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Research Paper

Impact of antibiotics on smell dysfunction

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Abstract *Objective:* Viral or bacterial respiratory infections can cause long-lasting olfactory dysfunction. Antibiotic therapy is indicated in severe cases; however, it is unclear whether antibiotic use produces a positive, negative, or null effect on olfactory function. This retrospective study sought to determine whether antibiotic use has an influence on odor identification and detection threshold test scores of patients with smell dysfunction secondary to upper respiratory infections (URIs), lower respiratory infections (LRIs), or rhinosinusitis.
Methods: Data from a total of 288 patients presenting to the University of Pennsylvania Smell and Taste Center were evaluated.
Results: Patients with a URI etiology who had taken bactericidal antibiotics had lower detection thresholds than did patients who had not taken antibiotics ($P < 0.023$; analysis of covariance with age and time since infection onset as covariates). Moreover, thresholds were lower for bactericidal antibiotic users than for bacteriostatic antibiotic users with either URI ($P = 0.023$) or rhinosinusitis ($P = 0.028$) etiologies. No meaningful influences of antibiotics on the odor identification test scores were evident.
Conclusions: These findings, which need to be confirmed in prospective double-blind studies, suggest that bactericidal antibiotic therapy may be beneficial in mitigating, at least to some degree, chronic decrements in smell sensitivity due to URIs and rhinosinusitis.

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Introduction

The use of antibiotics in treating respiratory tract infections is common in medical practice, even in cases where viral infections are most likely.[1] In general, antibiotic therapy is not recommended in initial treatment for upper respiratory tract infections (URIs); on the contrary, avoidance of prescribing antibiotics in these patients is encouraged, largely to prevent antibiotic resistance. In chronic rhinosinusitis, which adversely influences smell function in approximately three-quarters of patients,[2] bacterial infection or colonization may directly induce inflammation or serve as a disease modifier of a preexisting inflammatory state.[3] Therefore, antibiotic therapy is generally indicated to lower bacterial burden in such cases.

A standard classification of antibiotics differentiates bactericidal antibiotics, which specifically kill bacteria, from bacteriostatic antibiotics, which impede bacterial growth. However, overlap exists between these two classes of antibiotics.[4] While bactericidal antibiotics strongly and directly attack bacteria, the milder bacteriostatic antibiotics rely on phagocytosis and intracellular killing.[5] Ocampo et al[6] quantified death rates of both these classes of antibiotics and showed a substantial increase in killing rates for bactericidal antibiotics compared to those of bacteriostatic antibiotics. Although Nemeth et al[7] found minimal differentiation of efficacy between bactericidal and bacteriostatic antibiotics for abdominal infections, soft tissue infections, and pneumonia, differentiation has not been established for URIs that impact olfactory function. Importantly, interactions between viruses and bacteria are known to occur within the upper respiratory tract, decreasing or increasing the potency of some antibiotics in complex microbial communities.[8] In addition to antibacterial and anti-inflammatory effects, the bacteriostatic antibiotic minocycline has anti-apoptotic effects, delaying, for example, photoreceptor degeneration in the retina of the *Prph2*$^{Rd2/Rd2}$ (*rds*) mouse.[9]

The efficacy of antibiotics in improving smell function has been previously found to be negative, both when used for bacterial and viral infections. Van Zele et al,[10] in a double-blind, placebo-controlled, multicenter study, found no influence of doxycycline treatment on self-reported olfactory loss in 14 chronic rhinosinusitis patients with bilateral nasal polyps. Videler et al[11] administered azithromycin to 29 chronic rhinosinusitis patients (62% with nasal polyps) and a placebo to 31 such patients (42% with polyps). A 12-odor smell identification test was administered at the beginning of the treatment period and at 6 and 12 months during the treatment period. No influence of azithromycin was found. More recently, Reden et al[12] administered, in a randomized double-blind placebo-controlled study, either minocycline ($n = 26$) or a placebo ($n = 29$) to patients whose olfactory dysfunction was due to an upper respiratory infection. No influence of the antibiotic on tests of odor identification, detection, and discrimination was observed.

Taking a somewhat different tact, Ramakrishnan et al[13] examined, in a study of 434 medically refractory chronic rhinosinusitis patients, whether the number of days of reported antibiotic use in the 90 days before endoscopic nasal sinus surgery was related to pre-surgical scores on a 12-item smell identification test. No meaningful differences in the olfactory test scores were evident among the groups who had used no antibiotics ($n = 163$) or had used antibiotics for 1–14 days ($n = 102$), 15–28 days ($n = 69$) or more than 29 days ($n = 100$).

