

Classics in Rhinology

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Introduction

Classics in Rhinology has been created to bring together the premier articles in the rhinologic literature so that the reader can access these articles in one convenient reference. We have taken great care to identify these articles through a thorough search of the literature and a formal prioritization of the most highly cited articles. Although we believe this to be the most pristine approach, some of the most important contributions to the literature were not identifiable through the literature search. We therefore have added articles that will be recognized as “Editors’ Choices.”

To identify articles, we completed a literature search through Web of Science and Scopus. The search was confined to Science and Technology and Social Science and English-language articles, and the search terms used were *nose, nasal, sinus, sinusitis, rhinosinusitis, rhinitis, allergic rhinitis, acute sinusitis, acute rhinosinusitis, chronic sinusitis, chronic rhinosinusitis, sinus diagnosis, sinus treatment, nasal tumors/neoplasms, sinus tumors/neoplasms, nasal surgery, and sinus surgery*. The initial search was from the years 1930 to present. Since the results from both Web of Science and Scopus were similar in the first pass and since Web of Science seemed to focus more on US published articles, we elected to conduct the rest of the review through Web of Science exclusively. In addition, very few articles were identified from prior to 1970, and none were among the most highly cited articles, so the search was further confined to 1970 to 2012. We realize that with the increasing number of journals and number of journal pages, there is a clear bias for more recent articles and newer concepts. Since we had no objective way to compare the impact of earlier articles that may have had as much influence on the practices of their times as the newer, more highly cited articles, we elected to not to include those in the book, except for the “Editors’ Choices” papers that are described in more detail below.

The articles from all of the searches were combined in a database and listed according to frequency of citation. Many of the articles were listed in more than one search. We initially created an arbitrary cutoff of 50 cita-

tions or more to make the initial cut. The articles were then sorted by large topics, and general groupings were made to allow for a more robust review of redundancies and to make sure that the book would have a good balance of topics. Although some of the articles appeared to fit more than one large topic, it was simpler to identify a single topic for each. For example, computed tomography (CT) evaluation of the sinuses was included in diagnosis and not sinusitis. Once the articles were sorted, the individual lists were evaluated in detail. We noted that a few of the topics that we had initially felt should have a category had no cited articles. A good example of this was surgery for a specific indication, such as septal deviation or rhinoplasty. Other specific surgical topics, such as endoscopic repair of cerebrospinal fluid leaks and dacryocystorhinostomy, were cited enough to be included. Another area that seemed to be underrepresented was open surgical techniques for sinus disease. If there were multiple articles to a single topic, even if they were highly rated, we elected to reduce the number of articles to no more than 2 to 5 on a single topic. A very good example of this is fungal sinusitis, for which there were very many highly rated articles.

We did take some liberties in our final article list. We tried to limit articles that were by the same first author on similar topics. For example, if an author had articles discussing endoscopic sinus surgery principles, techniques, and outcomes, or if an author described surgery for the frontal and ethmoid sinuses, these were limited. Similarly, we limited the articles that were from the same institution or group of authors but with different orders of authors and varying primary authors. In allergic rhinitis, for which there were articles from many different disciplines, we primarily limited the final articles to the otolaryngology and allergy literature.

Many of the most highly cited articles were large reviews, evidence-based reviews, or recommendations or guidelines from national or international organizations. These usually included a large number of authors from a number of different institutions and were too lengthy to include in their entirety. Since most of these

were highly influential articles, we felt that they needed to be included in some way. If there was an executive summary that highlighted the key aspects of the study, this was included if possible. Otherwise, a summary of the article was provided and, where possible, the full abstract.

One of the obvious limitations to this search process was that a few of the most significant contributions to the literature did not make the final list. An excellent example of this is the original article that describes the Lund-Mackay CT score for sinus severity. It was not cited often enough to make the list, yet a number of the articles that did make the list devoted part or most of the article to the use of the Lund-Mackay scale. We therefore elected to include the original and less cited article.

