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Management of acute bronchitis in healthy adults

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Acute respiratory infections (ARIs) are the most common infections in humans. ARIs (nonspecific upper respiratory infections, otitis media, sinusitis, pharyngitis, bronchitis, and pneumonia) account for half of acute conditions each year [1], and consistently rank among the top 10 reasons for ambulatory visits in the United States [2–12]. Acute bronchitis episodes represent a significant portion of these illnesses. Data from the National Health Interview Survey suggest that 4% to 5% of all adults experience one or more episodes of acute bronchitis each year [1]. Furthermore, over 90% of acute bronchitis episodes will come to medical attention [1].

Acute bronchitis is a clinical diagnosis applied to otherwise healthy adults with acute respiratory illness of 1 to 3 weeks' duration. Acute bronchitis usually is distinguished from other ARIs by the predominance of cough, often accompanied by other respiratory and constitutional symptoms, and the absence of findings suggestive of pneumonia. The importance placed on sputum production and wheezing when making the diagnosis of acute bronchitis varies by physician [13–16]. Cough lasting longer than 3 weeks should be considered “persistent” or “chronic” cough [17,18], and is not discussed here because the diagnostic considerations are significantly different than those of acute bronchitis.

This article focuses on acute bronchitis in otherwise healthy individuals, not on patients who have underlying heart or lung disease or immunosuppression, who generally have been excluded from trials evaluating etiology of and treatment for acute bronchitis. The extent to which one can generalize from the data presented herein is unknown.

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Acute bronchitis: a transient form of asthma

Clinical features of uncomplicated acute bronchitis develop in sequential phases. Acutely, there is direct inoculation of the tracheobronchial epithelium, characterized clinically by variable constitutional symptoms, including fever, malaise, and myalgias. These symptoms usually last 1 to 5 days, depending on the infectious agent. This phase of illness is often indistinguishable from other acute upper respiratory tract infections. Most uncomplicated upper respiratory infections improve substantially within 5 to 7 days [19,20]. In patients for whom the diagnosis of acute bronchitis would be appropriate, however, the acute phase is followed by a second, protracted phase characterized by persistent cough, often accompanied by phlegm production or wheezing. This second phase usually lasts 1 to 3 weeks, and has as its underlying pathophysiology the hypersensitivity of the tracheobronchial epithelium and airway receptors (reactive airway disease).

During the protracted phase, pulmonary function tests (PFTs) are frequently abnormal and do not seem to be related to either the acute cytopathic effects of the infection or the type of infection (bacterial or viral) [21–25]. Vagal-mediated airway hyperresponsiveness has been shown to coincide with repair of the bronchial epithelium [26]. Other mechanisms of bronchial hyperresponsiveness, such as adrenergic-cholinergic tone imbalance and IgE-mediated histamine release, also may be present. PFT abnormalities seem to be common in acute bronchitis, with approximately 40% of patients demonstrating significant abnormalities by forced expiratory volume (FEV1) or histamine challenge [27,28]. PFT abnormalities are usually transient, typically resolving after 2 to 3 weeks, although they may last as long as 2 months [27–29]. Recurrent episodes of “acute bronchitis” may suggest underlying asthma [30,31]. Although undiagnosed asthma should be considered in patients who have acute cough illness, this diagnosis is difficult to establish because bronchial hyperresponsiveness and PFT abnormalities are frequent in patients who have acute bronchitis. Suspicion and work-up for asthma should be reserved for patients with cough lasting longer than 3 weeks [17].

Microbiology of acute bronchitis

Most acute bronchitis cases seem to have a nonbacterial etiology [29,32,33]. Microbiologic study of acute bronchitis, however, similar to community-acquired pneumonia, can identify a pathogen in only 16% to 55% of cases [32,34]. The significant variability in the frequency of isolation of any pathogen and the types of pathogens identified reflects the patients studied, available technology to identify certain viral and atypical pathogens, and the epidemic nature of the agents that cause acute bronchitis. Additionally, noninfectious causes of acute bronchitis also likely represent some of these cases. Occult asthma, allergic, and occupational exposures should be considered, although their prevalence in adults with acute cough illness remains unclear.

