham MJ. Tubal tonsil hypertrophy: a cause of recurrent symptoms after adenoidectomy. *Arch Otolaryngol Head Neck Surg.* 2006;132(2):153-156.
- Kerschner JE, Lindstrom DR, Pomeranz A, Rohloff R. Comparison of caregiver otitis media risk factor knowledge in suburban and urban primary care environments. *Int J Pediatr Otorhinolaryngol.* 2005;69(1):49-56.
- 20. Juntti H, Tikkanen S, Kokkonen J, Alho OP, Niinimaki A. Cow's milk allergy is associated

with recurrent otitis media during childhood. *Acta Otolaryngol.* 1999;119(8):867-873.

- Marshall SG, Bierman CW, Shapiro GG. Otitis media with effusion in childhood. *Ann Allergy.* 1984;53(5):370-378, 394.
- Stahlberg MR, Ruuskanan O, Virolainan E. Risk factors for recurrent otitis media. *Pediatr Infect Dis J.* 1986;5(1):30-32.
- Mattila PS. Amoxicillin treatment increases rate of late recurrence of acute otitis media in young children. *J Pediatr.* 2010;156(1):163.
- 24. Smit A. Editorial. J Biomed Ther. 2006; Winter: 3.
- Luotonen M, Uhari M, Aitola L, et al. Recurrent otitis media during infancy and linguistic skills at the age of nine years. *Pediatr Infect Dis J.* 1996;15(10):854-858.
- 26. Smit A, O'Byrne A, Van Brandt B, Bianchi I, Küstermann K. The three pillars of antihomotoxic treatment. In: Smit A, O'Byrne A, Van Brandt B, Bianchi I, Küstermann K. *Introduction to Bioregulatory Medicine*. Stuttgart, Germany: Thieme; 2009:49-143.
- 27. Hoban TF. Sleep disorders in children. *Ann N Y Acad Sci.* 2010;1184:1-14.
- Bonsignori F, Chiappini E, De Martino M. The infections of the upper respiratory tract in children. *Int J Immunopathol Pharmacol.* 2010;23(suppl 1):16-19.
- 29. Freud AG, Caligiuri MA. Purification of human NK cell developmental intermediates from lymph nodes and tonsils. In: Campbell KS, ed. *Natural Killer Cell Protocols*. 2nd ed. New York, NY: Humana; 2010. *Methods in Molecular Biology*; vol 612.
- Burton MJ, Glasziou PP. Tonsillectomy or adeno-tonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis. *Cochrane Database Syst Rev.* 2009;(1):CD001802. doi:10.1002/14651858.CD001802.pub2.
- Karaman E, Enver O, Alimoglu Y, et al. Oropharyngeal flora changes after tonsillectomy [published online ahead of print October 1, 2009]. Otolaryngol Head Neck Surg. 2009;141(5):609-613. doi:10.1016/j. otohns.2009.07.010.
- Acioglu E, Yigit O, Alkan Z, Server EA, Uzun H, Gelisgen R. The role of matrix metalloproteinases in recurrent tonsillitis. *Int J Pediatr Otorbinolaryngol.* 2010;74(5):535-539.
- Schechter GL, Sly DE, Roper AL, Jackson RT. Changing face of treatment of peritonsillar abscess. *Laryngoscope*. 1982;92(6, pt 1):657-659.
- Bussi M, Carlevato MT, Panizzut B, Omede P, Cortesina G. Are recurrent and chronic tonsillitis different entities? An immunological study with specific markers of inflammatory stages. *Acta Otolaryngol Suppl.* 1996;523:112-114.
- 35. Page C, Chassery G, Boute P, Obongo R, Strunski V. Immediate tonsillectomy: indications for use as first-line surgical management of peritonsillar abscess (quinsy) and parapharyngeal abscess [published online ahead of print April 20, 2010]. J Laryngol Otol. April 2010:1-6. doi:10.1017/ S0022215110000903
- 36. Jesic S, Stojiljkovic L, Stosic S, Nesic V, Milovanovic J, Jotic A. Enzymatic study of tonsil tissue alkaline and acid phosphatase in children with recurrent tonsillitis and tonsil hypertrophy. Int J Pediatr Otorhinolaryngol. 2010;74(1):82-86.

- Bertelsen RJ, Lødrup Carlsen KC, Carlsen KH. Rhinitis in children: co-morbidities and phenotypes [published online ahead of print April 27, 2010]. *Pediatr Allergy Immunol.* 2010;21(4, pt 1):612-622. doi:10.1111/ j.1399-3038.2010.01066.x
- Craig TJ, Sherkat A, Safaee S. Congestion and sleep impairment in allergic rhinitis. *Curr Allergy Asthma Rep.* 2010;10(2):113-121.
- Matheson MC, Walters EH, Simpson JA, et al. Relevance of the hygiene hypothesis to early vs late onset allergic rhinitis. *Clin Exp Allergy*. 2009;39(3):370-378.
- Heijink IH, Van Oosterhout AJM. Strategies for targeting T-cells in allergic diseases and asthma [published online ahead of print July 11, 2006]. *Pharmacol Ther.* 2006;112(2):489-500. doi:10.1016/j. pharmthera.2006.05.005
- Schleimer RP, Lane AP, Kim J. Innate and acquired immunity and epithelial cell function in chronic rhinosinusitis. *Clin Allergy Immu*nol. 2007;20:51-78.
- 42. Schleimer RP, Kato A, Peters A, et al. Epithelium, inflammation, and immunity in the upper airways of humans: studies in chronic rhinosinusitis. *Proc Am Thorac Soc.* 2009;6(3):288-294.
- Duplantier JE. Immunopathology of chronic rhinosinusitis in young children. *Pediatrics*. 2009;124(suppl 2):S135.
- Roth D, Ferguson BJ. Vocal allergy: recent advances in understanding the role of allergy in dysphonia. *Curr Opin Otolaryngol Head Neck Surg.* 2010;18(3):176-181.
- Ciprandi G, Castellazzi AM, Fenoglio D, Battaglia F, Marseglia G. Peripheral TH-17 cells in children with allergic rhinitis: preliminary report. Int J Immunopathol Pharmacol. 2010;23(1):379-382.
- 46. Bogefors J, Rydberg C, Uddman R, et al. Nod1, Nod2 and Nalp3 receptors, new potential targets in treatment of allergic rhinitis [published online ahead of print April 7, 2010]? *Allergy*. 10.1111/j.1398-9995.2009.02315.x
- Peters AT, Kato A, Zhang N, et al. Evidence for altered activity of the IL-6 pathway in chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol.* 2010;125(2):397-403.
- Okano M. Mechanisms and clinical implications of glucocorticosteroids in the treatment of allergic rhinitis. *Clin Exp Immunol.* 2009;158(2):164-173.
- Baldwin CM, Scott LJ. Mometasone furoate: a review of its intranasal use in allergic rhinitis. *Drugs.* 2008;68(12):1723-1739.
- Lumry WR. A review of the preclinical and clinical data of newer intranasal steroids used in the treatment of allergic rhinitis. *J Allergy Clin Immunol.* 1999;104(4):S150-S158.
- 51. Tamaki A. Side effects of topical steroids. *Skin Res.* 1999;41(suppl 21):26-30.
- Immune system. Anabolic Bible Web site. http://www.anabolic-bible.org/ShowPage. aspx?callpage=side_effects#. Accessed July 6, 2010.
- Naclerio RM, Hadley JA, Stoloff S, Nelson HS. Patient and physician perspectives on the attributes of nasal allergy medications. *Allergy Asthma Proc.* 2007;28(suppl 1):S11-S17.