

Approaching Chronic Sinusitis

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Abstract: Chronic sinusitis is a common disease that encompasses a number of syndromes that are characterized by sinonasal mucosal inflammation. Chronic sinusitis can be defined as two or more of the following symptoms lasting for more than 12 consecutive weeks: discolored rhinorrhea, postnasal drip, nasal obstruction, facial pressure or pain, or decreased sense of smell. Chronic sinusitis is further classified as chronic sinusitis with polyposis, chronic sinusitis without polyposis, or allergic fungal sinusitis using physical examination, and histologic and radiographic findings. Treatment methods for chronic sinusitis are based upon categorization of the disease and include oral and inhaled corticosteroids, nasal saline irrigations, and antibiotics in selected patients. Understanding the various forms of chronic sinusitis and managing and ruling out comorbidities are key to successful management of this common disorder.

Key Words: chronic rhinosinusitis, chronic sinusitis, nasal airway obstruction, nasal irrigation, rhinosinusitis

Chronic rhinosinusitis (CRS) is a common disease affecting approximately 15% of the US population each year.¹ A diagnosis of CRS is made >29 million times per year, placing a >\$4.3 billion burden on the American economy.² Although common in all age groups, the peak prevalence of CRS is in patients between 44 and 64 years old.² It affects all races and socioeconomic backgrounds. Quality of life (QOL) scores for chronic sinusitis parallel serious illnesses such as congestive heart failure and angina pectoris.³

The primary aspect separating chronic sinusitis from acute or subacute rhinosinusitis is its temporal course. A diagnosis of

CRS requires at least two of the following symptoms for 12 consecutive weeks: anterior or posterior mucopurulent or discolored drainage, nasal obstruction, facial pressure or pain, or decreased sense of smell.⁴ Because these symptoms are nonspecific, the diagnosis of CRS requires that a physical examination or imaging demonstrates evidence of inflammation such as purulent mucous, nasal cavity edema, or polypoid mucosal changes.⁴ Although anterior rhinoscopy with a nasal speculum often is sufficient for evaluation, nasopharyngeal endoscopy offers superior visualization of underlying abnormalities. Septal deviation, nasal polyps, or a pneumatized middle turbinate (concha bullosa) may predispose a patient to CRS. In addition, nasopharyngoscopy allows visualization of the posterior nasal cavity, nasopharynx, and, when present, sinus drainage from the middle and superior meatus.

In addition to patient symptoms and physical examination, the 2007 American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) guidelines recommend corroborating the diagnosis by using computed tomography (CT) in certain situations.⁴ Imaging aids in ruling out other etiologies and identifies potentially correctable anatomic abnormalities. CT demonstrates superior anatomic detail compared with plain films and is more sensitive and specific than history and physical examination alone.^{5,6} In addition, CT may identify more aggressive disease processes such as extrasinus extension that may warrant an urgent evaluation by an otolaryngologist.^{4,6} Precise timing of CT in the management of CRS

Key Points

- Chronic sinusitis is defined as 12 weeks of consecutive symptoms in addition to physical examination confirming mucosal inflammation or infection.
- Chronic sinusitis consists of many phenotypes including chronic rhinosinusitis with nasal polyposis, chronic rhinosinusitis without nasal polyposis, and allergic fungal sinusitis. Although symptoms are similar, the pathophysiology of each is different.
- Biofilms and coexisting medical diseases may contribute to chronic sinusitis.
- Treatment is multifaceted, driven by the type of disease present, and typically includes intranasal steroids and nasal saline irrigation. Other contributing diseases also should be controlled.

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remains controversial. An AAO-HNS consensus statement regarding the appropriate use of CT in paranasal sinus disease concluded that obtaining a CT scan to aid in the diagnosis of CRS was appropriate.⁶ A sinus CT allows providers to confirm the diagnosis and identify potential surgically correctable anatomic abnormalities. CT findings also may avoid inappropriate medication administration and spur physicians to seek alternative diagnoses when no sinonasal pathology is identified.