The "Editors' Choices" papers clearly did not fit the rigid and objective methods of the rest of the book. As we went through the lists, and partially because we limited the articles to the past 40 years, we realized that some of the critical articles that paved our knowledge of nasal and sinus disease, as well as their evaluation and treatment, were missed. We decided to independently put together a list of what we each felt were those other "classics." We then combined our lists and agreed on the additions. We purposely kept these to a minimum to not dominate the rest of the book, and we included them in the sections related to their major topics. We realize that these decisions were arbitrary, and some very influential articles were likely missed.

Once the final lists were pared down for the overall book and each category or grouping, we further limited

articles to fit the page volume of the book. To comply with copyright law and ethical publication of previous published articles, we sought to obtain permission to republish the works from the original journals. In some cases, permission was not granted, and in others, the cost of reprinting was prohibitively expensive, so some of the articles that made the list do not appear in the book, or a summary or abstract are published.

In keeping with the highly effective concept of having an expert discuss the impact and influence of the various articles in *Classics in Voice and Laryngology* by Branski and Sulica, we elected to invite discussants for articles with similar topics. Dissimilar to *Classics in Voice and Laryngology*, we chose our discussants based on their reputation and influence in rhinology and their publication history. They were not, however, asked to review the impact of their own articles but rather related topics. Since most of the most highly cited authors are also highly influential, we tried to avoid having them also serve as discussants, even though they would have made excellent contributors as discussants. Rather, we tried to bring in many of the "Classics" authors of the future as our discussants and to hear their view of the impact of these articles on the specialty and their practices.

We have done our best to identify the critical articles that have shaped the face of rhinology and sinusology. We have also tried to do this in a way that was objective and transparent. Finally, we hope that *Classics in Rhinology* will serve as a simple and ready resource for anyone who wants to review the history of rhinology for patient care, education, or just for pure enjoyment.

—Michael S. Benninger and Marvin P. Fried

1

Definitions of Rhinosinusitis

Classic Articles

- Abstract or Executive Summary only.

Lanza DC, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg.* 1997;117(3):S1–S7.

- Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology [Review]. *Otolaryngol Head Neck Surg.* 2003;129(3)(suppl):S1–S32. For the full article, see http://oto.sagepub.com/content/129/3_suppl/S1.full

- Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. *J Allergy Clin Immunol.* 2004;114(6)(suppl):S155–S212. For the full article, see [http://www.jacionline.org/article/S0091-6749\(04\)02484-4/abstract](http://www.jacionline.org/article/S0091-6749(04)02484-4/abstract)

- Kaliner MA, Osguthorpe JD, Fireman P, et al. Sinusitis: bench to bedside: current findings, future directions.

J Allergy Clin Immunol. 1997;99(6)(suppl):S829–S848. For the full article, see [http://www.jacionline.org/article/S0091-6749\(97\)80037-1/abstract](http://www.jacionline.org/article/S0091-6749(97)80037-1/abstract)

- Lindberg S, Cervin A, Runer T. Nitric oxide (NO) production in the upper airways is decreased in chronic sinusitis. *Acta Otolaryngol.* 1997;117(1):113–117. For the full article, see <http://informahealthcare.com/doi/abs/10.3109/00016489709118001?journalCode=oto>

Uluap SO, Toohill RJ, Hoffmann R, Shaker R. Possible relationship of gastroesophagopharyngeal acid reflux with pathogenesis of chronic sinusitis. *Am J Rhinol.* 1999;13(3):197–202.

Kennedy DW, Senior BA, Gannon FH, Montone KT, Hwang P, Lanza DC. Histology and histomorphometry of ethmoid bone in chronic rhinosinusitis. *Laryngoscope.* 1998;108(4):502–507.

Commentary

Wytske J. Fokkens

Rhinosinusitis is the term currently used to describe a spectrum of inflammatory and infectious diseases concurrently affecting the nose and paranasal sinuses. Because sinusitis is almost always preceded by rhinitis and rarely occurs without concurrent nasal airway inflammation, the term *sinusitis* is mostly abandoned. In this discussion, I will mainly concentrate on chronic rhinosinusitis (CRS). CRS can be divided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). For a more thorough discussion, see later in this discussion.

