Chronic Rhinosinusitis: The Unrecognized Epidemic

Rhinosinusitis is defined on the basis of the four cardinal symptoms of obstruction, drainage, smell loss, and facial pain or pressure in both acute (ARS) and chronic (CRS) rhinosinusitis, with CRS distinguished by a duration of symptoms of 3 or more months. The determinants of progression from ARS to CRS remain underexplored, but CRS differs from ARS in microbiology, with the most commonly cultured ARS pathogens rarely found in CRS. For the diagnosis of CRS, guidelines further recommend that symptoms be accompanied by objective evidence of sinus inflammation on the basis of sinus computed tomography (CT) scan or nasal endoscopy (1–3). These recommendations were necessary because it remains difficult to accurately differentiate whether a patient presenting with a chief complaint of 4 months of symptoms of facial pain or pressure, bilateral nasal obstruction, and nasal discharge has recurrent ARS, CRS, allergic rhinitis, or migraine without results from diagnostic tests such as nasal endoscopy, a CT scan, or atopy testing. Using symptoms alone, it is also difficult to differentiate important clinical subtypes of CRS such as CRS with nasal polyps (CRSwNP). Indeed, studies from tertiary care institutions report that only about half the patients with characteristic CRS symptoms have objective evidence of sinus inflammation (4, 5). Because diagnosis at the point of encounter has significant impact on treatment, the assumption of a CRS diagnosis on the basis of characteristic symptoms alone likely leads to excessive diagnosis and treatment.

Although directly attributable severe morbidity and mortality from CRS are infrequent, the symptoms and quality-of-life impairment attributed to CRS drive 11.1 million healthcare visits, 250,000 sinus surgeries (CRS being the most common indication), 7.1% of all adult outpatient antibiotic prescriptions, and a conservatively estimated $8.6 billion in direct healthcare costs; placing CRS among the top 10 most costly conditions to U.S. employers (6, 7). Because indirect costs such as workdays missed, increased antibiotic resistance, or antibiotic-related complications have not been fully characterized, the true costs associated with CRS may be significantly higher. Despite these high rates of healthcare use, the epidemiologic study of CRS is in its infancy. Comprehensive multi-institutional research networks have only just begun to apply consensus diagnostic criteria, establish clinical subphenotypes, and use validated disease outcome measures. Thus, there is a paucity of transformative longitudinal studies akin to the National Heart, Lung, and Blood Institute Severe Asthma Research Program or the U-BIOPRED (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes) studies, which have added exciting new information on the phenotyping of asthma. At present, there remains poor information on the incidence, prevalence, natural history, and etiology of CRS and even fewer comprehensive biobanks upon which analysis of biomarkers of CRS severity can be performed. Currently, the World Health Organization has provided no plans for surveillance or prevention and control in its global action plan for chronic respiratory disease (8), and the National Institutes of Health has only recently provided funding for initial studies into the epidemiology of CRS.

In the United States, frequently cited National Health and Nutrition Examination Survey data estimated the prevalence of rhinosinusitis at between 13 and 17% of adults (9). In the National Health and Nutrition Examination Survey, respondents were asked whether they had received a diagnosis of "sinusitis" from a healthcare professional in the previous 12 months. However, the survey did not ascertain duration of symptoms, so ARS and CRS could not be separated; it depended on a healthcare provider diagnosis of sinusitis; not all patients may seek care; and it failed to ascertain and distinguish important variants such as CRSwNP. In 2011, the first population-based epidemiologic study was conducted in Europe using questions about CRS symptoms or prior physician diagnosis and estimated overall adult prevalence at 10.9% (10). In Korea, a population-based survey revealed a prevalence of only 1% in 1991, but this rose to 7% when results were reported again in 2011 (11, 12).

We recently analyzed electronic health records of the primary care patients of the Geisinger Health System and, relying on ICD-9 codes, estimated the incidence for this common condition at 1.1 cases per 100 person-years. Incidence among adults peaked between ages 45 and 54 years. There were sex differences, as more females had CRS without nasal polyps and more males had CRSwNP (13). Our study further demonstrated that CRS was strongly associated with premorbid episodic and chronic conditions of the upper *and* lower airway with particularly strong associations between CRS and asthma, especially CRSwNP. A number of airway conditions less frequently associated with CRS, including bronchitis, pneumonia, obstructive sleep apnea, and gastroesophageal reflux disease, were also significantly more prevalent in patients who developed CRS, lending strong support for the concept of the unified airway. There is a present need to systematically evaluate the natural history of CRS; the role of developmental, environmental, and occupational risk factors; the long-term effects of CRS on comorbid conditions of the airway; and whether CRS is associated with the development of postmorbid conditions outside the airway.