There have been many approaches to minimizing sinus CT radiation dose.⁷⁻¹⁰ Hojreh et al reported that the diagnostic quality of low-dose scans is equal to higher doses in examining important sinonasal landmarks. They recommend using a tube current of 50 mA (with 120 kV and collimation of 16×0.75 mm).⁸ This protocol reduces the radiation dose from 30 to 6.1 mGy, a dose that is equivalent to a four-view x-ray of the sinuses.⁷⁻¹⁰ Given the widespread use of ionizing radiation in evaluating disease processes, it is prudent to minimize the radiation dose for a diagnostic CT scan; therefore, communication with the radiologist is critical to avoiding unnecessary radiation exposure.

Pathophysiology

CRS is primarily a disease of inflammation and can result from several triggers, which may explain why it has many different phenotypes. The two most common phenotypes are CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP). Fig. 1 is an anterior view comparing normal anatomy to that of nasal polyposis. Although symptoms may be identical histologically and immunologically, these two phenotypes differ greatly.¹¹

Traditional thought held that immunologically CRSsNP was primarily the result of a T-helper 1 (Th1)-driven immune response and that CRSwNP resulted from a Th2-driven response.¹² In a basic immune response, CD4⁺ lymphocytes are driven to produce cytokines to eliminate the pathogen. Antigen-presenting cells alert T cells via the major histocompatibility complex type II. The interaction of the antigen-presenting cells

and cosignaling molecules polarize a naïve T cell into a Th1 or a Th2 pathway.¹³ The Th1 pathway produces a cascade of cytokines that trigger cell-mediated immunity and phagocytic inflammation by natural killer cells and cytotoxic T cells. This triggers a significant proinflammatory response, with an increase in transforming growth factor- β , interleukin (IL)-2, and IL-10. The Th2 pathway leads to the recruitment of eosinophils, polymononuclear cells, and immunoglobulin E (IgE) antibody production.¹³ Although prevailing opinion may have been that CRSwNP and CRSsNP is simply a spectrum of the same disease, analysis of inflammatory mediators beyond neutrophil versus eosinophil is distinctly different. CRSsNP shows an increased number of activated T cells, increased fibrosis and high levels of transforming growth factor- β ; CRSwNP shows increased IL-5, eosinophils, and high levels of IgE with significant edema but little to no fibrosis^{11,12,14,15}; however, it has been found that both Th1 and Th2 responses can drive the formation of nasal polyps, with white populations typically having the established Th2 eosinophilic polyposis and some Asian populations having Th1-driven neutrophilic polyposis.^{11,15} This indicates that there is partial overlap and that these diseases may not be mutually exclusive. At present, researchers are separating and defining these two phenotypes to eventually predict comorbidities, recurrence after surgery, or response to innovative treatment.^{14,16-20} Clearly, the ability to distinguish these two entities will become increasingly important.

Allergic fungal sinusitis (AFS) is a third subtype of CRS that is radiographically and histologically distinct. Typically, type 1 hypersensitivity, nasal polyps, characteristic CT findings, presence of fungi on direct microscopy or culture, and allergic mucin are the five characteristics that describe AFS.²¹ Although clinical symptoms may appear identical to other forms of CRS, AFS may be easily distinguished radiographically because often there is unilateral or asymmetric involvement of the sinuses.^{22,23} Bony expansion and remodeling can be impressive and is seen in approximately 20% of patients.²³ The double density sign frequently is used to describe the

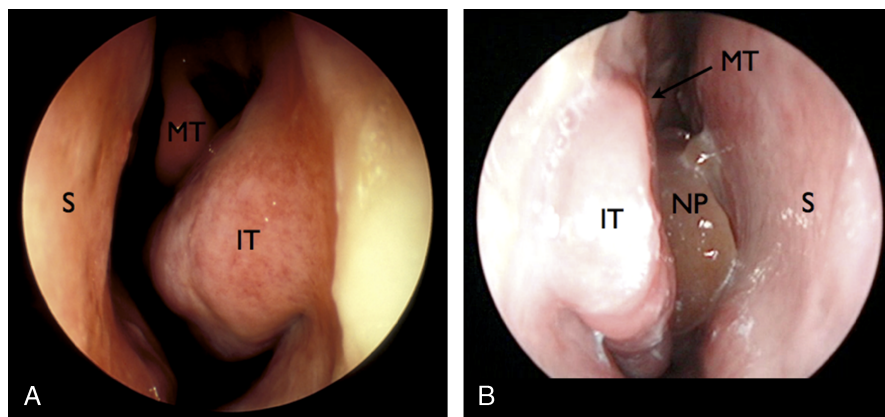


Fig. 1. A, Normal anatomy of left nasal cavity. B, Right nasal cavity with nasal polyp. IT, inferior turbinate; MT, middle turbinate; NP, nasal polyp; S, septum.

serpiginous appearance of mucin, fungal debris, and polypoid concretions within the sinuses.