In the 1990s, most emphasis was placed on the pathophysiology and differential diagnosis of rhinosinusitis. Lindberg and colleagues¹ were the first to describe that patients with CRS had lower nasal nitric oxide (NO) than did patients with the common cold or healthy controls. Inspired by the possibilities in the lower airways, where it was shown that exhaled NO was a good marker for asthma, to be more precise for eosinophilic airway inflammation, Lindberg et al tried to find an easy way to diagnose CRS. NO is found in both the upper and lower airways of humans and plays a role in vasodilation, neurotransmission, bronchodilation, and mucociliary regulation and might also have antimicrobial and anti-inflammatory and antitumor properties. It is found at concentrations less than 3 ppb in the normal lower airways and at about 600 ppb in the normal upper airways. The NO found in the upper airways is thought to arise from the sinuses and to play a role in maintaining the sterility of the paranasal sinuses. Since the study of Lindberg et al,¹ 4 other studies have used nasal NO measurements in CRS.

The results of these studies were very variable, usually not significantly different from normal, unless nasal polyps were found.² Nasal NO measurements were also used in acute rhinosinusitis (not different from controls), allergic rhinitis (conflicting results), effect of surgery in CRS (conflicting results), and cystic fibrosis and primary ciliary dyskinesia (PCD). In the latter two, nasal NO is consistently very low, and measurement of nasal NO may be a valuable tool to exclude these diseases, as whenever nasal NO is not low, the diagnosis of cystic fibrosis or PCD is less likely. Although the measurement of nasal NO as an easy way to diagnose CRS was attractive, it has not worked out that way, and the measure-

ments have never made it into the clinic and have been limited to clinical research in the upper airways.

In the second half of the 1990s, when endoscopic sinus surgery found its way into the otorhinolaryngologic society, the leaders in the field started to realize the need for standardization of nomenclature. Lund and Kennedy³ and Lund and Mackay⁴ wrote 2 very important articles on the scoring of computed tomography (CT) scans and endoscopy. To identify critical directions for research on sinus disease, the American Academy of Allergy, Asthma, and Immunology and the American Academy of Otolaryngology-Head and Neck Surgery Foundation convened a meeting in January 1996 in collaboration with the National Institutes of Allergy and Infectious Disease. This led to the first review paper with definitions of rhinosinusitis, although the title of the article is "Sinusitis: Bench to Bedside."⁵ "Sinusitis requires a more precise definition and classification. Because the inflammatory process that causes sinusitis is frequently associated with inflammation of the nasal passages, the term rhinosinusitis might more precisely define this disease state."^{5(pS830)} The article classifies rhinosinusitis chronologically into acute, recurrent acute, subacute, or chronic (persistent) disease. Acute sinusitis is defined as the symptom complex accompanying inflammation of the sinuses present for less than 8 weeks in adults and less than 12 weeks in children. Subacute sinusitis is defined as the manifestation of persistent minimal to moderate signs and symptoms of sinus inflammation, sometimes lasting for long periods. Chronic sinusitis is defined as signs and symptoms of inflammation of the sinuses persisting more than 8 to 12 weeks. It is mentioned that in contrast to acute sinusitis, the role of bacterial infection in subacute and chronic sinusitis is less certain. The term *recurrent acute* is not defined, nor is there any guidance on the diagnosis of rhinosinusitis. Symptoms, endoscopy, and CT scan of the sinus are not mentioned in the definition. However, important emphasis is placed on the high prevalence of the disease, the impact of rhinosinusitis on health-related quality of life, and the costs for society. This article has been a milestone in the definition of rhinosinusitis, and the criteria, although not very precisely defined, have been used in many later studies.

In 1998, an important study was published by Kennedy et al,⁶ showing for the first time that not only the mucosa but also the underlying bone are involved in chronic rhinosinusitis. In a very elegant experiment, 33 individuals with CRS and 16 patients having surgery for non-CRS were treated with tetracycline and demeclocycline at fixed intervals before undergoing surgery. The amount of tetracycline/demeclocycline-labeled bone was evaluated. Within the chronic sinusitis group, one-third of the patients showed no activity, one-third of the patients showed mild activity, and one-third of the patients showed marked activity. The average score assigned to chronic sinusitis specimens was 2.1. Within the control group, 70% showed no activity; of the other 30%, most showed mild activity. The authors conclude that a very active inflammatory process occurs in the ethmoid bone in patients with CRS, and this may be a significant factor in the persistence of overlying mucosal disease. Although not taken into definitions in future studies, chronic rhinosinusitis was shown in this article to be an inflammation not only of the mucosa but also possibly the underlying bone. Future studies have shown the findings can better be explained as neo-osteogenesis than as real inflammation of the bone.^{7,8} Whether neo-osteogenesis can lead to inflammation of the overlying mucosa is not clear at the moment.

