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34 (2007) 39–58

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Treating the Immunocompetent Patient Who Presents with an Upper Respiratory Infection: Pharyngitis, Sinusitis, and Bronchitis

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Infections of the upper respiratory tract are among the most common conditions seen in primary care [1]. The upper respiratory tract consists of the oropharynx, nares, and nasopharynx, which are lined by stratified squamous epithelium; and the sinuses, larynx, and trachea, areas generally lined by columnar, goblet, and gland cells. There are normal flora occupying the former, and the evaluation of infections is complicated by the presence of colonizing species, which may have no role in infection. The latter group is generally sterile, and requires invasive measures to access and obtain material for culture [2]. Physiological mucous production may be altered here by nonspecific and noninfectious causes, further complicating diagnosis.

Because the specific etiological agent of an upper respiratory infection (URI) is often not identified, clinical judgment is required in the approach to their diagnosis and treatment. The causative agent of these infections is typically a virus, yet studies have reported rates for antibiotic prescriptions of 46% for pediatric patients [3] and of 52% for adults [4]. In this article, the author reviews the evidence-based approach to treatment of the immunocompetent patient who has URI, with a focus on the rational use of antibiotics in treating pharyngitis, sinusitis, and bronchitis.

Upper respiratory infection

The management of URIs is complicated by the confusing terminology that has arisen to define their anatomic locations, while ignoring their

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doi:10.1016/j.pop.2006.09.009 *primarycare.theclinics.com*

usually diffuse nature. As such, the term URI has come to encompass multiple clinical entities including pharyngitis, sinusitis, and bronchitis, as well as nonspecific respiratory infections, a designation that includes the common cold. The classification scheme based upon the predominate anatomic site of the presenting symptom complex tends to be poorly specific for directing therapy [5]. These diagnoses and their treatment will be examined relative to the nonspecific URI. Determining the evidence-based indications and relative value of antibiotic therapy for each may limit unnecessary use. Although a thorough examination of the viral URI is beyond the scope of this article, brief review of the nonspecific or undifferentiated URI and its treatment may provide some context for a discussion of these more specific conditions.

The inappropriate use of antibiotics, for respiratory infections in particular, has been implicated in the emergence of antibiotic resistance, especially in *Streptococcus pneumoniae* [6]. Guidelines for diagnosis and treatment of the URI based upon a nonfocal presentation have been developed in an effort to limit the indiscriminate use of antibiotics for what are generally viral illnesses [7]. The course of the viral URI, also termed acute rhinopharyngitis, is generally self-limited in nature and mild in severity. Symptoms may persist for greater than 1 week in duration in more than 50% of cases, and persist for 2 weeks in 25% [8]. The cause is most commonly rhinovirus and to a lesser extent coronavirus (typically in midwinter), and adenovirus (typically in spring to fall). Although laboratory identification can be accomplished, the time required to identify the cause may exceed the duration of the illness and the yields may be highly variable [2]. Syndromes involving symptoms of greater severity and more commonly including the lower respiratory tract are caused by influenza, parainfluenza, and respiratory syncitial virus [9]. There may be some benefit in the prompt identification of influenza to initiate timely neuraminidase inhibitor therapy [10,11]. It appears, however, that neither a rapid influenza test nor a clinical prediction rule is superior to clinical judgment in establishing the diagnosis [12].

Treatment of the URI is essentially symptom-directed, because antibiotic treatment does not appear to contribute to resolution of the illness. Their benefit in preventing life-threatening complications, such as meningitis, sepsis, or abscess, in such patients has not been adequately assessed [8]. Bacterial sinusitis may develop as a complication in a minority of patients and is reviewed later. Improvement is expected in the URI by the first week, notwithstanding reports that sinus changes may be demonstrated on CT studies in most patients in the first few days of illness [13]. A recent systematic review of the literature has found insufficient evidence to warrant the use of antibiotics for URIs in adults or children [14]. Adults experienced a greater rate of adverse effects with antibiotics than with placebo. Patients who have respiratory infections may have certain expectations for antibiotic prescriptions, and physicians may prescribe antibiotics based on their perceptions of these expectations; however, patient satisfaction has been correlated with physician

time spent with them and the patient's understanding of their diagnosis to a greater extent than the prescription of an antibiotic [15]. When patients who had upper respiratory symptoms were randomized to receive immediate antibiotics, or to have antibiotic use delayed by 48 hours, clinical outcomes were not significantly different for most symptoms, although some symptom scores worsened in the delayed use groups who had sore throat and otitis media [16]. Significant variability of symptom scores was noted between these trials. Clinical decision support systems, guiding physicians in appropriate antibiotic use for respiratory infections may reduce inappropriate use [17].