To date, an incomplete understanding of the etiology and pathogenesis of the disorder, the lack of accepted animal models arising from the uniquely complex paranasal sinus anatomy of humans compared with model organisms, and the paucity of large population-based studies have impeded progress in CRS research (14). Most data on patients with CRS, defined using consensus guidelines requiring evidence of sinus inflammation, are from highly selected patients in tertiary care. Studies of CRS in the general population have generally relied on ICD-9 codes, often from the primary care physician (13), self-reported symptoms without objective determination of sinus inflammation, or self-reported physician diagnosis of CRS. Important unresolved issues include whether etiology, pathophysiology, natural history, and need for treatment differ in the patients described in general population studies and tertiary care populations. Nonetheless, population-representative studies of accurately identified patients with CRS are critical to provide the observations of phenomena and disease history necessary for genetic, epigenetic, immunologic, microbiologic, and other mechanistic investigations.

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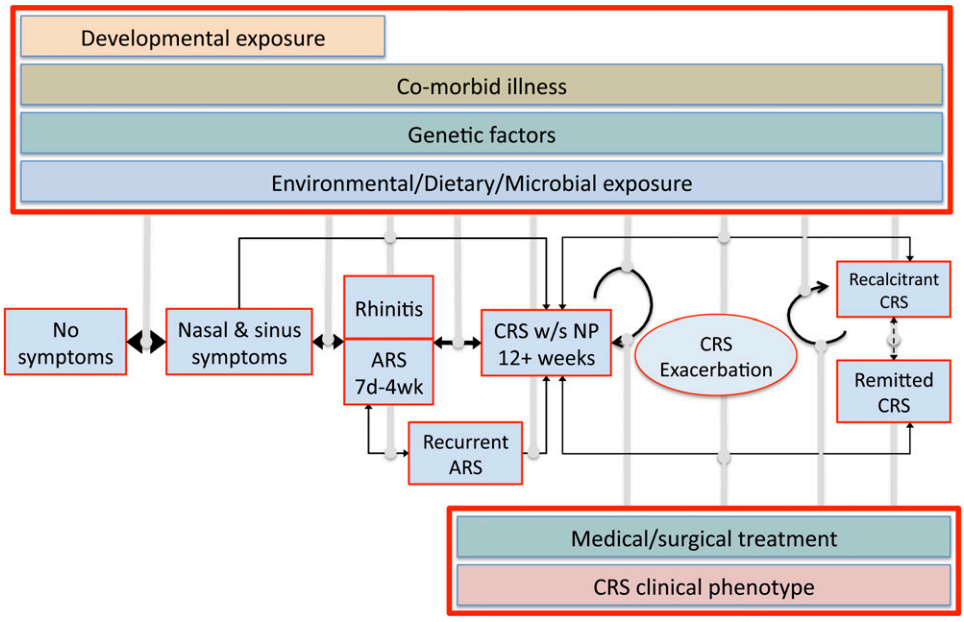

Figure 1. Application of a dynamic chronic episodic disease model to the natural history of chronic rhinosinusitis (CRS). Ordinary nasal and sinus symptoms progress through a transition through a state of rhinitis or acute rhinosinusitis (ARS) into CRS. In the model, CRS can be worsened by exacerbations of disease, durably remit at various points, or transition to recalcitrant CRS after exacerbations. Environmental, genetic, dietary, and developmental factors, the presence of comorbid diseases such as asthma, and specific microbial exposures, CRS phenotype, and surgical or medical management all likely affect transition rates to the various disease states.

We can make several recommendations for studies that are needed to address the aforementioned limitations in CRS epidemiology. First, to facilitate studies in the general population, a validated questionnaire is needed that can identify patients with sinus inflammation as well as distinguish patients with and without nasal polyps. Second, studies should recruit patients from community and tertiary care populations and biobank samples upon which analyses for biomarkers of severity or phenotype can occur. Third, new natural history models must be investigated because evidence suggests that CRS prevalence plateaus with increasing age, implying that disease remission occurs in a substantial segment of the patient population. CRS should be reevaluated using a conceptual framework applied for the analysis of several other chronic episodic conditions, including asthma, migraine headache, and gastroesophageal reflux disease. In this framework (Figure 1), CRS is hypothesized to begin with a transition from ARS or rhinitis. With continuing insults, including environmental exposures, and influenced by genetic predispositions, disease can progress to a period of durable symptoms meeting the definition of CRS. Once CRS is established, transitions can occur, allowing for extended periods of remission without symptoms; relapse into the symptomatic state after exacerbations, during which healthcare use is likely to occur; and for some, a progressive recalcitrant course with persistent symptoms not durably altered by the effects of treatment. The incidence, prevalence, transition rates, and risk factors for each of the states in the framework are currently unknown, but we believe this model can account for and explain the clinical experience and natural history of the various clinical phenotypes of CRS (e.g., CRS without nasal polyps, CRSwNP, allergic fungal rhinosinusitis, and aspirin-exacerbated respiratory disease) in an epidemiologic framework. In evaluation of this model in the context of published literature, it is apparent that factors such as asthma likely increase rates at which ARS transitions toward CRS and treatment recalcitrance. This explains the high prevalence of individuals with asthma in studies of CRS in tertiary care. Similarly, patients with specific disease phenotypes, such as aspirin-exacerbated respiratory disease, are significantly more likely to remain recalcitrant, receiving repeated surgeries and courses of medication without disease remission. Further studies that carefully elucidate the drivers of these transitions between states are likely to provide novel and critical insights regarding potential mechanisms and thus more effective prevention and management of CRS.

