Controversies in Medicine: An Integrative Approach to the Management of Cough and Cold Symptoms in Sinusitis CME/CPE

Goal
The goal of this activity is to update the participant’s knowledge of the latest controversies and advancements in the treatment of sinusitis with a focus on the signs and symptoms complex of cough and cold. The article will focus on an integrative approach to management of this multifactorial disease process.

Learning Objectives
Upon completion of this activity, participants will be able to:
1. Discuss the current epidemiology and multifactorial pathophysiology of rhinosinusitis.
2. Review recent controversies with over-the-counter therapies.
3. Describe some of the current approaches and limitations in treating rhinosinusitis.
4. Identify appropriate pharmacologic and nonpharmacologic therapies for optimum treatment of rhinosinusitis.
5. Review the current evidence-based phytopharmaceutical options for treating rhinosinusitis.

Target Audience
This activity is intended for Pharmacists, Family Physicians, Primary Care Physicians, Physician Assistants, and Nurse Practitioners.

Needs Assessment
Upper respiratory symptoms of cough and cold are recognized as harbingers for the subsequent development of more complex medical conditions such as sinusitis. The formal terminology change of sinusitis to “rhinosinusitis” emphasizes the anatomic and pathologic relationship between nasal mucosal inflammation and disease of paranasal sinuses. Controversy exists in the correct approach to managing cough and cold symptoms. Several of the over-the-counter products for children have come under FDA review and restriction due to significant safety issues and lack of efficacy data. The need is imperative for an integrative pharmacological and physiological rational evidenced based approach to the management of upper respiratory symptoms.

Continuing Education Credit
CME Credit
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Contents of this CME/CPE Activity
1. Introduction
2. Epidemiology
3. Pathophysiology
4. Sinus Imaging and Other Diagnostic Tests
5. Treatment
6. Non Pharmacological and Pharmacological Therapies
7. Evidence based Phytopharmaceuticals

Introduction
Acute rhinosinusitis is defined as inflammation of one or more of the paranasal sinuses (frontal, maxillary, ethmoid, or sphenoid), along with inflammation of the mucosa of the nose. Acute rhinosinusitis is a common ailment which has a negative effect on a large segment of the population. Each year in the United States, one billion viral respiratory illnesses occur. Ten percent of these cases (100 million) are associated with impaired nasal drainage and retained secretions. One percent of these cases (1 million) are secondary to bacterial infections [1,2]. Approximately 10% of childhood cases of acute rhinosinusitis and 0.5-2% of adult cases will progress to a secondary acute bacterial rhinosinusitis (ABRS) [3]. Acute rhinosinusitis, as a whole, affects approximately 37 million Americans (16%) each year, which accounts for about 16 million office visits each year and on average, an estimated $3.5 billion in healthcare cost [2].

Rhinosinusitis can be described based on duration of illness; acute (symptoms present for less than 4 weeks), subacute (symptoms present 4-12 weeks) recurrent (3 or more episodes per calendar year) or chronic (symptoms present for more than 12 weeks). Acute and subacute rhinosinusitis are often without complications if treated appropriately; however, chronic rhinosinusitis can lead to more serious complications with long lasting effects if not appropriately managed [1,4].

In 1999, the Agency for Healthcare Research and Quality deemed Rhinosinusitis, rather than sinusitis, as the correct terminology due to the integral involvement of the nasal passages in acute and chronic sinusitis. Furthermore, the Joint Council of Allergy, Asthma and Immunology (JCAAI) practice parameter guidelines states “rhinitis typically precedes sinusitis; sinusitis without rhinitis is rare; the mucosa of the nose and sinuses are contiguous; and the symptoms of nasal obstruction and nasal discharge are prominent in sinusitis [1].”

Significant controversies currently exist in the management of rhinosinusitis

1. Antibiotic Resistance: Antibiotic resistance is of global concern. Acute bacterial rhinosinusitis is the fifth leading reason for antibiotic prescribing thus accounting for 9% of all pediatric and 21% of all adult antibiotic prescriptions in 2002. As stated earlier, many of these cases (greater than 90%) are not bacterial in origin and as a result, a major cause of inappropriate antibiotic

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<tr>
<th>Classification</th>
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<tr>
<td>Acute</td>
<td>&lt;4 weeks</td>
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<td>Sub acute</td>
<td>8 weeks (4-12 wks)</td>
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<td>Chronic</td>
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<td>Recurrent acute</td>
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<td>Acute exacerbations of chronic sinusitis</td>
<td>Sudden worsening of chronic sinusitis than return to baseline</td>
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Table 1: Classification of Sinusitis

**Figure 1: Anatomy of Paranasal Sinuses**

- **Frontal sinuses**: over the eyes in the brow area
- **Ethmoidal sinuses**: just behind the bridge of the nose and between the eyes
- **Sphenoidal sinus**: behind the ethmoids in the upper region of the nose and behind the eyes
- **Maxillary sinuses**: inside each cheekbone
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FDA Withdrawal of Cough and Cold Products: Due to escalating concerns with the safety and efficacy of many available cough and cold products, the FDA has issued a statement restricting the use of these products in the marketplace for children less than 4 years of age. Additionally, the Centers of Disease and Control and Prevention reported that more than 1,500 toddlers and babies were seen in emergency rooms over a two-year period because of side effects from these products [6].