The purpose of this retrospective study was to assess, in a comparatively large number of subjects presenting with complaints of chemosensory disturbances, the potential influences of bactericidal or bacteriostatic classes of antibiotics on odor identification and detection threshold test scores of individuals whose olfactory dysfunction followed URIs, rhinosinusitis, or lower respiratory infections (LRIs). This study is the first to differentiate between the potential effects of bactericidal and bacteriostatic antibiotics on smell function and, unlike previous studies, focused on a patient group specifically seeking help for their chemosensory disturbance.

Materials and methods

Subjects

Data from 288 patients who had used or not used antibiotics at the time of their infection and whose chronic smell problem was attributed to URIs, LRIs, or rhinosinusitis were evaluated. The data were obtained from the clinic database of the University of Pennsylvania Smell and Taste Center from 1990 to 2013 (Table 1). This retrospective use of our clinic database information was approved by the Institutional Review Board of the University of Pennsylvania's Office of Regulatory Affairs.

In order to minimize the effect of other major etiologies such as head trauma or surgery, we included only data from patients who had URI, LRI, or rhinosinusitis as their principle etiologies. To minimize the confounding effect of the use of multiple types of antibiotics by the same patient, only patients who had used the same antibiotic during their treatment period were included in the sample.

In addition to detailed chemosensory testing described below, information regarding each person's current health, medical history, and chemosensory complaint was obtained from the patient's intake interview, physician reports, and an intake questionnaire completed by the patient prior to their visit to the Center. Medical information included a history of physician visits and physical examinations, as well as, in some cases, specific test results. The questionnaire was comprised of seven sections: (1) General Information (e.g., questions regarding demographics, referral source, and drinking and eating habits); (2) Medical History (listing of major illnesses and injuries, hospital admissions, and medications taken in the year prior to and since symptom onset); (3) History of Present Illness (report of the problem, in the patient's own words, including date of onset, duration, antecedent conditions, and treatments received); (4) Smell Symptoms (questions concerning problems with the sense of smell, general nasal health and abnormal nasal sensations, including nasal obstruction, rhinorrhea, and postnasal drip); (5) Taste Symptoms (questions related to problems with the sense of taste, general oral health, and abnormal oral sensations); (6)

Table 1 Demographics of study population.

Group	Antibiotic type	N	Mean age (SD)	Sex (% F)	Current or past smokers (%)
Entire group	Bactericidal	81	55.5 (12.4)	71.6	35.8
	Bacteriostatic	70	54.0 (11.9)	78.6	32.9
	No antibiotic	137	54.6 (13.3)	61.9	40.1
Upper respiratory infection/Viral infection	Bactericidal	32	55.0 (12.4)	65.6	40.6
	Bacteriostatic	32	50.9 (10.8)	81.2	37.5
	No antibiotic	94	54.4 (12.9)	56.4	38.3
Rhinosinusitis	Bactericidal	35	55.4 (13.2)	71.4	37.1
	Bacteriostatic	22	54.0 (14.3)	72.7	22.7
	No antibiotic	25	51.7 (15.2)	60.0	32.0
Lower respiratory infection	Bactericidal	14	56.7 (10.7)	85.7	21.4
	Bacteriostatic	16	60.2 (7.6)	81.3	37.5
	No antibiotic	18	59.4 (12.2)	66.7	61.1

Endocrine Information (questions regarding endocrine status, including endocrine operations (e.g., oophorectomy and thyroidectomy) and in women, menstrual cycle length and oral contraceptives usage); and (7) Depression (the Beck Depression Inventory II). The likely etiology of each patient was determined based upon self-report, medical records (when available), and the coincidence with the onset of the problem.