Evidence is mounting that biofilms play an important role in the etiology and persistence of CRS. Pathogens can exist in a protected state called a “biofilm.” A biofilm is a sessile community of bacteria that forms a protective mucoid matrix. Biofilms irreversibly adhere to the sinus mucosa and bacteria within the colony exist at multiple different levels of metabolic activity. These characteristics allow the colony to be extremely resistant to both host defenses and antimicrobial agents²⁴ (Fig. 2). Various studies have identified biofilms on the mucosa of patients with CRS.²⁵ In a study that evaluated sinus surgical outcomes, the presence of biofilm was found to significantly reduce the success rates of surgery.²⁶ Specifically, the presence of *Staphylococcus aureus* as a single biofilm or in a colony of multiple species was strongly associated with worse postoperative symptom scores and signs of continued mucosal inflammation.²⁷

There are many comorbidities to consider with CRS. Researchers developed the unified airway concept during the past 15 years,²⁸ which proposes that because the respiratory mucosa from the middle ear and nose to the bronchioles is identical, it shares the same physiology and susceptibility to inflammation. The unified airway model explains the overlap and comorbidities that are associated with inflammatory diseases such as allergic rhinitis, chronic rhinosinusitis, and asthma.

Epidemiologic studies report that the prevalence of asthma in patients with allergic rhinitis is 20% to 35%. Patients with chronic sinusitis have a 20% prevalence of asthma and a 40% to 85% prevalence of allergic rhinitis.²⁹ Consistent with the

unified airway theory, multiple studies demonstrate that medical treatment of sinusitis and allergic rhinitis leads to better control of a patient’s asthma and vice versa. The 2007 National Asthma Prevention Expert Panel Report 3 recognized sinusitis and allergies as comorbid conditions that aggravate asthma and impede its treatment.³⁰ If skin testing for aeroallergens is clinically indicated, the panel recommends it in patients with asthma and maximally treating identified allergies with medications or immunotherapy.³⁰ Similarly, the AAO-HNS recommends allergy testing and treatment to control chronic sinusitis.⁴ There also is emerging evidence that immunotherapy may play a role in the treatment of AFS.³¹

In some patients with CRS and asthma, the disease is exacerbated by aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). Often, this sensitivity occurs as part of a triad that includes nasal polyposis, asthma, and aspirin sensitivity, and is known as aspirin-exacerbated respiratory disease or Samter’s triad. Aspirin and some NSAIDs block cyclooxygenase-1, thereby decreasing the production of anti-inflammatory prostaglandins such as prostaglandin E2.³² Arachidonic acid metabolites are shunted toward the production of leukotrienes, which are potent mediators of inflammation in the upper and lower airways. In this subgroup of patients, these metabolites can cause symptoms ranging from rhinorrhea and nasal obstruction to chest tightness and bronchospasm. Treatment requires the avoidance of all NSAIDs, and in some cases, aspirin desensitization is necessary.³²

Patients with immunodeficiency may account for 8% to 20% of patients with persistent or recurrent sinusitis.^{33–35} Patients with recurrent sinus infections, pneumonias, skin abscesses, or gastrointestinal symptoms should be evaluated for