Viral bronchitis

Respiratory viruses seem to cause or serve as a copathogen in most cases of acute bronchitis in epidemiologic studies. The specific viruses most frequently associated with acute bronchitis, in order of frequency of occurrence, are influenza, parainfluenza, respiratory syncytial virus (RSV), coronavirus, adenovirus, and rhinoviruses.

Recent studies have demonstrated the importance of RSV as the etiology of ARIs in adults [35,36]. The impact of RSV is greatest in the elderly, particularly those living in long-term care facilities, and those with underlying heart and lung disease and malignancy [37]. Infection among exposed adults is common, with attack rates approaching 50%, particularly in households with children infected with RSV and in institutional settings [24,37]. Most young and middle-aged adults develop asymptomatic or mildly symptomatic disease, often closely resembling influenza [38]. RSV can be associated with more severe clinical disease and significant morbidity, even in otherwise healthy adults [24]. This morbidity seems to be in part secondary to induced airway hyperreactivity.

In the elderly and institutionalized, lower respiratory illness with RSV is common, with most studies reporting rates of pneumonia and death from 10% to 20% and 2% to 5%, respectively [37]. One report of an outbreak on a geriatrics ward found intense coughing and fever in 96% of patients, productive cough in 64%, and evidence of bronchopneumonia in 40% [39]. In this study, it is unclear whether RSV or secondary bacterial infection caused these pneumonias.

Human metapneumovirus (hMPV), a paramyxovirus [33,40], has emerged recently as an important cause of lower respiratory tract illness and acute bronchitis. Human MPV has been detected in children, adults, the elderly, and the immunocompromised in the Netherlands, Australia, North America, the United Kingdom, and Finland [41–45]. In one study, hMPV was second only to RSV as a cause of respiratory tract illness presenting to a university hospital in the Netherlands [45].

Similar to RSV, hMPV is primarily an illness of the winter months, most commonly causing significant illness in young children and immunocompromised and elderly individuals. Studies suggest that 25% to 50% of hMPV-positive patients who have significant respiratory tract illness have underlying disease [46,47]. Among otherwise healthy adults, hMPV likely causes predominantly mild respiratory illness, but may cause a small but significant portion (approximately 3%) of acute respiratory illness requiring medical attention [46–48].

Bacterial bronchitis

When microbiologic studies are performed on select patients who have uncomplicated acute bronchitis in nonoutbreak settings, less than 10% of

patients have a clear bacterial etiology [29,32,33]. *Bordetella pertussis*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* are the only bacterial pathogens that have been established as causes of acute bronchitis. Although studies have reported the presence of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in adults with acute bronchitis, these studies generally failed to exclude patients who had underlying lung disease, failed to distinguish between colonization and infection [49], or did not differentiate adequately patients who had pneumonia from those who had acute bronchitis when determining causative agents [33]. Furthermore, acute viral respiratory infections seem to increase the proliferation of these bacteria among the oropharyngeal flora [50], further complicating the issue of colonization versus infection. Therefore, sputum Gram stain and culture for common bacterial pathogens have no clinical usefulness in patients who have acute bronchitis.

Mycoplasma pneumoniae and *C pneumoniae* have been recognized as possible causes of acute bronchitis since the 1980s [51,52]. Attack rates vary highly, reflecting the seasonal, geographic, and epidemic nature of these infections [21,27,33,53–60]. Studies attempting to distinguish these atypical bacterial pathogens from viral etiologies have shown that patients infected with atypical bacterial pathogens tend to present to medical attention much later than those with confirmed viral bronchitis [21,60,61], and are more likely to have wheezing on clinical examination [21]. In several studies, although these pathogens were present by antibody titer or gene amplification, treatment with antibiotics appropriate to atypical pathogens did not change outcome [33,62–65]. This suggests that in acute bronchitis, *C pneumoniae* and *Mycoplasma pneumoniae* may reflect copathogens or inciting factors for secondary infectious processes, rather than the etiologic agent. Alternatively, because patients with atypical bacterial pathogens present late in the course of illness, the acute infectious process may have resolved with only residual reactive airway disease present at the time of presentation for medical care.