Pseudoephedrine - Precursor to Methamphetamine: The cost of pseudoephedrine adulteration to society is not of insignificance. In order to curtail society's cost and the illicit production of methamphetamine, legislation signed into law on March 9, 2006, the Combat Methamphetamine Epidemic Act of 2005 (CMEA). The CMEA regulates retail over-the-counter sales of ephedrine, pseudoephedrine, and phenylpropanolamine products. Furthermore, the Cochrane Collaboration found that decongestants provide very little statistical benefit when compared to placebo therapies [7].

Sinus Development
Paranasal sinuses are air-filled cavities within the craniofacial skeleton. These small, aerated cavities function to lighten the weight of the skull, produce a portion of upper airway respiratory mucus and help with vocal resonance [8]. Contrary to belief, not all of the paranasal sinuses are present at birth. Only the maxillary and ethmoid sinuses are present at birth and will continue to grow into adolescence. The frontal sinus is not present until the fifth year of life and then matures through late adolescence. The sphenoid sinus is the last to develop at the sixth year of life and reaches complete growth in early adulthood. This later development of the frontal and sphenoid sinuses reduces the risk of infection occurring in these sinuses. In fact, 15% of the population will have hypoplasia or be without frontal sinuses, while 25% of the population will have underdeveloped sphenoid sinuses [11].

Anatomy/Pathophysiology
The most important anatomical aspect of the sinus labyrinth system is the relationship of the sinus ostia (openings) with nasal turbinates. Located on the lateral nasal wall are 3 nasal turbinates (the inferior, middle, and superior). Lying beneath the middle turbinate is the middle meatus, where the drainage gates (ostia) from the maxillary, frontal, and anterior ethmoid sinuses are found [12]. This intricate area is referred to as the ostiomeatal complex.
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Figure 3: Sinus Mucosal Anatomy

(OMC). The convolution and narrow structure of the OMC makes it prone to blockage when the immune mucous layer thickens due to acute inflammation of the sinus mucosa. Our current understanding of sinus physiology indicates that the blockage of the OMC impedes normal sinus drainage, predisposing patients to sinusitis. This can be likened to a “stagnant pond of water” which is a breeding ground for infectious pathogens. The immune mucous layer is propelled by the mucociliary clearance activity of the pseudostratified ciliated columnar epithelium. Upon inflammation of the sinus mucosa the mucocilliary system becomes dysfunctional, resulting in decreased propelling of the immune mucous layer and increased risk of sinusitis complications. Complications of severe sinusitis can arise due to the close approximation of the sinuses to the orbits and central nervous system [13].

Healthy sinuses are normally filled with air and are fringed with pseudostratified ciliated columnar epithelium with interrupted goblet cells [1]. Acute inflammation of swollen mucosa or other anatomic abnormality obstructs the ostium of a sinus, resulting in poor sinus ventilation. The drainage becomes impaired and an anaerobic environment is created. Oxygen concentrations within the sinus may fall, and this may further inhibit mucociliary clearance and further facilitate an anaerobic environment [13].

Other inciting predisposing factors, include allergic rhinitis, immunodeficiency (such as immunoglobulin [Ig] A, IgG or IgG subclass deficiency, HIV infection, abnormal cellular immunity, etc), cystic fibrosis, immotile cilia syndrome, and other environmental factors [13].

Sinus pain may result from acute alterations in intrasinus pressure. During acute sinusitis, the pressure within the affected sinus increases. The sinus ostium is obstructed and ongoing mucosal metabolism may result in a lowering of pressure within the sinus. Given the innervation of sinuses with pain receptors, pain may arise even in the absence of infection. Lower pressure within a given sinus may also result in osmotic transudation of fluid into that sinus.

The pathophysiology of rhinosinusitis is related to three factors: obstruction of sinus drainage pathways (sinus ostia), ciliary impairment, and mucus quantity and quality [13].

• Obstruction of the natural sinus ostia appears to be pivotal in the disease progression. Inflammation, edema, polyps, tumors, trauma, scarring, anatomic variants (eg, concha bulbosa-pneumatized middle turbinate, septal deviation), and nasal instrumentation (nasogastric tubes or packing) can result in decreased patency of sinus ostia. Hypoxia within the obstructed sinus is thought to cause ciliary dysfunction and alterations in mucus production, further impairing the normal mechanism for mucus clearance [13].

• Earlier disease models of sinus physiology hypothesized that drainage patterns of the paranasal sinuses depend on gravity, but it is now clear that the mucociliary transport mechanism is paramount in drainage of the sinus labyrinth. The metachronous coordination of the ciliated columnar epithelial cells propels the sinus immune stream contents toward the natural sinus ostia. Disruption of the ciliary function results in fluid accumulation within the sinus. Poor ciliary function can result from the loss of ciliated...
Figure 4: Pathophysiology of Sinusitis

Secretions stay fluid; contain antibodies and IgA

Soluble pollutants are absorbed in the mucosa

Particulate matter and bacteria are removed by mucociliary clearance

Mucociliary flow prevents local mucosal damage

Host defenses resist infection

Mucous composition is normal

Mucous secretion is normal

Ostium is Open

Secretions thicken, pH changes

Secretions stagnate

Mucosal congestion (often due to viral rhinitis) or anatomic obstruction blocks air flow and drainage