Use of oral and topical nasal decongestants provides benefit for short-term use in adults; there is no evidence supporting their use in children [18]. Studies of treatment with antihistamines alone for the common cold have shown no faster recovery, and only small benefit for sneezing and rhinorrhea at the expense of sedation. In combination with decongestants, no effect was seen in small children, but some benefit in general recovery and nasal symptoms was noted in older children and adults [19]. Intranasal ipratropium decreases rhinorrhea, and may decrease sneezing and promote nasal drying [20]. Evidence for the use of zinc in the treatment of URI is inconclusive [21], and Echinacea extract showed no significant effects in either infection rates with rhinovirus or symptom severity [22]. The role of vitamin C in prevention appears to be limited to perhaps those individuals exposed to severe physical or low-temperature stress, and therapeutic benefit was limited or equivocal [23].

Pharyngitis

The pharynx is the common portal to the human respiratory and digestive tracts and is exposed to multiple potential pathogens. Pharyngitis is predominantly viral in etiology, accounting for as much as 80% of all cases in adults [24]. The cardinal feature, sore throat, is also a feature of the common cold. In adenovirus infections it is usually accompanied by adenitis and conjunctivitis, and is associated with erosive stomato-pharyngitis in herpes simplex [2]. In Coxsackie virus infections sore throat is associated with pharyngeal vesicles (herpangina) or with hand and foot vesicles [25]. Epstein-Barr virus infection is characterized by the fatigue, functional impairment, and cervical lymphadenopathy of mononucleosis [26]. Bacterial causes of sore throat include group A β-hemolytic streptococcus (GABHS), the most common cause of bacterial pharyngitis, and non-group–A streptococcus. Less common causes are *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Neisseria gonorrhoeae*. A rare cause is *Arcanobacterium haemolyticum*, which is associated with an exanthema that may mimic the rash of scarlet fever [27]. Among these various causes, the only commonly occurring infection for which antibiotic therapy is beneficial is GABHS.

The goals of treating GABHS include expediting clinical recovery, decreasing the likelihood of suppurative complications (such as abscess),

preventing acute rheumatic fever, and limiting transmission of the disease [28]. At the same time, by excluding from treatment those patients who have pharyngitis who are not infected by GABHS, the adverse effects of treatment and the emergence of antibiotic-resistant bacteria are avoided [29]. GABHS may account for 5% to 15% of pharyngitis in adults and 12% to 35% in school age children, yet in a national survey 73% of adults [30] and 53% of children [31] who had pharyngitis were treated with antibiotics.

Clinical features and diagnostic strategies

The typical symptoms of streptococcal pharyngitis are sudden onset of sore throat accompanied by fever. In children, abdominal pain and vomiting are also reported. The presence of cough and rhinorrhea suggest a non-GABHS etiology. The physical findings may include pharyngeal erythema, tonsillar exudates, and enlarged cervical lymph nodes. Fever, palatal petechiae and uvular swelling, none of which are specific for streptococcal infection, are also found. All of these historical and physical features are common to infections by other agents, including group C and group G streptococcus [32].

Because a physician may be unable to clinically distinguish GABHS from the causes of pharyngitis for which antibiotics should be withheld, a laboratory test will in some cases be necessary to confirm the diagnosis [28]. A throat culture, consisting of a throat swab incubated on blood agar and confirming GABHS growth by the inhibitory effects of bacitracin, has been the standard for diagnosis; however, results of this culture are only available after 24 to 48 hours, with a delay in immediate and appropriate therapy. With this delay, the benefits of timely treatment, which include reducing risk of disease transmission, diminishing symptoms, and speeding recovery, are jeopardized [32]. Rapid antigen detection testing (RADT) for GABHS was developed to provide more immediate, albeit more costly results, with a demonstrated specificity exceeding 95% relative to blood agar culture [33].

A clinical score based on the cumulative presence or absence of specific clinical features may be used to exclude or entertain the diagnosis of GABHS, thereby reducing the need for both throat cultures and unnecessary antibiotics [34,35]. Use of a sore throat score to determine treatment of children and adults in a university-based family practice demonstrated a 48% reduction in antibiotic prescription compared with usual care [35]. In a community-based family practice, McIsaac and colleagues [36] assessed a clinical score for validity that resulted in a reduction in antibiotic prescription of 63.7%, and a reduction in throat cultures of 35.8%. Sensitivity and specificity of the score relative to culture was 85.0% and 92.1% respectively (Table 1).