Description of smell tests

Odor identification was assessed using the University of Pennsylvania Smell Identification Test (UPSIT).[14,15] This 40-odor test focuses on the comparative ability of subjects to identify odorants at the suprathreshold level. It is comprised of four envelope-sized booklets, each containing ten "scratch and sniff" odorants embedded in polymer microcapsules individually positioned on brown strips at the bottom of each booklet page. The specifics and criteria for item selection and standardization of this test is described in detail elsewhere.[14] *Detection threshold sensitivity* was measured by a single-staircase detection threshold test employing the odorant phenyl ethyl alcohol.[16] On a given trial, the task was to report which of two randomly presented stimuli, an odorant and a blank, was perceived as strongest. A response was required even if no smell could be perceived; i.e., the test was forced-choice. The first odorant stimulus was presented at the −6.00 log concentration step of a half-log step (vol/vol) dilution series that ranged from −10.00 to −2.00 log concentration in USP grade light mineral oil. The odorant concentration was increased in full log steps until correct detection occurred on five consecutive trials at a given concentration. For each incorrect response, the staircase was moved up one full log step. When correct responses were made on all five trials, the staircase was reversed and moved down one 0.50 log concentration increment. Subsequently, the staircase was moved up or down in 0.50 log increments or decrements, depending upon the subject's performance on two pairs of trials at each concentration step. If the subject missed the first of these two trials, the second was not administered, and the next higher 0.50 log concentration was presented. When both were correct, the next lower 0.50 log concentration was presented. The mean of last four of seven staircase reversals served as the threshold estimate.

Classification of antibiotics

Following literature precedence,[7,17] penicillins, quinolones and cephalosporins were classified as the primary bactericidal antibiotics. Macrolides, tetracyclines, sulfonamdies and lincosamides were classified as the primary bacteriostatic antibiotics.[18] These antibiotics were generally prescribed at the time of infection onset; in rare instances, additional treatment with the same antibiotic was presented at a later time.

Etiology grouping

The subjects were classified by the etiology with which they presented to the clinic: viral URIs, rhinosinusitis, and LRIs such as bronchitis and pneumonia. Because most patients had been referred to our center by their own primary care physician or ORL specialist, we determined their etiology based on their provided medical history and responses to the intake questionnaire.

Statistical analyses

The UPSIT and PEA test scores for each etiologic category were subjected to separate analyses of covariance (ANCOVAs), with the between subject factor of antibiotic group (none, bactericidal, bacteriostatic) and the covariates of age and the time between testing and the infection.[19] Post-hoc comparisons were assessed using Tukey's HSD test.

Results

The mean (SEM) UPSIT and PEA threshold test scores are shown in Table 2, along with the *P* and η^2 values for the ANCOVA comparison of scores across the three groups. Comparisons among the antibiotic groups are shown in the three columns on the far right. *P*s$<$ 0.05 are bolded.

It is apparent from Table 2 that detection threshold values were nominally lower, i.e., sensitivity was higher, for those individuals in the URI and rhinosinusitis study

Table 2 Mean (SEM) olfactory test scores in subjects taking or not taking antibiotics in response to rhinosinusitis and upper and lower (e.g., pneumonia/bronchitis) respiratory infections. *P* values from analyses of covariance with age and time since infection onset as covariates. Bolded values indicate significance $P < 0.05$. See text for details.

Group	Smell test	Antibiotic group			*P*	η^2	None vs Bacteriostatic *P*	None vs Bactericidal *P*	Bacteriostatic vs Bactericidal *P*
		None	Bacteriostatic	Bactericidal					
Upper respiratory infection	UPSIT	24.3 (0.90)	25.4 (1.55)	25.3 (1.53)	0.758	0.004	0.815	0.833	0.999
	Threshold	−3.97 (0.18)	−3.67 (0.32)	−4.84 (0.31)	**0.020**	0.048	0.702	**0.044**	**0.023**
Rhinosinusitis	UPSIT	23.1 (1.75)	21.9 (1.83)	25.7 (1.51)	0.255	0.030	0.892	0.512	0.255
	Threshold	−3.81 (0.40)	−3.37 (0.41)	−4.76 (0.34)	**0.028**	0.084	0.721	0.177	**0.028**
Lower respiratory infection	UPSIT	21.5 (1.73)	19.4 (1.83)	22.6 (1.97)	0.471	0.032	0.659	0.917	0.462
	Threshold	−3.59 (0.34)	−3.53 (0.36)	−3.65 (0.38)	0.975	0.0009	0.992	0.993	0.973

UPSIT scores can range as high as 40; scores below 18 typically reflect total anosmia; detection threshold scores (phenyl ethyl alcohol) reflect log vol/vol concentrations in USP grade mineral oil.

groups who had taken bactericidal antibiotics for their chemosensory deficit compared to those who had taken either no antibiotic or a bacteriostatic one. This effect reached statistical significance for both the URI group ($P = 0.020$) and the rhinosinusitis group ($P = 0.028$). For both of these groups, thresholds were lower for those who had taken bactericidal antibiotics than for those who had taken bacteriostatic antibiotics (respective $P = 0.023$, $P = 0.028$). For individuals in the LRI study group, the use or type of antibiotic did not impact olfactory thresholds (all $P > 0.50$). The odor identification test scores did not meaningfully differ among any of the subject groups, although they were nominally larger in the bacteriocidal group with a rhinosinusitis etiology.