Ostium is Closed

Mucosal thickening creates further blockage

Mucosal thickening creates further blockage

Bacterial infection develops in the sinus cavity

Cilia and epithelium are damaged

Change in host milieu creates culture medium for bacterial growth in closed cavity

Retained secretions cause tissue inflammation
Sinonasal secretions play an important role in the pathophysiology of rhinosinusitis. The mucus that lines the paranasal sinuses is composed of a thin periciliary layer, which enables ciliary mobility, and a thick gel layer, which anchors the tips of the cilia. This mucous immune stream contains mucoglycoproteins, immunoglobulins, and inflammatory cells. Alterations in the water content of the mucous blanket can impair ciliary mobility. Overproduction of mucus can overwhelm the mucociliary clearance system, resulting in retained secretions within the sinuses.

**Microbiology**

An essential component of understanding the pathology of rhinosinusitis is establishing a baseline understanding of the microbiology composition of the upper respiratory tract. As previously mentioned, the upper respiratory tract is lined by epithelial cells with a mucosal layer that varies in oxygen concentration. This variation in oxygen concentration leads to colonization of these mucosal surfaces by anaerobic microorganisms. Anaerobic microorganisms will always outnumber aerobic microorganisms due to the oxygen deficient environment and increased pH of mucosal surfaces.

The nose and pharynx harbor many pathogenic viruses, bacteria, and fungus, which have the potential to cause various respiratory infections. The pathophysiology of acute rhinosinusitis is usually initiated by a two step mode of disease evolution. The first phase is usually hallmarked by a “rhinitis” viral respiratory infection, lasting approximately 10 days. Most healthy individuals will recover completely; however, an estimated 1% of adults and 10% of children will develop a secondary acute bacterial rhinosinusitis infection. During acute bacterial rhinosinusitis the most common bacterial pathogens isolated are facultative aerobic bacteria: Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. As the inflammatory process continues acute rhinosinusitis progresses into subacute rhinosinusitis which progresses into chronic rhinosinusitis. The persistent obstruction of the ostia leads to decreased transport of mucus, limited gas exchange and reduced pH in the sinuses. These stagnant secretions reduce oxygen concentration and increase acidity, creating an environment that fosters the growth of anaerobes. The most likely bacterial species to be recovered are: S. aures, S. Pneumonia, H. Influenza, P. aeruginosa, and anaerobes. Occasionally, chronic sinusitis will be due to colonization of the nasal cavity by fungi. The most likely fungal species isolated are: Aspergillus, Zygomycetes, Phaeohyphomycoses, Sporothrix, and Pseudallescheria.

**Symptoms**

Patients’ symptoms are variable but the typical symptoms of acute sinusitis include nasal congestion, facial/dental pain, purulent rhinorrhea, headache, postnasal drainage, and cough. Similar to the cough caused by gastroesophageal reflux, the cough that is associated with sinusitis may be worse when the patient lies down at night-positional orientation. This

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**Figure 5: Life Cycle of Sinusitis**
finding is still a clue to the diagnosis. Furthermore, patients may comment on halitosis, fever, malaise, sore throat, and diminished sense of smell. Children with acute sinusitis may be irritable and experience vomiting, presumably after swallowing tenacious mucous drainage, or prolonged coughing [13].

Patients with chronic rhinosinusitis may have a much more subtle presentation, with symptoms of persistent nasal congestion, postnasal drainage, slight headache, fatigue, and a "foggy feeling" with lack of mental acuity. Chronic nasal congestion appears to interfere with restful sleep and it logically follows that fatigue tends to be a common complaint in patients with either acute or chronic rhinosinusitis [13].

The most important aspects of the patient's history include the temporal sequence of the duration of symptoms and the presence of predisposing factors, such as allergic rhinitis, immunodeficiency, and known anatomic abnormalities. Patients with a history of nasal polyposis should be asked about allergies to aspirin or nonsteroidal anti-inflammatory drugs, because there is a significant relationship between these drug allergies, nasal polyposis, and asthma (termed "Samter's triad" or "triad asthma") [13].

Clinical acumen and focus should also be paid to symptoms that suggest the possibility that infection may have spread to tissues adjacent to the sinuses; these include swelling of the forehead or periorbital area, diplopia, and other neurologic symptoms.

**Signs**

Examination of the patient suspicious of rhinosinusitis begins with inspection of the anterior nares, oropharynx, and face. Look for signs of inflammation of the nasal mucosa, including edema and erythema, as well as purulent secretions. However, purulent secretions may not be visualized at the time of the examination, even when acute infection is present. The oropharyngeal exam may reveal purulent postnasal discharge, pharyngeal infection, and/or lymphoid hyperplasia. Increase in pigmentation or circles under the eyes, result from interference with venous blood flow accompanying the inflammatory process. Palpation of the face may reveal regions of tenderness over infected paranasal sinuses [13].

Examination of the nasal cavity with flexible fiber-optic nasopharyngoscopy may also provide clues to predisposing factors that are not well seen on anterior rhinoscopy. This requires referral to an otolaryngologist where intranasal abnormalities may be discovered [13].

The examiner should also look carefully for any evidence of factors complicating acute sinusitis, including facial or periorbital swelling, visual changes, abnormalities in extraocular muscle function, proptosis, or any suggestion of neurologic signs that could suggest intracranial involvement. If these are present immediate referral is needed and acute intervention is imperative.