In the changing environment of a healthcare system that places increasingly heavy emphasis on preventing costly escalations in care and demands metrics of efficacy to justify resource use, CRS appears to be an inviting disease for careful evaluation of current clinical practice and reconceptualization of our current disease paradigm. It is clear that critical new tools are needed to understand the natural history of the disease and identify factors leading to disease onset, symptomatic exacerbation, and remission in CRS. Epidemiologic studies are urgently needed to fill the immense gaps in knowledge and a fundamental reconsideration of CRS as a chronic episodic disease may provide a critical framework with which future studies can conceptualize this epidemic that silently claims a heavy individual and societal toll.

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Are the Smoking-induced Diseases an Acquired Form of Cystic Fibrosis?

Cystic fibrosis, the most common autosomal recessive disorder of whites, is caused by inheritance of variants of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, coding for an ABC transporter class cyclic AMP–responsive ion channel that provides functions in airway, pancreatic, bowel, sweat gland, and vas deferens epithelium (1). When both parental genes have deleterious variants of the CFTR gene, the result is an insufficient amount or function of the CFTR protein on the epithelial surface, resulting in chronic bronchitis, pancreatic insufficiency, and male infertility. The classic test for cystic fibrosis is measurement of sweat chloride levels in the skin after administration of pilocarpine (2, 3).

Whereas cystic fibrosis is considered a classic monogenic Mendelian "genetic disease," disorders associated with chronic cigarette smoking, including chronic obstructive pulmonary disease (COPD), are thought to be "acquired diseases," caused by the direct and indirect effects of cigarette smoke. Although there is a genetic component to susceptibility for COPD in smokers, these genetic variants each contribute only a minor increased risk, and there is no link between genetic variants of CFTR and susceptibility to smoking (4).

In a provocative study in this issue of the *Journal*, Raju and colleagues (pp. 1321–1330) present evidence that smokers with normal CFTR genes have dysfunctional CFTR protein in organs other than the lung (5). Although others have previously shown that CFTR function is suppressed in the nasal epithelium in cigarette smokers and that cigarette smoke extract inhibits CFTR function in bronchial epithelial cells *in vitro* (6, 7), Raju and colleagues (5) have extended this concept to show that the effect of smoking on CFTR function is systemic. On average, Raju and colleagues (5) found that compared with nonsmokers, there was a twofold increase in sweat chloride levels in normal smokers, smokers with COPD, and ex-smokers with COPD. Consistent with the sweat chloride observations, quantification of rectal biopsy short-circuit currents in Ussing chambers (a measure of CFTR function) in smokers showed a 65% decrease compared with nonsmokers. Further supporting the overall concept, mice exposed to cigarette smoke had decreased airway and intestinal epithelial CFTR activity. Finally, exposure of human bronchial cells to plasma from smokers decreased CFTR activity, and exposure of these cells to acrolein, a component of cigarette smoke elevated in plasma of smokers, blocked CFTR function. Essentially, the conclusions of the study by Raju and colleagues (5) are that cigarette smoking modifies the function of CFTR proteins throughout the body, causing the functional equivalent of a mild form of cystic fibrosis in the airways and tissues as far-flung as the skin and the rectal epithelium.

Does smoking essentially create the systemic equivalent of a monogenic disorder? A link between cystic fibrosis and diseases caused by cigarette smoking is not far fetched. Although we usually think of cystic fibrosis as a genetic disorder with a characteristic lung, bowel, and reproductive phenotype (2, 3), the pulmonary manifestations of cystic fibrosis are essentially a very aggressive form of chronic bronchitis, and cigarette smoking is associated with both weight loss and reduced fertility. The pulmonary manifestations of cystic fibrosis, the most common hereditary lung disease, and cigarette smoking, the most common cause of acquired lung disease, have much in common. At the biologic level, the earliest abnormalities of the pulmonary manifestations of both are in the airway epithelium, with disordered differentiation including secretory cell hyperplasia, airway inflammation, and eventual development of chronic airway infection. At the clinical level, there are also similarities, with fixed airflow obstruction. Both are progressive, and both are associated with a shortened life span. The recent study by Okada and colleagues (8) demonstrating the marked differences in the appearance of the skin of monozygotic identical twins, where one twin was a chronic smoker and the other a nonsmoker, provides dramatic evidence that smoking may cause systemic disease.

Although the study by Raju and colleagues (5) provides evidence for a new way to think about smoking-induced disease, it also raises several issues.

First, what is the relevance of these findings to the skin sweat chloride test, the classic test to diagnose cystic fibrosis, and assessment of nasal potential difference, a more sophisticated test used by some research laboratories? As Raju and colleagues (5) point out, smoking status may need to be considered a covariate