Discussion

This retrospective study suggests that antibiotic use, particularly bactericidal antibiotic use, may protect to some degree against decrements in olfactory sensitivity secondary to upper respiratory and rhinosinusitis infections, but not to lower respiratory infections. Such protection, however, was not mirrored by scores on a standardized odor identification test. Our findings lend no support to the concept that commonly administered antibiotics have toxic influences on the olfactory system when prescribed for nasal inflammatory disorders. In general, bactericidal antibiotics appeared to be more effective than bacteriostatic antibiotics in protecting against the olfactory threshold deficits, although regardless of treatment condition considerable dysfunction remained.

Our study is in agreement with earlier studies that found no influence of antibiotics on odor identification test scores of patients whose olfactory disturbances were due to chronic rhinosinusitis[10,13] or URIs.[12] They differ, however, from the negative findings of the sole study that measured olfactory thresholds in patients whose chemosensory dysfunction was secondary to URIs.[12] The basis for this difference is not clear. Although our patient population was specifically comprised of persons with olfactory dysfunction significant enough for them to seek help from a specialized smell and taste center, this was also the case with their study.[12] Our sample size was considerably larger (158 vs 55), presumably providing more power to see effects. The possibility also exists that our threshold test is more sensitive than that used in their study. It is noteworthy that some previous studies have found threshold tests to be somewhat more sensitive than odor identification tests to olfactory alterations secondary to chronic renal failure,[20] migraine headaches,[21] iron deficiency anemia,[22] and continuous positive airway pressure (CPAP).[23,24]

While we chose to divide our etiologies into three categories, it should be noted that such division has certain limitations. Even though URIs and the common cold[25] are considered mainly viral in origin and rhinosinusitis mainly bacterial in origin,[26,27] there is considerable overlap between these conditions in terms of bacterial involvement.[28] The same is the case with bronchitis and pneumonia, although bronchial infections are more commonly viral in nature.[1] URIs, including those due to rhinosinusitis, often undergo two phases. The first phase typically involves a

viral infection and lasts a relatively short period of time (<10 days). If recovery does not occur, a longer-lasting second phase of bacterial infection may ensue. In this case, aerobic bacteria initially predominate, but later anaerobic bacteria do so.[29] Anaerobic activity is promoted by the blockage of mucosal blood flow, poor sinus drainage, and increased inflammation-related pressure within the sinuses that result in the lowering of pH and the partial pressure of oxygen. The clinical classification of chronic rhinosinusitis is a sinusitis infection that persists for more than 12 weeks, which is the same time frame when anaerobic bacteria begin to dominate the sinuses.[29,30] This progression from a viral to bacterial infection over a long time frame could explain the efficacy of bactericidal antibiotics in improving the olfactory function of those whose dysfunction was attributed to severe common colds. It should also be noted that because some patients classified as having a rhinosinusitis etiology may have had short-term viral rhinosinusitis, the aggregate effect of the antibiotics on these particular patients may have been minimal, increasing the variance in our test measures.

Because the initial olfactory deficits observed in sinusitis patients are often attributed to nasal obstruction and mucosal edema, rhinosinusitis produces, in the short run, olfactory deficits by restricting access of molecules to receptors within the olfactory neuroepithelium.[31] However, by the time the smell function of the patients of this study was evaluated at the Center, the nasal inflammation phase had likely passed and nasal congestion and other related components were no longer of significance [median (IQR) times in days between olfactory testing and bacteriocidal and bacteriostatic treatments = 178 (131–287) and 163 (103–305), respectively]. The period of efficacy of antibiotics would have also passed and the degree of function that was left likely reflected damage induced by viral or bacterial processes. Olfactory biopsies of persons with post-viral anosmia or hyposmia reveal large numbers of aciliated olfactory receptor neurons and a greatly reduced number of intact ciliated receptor neurons.[32] While it is widely accepted that such damage can be induced by viruses, directly or via the immune response,[33] the degree to which bacteria are also involved is not clear. Our findings of better function in those who received antibiotics at the time of the infection suggest that bacteria may well be more important in this process than generally appreciated.