**Common Signs and symptoms**

- Purulent nasal secretions
- Purulent posterior pharyngeal secretions
- Mucosal erythema
- Periorbital edema
- Tenderness overlying sinuses
- Air-fluid levels on transillumination of the sinuses (60% reproducibility rate for assessing maxillary sinus disease)
- Facial erythema

**Differential Diagnosis**

Other clinical conditions that may present with a clinical picture that is similar to rhinosinusitis or that may coexist with rhinosinusitis include [1]

- Viral URI;
- Allergic rhinitis;
- Nonallergic rhinitis;
- Nasal polyposis;
- Nasal or sinus tumor;
- Dental infection with adjacent spread; and
- Adenoidal enlargement obstructing the nasopharynx.

Inquire about preexisting history of allergic or occupational rhinitis, vasomotor rhinitis, nasal polyps, rhinitis medicamentosa, or an immunodeficiency. Rhinosinusitis is more common in patients with congenital defects that affect humoral immunity and ciliary motility, in those with cystic fibrosis, and in patients with AIDS. Obtain a history of diabetes or organ transplant if invasive fungal sinusitis is being considered.

Overdiagnosis of acute bacterial rhinosinusitis is common. Acute bacterial rhinosinusitis is the correct diagnosis in 40-50% of cases in which a primary care physician initially classifies a patient as likely having the condition [19].

The natural history of rhinovirus infection, as described by Gwaltney et al, lasts from 1-33 days. One fourth of patients have symptoms that last longer than 14 days [20].

Patients with uncomplicated upper respiratory infections usually report some of the following symptoms: sneezing, rhinorrhea, nasal congestion, hyposmia/anosmia, facial pressure, postnasal drip, sore throat, cough, ear fullness, fever, and myalgia.

- Diagnostic criteria for acute rhinosinusitis have been proposed; no single sign or symptom has strong diagnostic value for bacterial rhinosinusitis [21, 22]. The temporal sequence in the history is the most important distinguishing factor and as such acute bacterial rhinosinusitis should be suspected in patients who exhibit symptoms of a viral upper respiratory infection that do not improve after 10 days or worsen after 5-7 days. Another clue is a bimodal pattern to the infection or "doublesickening." This occurs when a patient states they had a URI and felt better but now are worse again indicating a potential secondary AFRS [19].
- Symptoms of acute bacterial rhinosinusitis include the following:
  - Facial pain or pressure (especially unilateral)
  - Hyposmia/anosmia
  - Nasal congestion
  - Nasal drainage
  - Postnasal drip
  - Fever
An accurate and timely diagnosis of ABRS is imperative for an appropriate choice of therapy. Making an unambiguous diagnosis of ABRS is very difficult, especially in the primary care setting. Two reasons for this are:

1) ABRS signs and symptoms are not specific to bacterial sinusitis and are difficult to differentiate from viral RTIs; or
2) other non-infectious causes and the lack of reliable, convenient and practical diagnostic tools. Definitive diagnosis of ABRS requires the use of a method (sinus puncture with culture) that is impractical in the primary care setting and requires substantial technical proficiency.

Despite a wealth of methods for the diagnosis of ABRS, which include clinical examination, sinus puncture with aspiration and culture, endoscopy, radiography, ultrasonography and computed tomography (CT), each of these approaches has significant limitations.

Clinical history and examination is an essential step in the diagnosis of ABRS, it is limited by the fact that it does not allow for differentiation of ABRS from viral infection. Despite its shortfalls it remains the most accurate method of diagnosis. The dilemma arises because viral and bacterial infections are very similar. Symptoms may include nasal congestion, nasal drainage, postnasal drainage, facial pressure/pain, fever, cough, fatigue, maxillary dental pain and ear pressure/fullness [23, 21]. The difficulty is additionally compounded by the fact that most, if not all, ABRS infections are preceded by viral infections the “rhinitis phase.” Differentiation between the two types of infection is even more difficult in pediatric patients because their symptoms tend to be more diffuse than those in adults [24]. Change in the color of the nasal discharge, which has been proposed as a potentially useful indicator of ABRS, has not been definitively demonstrated to be a sign of bacterial infection. Again the temporal duration of ABRS signs and symptoms may be a better diagnostic tool than simply the presence of symptoms, although definitive clinical evidence for this criterion is also lacking general consensus exist. Viral sinusitis usually resolves after 7 days, whereas patients with ABRS typically have worsening or persistent symptoms beyond 7 days. Thus, symptom persistence for over 7 days may be a valid sign of a bacterial infection [21]. Sinus puncture with culture of the aspirate is generally accepted as the ‘gold standard’ for the diagnosis of maxillary ABRS. It is performed by puncture of the maxillary sinus.
Sinonasal endoscopy allows a visual inspection of the middle meatus and provides an avenue for acquisition of a direct culture. Endoscopy is less invasive than sinus puncture and thus is better accepted by patients. This procedure shows a good correlation with sinus puncture results for diagnosis of maxillary ABRS, but its clinical validation requires more definitive study [24].