B pertussis causes acute bronchitis in previously immunized adults. Natural infection and vaccination with whole-cell and acellular vaccines induce protection from infection for a limited time [21,66–71]. Thus, adolescents and adults gradually may become susceptible to infection again. Symptomatic adult pertussis requiring medical attention occurs at a rate of 71 to 507 per 100,000 population per year (0.1%–0.5% of the population per year) [72–76]. This pool of frequently undiagnosed pertussis [77] provides a reservoir for potentially serious infections in young infants who either are unvaccinated or whose vaccinations are not yet fully effective [78].

The gradual decrease in protection against pertussis likely explains part of the wide variation in presenting symptoms in previously immunized adults. Adults with pertussis generally present with persistent cough, with a mean duration of 36 to 48 days [72,75,77,79–82]. When prolonged cough (longer than 1 week) is present, a significant portion of patients will have

B pertussis infection, with a frequency ranging from 12% to 32% [71,72,74, 75,79,83–88]. Cough is mostly paroxysmal, and often disturbs sleep. Choking or vomiting and whooping can be present, but less commonly than in children or previously unimmunized adults.

Some have suggested that booster pertussis immunizations for adults or adolescents may curb illness in infants [89]. Whole-cell and acellular pertussis vaccines are well tolerated, with primarily local side effects [90–92]. Only one study has assessed the efficacy of acellular (aP) vaccines in adults [93]. Because of the small sample size of the trial, few pertussis cases were reported ($n = 12$), and no point estimate of efficacy could be given. The incidence of primary pertussis cases was decreased in the aP group (0.8 per 1000 person-years; 95% CI 0.0–2.1), however, compared with the control group (3.7 per 1000 person-years; 95% CI 1.2–6.2). An epidemiologic model has suggested that a high coverage of adults (greater than 85%) would be needed to reduce effectively the number of cases of infant pertussis [94].

Antibiotic therapy does not seem to decrease duration of symptoms for pertussis unless initiated within 7 to 10 days of the onset of illness [95–97]. Macrolide prophylaxis during outbreak situations and after intrafamilial contacts seems effective [77,98], however, and decreases spread of disease [96,97].

Distinguishing pneumonia from acute bronchitis

In the absence of significant comorbid conditions or asthma, the primary objective when evaluating patients who have acute cough illness is excluding pneumonia. The prevalence of pneumonia in patient populations presenting with ARIs varies significantly across study populations, ranging from 3% to 10% in most studies [33,99–101]. Cohort studies have identified clinical features useful for determining which patients do not have pneumonia [99,101–104]. The absence of abnormal vital signs (heart rate greater than 100 beats/minute, respiratory rate greater than 24 breaths/minute, oral temperature above 100.5°F) and chest examination (focal consolidation; eg, rales, egophony, fremitus) reduces the likelihood of pneumonia sufficiently to render further diagnostic testing unnecessary [101]. The specificity (67%–76%), but not sensitivity (62%–71%), of these clinical prediction rules for radiographic pneumonia exceeded physician judgment in a well-designed validation study of 290 adult patients who had acute cough illness [100]. Notably absent from these decision rules is the presence or absence of purulent sputum because purulence (by itself) is a poor predictor of bacterial infections [105,106].