A systematic review of the clinical diagnosis of strep throat by Ebell and coworkers [37] showed that the presence of tonsillar or pharyngeal exudates

Table 1
McIsaac clinical score for pharyngitis

Points	Clinical feature
1	History of fever (or measured temperature $>38^{\circ}C$)
1	Absence of cough
1	Tender anterior cervical adenopathy
1	Tender swelling or exudate
1	Age <15
−1	Age ≥ 45
Score	**Recommended action**
≤ 1	No culture or therapy
2–3	Culture
≥ 4	Culture or therapy

Adapted from McIsaac WJ, White D, Tannenbaum D, et al. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. CMAJ 1998;158(1):79; with permission.

or exposure to strep throat infection in the previous 2 weeks were reliable in predicting the likelihood of GABHS pharyngitis (positive likelihood ratio [LR] of 3.4, 2.1, and 1.9, respectively). The absence of tender anterior cervical nodes, tonsillar enlargement, or exudates were reliable predictors that GABHS was not present (negative LR of 0.60, 0.63, and 0.74, respectively). No single element of the history or physical examination alone was sufficient for excluding or diagnosing strep throat. Based on the prevalence of GABHS in a given population, clinical prediction rules can be used to calculate the individual's probability of GABHS pharyngitis (Table 2).

The American College of Physicians (ACP) developed guidelines for the diagnosis of pharyngitis in adults based upon clinical prediction rules [29]. Throat culture is excluded from this diagnostic algorithm because the delay in its result precludes an immediate treatment decision and the potential benefit of symptom relief. An additional concern is the failure of culture to discriminate between infection and the carrier state. Instead, recommendations are to assess by RADT the patient who have two to three clinical criteria (intermediate risk) and treat only for a positive test. Patients who have three or four criteria are treated empirically. All others are neither

Table 2
McIsaac clinical prediction rule for the diagnosis of GABHS in adults and children

Score	Likelihood ratio	% of patients with strep[a]
−1 or 0	0.05	1
1	0.52	10
2	0.95	17
3	2.5	35
4 or 5	4.9	51

[a] Baseline prevalence = 17%.

Data from Ebell MH, Smith MA, Barry HC, et al. The rational clinical examination. Does this patient have strep throat? JAMA 2000;284(22):2912–8.

tested nor treated. This approach acknowledges the chance of undertreatment based on testing only those designated as intermediate to high risk by criteria (both sensitivity and specificity of approximately 75%), while emphasizing the relatively low likelihood of suppurative complications and acute rheumatic fever.

A cost-effectiveness analysis compared five strategies in the diagnosis and management of pharyngitis in adults assuming a GABHS prevalence of 10% [38]. A decision model was constructed to evaluate the strategies of observation only, empiric therapy, two-plate throat culture, RADT (optical immunoassay) followed by culture to confirm negative results, or RADT alone. The findings of this analysis generally supported the ACP guidelines, except that a marginal superiority in costs and effectiveness is seen with culture. The other strategies differed little in cost-effectiveness; however, empirical therapy achieved reasonable cost-effectiveness only when very high GABHS prevalence is assumed.

Guidelines provided by the Infectious Disease Society of America for the diagnosis and management of GABHS pharyngitis calls for laboratory testing based on epidemiological and clinical features and exclusion of those who appear at low risk [28]. Confirmatory culture of negative RADT results in adults is not recommended. A confirmatory throat culture is advised for RADT negative children and adolescents because there is a higher prevalence of GABHS and acute rheumatic fever. Follow-up cultures are not recommended after appropriate therapy in asymptomatic individuals except under circumstances of an epidemic in a closed community or recurrent infection in a household when carriage is suspected.

Therapy

Treatment of GABHS is aimed at eradication of the organism from the upper respiratory tract [28]. A Cochrane review [39] assessed the benefits of antibiotic treatment of sore throat. Studies demonstrating a reduction in rheumatic fever with antibiotic therapy found benefits were modest, with large numbers of individuals needed to treat to derive meaningful benefit [39]. A reduction in symptoms (sore throat, headache, or fever) by about one half was seen with antibiotic therapy at 3.5 days of illness. Five patients would need to be treated with antibiotics to eliminate one sore throat by day 3 and seven patients would need to be treated to eliminate one sore throat by day 7. A subgroup analysis of patients evaluated with a throat swab for streptococcus revealed significantly greater symptom reduction with antibiotic treatment in those who had a positive swab than a negative swab. Antibiotic therapy resulted in a reduction in the incidence of suppurative complications, including otitis media, sinusitis, and quinsy (peritonsillar abscess) compared with placebo.

Penicillin is recommended for the treatment of GABHS pharyngitis [29]. In penicillin-allergic patients, erythromycin is recommended. GABHS

resistance to penicillin has not been reported; however, some resistance to macrolides, including erythromycin, has been seen [28]. First-generation cephalosporins are acceptable alternatives for patients who have a history of non-anaphylactic allergy to β-lactam antibiotics. Although a 10-day course of penicillin is recommended for eradication of GABHS, shorter courses of therapy with other agents have been shown to be effective [28,40]. Providing written instructions on the use of the antibiotics for sore throat has improved compliance [41].