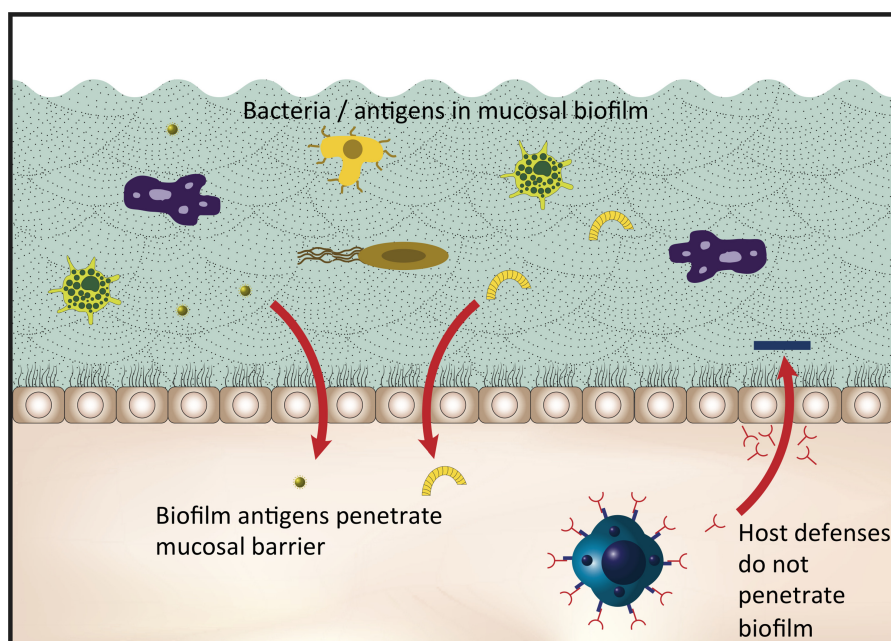


Fig. 2. The role of biofilms.

immunodeficiency with quantitative Ig levels (IgA, IgM, IgG) and vaccine responsiveness status through titer evaluation such as antipneumococcal titers.³⁴⁻³⁶ Human immunodeficiency virus testing, and if positive, CD4⁺ counts are warranted.³⁷ Typically, these patients complain of symptom recurrence shortly after the completion of antibiotic therapy. In patients with chronic sinusitis, Chee et al found an unexpectedly high incidence of immune dysfunction, the majority of which were common variable immune deficiencies.³⁸ Culture-directed antibiotic therapy is the treatment of choice in patients with immunodeficiencies and specific deficiencies may be supplemented by intravenous or subcutaneous immunoglobulin.³⁹⁻⁴¹

In patients who continually fail medical management for chronic sinusitis, genetic evaluation is warranted. Children presenting with nasal polyposis should have a workup to rule out cystic fibrosis (CF). Nasal polyps are present in 20% to 50% of patients with CF.⁴²⁻⁴⁴ Although the role of endoscopic sinus surgery to improve lung function in CF is debatable, multiple studies have shown a significant improvement in QOL in these patients following sinus surgery.⁴⁵⁻⁴⁷ In addition, other ciliary dyskinesia, including primary ciliary dyskinesia, Kartagener syndrome, and Young syndrome, is associated with an increased incidence of CRS and nasal polyps.^{4,42,66}

Many patients with hypereosinophilic syndromes or autoimmune diseases may present with chronic sinusitis.^{4,33,42,66} In middle-aged patients with asthma and new-onset chronic sinus symptoms, Churg-Strauss disease may be considered. The four cardinal symptoms of Churg-Strauss are bronchial asthma, chronic sinusitis, eosinophilic vasculitis, and granulomas. Anterior rhinoscopy may demonstrate severe crusting, open sores, and nasal polyposis. Wegener granulomatosis is an autoimmune disease that typically presents in adulthood and frequently has physical examination findings similar to Churg-Strauss. The list below provides a differential diagnosis to consider when evaluating the confounding factors as well as the possible comorbidities to consider in chronic sinusitis.

Inflammatory

- Gastroesophageal reflux
- Rhinitis
- Allergies
- Churg-Strauss disease

Trauma

- Orbital fracture
- Nasofacial fractures

Autoimmune

- Wegener granulomatosis
- Sarcoidosis

Metabolic

- Pregnancy
- Hypothyroidism

Infectious

- Human immunodeficiency virus
- Dental abscess

Iatrogenic

- Foreign body
- Smoking

Neoplastic

- Juvenile nasal angiofibroma

Congenital

- Adenoid hypertrophy
- Thronwaldt cyst
- Young syndrome
- Kartagener syndrome
- CF
- Common variable immunodeficiency