In search of other factors that might influence CRS or the outcome of treatment of CRS, Ulualp et al⁹ investigated the role of gastroesophagopharyngeal reflux (GEPR). Over a 2-year period, they investigated 11 patients with CT-confirmed chronic sinusitis who had not responded to conventional therapy, and in 11 healthy controls, they measured GEPR with ambulatory pH monitoring. GEPR was found in 7 of 11 patients with CRS (1–12 episodes) and 2 of 11 healthy controls (1–2 episodes). Interesting aspects of this study were that 9 of 11 patients with CRS had involvement of the sphenoid, but only 6 had involvement of the ethmoid and 6 involvement of the maxillary sinus. Also, only 2 patients with CRS had had surgery, and 5 already spontaneously complained of heartburn. One might wonder whether this CRS population is representative of the general CRS population. Moreover, the healthy volunteers did not have symptoms of gastroesophageal reflux (GERD) or sinusitis, with the prevalence of GERD in the healthy population being around 20%.¹⁰ The authors conclude that compared with healthy controls, the prevalence of pharyngeal reflux of gastric acid is significantly higher in patients with chronic sinusitis unresponsive to conventional therapy, and they suggest a different esoph-

agopharyngeal distribution pattern of GERD in this patient group.

Ulualp et al⁹ suggest that GERD may contribute to the pathogenesis of chronic sinusitis in some adult patients. The relationship between GERD and rhinosinusitis has remained controversial over the past 15 years, but several large epidemiologic studies of adults and children have demonstrated an association between GERD and sinusitis.^{11,12} However, the differential diagnosis between GERD and postnasal drip can be difficult, and more controlled studies are required to strengthen this association and study whether treating GERD has a positive influence of CRS symptomatology.

A new US task force, the Task Force for Defining Adult Chronic Rhinosinusitis, was convened in January 2002.¹³ It was emphasized that the definition of CRS should not only be based on symptomatology, as was done in Kaliner et al,⁵ but that physical findings of mucosal swelling or discharge should be present for an appropriate length of time. Nasal endoscopy is, therefore, recommended. Furthermore, it is stated that although the current “imaging” standard for evaluation of the sinuses is a CT scan, plain sinus radiographs are helpful in confirming the diagnosis of symptomatic patients with equivocal physical findings. With the further availability of the CT scan, nowadays studies do not support the use of plain sinus radiographs.^{14–16} This study for the first time gives more rigorous criteria to establish the research criteria for the diagnosis of CRS, and it is recommended that in research, all patients who meet the clinical criteria for CRS should have a CT scan or nasal endoscopy performed to confirm the diagnosis. Moreover, other relevant measurements for research, such as allergy testing, validated outcomes instruments to measure quality of life, rhinomanometry and acoustic rhinometry instruments to objectively measure nasal patency and resistance, mucociliary clearance testing, olfactory evaluations, nasal cytology, and laboratory evaluation to detect underlying associated systemic disease such as measurement of serum eosinophilia, IgE levels, and genetic testing, are mentioned. This study is the first to highlight the importance of supporting evidence on which the definitions are based. The start made in Benninger et al¹³ to describe definitions for rhinosinusitis in research was extended by a joint effort of 5 US societies: the American Academy of Allergy Asthma and Immunology (AAAAI), American Academy of Otolaryngic Allergy (AAOA), American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), American College of Allergy, Asthma & Immunology