Radiography is commonly used for patients with persistent or recurrent sinus infections. It is a suitable method for the visualization of maxillary and frontal sinuses but not for the visualization of the ethmoid sinuses. The main limitation of radiography is the lack of specificity, as this method cannot readily distinguish between an infection and other sinus-related anomalies, such as mucosal thickening, tumors and polyps. In fact, only complete opacification or presence of an air fluid level is indicative of ABRS. In addition radiographs are not cost effective in ABRS as stated by the United States Agency on Healthcare Policy and Research [26].

Ultrasonography enjoys popularity in northern Europe and the Netherlands but less so in the United States and southern Europe. It is a relatively simple and non-invasive procedure, but like radiography, it can be used to evaluate only maxillary and frontal sinuses. In addition, it requires fairly high technical proficiency to ensure consistent and reproducible results [26].

CT allows for good anatomical visualization of paranasal sinuses, and two types of the technique are used: screening CT and complete sinus CT. The fast-spin CT scanners, digital imaging and less of a need to print all the images, the economic advantage of screening CT scans largely made less of a concern. The complete sinus CT is becoming the imaging of choice for anatomical visualizes paranasal sinuses in more detail and provides a high-resolution view of the ostiomeatal anatomy. CT can detect anatomy but not make a specific diagnosis of viral vs. bacterial specificity. CT scans are the gold standard for anatomical view but not for diagnostic disease pathology [27].

Despite its impracticality, sinus puncture thus remains the only well-established technique for diagnosis accurate firm diagnosis of ABRS, emphasizing the need for new diagnostic methods that are reliable, practical to perform and have patient acceptance. The data showing a high concordance between maxillary sinus puncture and culture with endoscopically guided, selective middle meatal cultures hold promise for a simpler technique with less morbidity [28].

Laboratory Studies
- Erythrocyte sedimentation rate and C-reactive protein level may be elevated, but are nonspecific.
- The findings of CBC count with differential may be within reference ranges.
- Nasal cytology examinations may be useful to elucidate the following entities:
  - Allergic rhinitis
  - Eosinophilia
  - Nasal polyposis
  - Aspirin sensitivity
- Sweat chloride test screening should be performed if cystic fibrosis is suggested.
- Ciliary function studies help screen for Kartagener syndrome.
- Tests for immunodeficiency are indicated if history findings indicate recurrent infection, to include the following:
  - Immunoglobulin levels
  - HIV serology
- Cultures of nasal secretions are of limited value because they are usually contaminated by normal flora.

Imaging Studies
- Findings on standard radiographs are insensitive, especially for ethmoidal disease. Waters view is best.
- CT scanning is the preferred imaging method.
- A screening sinus CT scan is adequate for diagnosis and less expensive than other methods but is necessary only in cases of treatment failure or chronic disease.
- A complete sinus CT scan with frontal and coronal planes is used if an alternate diagnosis (eg, tumors) must be excluded.
- CT scan findings are used to differentiate orbital cellulitis from periorbital cellulitis as a complication or to evaluate extension into intracranial space.
- MRI is useful only if fungal infection or a tumor is suggested.

Treatment
The treatment of sinusitis can be divided into three categories: non-pharmacological therapies, pharmacological therapies, and phytopharmaceutical therapies. These therapies can be use alone or in combination to accomplish the eight treatment objectives of sinusitis outlined in Figure 7 [29].

Nonpharmacological Therapies
Although the data on the efficacy of the nonpharmacological intervention is limited, the benefit of these therapies far outweighs any risks and is considered by many providers to be a form of comfort therapy. Furthermore, they address the physiological aspect of an adjunct to maintaining ostia patency and mucociliary clearance [30].
- Recommend adequate hydration. At least 8+ glasses of water daily.
- Recommend avoidance of beverages that act as a "natural" diuretic (i.e. alcohol, caffeinated beverages).
• Recommend steam inhalations 20-30 minutes TID.
• Recommend saline irrigation or saline nasal drops.
• Recommend getting adequate rest.
• Recommend sleeping with head of bed elevated.
• Recommend avoidance of exposure to irritants.
• Recommend good nasal and oral hygiene as both the mouth and nose are anatomically contiguous.

Pharmacological Therapies
Pharmacological interventions for treating sinusitis continue to be controversial. In the absence of definitive data, choosing when to treat and what to treat with becomes very challenging. In this article treatment options and the evidence supporting use will be examined.

Antibiotic Therapy
Treatment of uncomplicated acute sinusitis rarely requires antimicrobial therapy. In uncomplicated cases, it is reasonable to watch-and-wait for spontaneous resolution for 7 to 10 days prior to prescribing antibiotics [30]. Nevertheless, those patients who present with severe signs and symptoms of sinusitis, or are immunocompromised due to disease co-morbidity should be treated with antibiotics regardless of the duration of illness. Antibiotic selection for treating sinusitis is based on predicted effectiveness, cost, and side effects. Patients presenting with signs and symptoms associated with acute bacterial sinusitis will most likely require narrow spectrum antibiotics that are active against the most common bacteria observed S.pneumoniae, M. Catarrhalis, and H. influenzae [31]. It is important to note that approximately 90% of S. pneumoniae and 33% of H. influenzae produce beta-lactamases, which increases the chance of first-line antibiotic failure. Patients presenting with signs or symptoms associated with chronic bacterial sinusitis or who experience first-line treatment failure will require antibiotics with a broader spectrum of activity. A reasonable approach would be to prescribe patients a 7-10 day course of an aminopenicillin, or first or second generation cephalosporin. After 7-10 days of therapy re-evaluate the patient and determine whether the signs and symptoms are improving. If improving then continue for 10 to 14 days or until patient is free of symptoms plus 7 days. If no improvement or signs and symptoms have worsened, then switching therapy to an aminopenicillin with a beta-lactamase inhibitor or second generation cephalosporin with activity against beta-lactamase enzymes is recommended. Respiratory fluoroquinolones are also acceptable for treatment failures or patients with allergies to cephalosporins or penicillin analogs [31-35].