Treatment of pharyngitis with corticosteroids has demonstrated inconsistent results. In one study [42], a single dose of oral dexamethasone (0.6 mg/kg) provided greater pain relief than placebo in children who had moderate to severe pharyngitis caused by GABHS and non-GABHS. In a somewhat smaller study with a similar design [43], the antigen-positive subset of children reported an improvement in time to onset of pain relief with dexamethasone treatment compared with placebo. No significant decrease in time to onset of pain relief or time to complete pain relief was seen in the antigen-negative treatment group compared with placebo.

Acute sinusitis

Inflammation of the mucosa of the paranasal sinuses, or sinusitis, is among the group of respiratory illnesses (excluding pharyngitis) which was ranked second in frequency of visits to outpatient clinics in 2003 [44]. The term rhinosinusitis may more accurately describe the condition, because inflammation of the nasal mucosa is usually present as well [45]. Although it is usually caused by a viral infection, rhinosinusitis is often attributed by patients and physicians to bacterial cause. Noninfectious causes of sinusitis include allergy, foreign body, deviated septum, tumor, polyps, and barotrauma [25]. Although bacterial sinusitis may complicate only 0.5% to 2% of URIs, it accounts for a disproportionate 21% of antibiotic prescriptions written [46]. Acute bacterial rhinosinusitis (ABRS) shares symptoms with the viral URI, including rhinorrhea, nasal congestion, facial pressure, and fever, which may lead the patient to request antibiotics from their physician. Though antibiotic therapy may be beneficial for bacterial sinusitis, the definitive diagnosis is made by sinus aspiration, an invasive procedure not typically performed in the office setting. Instead the physician must rely on the presentation of a persistent symptom complex, including facial pressure, nasal obstruction, nasal discharge, hyposmia, and fever [47]. The treatment guidelines for sinusitis have generally been directed at reducing the inappropriate use of antibiotics for viral respiratory infections [48]. This article addresses the evaluation and therapy of ABRS in immunocompetent adults and children aged 2 years and older.

The paranasal sinuses typically involved in ABRS are the maxillary and ethmoid sinuses. These sinuses are present at birth, having formed in the

third and fourth gestational month [49]. The sphenoid sinus develops through early childhood and the frontal sinuses develop by adolescence. Infections of the frontal sinuses typically present with greater intensity and severity and may require hospital admission. Bacterial infection typically follows the impairment of mucus clearance and the obstruction of sinus ostia caused by viral respiratory infection. The paranasal sinuses are ordinarily sterile. With infection, the most common microorganisms isolated from maxillary sinuses are *S pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

Clinical features and diagnostic strategies

Sinusitis has been defined as acute when symptom duration is of less than 4 weeks, and chronic when symptoms persist for more than 12 weeks [45]. Complications are potentially quite serious because of the anatomical relationship of the sinuses to the eyes and brain. These complications include orbital cellulitis, orbital abscess, and potentially life-threatening intracranial complications such as cavernous sinus thrombosis, meningitis, and brain abscess.

Chronic sinusitis is defined by the presence of two major, or one major and two minor criteria. Criteria are listed in Box 1 [50]. Noninfectious factors such as allergy and irritants appear to initially cause inflammation, and then bacteria may have some role in its persistence. Antibiotic therapy for chronic rhinosinusitis has not been shown to improve outcomes in children, whereas the benefits of antibiotic therapy for adult chronic sinusitis have not been studied [51]. Endoscopic surgery may be used in the treatment of

Box 1. Diagnostic criteria for chronic rhinosinusitis

Major criteria
- Facial pain/pressure
- Nasal obstruction
- Nasal discharge
- Nasal purulence
- Hyposmia/anosmia

Minor criteria
- Fever (nonacute)
- Halitosis
- Fatigue
- Dental pain

Adapted from Lanza DC. Diagnosis of chronic rhinosinusitis. Ann Otol Rhinol Laryngol Suppl 2004;193:11.

chronic rhinosinusitis that has failed to resolve with conservative therapy [52].

The diagnosis of ABRS is complicated by the symptoms it shares with viral URI and by the lack of data correlating these symptoms with sinus aspirate findings [25]. Clinical impression alone may result in 40% to 50% accuracy in diagnosis by the primary care physician [45]. Current guidelines provide for a diagnosis of ABRS in patients who have duration of illness with typical symptoms of more than 7 to 10 days [45,48,49]. Patients who have rhinovirus infection may have symptoms from one to 33 days, but most are well by 10 days, and 75% have resolution of symptoms by 14 days [53].