(ACAAI), and American Rhinologic Society (ARS) convened a group of 30 physicians from a wide range of disciplines, including allergy-immunology, otolaryngology, infectious disease, and radiology, to develop definitions of rhinosinusitis for clinical research and to suggest clinical trial designs. The group was able to reach consensus on definitions and clinical research strategies for acute presumed bacterial rhinosinusitis, CRS without polyps, CRS with polyps, and allergic fungal rhinosinusitis (AFRS). An important issue discussed at the conference was whether current evidence was sufficient to subclassify CRS into distinct subcategories. The group decided by consensus to accept the term *rhinosinusitis* instead of *sinusitis*. The group agreed to endorse and adopt the previously developed definition¹³ for rhinosinusitis: "Rhinosinusitis is a group of disorders characterized by inflammation of the mucosa of the nose and the paranasal sinuses." Acute rhinosinusitis is defined as an inflammatory condition involving the paranasal sinuses, as well as the lining of the nasal passages, and it lasts up to 4 weeks. As research criteria for diagnosis, patients with acute (presumed bacterial) rhinosinusitis must have symptoms, including anterior purulent drainage, posterior purulent drainage, or both, plus nasal obstruction or facial pain, pressure, or fullness present for a minimum of 10 days up to a maximum of 28 days. Additional individuals who have patterns that might qualify for inclusion are patients with severe disease who have the presence of nasal or postnasal purulent secretions for 3 to 4 days with high fever and patients whose symptoms initially regress but then worsen within the first 10 days. For objective documentation for the diagnosis, either nasal airway examination (purulent drainage beyond the nasal vestibule or posterior pharyngeal drainage) or radiographic evidence of acute rhinosinusitis (plain sinus films, CT, or magnetic resonance imaging [MRI]) is advised. It is not clear from this definition how many symptoms are necessary or what findings are considered relevant at imaging. Fulfilling this definition would be a patient with (objective) anterior purulent drainage and nasal obstruction for 12 days without any other symptoms. No differentiation is made to other diseases that might have the same symptoms, such as common cold (severe [not defined] disease with nasal purulent secretions for 3–4 days and high fever) or postviral rhinosinusitis.¹⁶

CRS with or without nasal polyps is defined as an inflammatory condition involving the paranasal sinuses, as well as the lining of the nasal passages, with symp-

tomts that persist beyond 12 weeks.¹⁵ For CRSsNP, 2 or more symptoms (anterior and/or posterior mucopurulent drainage, nasal obstruction, and/or facial pain, pressure, or fullness) are required. For CRSwNP, 2 or more symptoms (anterior and/or posterior mucopurulent drainage, nasal obstruction, and/or decreased sense of smell) are required.¹⁵

Objective documentation is required by means of direct visualization of the middle meatus through anterior rhinoscopy (after decongestion) or nasal endoscopy to assert the accurate diagnosis of CRS. Bilateral nasal polyps (NPs) are recorded as absent or present in the middle meatus to distinguish between CRSwNP and CRSsNP. A positive sinus CT scan is required for the research definition of both CRSsNP and CRSwNP.

A differentiation is made in the definition for patient care compared with research. For patient care, sinus CT imaging is not considered essential as symptoms and nasal endoscopy should be sufficient. In the past decade, these definitions for CRSsNP and CRSwNP in patient care and research have been proven to be very useful and have been used with small modifications in more recent guidelines and position papers.^{16,17}

Finally, in this paper, AFRS is clinically defined by meeting the criteria for CRS (with or without polyps) while demonstrating the presence of allergic mucin and evidence of fungal hypersensitivity by means of skin testing or in vitro blood testing.^{18,19} For research, the following is required, only one of the symptoms (anterior and/or posterior nasal drainage, nasal obstruction, decreased sense of smell, and/or facial pain, pressure, or fullness), endoscopy to document the presence of allergic mucin (without indicating how that is defined at endoscopy), and evidence of fungal-specific IgE by means of skin testing or in vitro blood testing.^{18,19}

From the millennium onward, the research on rhinosinusitis has been booming with at least a triplicate of studies, especially randomized controlled trials and other high-level studies compared to before 2000. Clear definitions of rhinosinusitis and conditions for clinical trials have been of great importance to ensure the level of our research and consistency of results. From the first attempts in the mid-1990s to the recent, sometimes very elaborate studies, a significant progression has been made. What we now need is a world consensus paper on the definition of rhinosinusitis and strict guidelines of journals to stick to the definitions and guidelines included in this world consensus.

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