Antihistamines
Currently there are no data that support the use of antihistamines in the treatment of acute or chronic sinusitis in patients without an underlying risk of allergic rhinosinusitis. Often use of antihistamines leads to drying of mucous membranes, decrease clearance of secretions, and increased ciliary dysfunction [31].

Alpha-Adrenergic Decongestants
Clinical evidence supporting the use of alpha-adrenergic decongestants in sinusitis is lacking. Theoretically, using topical or oral decongestants might lead to reduction of turbinate swelling and ostia widening through vasoconstriction, thus promoting sinus and nasal ventilation [36]. However, the unwarranted side effects of rhinitis medicamentosa with chronic use, blood pressure elevations, and narrow therapeutic index often make decongestants more of a risk for harm then benefit. Because of the potential risk to cause harm the US Food and Drug Administration has mandated the withdrawal of all over-the-counter products that contain phenylpropanolamine due to the increased risk of hemorrhagic stroke in women; and combination cough-and-cold products for pediatrics and children [37-38]. Although popular in numerous over-the-counter remedies they lack both safety and efficacy data.
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for their use. 

**Glucocorticosteroids**
Clinical evidence attesting to the efficacy of inhaled-topical corticosteroids in sinusitis has demonstrated that as an adjunct therapy, inhaled-topical corticosteroids might be modestly beneficial in the treatment of patients with recurrent acute or chronic sinusitis. Treatment of the nasal mucosa with an inhaled topical corticosteroid leads to a reduction in inflammatory mediators, decreased vascular permeability, formation of mucous secretagogues, and inhibition of inflammatory cell infiltration; however, these effects often require at minimum 2-4 weeks to take complete effect [39-40]. Most clinicians agree on the potential usefulness of intranasal corticosteroids and their documented efficacy and safety profile make them reasonable choices in treatment of sinusitis.

**Mucolytics:** Mucolytic therapy consists of pharmacologic agents that help facilitate drainage of retained secretions by reducing the viscosity of secretions, thus improving mucociliary clearance. Evidence to support mucolytic therapy is specific to the mucolytic agent. Guaifenesin works as an expectorant to loosen phlegm and bronchial secretions within the upper and lower respiratory tract. Evidence supporting the use of guaifenesin as adjunctive treatment in sinusitis is based on its clinical efficacy in thinning secretions in patients who have chronic bronchitis. Therefore, there are currently no clinical trials demonstrating its efficacy in adjunctive treatment of sinusitis [41].

Saline works by limiting the crusting of secretions in the nasal cavity. This aids in the removal of retained nasal secretions, which cause nasociliary dysfunction and may contain virus, bacteria, or other cellular debris that contributes to more sinus inflammation [42-45]. Hypertonic nasal saline irrigation has clinical evidence that proves it reduces symptoms and improves quality of life in patients with sinusitis. This should be foundational therapy in most cases of acute or chronic sinusitis.

**Phytopharmaceutical Medicine**
The recent FDA restriction and limitation of many over-the-counter cough and cold products in children due to significant concerns of safety and efficacy has called to question what and if other evidence-based options are available. Recent data reveals 32% of our patients with chronic rhinosinusitis have used