Although we found it useful to classify antibiotics into bactericidal and bacteriostatic categories, it should be emphasized that these classes are not mutually exclusive, and some antibiotics are considered bacteriostatic at low concentrations and bactericidal at higher concentrations.[34,35] Thus, most bacteriostatic agents can kill 90–99% of some bacteria within 18–24 h after their application, even though they don't reach the >99.9% criterion typically applied by bactericidal agents.[4] Similarly, bactericidal agents fail to kill every organism within this same period. This overlap may explain, in part, why we saw only relatively small differences in the efficacy of these two classes of antibiotics. In any form of antibacterial therapy, inadequate penetration of the infection site is a leading factor because it prevents the drug from traveling through necessary body fluids at effective concentration levels.[4] In light of our findings, and the fact that bacteriostatic antibiotics are limited by the host's own immune response, bactericidal antibiotics could be more effective not only because of their greater killing potential, but because they more readily access the inflammation site under harsh inflammation conditions.

This retrospective study has both strengths and weaknesses. Among its strengths are the use of reliable and well-validated tests of both odor identification and detection, the employment of subjects for whom considerable demographic, medical, and sensory testing data were available, and a relatively large sample size. Its weaknesses include the lack of availability, in most cases, of detailed information regarding the duration and doses of antibiotic administrations that were employed, the varying time periods between the olfactory testing and illness onset, and reliance on subject self-report for information regarding antibiotic use and details the nature of the involved infection. Although most referrals were from otolaryngologists, specific information regarding nasal examinations was generally lacking. We have made the assumption that normal clinical doses of antibiotics prescribed for the conditions was made, although exceptions may have been present. Nonetheless, in most cases adequate information regarding the antibiotic use was available from the patient questionnaire filled out before the patient came to the Center for assessment, suggesting that our overall conclusions were unlikely affected by this problem. It is important to note that without performing viral and bacterial assays on our subjects, we cannot be certain of the relative contributions of viruses and bacteria in influencing smell function. This information, if present, would have been obtained from the patient's previous medical diagnoses. However, even if one combines these two categories, our general findings would remain the same.

Conclusion

By employing a large and unique patient population for which extensive olfactory testing had been performed, the present study provides preliminary retrospective evidence that bactericidal antibiotics may quell, to some degree, olfactory dysfunction associated with URIs and rhinosinusitis, particularly when compared to bacteriostatic antibiotics. However, the magnitude of the observed effects is not large, and our findings beg for prospective confirmation. A major need is to establish whether the bacterial titer of those URI and rhinosinusitis patients who experience olfactory dysfunction or respond to antibiotics differs from that of URI and rhinosinusitis patients who do not experience such dysfunction or fail to respond to such treatments. It is conceivable, for example that there are more bacterial or mixed upper respiratory infections than generally expected in those URI patients with olfactory dysfunction. Clearly, a double-blind placebo-controlled prospective study on this topic is needed to confirm our findings. If confirmed, the underlying mechanisms should be better defined and the optimal drug dose regimen identified.