Evaluation of patients' symptoms and physical features relative to radiological findings has been studied. Features associated with significant CT findings (air-fluid levels or complete sinus opacification) included purulent rhinorrhea, erythrocyte sedimentation rate greater than 10, purulent nasal secretions, and "double sickening," or symptom worsening after an initial resolution [54]. CT findings are, however, not specific for ABRS, and are seen in patients who have URI [13]. Williams and colleagues [55] used sinus radiographic changes to identify five predictors of ABRS, namely, maxillary toothache, poor response to decongestants, history of discolored nasal discharge, mucopurulent nasal discharge on examination, and abnormal transillumination. No single finding had sufficient specificity and sensitivity to be diagnostic [55].

Although transillumination of the sinuses was found to be an independent predictor of sinusitis, its utility is limited to the maxillary and frontal sinuses, it is difficult to perform and is likely unreliable in younger children; its practical use appears limited [49]. Hansen and coworkers [56] found a relationship between positive bacterial culture of sinus aspirates and unilateral tenderness of the maxillary sinus, maxillary pain, maxillary toothache, and mucopurulent nasal discharge. A study of emergency room patients who had symptoms of sinusitis [57], some for more than 30 days, found an increased likelihood of ABRS (with purulent sinus aspirate, not cultured) in those who had unilateral predominate purulent nasal discharge and unilateral predominate facial pain by history, bilateral purulent nasal discharge, and pus in the nasal cavity. Reviewing the studies to identify clinical signs and symptoms of ABRS, it appears that purulent nasal discharge, unilateral maxillary tenderness, and worsening of symptoms after initial improvement predict a higher likelihood of the diagnosis [45].

Radiography has been employed in the evaluation of ABRS, but there are significant limitations in its ability to reliably predict this diagnosis. In particular, mucosal thickening lacks specificity as a finding in ABRS, and is no more predictive than clinical judgment. Patients who had either complete sinus opacification or air fluid levels benefited from treatment for ABRS with amoxicillin [58]. These findings have relatively high specificity, approximately 85% and 80% respectively. The sensitivity of a radiographic negative for these three findings is about 90%, and the normal study can be

powerful evidence for excluding ABRS [45,49]. Management guidelines exclude radiography from the routine evaluation of sinusitis in both children and adults [47–49]. CT has the ability to visualize the paranasal sinuses and the osteomeatal complex, the anatomic entity central to the diagnosis of ABRS. Lindbaek and colleagues [59] found no difference in outcomes for patients who had a clinical diagnosis of sinusitis, but only mucosal thickening on CT treated with either amoxicillin or placebo. In patients undergoing CT examination for reasons other than sinusitis but who had a history of recent URI, 31% were found to have sinus abnormalities [60]. The changes seen in CT examination are not sufficiently specific for sinusitis, and CT should be used carefully and within the clinical context. When surgical management is being considered, as in cases of persistent infection or complicated infections, CT may be indicated in planning therapy [49,61].

Therapy

The rational approach to treatment of ABRS is somewhat limited by the diagnostic uncertainties that have been described. Nevertheless, guidelines have been published that advocate antibiotic therapy dictated by the severity and duration of symptoms [47–49]. Antibiotic therapy has been shown to shorten the duration of symptoms in patients who have purulent rhinorrhea compared with placebo; however, no difference in overall recovery was seen, and the antibiotic group had a higher frequency of diarrhea [62]. When study participants were limited to those who had pus in the nasal cavity, facial pressure, or nasal discharge lasting longer than 7 days, the group treated with antibiotics experienced symptom improvement earlier (8 versus 12 days), but there was no significant difference in improvement at 14 days [63]. A Cochrane review of antibiotic therapy for persistent (more than 10 days) nasal discharge in children found a reduction in the probability of persistent symptom in the short to medium term, with eight children needed to be treated to achieve one additional cure [64]. A systematic review of antibiotic therapy for acute maxillary sinusitis in adults included 49 studies with significant variability among them that compared antibiotic to control or antibiotics from different classes [65]. Penicillin improved clinical cures and radiographic outcomes. No significant differences were seen between classes of antibiotics.