Treatment

CRS is a disease of inflammation; therefore, inflammatory triggers should be sought and treated. The Table outlines treatment recommendations for CRSsNP and CRSwNP from available data. Historically, there has been an overreliance on antibiotics. The 2012 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS2012) downgraded their previous recommendation in favor of long-term antibiotics to a treatment option if steroids and nasal saline irrigation fail.^{47a} This change was a result of a placebo-controlled randomized study,⁴⁸ as well as other smaller studies. The authors note that several other factors could have affected the response to treatment, with smokers having a lower response rate and those with normal IgE levels having a higher response rate. The Cochrane Database attempted a meta-analysis of systemic antibiotics for CRSwNP in adults and only one study met the inclusion criteria. In that study, 3 months of low-dose roxithromycin (a drug not available in the United States) reduced the mean response score of patients modestly (by 0.73 points on a 1- to 6-point scale) at 3 months after the start of treatment. Comparisons of pre- and posttreatment scores of the sinonasal-outcome test, a validated, disease-specific QOL instrument,⁴⁹ show that the roxithromycin group fared no better than the placebo group. The study concluded that routine long-course antibiotics in patients with chronic rhinosinusitis are not warranted⁵⁰; however, roxithromycin is a semisynthetic macrolide, a class of antibiotic with known anti-inflammatory effects. Multiple studies have demonstrated both

Table. Treatment recommendations for CRSsNP and CRSwNP*

| Therapeutic intervention | CRSsNP | | CRSwNP | |
|--------------------------|--------|---------------------------------------|--------|---------------------------------------|
| | Mild | Moderate or severe | Mild | Moderate or severe |
| Nasal saline irrigation | Yes | Yes | Yes | Yes |
| Topical steroids | Yes | Yes | Yes | Yes |
| Oral steroids | — | — | — | Yes |
| Oral antibiotics | — | Option: long term if IgE not elevated | — | Option: long term if IgE not elevated |

CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; IgE, immunoglobulin E.

*Including severity based on best current evidence, including the 2012 European position paper on rhinosinusitis and nasal polyps.^{47a,66}

in vitro and in vivo effects of macrolides to decrease bacterial virulence and biofilm formation, as well as to downregulate proinflammatory cytokines.^{16–18,51} Additional prospective randomized controlled trials with strict inclusion criteria are required before the subset of patients with CRS who will benefit from antibiotics are identified. Perhaps prescribing a long course of antibiotics for any patient with CRS should be decided on a case-by-case basis, taking into account the individual's symptoms, physical examination findings, risk factors, and comorbidities.

Topical antibiotic therapy can provide high local drug concentrations in the sinuses while minimizing systemic absorption of the drug. This treatment method has significant appeal for biofilm-related diseases, which can require antibiotic concentrations up to 1000 times the minimum inhibitory concentration to eradicate. There have been a small number of retrospective studies and one prospective study supporting the efficacy of this treatment method.^{52–54} Although further studies are necessary to determine the exact pharmacodynamics of topical antibiotics, their use is promising in the treatment of recalcitrant disease after sinus surgery.

Intranasal steroids have been proven effective in improving nasal polyps, decreasing nasal congestion and drainage, and improving overall QOL. Effective treatment may require higher dosages than those used for allergic rhinitis. Double-blind, randomized controlled studies of CRSwNP have shown benefit, with fluticasone using dosages of 400 to 800 $\mu\text{g}/\text{day}$ for durations ranging from 12 to 26 weeks.^{55–58} Mometasone 200 to 400 μg once or twice daily for 16 weeks also improved symptoms of CRSwNP.^{59–61} With such relatively high doses of steroids, much attention is focused on the systemic adverse effects of intranasal application. Both fluticasone and mometasone have systemic bioavailability of <1%.⁶² No significant effects have been shown on the hypothalamic–pituitary axis with prolonged treatment.^{62–64}

Oral corticosteroids are another common modality of treatment for CRS because of their ability to decrease inflammation. Lal and Hwang conducted a systematic review of 33 publications showing that oral steroids, in combination with other treatment modalities, increased the time interval to recurrence and improved both nasal endoscopy and CT scores.⁶⁵ Oral steroids appear to be especially beneficial in patients with AFS and with CRSwNP.^{4,20,30,31,67,68} Dosing and duration of treatment have not been standardized. In a double-blind placebo-controlled study, Van Zele et al showed that a steroid taper starting at 32 mg of methylprednisolone daily and tapering to 8 mg during a period of 20 days significantly decreased polyp size and levels of inflammatory cytokines.²⁰