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<tr>
<td>Richstein [49]</td>
<td>Randomized, double-blind, placebo controlled prospective study</td>
<td>50 drops 3 times daily or 2 tablets 3 times daily (n=16); Placebo (n=15)</td>
<td>Symptoms, endoscopic, radiologic, ultrasound findings at day 16 after start of treatment.</td>
</tr>
<tr>
<td>Neubauer [54]</td>
<td>Doxycycline + Xylometazolin + Sinupret 2 tabs 3 times daily (n=81) or doxycycline + xylometazine + Placebo (n=79)</td>
<td>Radiographic finding, Patient assessment, and Secondary variables</td>
<td></td>
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<tr>
<td>Berghorn [48]</td>
<td>Doxycycline + Xylometazolin + Sinupret 50 drops 3 drops (n=81) or doxycycline + xylometazine + Placebo (n=79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Braun [57]</td>
<td>Sinupret 2 tablets 3 times daily + antibiotics or N-Acetylcystein 200 mg 3 times daily</td>
<td>Radiographic finding, and patient assessment.</td>
<td></td>
</tr>
<tr>
<td>Sim [60]</td>
<td>Sinupret 50 drops 3 times daily +/- decongestant nose drops or Ambroxol +/- decongestant nose drops</td>
<td>Sinusitis score and patients assessment</td>
<td></td>
</tr>
<tr>
<td>Wahl [63]</td>
<td>Sinupret 50 drops 3 times daily +/- decongestant nose drops or Ambroxol +/- decongestant nose drops</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biebach [64]</td>
<td>Sinupret drops, dosage according to age, co-medication, and antibiotics or co-medication</td>
<td>Symptoms, Tolerability</td>
<td></td>
</tr>
<tr>
<td>Garaschenko [65]</td>
<td>Sinupret drops dosage according to age, co-medication, and antibiotics or only co-medication</td>
<td>Mucociliary transport time, endoscopic ENT examination, and general patient assessment.</td>
<td></td>
</tr>
<tr>
<td>Ismail [66]</td>
<td>Sinupret for at least 24 hours</td>
<td>Systemic evaluation of all pregnancies, questionnaires, neonatal examinations, and analyst of clinically abnormal findings.</td>
<td></td>
</tr>
</tbody>
</table>
natural therapies alone or as an adjunctive treatment for their condition [46]. One comprehensive systematic review to assess the efficacy of phytopharmaceuticals for rhinosinusitis in the clinical world literature was conducted by Guo, et al. and published in Otolaryngology – Head and Neck Surgery in 2006. This systematic review was conducted to evaluate randomized controlled trials of phytopharmaceutical medicines in rhinosinusitis. Ten randomized controlled trials met the inclusion criteria. Six different phytopharmaceuticals were identified: Bi Yuan Shu, Bromelain, Cineole, Esberitox® (manufactured by Schaper & Bruemmer GmbH & Co. KG, Salzgitter Germany; imported by Enzymatic Therapy, Green Bay, WI), Myrtol, and Sinupret® (manufactured by Bionorica in Neumarkt, Germany; imported by Bionorica LLC, San Clemente, CA) [47-57]. The phytopharmaceutical with the largest number of trials, 4 trials was Sinupret® [58-61]. The systematic analysis conducted by Guo, et al. noted the natural literature was limited but it did show the evidence was in favor of Sinupret® and bromelain[48, 49, 54, 57, 59, 60, 63-66].

Sinupret® is a trademarked preparation developed in Germany for sinusitis and cough and cold symptoms. It is composed of five standardized “phyto-engineered” herbal extracts: Gentiana lutea, root; Primula veris, flower; Rumex species-acetosa., herb; Sambucus nigra, flower; Verbena officinalis, herb. Sinupret® is available in the United States for promoting upper respiratory health, and in over 40 countries for the treatment of sinusitis. Sinupret® has randomized control trials assessing the efficacy and safety of Sinupret®. These trials show that Sinupret® significantly improves acute and chronic sinusitis symptoms. Bromelain is a protease containing extract from the stem and fruit of the Ananas comosus (pineapple). The evidence assessing the efficacy of bromelain for the use as adjunctive treatment for acute or chronic rhinosinusitis were conducted in the late 1960s. Although there were three randomized controlled studies assessing its efficacy as adjunctive treatment for acute or chronic rhinosinusitis the studies were conducted in the late 60s. These studies showed bromelain to provide a favorable small but statistically significant difference for improving nasal mucosal inflammation, nasal discomfort, breathing difficulty, and patient over all rating. Change in nasal discharge was not significant [47,51,53].

Esberitox® is a phytopharmaceutical composed of three herbs:Thuja occidentalis, Echinacea angustifolia, and Baptisia tinctoria. One single blinded parallel trial comparing Esberitox® plus doxycycline, Sinupret® plus doxycycline, or doxycycline showed that both the Esberitox® and Sinupret® arm of the trial had significantly higher responder rates compared to doxycycline alone [47].

Myrtol is a phytoextract that contains three monoterpenes: (+)alpha-pinene, d-limonene and 1,8-cineole extracted from Pinus spp (Pine), Citrus aurantifolia(lime) and Eucalyptus globulus. One double-blind, placebo controlled RCT, involving patients with acute rhinosinusitis, evaluated myrtol’s efficacy in reducing the symptoms of acute rhinosinusitis. The results showed that the Myrtol group and other essential oil groups were superior for reducing acute rhinosinusitis symptoms than placebo; however, there is insufficient statistical data to verify the significance of these results [47,48].

Cineole is also a phytoextract derived from Eucalyptus globulus. A double-blind, placebo controlled trial evaluated Cineole as adjunctive treatment in the treatment of acute rhinosinusitis. The study used a symptom-sum-score to assess improvement in clinical symptoms. After 4-7 days of treatment Cineole showed significant differences in clinical symptoms but again, there is not sufficient data to verify the significance of these results [47].

Bi Yuan Shu (BYS) is an oral Chinese natural medicinal mixture containing an unknown number of natural medicinal agents. According to reports BYS is composed of at least the following natural agents: Magnolia Liliflora, Xanthium strumarium, Astragalus membranaceus, Angelica dahurica, and Scutellaria baicalensis. A multi-center randomized controlled trial assessed the efficacy of BYS as an adjunctive treatment in patient with CRS and nasal polps who had undergone FESS. Symptoms were evaluated on days 7, 14, 30, and 60, and showed significant improvements in pain, breathing difficulty, purulent nasal discharge, hyposmia, and halitosis but not for fever and cough [47,50].