Recommendations of the American College of Physicians-American Society of Internal Medicine (ACP-SIM) are for symptomatic treatment or reassurance for those who have mild to moderate symptoms [48]. Antibiotics are reserved for those who have severe or persistent symptoms of more than 7 days. It is surmised that the modest improvements seen in the studies using relatively nonspecific standards (clinical or radiographic) were caused by the inclusion of patients who have no bacterial infections. The agent with the narrowest spectrum active against the likely pathogens is recommended, and amoxicillin is preferred. The American Academy of Otolaryngology-Head and Neck Surgery recommends initial therapy of adults who have

mild disease and who have not received antibiotics in the previous 4 to 6 weeks with first-line agents such as amoxicillin. Those who have mild disease but antibiotic use in the previous 4 to 6 weeks or moderate disease are treated with second-line agents, including fluoroquinolones. Failure to respond after 72 hours of therapy should prompt a re-evaluation of therapy [47]. Likewise, for the treatment of children, severity of disease and prior treatment with antibiotics determine therapy choice, excluding fluoroquinolones. Efficacy is predicted according to a mathematical model based on the expected pathogens, spontaneous resolution rates, and in vitro activity. The American Academy of Pediatrics recommends antibiotic therapy for children who have sinusitis meeting the clinical definition and whose symptoms are severe or persistent [49]. Amoxicillin is recommended at usual doses (45 mg/kg) in two divided doses for children who have mild to moderate disease and who do not attend day care and have not recently been treated with antibiotics. Failure to improve (reduction in respiratory symptoms and in general well-being) within 48 to 72 hours should lead to reconsideration of the diagnosis or changes in therapy. High-dose amoxicillin (90 mg/kg) is advised if patients fail to improve with usual doses of amoxicillin, have moderate to severe illness, have been recently treated with antibiotics, or attend day care. Alternatives for β-lactam allergic patients include cefdinir, cefuroxime, or cefpodoxime. Clarithromycin and azithromycin are recommended in anaphylaxis-type, β-lactam allergic patients.

There are few data concerning the use of additional non-antimicrobial therapies for sinusitis. A 3-day course of prednisone (0.8–1.2 mg/kg) combined with cefpodoxime resulted in less pain and nasal obstruction in the first 3 days compared with placebo in adults who have radiograph- or endoscope-documented maxillary rhinosinusitis [66]. Daily hypertonic saline use for 6 months by patients who had a history of sinusitis resulted in improved symptom severity and sinusitis-related disability scores, and less antibiotic use [67]. The addition of intranasal steroids to antibiotic therapy for acute rhinosinusitis in patients who had [68] and did not have [69] a history of chronic or recurrent sinus symptoms achieved a higher and more rapid rate of patient-reported clinical success than placebo.

Acute bronchitis

Unlike the other diagnostic entities reviewed here, acute bronchitis refers to inflammation of a portion of the lower respiratory tract. Like pharyngitis and sinusitis, however, it is a condition that shares a primary symptom, in this case cough, with the nonspecific URI, an illness of viral origin not requiring antibiotic therapy. And as with these other specific conditions, there is evidence for benefit from antibiotic therapy in only the minority of cases. Because of its relationship to the viral URI, acute bronchitis, defined as an acute cough illness in an otherwise healthy adult, is included here for review [70].

Acute bronchitis generally refers to an infection of the respiratory tract in which cough is the predominate feature [71]. When surveyed on the definition of acute bronchitis, there is disagreement among family physicians, some qualifying the cough as purulent, and others indicating that it must only be productive [72]. Although a systematic review found antibiotic therapy for acute bronchitis offers only modest benefit [73], it is reported that 70% to 90% of office visits for this diagnosis result in a prescription for antibiotics [71]. Treatment guidelines have been developed in an effort to limit unnecessary antibiotic therapy for this condition [74].

The majority of cases of acute bronchitis are caused by infection by viruses, including influenza, parainfluenza, and respiratory syncytial virus, resulting in lower tract disease; and rhinovirus, coronavirus, and adenovirus, usually resulting in upper tract disease [71]. An etiological study of adults who had lower respiratory tract infection and controls identified rhinovirus in 33%, and influenza in 24% of patients [79]. Noninfectious causes of acute cough include allergy, asthma, environmental exposures, heart failure, gastroesophageal reflux, and tumor [75]. Cough-variant asthma may be difficult to distinguish from uncomplicated acute bronchitis, which may also be associated with transient bronchial hyperresponsiveness but typically resolves after 2 to 3 weeks [76]. The other causes are identified by unique epidemiological or clinical features (Table 3). Bacterial infection causes fewer than 10% of the cases of infectious bronchitis; only *Bordetella pertussis*, *M pneumoniae*, and *C pneumoniae*, have been identified as primary agents [71]. Pneumonia is a relatively frequent and important cause of cough that must be excluded as a diagnosis because it may be associated with significant mortality.