Nasal saline irrigation with isotonic or hypertonic saline is an effective, inexpensive treatment for all types of CRS. Benefits of nasal irrigation include improved mucociliary function, decreased nasal mucosal edema, and mechanical removal of infectious debris and allergens.⁶⁸ The symptomatic improvement from nasal irrigation has been demonstrated in many randomized controlled trials. A Cochrane Database

systematic review concluded that the beneficial effects outweigh minor adverse effects.^{69–71} The AAO-HNS recommends sinus irrigation as a primary preventive practice, a secondary preventive practice after surgery, and part of a combined treatment for all types of sinusitis.⁴

Finally, if CRS symptoms continue despite a thorough workup and medical treatment, and CT demonstrates persistent sinus disease, an otolaryngology consultation is indicated. For patients with AFS, sinus surgery is almost always warranted.³¹ Functional endoscopic sinus surgery via traditional endoscopy or under image guidance (used in revision or complex surgery to aid in orientation within the paranasal sinuses) allows for removal of inflammatory drivers (nasal polyps, purulence, or allergic fungal mucin). In addition, functional endoscopic sinus surgery opens and widens the natural drainage pathways to allow the mucociliary blanket to trap and transport antigens out of the sinonasal cavities and to create sinus access for topical medications. Balloon sinuplasty has become available as a minimally invasive therapeutic option to open the sinus ostia, but it has not been validated in any randomized controlled trials.^{72,73} Sinus ostia must be at least 4.7 mm for nasal irrigation to reliably penetrate the sinuses and the solution should penetrate all of the sinuses.³⁴ Irrigation with a high-volume, low-pressure irrigator (eg, NeilMed sinus rinse plastic squeeze bottle [NeilMed Pharmaceuticals, Santa Rosa, CA]) with the head tilted downward 45° and the bottle aligned on an axis parallel to the nasal dorsum and aimed toward the ipsilateral medial canthus is most effective.^{74,75}

In caring for postoperative patients with CRS, the treatment goals are controlling nasal mucosa inflammatory responses to optimize nasociliary function. This may be done almost entirely with topical medications delivered through a sinus rinse bottle or nebulizer. Topical medications include surfactants, antibiotics, and steroids. Surfactants work by decreasing mucous viscosity and altering the microbial–surface interface. They cause cell membrane disruption and increase cell membrane permeability, which disrupts the complex interactions and mechanical defenses of biofilms.¹⁹ Baby shampoo is a simple, inexpensive surfactant that is commercially available and safe to use. A University of Pennsylvania study determined the optimal concentration of Johnson's Baby Shampoo (Johnson & Johnson, New Brunswick, NJ) to nasal irrigation is 1% (approximately ½ teaspoon in an 8-oz irrigation bottle). Chiu et al found that it not only improved symptoms of thick mucous and postnasal drip but it also significantly inhibited the formation of *Pseudomonas* biofilms.⁷⁶ The duration of treatment was twice daily for 4 weeks. Although this was a small, uncontrolled study, no significant adverse effects were reported and it may prove beneficial in some patients while keeping costs at a minimum.

Summary

Chronic sinusitis is a clinical syndrome encompassing a heterogeneous group of diseases characterized by sinonasal

mucosal inflammation. Many distinct triggers contribute to the inflammatory pathophysiology, and treatment aims to identify and manage these triggers. CRSsNP and CRSwNP represent different diseases with similar symptomology. Topical and oral steroids and nasal irrigation play a central role in the management of both CRSsNP and CRSwNP. The use of oral antibiotics is controversial, whereas topical antibiotics may prove effective in eradicating recalcitrant disease. Confounding comorbidities and underlying systemic disease should be identified and treated. Symptoms that are recalcitrant to medical therapy or worrisome for complication warrant otolaryngology referral. Following a systematic approach to diagnosing and managing CRS will ultimately provide optimal patient outcomes.

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