Summary
Rhinosinusitis continues to be a common condition of children and adults. Studies suggest is mounting and now becoming clear that the rhinitis phase is a prodrome to the sinusitis phase of disease evolution. The importance of treating the early cough and cold symptoms with non-pharmacological and natural medicines as first line is important. Furthermore, we must continue these therapies in an integrative adjunctive manner when pharmacological agents are required. This multi-modality approach to respiratory health should be evaluated by evidence based scrutiny and vigor. This approach will also allow us to preserve antibiotic use in order to prevent inappropriate use of antibiotics and the ever increasing concern of antibiotic resistance. Natural therapies and over-the-counter remedies should not be recommended if the evidence does not support their use. The foundation of modern medicine is to look at the weight of the evidence and the totality of the world literature in order to make fair and reliable recommendations to our patients.
Continuing Education

References


Continuing Education


38. Safety issues of phenylpropanolamine (PPA) in over-the-counter drug products. In: Meeting of the Nonprescription Drugs Advisory Committee of the Food and Drug Administration Center for Drug Evaluation and Research; October 19, 2000; Gaithersburg, Md.


**Continuing Education Quiz for Pharmacists**

**Controversies in Medicine:**  
**An Integrative Approach to the Management of Cough and Cold Symptoms in Sinusitis CME/CPE**

1. Ninety-percent of childrens and ninety-eight percent of adult acute rhinosinusitis is virus mediated.  
   a. True  
   b. False

2. In contrast to the traditional paradigm, if a patient has acute rhinosinusitis an integrative approach to treatment should be utilized?  
   a. True  
   b. False

3. Based on current literature and guidelines the correct nomenclature for sinusitis is:  
   a. Acute sinusitis  
   b. Chronic sinusitis  
   c. Re-current sinusitis  
   d. Rhinosinusitis

4. The most accurate differential of the history to assist a clinician in making an accurate diagnosis of acute rhinosinusitis is:

<table>
<thead>
<tr>
<th></th>
<th>a. Temporal sequence of symptom complex.</th>
<th>b. X-ray imaging</th>
<th>c. Translumenation</th>
<th>d. Physical exam symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a. True</td>
<td>b. False</td>
<td>c. Increased risk of harm</td>
<td>d. Both a and b</td>
</tr>
</tbody>
</table>

5. Recent restriction of cough and cold products for children under age of four were due to:  
   a. Increased risk of harm  
   b. Lack of Efficacy  
   c. Increased safety  
   d. All of the above

6. Guaifenisin is an expectorant with strong clinical evidence to support use in rhinosinusitis.  
   a. True  
   b. False

7. Most acute rhinosinusitis is caused by:  
   a. Bacteria  
   b. Fungi  
   c. Viruses  
   d. All of the above

8. The definition of acute rhinosinusitis is symptoms:  
   a. Less than 4 weeks  
   b. Greater than 4 weeks but less than 8 weeks  
   c. Four or more episodes per calendar year  
   d. Greater than 8 weeks

9. Adjunct therapy for acute bacterial rhinosinusitis is:  
   a. Nasal saline irrigation  
   b. Sinupret  
   c. Good oral hygiene  
   d. All of the above

10. Based on the meta-analyst by Guo, et al. published in Otolaryngology Head and Neck Surgery 2006, which phytopharmaceutical had the most clinical evidence for use in rhinosinusitis?  
    a. Bromelin  
    b. Sinupret  
    c. Zinc  
    d. Airborne

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**Quiz Registration for Pharmacists**

Circle your answers on the quiz and send this entire page and a STAMPED, SELF-ADDRESSED ENVELOPE to:  
WSPA, 1501 Taylor Avenue S.W., Renton, WA  98057-3139. Contact WSPA at (425) 228-7171 with questions.

Name (Please print clearly)_________________________________________________________________

Address ________________________________________________________________________________

City|State|Zip ___________________________________________________________________________

Daytime Phone (____) ______________  Email Address: ______________________________  Completion Date :________

---

**Evaluation**

Please explain any “no” or “unsure” answers:

1. This course met the learning objectives:  
   a. Discuss the current epidemiology and multi-factorial pathophysiology of rhinosinusitis  
      Yes  No  Unsure  
   b. Review recent controversersies with over-the-counter therapies  
      Yes  No  Unsure  
   c. Describe some of the current approaches and limitations in treating rhinosinusitis.  
      Yes  No  Unsure  
   d. Identify appropriate pharmacologic and nonpharmacologic therapies for optimum treatment of rhinosinusitis.  
      Yes  No  Unsure

2. This course has improved my knowledge of the management of cough and cold symptoms in sinusitis  
   a. True  
   b. False  
   c. Unsure

3. This course will assist me in treating patients in practice  
   a. True  
   b. False  
   c. Unsure

4. Please list any barriers to putting this knowledge into practice: ________________________________________________

5. What other topics would be of interest to you? ____________________________________________________________

Practitioners completing this course and the quiz will earn 1.5 hours (0.15 CEUs) continuing education credit and will receive a statement of credit within six weeks.  
Initial release date: January 26, 2009

ACPE# 130-000-09-006-H01-P
Continuing Education Quiz for MDs or other Healthcare Professionals

Controversies in Medicine: An Integrative Approach to the Management of Cough and Cold Symptoms in Sinusitis CME/CPE

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**Quiz Registration for MDs or other Healthcare Professionals**


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[ ] _____ credits (up to 1.5 AMA PRA Category 1 Credit™) OR [ ] a certificate of participation

Signature ____________________________________________ Completion Date ______________________________

**Evaluation**

Please explain any “no” or “unsure” answers:

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