Clinical features and diagnostic strategies

The cough of acute bronchitis may be productive and may be accompanied by wheezing. This reflects hypersensitivity of the bronchial epithelium that can be measured by pulmonary function testing, with abnormalities

Table 3
Causes of cough

Disease	Signs and symptoms
Asthma	Evidence of reversible airway obstruction
Occupational exposures	Symptoms worsen during work week
Chronic bronchitis	Chronic cough with sputum production for minimum of 3 months, smoker
Sinusitis	Tenderness over sinuses, nasal discharge
Common cold	Upper airway inflammation, no wheezing
Pneumonia	Infiltrate on chest radiograph
Congestive heart failure	Rales, orthopnea, cardiomegaly, S3 gallop
Reflux esophagitis	Heartburn, especially when supine

Adapted from Hueston WJ, Mainous 3rd AG. Acute bronchitis. Am Fam Physician 1998;57(6):1273; with permission.

most prominent 1 or more weeks after infection [71]. These abnormalities typically persist for 2 to 3 weeks, but may last longer. In a study of patients presenting to a general medical practice who have acute cough, purulent sputum, or abnormal auscultory findings, it was 3 to 4 weeks before most patients were well and able to resume usual activities [77]. Although the productivity of the cough, and in particular the purulence of the sputum, is associated with antibiotic use by physicians [78], this feature, a nonspecific sign of inflammation, is not predictive of a bacterial infection [76]. Established criteria for the diagnosis of pneumonia do not include purulent sputum, and only 10% of patients presenting with purulent sputum have pneumonia [71]. A rule to exclude the diagnosis of pneumonia without the need for further evaluation is based on the absence of abnormal vital signs (tachycardia, tachypnea, and fever) and the absence of specific adventitious breath sounds (consolidation signs, such as rales, egophony, or fremitus) [79]. Although this may guide the physician in the decision to proceed with radiography, other factors that may influence this decision include the age and comorbidities of the patient, and the likelihood of a seasonal illness such as influenza. The use of C-reactive protein measurement to distinguish bacterial pneumonia from uncomplicated acute bronchitis has been studied but does not appear to offer an advantage in the evaluation of patients who have acute cough [71].

Infection with *B pertussis* should be considered if there is a history of exposure to an individual who has confirmed pertussis or when cough persists. Nasopharyngeal swab for polymerase chain reaction testing is particularly useful for diagnosis in previously vaccinated individuals who less frequently meet clinical criteria for the disease [80]. Increasing reports of pertussis appear to be due to waning vaccine immunity in adolescents and young adults [81]. Use of serology for the diagnosis of pertussis and for diagnosis of infection with *M pneumoniae* or *C pneumoniae* is limited, in part because seroconversion may occur in asymptomatic individuals [76,80]. Sputum culture is poorly sensitive for these species and is not recommended. *M pneumoniae* infection commonly produces an influenza-like tracheobronchitis with a self-limited course resolving in 2 to 4 weeks without treatment [82]. It may also produce an atypical pneumonia. *C pneumoniae* infection of the respiratory tract is usually asymptomatic, but may be associated with bronchitis or pneumonia. There has been speculation that *C pneumoniae* may be implicated in adult new-onset asthma based on serological findings in these patients [83].

Therapy

Treatment guidelines derived from the available evidence recommend against routine antibiotic therapy for uncomplicated acute bronchitis [74]. Systematic reviews have failed to discover more than marginal benefit in treatment with antibiotics of acute bronchitis patients, including smokers

[73,84]. Although a shorter duration of cough (by 0.58 days), productive cough (by 0.52 days), and feeling ill (by 0.58 days) was noted in the treated group in one review [73], there was no difference at follow-up for night cough, productive cough, or activity limitations. In another systematic review [84], there were significantly more side effects in the antibiotic treatment group. No trials have specifically examined antibiotic treatment for smokers who have acute bronchitis, but a review of existing data found the same or less benefit for smokers compared with nonsmokers [85]. In a trial of azithromycin or vitamin C therapy for adults who had acute bronchitis, there was no significant difference in health-related quality of life after 7 days [86].

Antibiotic therapy is recommended for acute bronchitis caused by pertussis [74]. A Cochrane review of antibiotics for pertussis [87] found that short-term therapy with azithromycin (3 days), clarithromycin (7 days), or erythromycin (7 days) was as effective as long-term therapy with erythromycin in eradicating infection from the nasopharynx with fewer side effects in the short-term treatment. Although the clinical course of the illness is not altered, treatment is recommended for individuals who have bronchitis and who have been exposed to documented pertussis in order to decrease spread of the disease [76].

Although there is scant evidence supporting the use of antibiotics for acute bronchitis, the evidence for use in chronic bronchitis and its exacerbation is mixed [88]. The US Food and Drug Administration (FDA) no longer considers antibiotic trials for acute bronchitis warranted because of lack of evidence of benefit [71]. Nevertheless many of the antibiotics with indications for chronic bronchitis are used by physicians for the treatment of acute bronchitis. Perhaps this is due in part to the failure to distinguish between the otherwise healthy patients with acute, self-limited cough and the patient who has worsening symptoms associated with irreversible lung disease [75].