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References

1. Evertsen J, Baumgardner DJ, Regnery A, Banerjee I. Diagnosis and management of pneumonia and bronchitis in outpatient primary care practices. *Prim Care Respir J*. 2010;19:237—241.
2. Kohli P, Naik AN, Harruff EE, Nguyen SA, Schlosser RJ, Soler ZM. The prevalence of olfactory dysfunction in chronic rhinosinusitis. *Laryngoscope*. 2017;127:309—320.
3. Kohanski MA, Tharakan A, Lane AP, Ramanathan M. Bactericidal antibiotics promote reactive oxygen species formation and inflammation in human sinonasal epithelial cells. *Int Forum Allergy Rhinol*. 2016;6:191—200.
4. Pankey GA, Sabath LD. Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of Gram-positive bacterial infections. *Clin Infect Dis*. 2004;38:864—870.
5. Forsgren A, Schmeling D, Quie PG. Effect of tetracycline on the phagocytic function of human leukocytes. *J Infect Dis*. 1974;130:412—415.
6. Ocampo PS, Lázár V, Papp B, et al. Antagonism between bacteriostatic and bactericidal antibiotics is prevalent. *Antimicrob Agents Chemother*. 2014;58:4573—4582.
7. Nemeth J, Oesch G, Kuster SP. Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: systematic review and meta-analysis. *J Antimicrob Chemother*. 2015;70:382—395.
8. Bosch AA, Biesbroek G, Trzcinski K, Sanders EA, Bogaert D. Viral and bacterial interactions in the upper respiratory tract. *PLoS Pathog*. 2013;9. e1003057.
9. Hughes EH, Schlichtenbrede FC, Murphy CC, et al. Minocycline delays photoreceptor death in the rds mouse through a microglia-independent mechanism. *Exp Eye Res*. 2004;78:1077—1084.
10. Van Zele T, Gevaert P, Holtappels G, et al. Oral steroids and doxycycline: two different approaches to treat nasal polyps. *J Allergy Clin Immunol*. 2010;125:1069—1076.e4.
11. Videler WJ, Badia L, Harvey RJ, et al. Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. *Allergy*. 2011;66:1457—1468.
12. Reden J, Herting B, Lill K, Kern R, Hummel T. Treatment of postinfectious olfactory disorders with minocycline: a double-blind, placebo-controlled study. *Laryngoscope*. 2011;121:679—682.
13. Ramakrishnan VR, Mace JC, Soler ZM, Smith TL. Examination of high-antibiotic users in a multi-institutional cohort of chronic rhinosinusitis patients. *Int Forum Allergy Rhinol*. 2017;7:343—351.
14. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav*. 1984;32:489—502.
15. Doty RL, Shaman P, Applebaum SL, Giberson R, Siksorski L, Rosenberg L. Smell identification ability: changes with age. *Science*. 1984;226:1441—1443.
16. Doty RL. *Odor Threshold Test™ Administration Manual*. Haddon Hts., NJ: Sensonics, Inc.; 2000.
17. Kohanski MA, Tharakan A, London NR, Lane AP, Ramanathan M. Bactericidal antibiotics promote oxidative damage and programmed cell death in sinonasal epithelial cells. *Int Forum Allergy Rhinol*. 2017;7:359—364.
18. Jelić D, Antolović R. From erythromycin to azithromycin and new potential ribosome-binding antimicrobials. *Antibiotics (Basel)*. 2016;5.
19. Wilkinson L. *SYSTAT: The System for Statistics*. Evanston, Il: SYSTAT, Inc.; 1990.
20. Koseoglu S, Derin S, Huddam B, Sahan M. The effect of non-diabetic chronic renal failure on olfactory function. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2017;134:161—164.
21. Kayabaşoglu G, Altundag A, Kotan D, Dizdar D, Kaymaz R. Osmophobia and olfactory functions in patients with migraine. *Eur Arch Otorhinolaryngol*. 2017;274:817—821.
22. Dinc ME, Dalgic A, Ulusoy S, Dizdar D, Develioglu O, Topak M. Does iron deficiency anemia affect olfactory function. *Acta Otolaryngol*. 2016;136:754—757.
23. Walliczek-Dworschak U, Cassel W, Mittendorf L, et al. Continuous positive air pressure improves orthonasal olfactory function of patients with obstructive sleep apnea. *Sleep Med*. 2017;34:24—29.
24. Koseoğlu S, Derin S, Yilmaz M, Kutlu G, Sahan M. Does positive airway pressure therapy improve olfactory function. *Int Forum Allergy Rhinol*. 2017;7:557—560.
25. Kirkpatrick GL. The common cold. *Prim Care*. 1996;23:657—675.
26. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl*. 2012;23(3). p preceding table of contents, 1-298.
27. Brook I. Microbiology of sinusitis. *Proc Am Thorac Soc*. 2011;8:90—100.
28. Snow V, Mottur-Pilson C, Hickner JM. Principles of appropriate antibiotic use for acute sinusitis in adults. *Ann Intern Med*. 2001;134:495—497.
29. Brook I. Acute and chronic bacterial sinusitis. *Infect Dis Clin North Am*. 2007;21:427—448. vii.
30. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis executive summary. *Otolaryngol Head Neck Surg*. 2015;152:598—609.
31. Kern RC. Chronic sinusitis and anosmia: pathologic changes in the olfactory mucosa. *Laryngoscope*. 2000;110:1071—1077.
32. Moran DT, Jafek BW, Eller PM, Rowley JC. Ultrastructural histopathology of human olfactory dysfunction. *Microsc Res Tech*. 1992;23:103—110.
33. van Riel D, Verdijk R, Kuiken T. The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. *J Pathol*. 2015;235:277—287.
34. Piccolomini R, Catamo G, Di BG. Bacteriostatic and bactericidal in vitro activities of clarithromycin and erythromycin against periodontopathic Actinobacillus actinomycetemcomitans. *Antimicrob Agents Chemother*. 1998;42:3000—3001.
35. Vishwanath P, Prashant A, Devanand D, Nayak N, D'souza V, Venkatesh T. Screening of school children for blood lead levels and attempts to reduce them by nonpharmacological means in a coastal city of India. *Indian J Med Sci*. 2008;62:185—192.

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