Various agents used to provide symptom relief for the patient who has acute bronchitis have been studied. Because bronchial hyperresponsiveness with bronchospasm is a feature of the disease in a significant percentage of patients [71], it is not surprising that the evidence supports the use of bronchodilators in individuals who demonstrate airflow obstruction [89]. Cough scores did not change after treatment in children who had no airway obstruction. In studies of adults, there was no difference in cough at 7 days for treatment or control groups; however subgroups who had airflow limitation had lower cough scores, and those who had wheezing at baseline had quicker resolution of cough [90].

There is little evidence to support the use of antitussives specifically for acute bronchitis. Guidelines suggest that there may be modest responses to dextromethorphan and codeine preparations [76]. Few studies have evaluated the efficacy of guaifenesin as an expectorant, although its use is widespread. It has been found to inhibit capsaicin-induced cough in patients who have URI [91]. An herbal agent, *Pelargonium sidoides* (EPs 7630) was

studied against placebo in adults who had acute bronchitis and less than 2 days of cough [92]. A significant decrease in symptom severity scores and in work disability was found in the treatment group, with no difference in adverse effects.

The approach to the patient who has acute cough should be to first identify, based on history and physical examination, individuals likely to have pneumonia who require further evaluation and specific therapy (strength of recommendation [SOR]: A) In the remaining patients there is a subset for whom treatment with antiviral therapy for influenza may be indicated based upon clinical judgment, and seasonal prevalence. If there is known exposure to pertussis, macrolide therapy should be considered. Antibiotic therapy is otherwise not indicated, and is unlikely to provide benefit to the patient. Symptomatic therapy, including inhaled-bronchodilators for those who show evidence of airway obstruction, and antitussives for those who have chest discomfort or sleep disturbance from cough, may be added.

Table 4
Evidence-based recommendations for the treatment of URI

Recommendations	Strength of recommendation
Antibiotics are not indicated in the treatment of a nonspecific URI in adults and children.	A
Delayed antibiotic therapy may decrease use with no effect on outcome except symptom score for otitis media and pharyngitis.	B
Oral and topical decongestants are beneficial in adults with URI.	A
Decongestant/antihistamine combinations improve recovery and nasal symptoms in older children and adults with URI.	B
RADT for GABHS is recommended if pretest likelihood is intermediate to high.	A
Culture for GABHS is recommended to confirm negative RADT in children and adolescents.	C
Penicillin is recommended therapy for GABHS if no allergy history.	A
Oral dexamethasone is recommended to speed pain relief in pharyngitis.	B
Antibiotic therapy does not improve outcomes in children with chronic sinusitis.	A
Radiographs are not recommended for routine evaluation of acute sinusitis in children and adults.	B
Antibiotics are recommended for persistent or severe symptoms in acute sinusitis.	B
Combination prednisone and antibiotics decrease symptoms in acute sinusitis.	B
Antibiotic therapy is not indicated for acute bronchitis unless symptoms persist after pertussis exposure.	A
Bronchodilator therapy is recommended in bronchitis with evidence of airway obstruction.	B
Antitussive therapy may improve cough in bronchitis.	C
Patient education on appropriate antibiotic use decreases use of antibiotics for URI.	A

Patient education by the physician on the appropriate treatment of acute bronchitis can result in lower antibiotic usage without affecting clinical outcomes [93]. These efforts may include providing an informational leaflet, or during the visit reviewing with the patient the following.

- There is a very high likelihood that the illness will resolve with or without antibiotics.
- Inappropriate antibiotic use is associated with emergence of antibiotic-resistant bacteria.
- Antibiotic use is associated with risk of adverse events, including serious allergic reactions.
- Avoid terms such as bronchitis that engender fear but have no value in specifying treatment.

Summary

The patient presenting to the primary care physician with infection of the upper respiratory tract is most likely experiencing a frequent and usually self-limited viral infection. The viral URI is characterized by nonspecific symptoms including sore throat, nasal congestion, and cough that may respond to symptom-targeted measures. In those who have pharyngitis and features typical of streptococcal infection, rapid in-office testing may guide antibiotic treatment and limit their unwarranted use. The appropriate treatment of acute sinusitis is dictated by an assessment of historical and physical features generally not requiring diagnostic imaging. When cough is the predominate symptom in the immunocompetent individual and pneumonia is excluded, then treatment with antibiotics is not indicated. Physician responsibility in the judicious use of antibiotics may reduce the emergence of bacterial resistance and also decrease adverse reactions. Patient education may mitigate demands for unnecessary therapy and preserve satisfaction with their care. Table 4 summarizes the evidence-based recommendations for the treatment of URI.

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