Applying the pneumonia clinical prediction rules should help inform the decision about ordering a chest radiograph, but cannot substitute for clinical judgment. The pneumonia clinical prediction rules have limited application in

the elderly because they may present with atypical manifestations of pneumonia (and without vital sign or examination abnormalities) [107]. Conversely, during the influenza season many patients will have fever or tachycardia but not pneumonia. As a result, chest radiography often is overused in the elderly and during influenza season. In settings where chest radiography is not available readily (eg, many private office practices or rural locations), patients who have cough illness (particularly elderly) may be prescribed antibiotics to safeguard against missing a case of pneumonia.

Rapid blood tests for bacterial infections

C-reactive protein

A rapid, office-based diagnostic test that improves sensitivity and specificity of detecting pneumonia could be a valuable addition to the current evaluation strategies for patients who have acute cough illness [108]. European experience with an office-based, rapid c-reactive protein (CRP) test, as well as a recent study conducted in the United States, suggests considerable potential to improve diagnostic and treatment decisions for adults with cough illness [109–117]. CRP synthesis is stimulated in response to many inflammatory conditions, and levels increase preferentially (but not exclusively) by bacterial (versus viral) infections. The serum levels of CRP associated with bacterial infections are 10 to 50 fold higher than those used to predict atherosclerotic heart disease.

Despite widespread use in Europe, and recent US Food and Drug Administration approval of a rapid CRP test in the United States, the role of rapid CRP testing in the management of adults with acute cough illness has not been defined rigorously. Most studies found a high sensitivity (80%–100%), but CRP levels may lack the specificity (60%–70%) necessary to diagnose bacterial infections in isolation. Integrating CRP testing into a clinical algorithm is one strategy to improve on its specificity while taking advantage of its sensitivity for detecting acute bacterial infections such as pneumonia. Future studies assessing the effectiveness of a CRP-based clinical algorithm are necessary.

Procalcitonin

Recent studies of procalcitonin in serum also have shown levels to distinguish bacterial from viral illnesses [118,119]. Early procalcitonin assays had a limited functional assay sensitivity (0.3–0.5 µg/L), and therefore were not accurate for the diagnosis of early or localized infections [120,121]. A newer assay with improved functional sensitivity (0.06 µg/L) has become available in Europe, however. One recent study adopting a test-based clinical algorithm with this rapid procalcitonin testing among adults admitted to the hospital with lower respiratory tract infection demonstrated a large reduction in antibiotic use, and equivalent outcomes [122].

Acute bronchitis and antibiotics

Should antibiotics ever be used?

Antibiotic prescription rates for acute bronchitis range from 50% to 80% in studies from multiple settings and countries [123–125]. Studies have failed to show any meaningful benefit from antibiotics in the treatment of acute bronchitis, however. Systematic reviews and meta-analyses of nine randomized placebo-controlled trials conducted between 1970 and 2000 conclude that routine antibiotic treatment of acute bronchitis has no consistent effect on either the duration or severity of illness. In one meta-analysis, there was no significant impact on the duration of cough [126], but two other meta-analyses reported a small but statistically significant decrease in cough duration (one third days fewer of cough after 7 days) associated with treatment with antibiotics [127,128]. In all three meta-analyses, there was no significant impact on overall illness duration, activity limitation, or work loss. A recent randomized, double-blind, controlled study comparing azithromycin with vitamin C has addressed concerns that the earlier trials were performed with older antibiotics, some of which had no activity against the atypical agents implicated in acute bronchitis [129]. This study found no advantage to antibiotic treatment on illness outcomes or return-to-work status.

As discussed earlier, antibiotic prescription is appropriate when the physician suspects pertussis infection. Antibiotics should be reserved for adults exposed to known pertussis infection, or to patients who have acute bronchitis in the setting of a documented pertussis epidemic. Although antibiotics do not decrease the duration of illness in this setting, they can decrease bacterial shedding and spread. Antibiotics also may be considered in the setting of a known mycoplasma or *C pneumoniae* outbreak, although data are lacking on their effectiveness in this setting.

The harm of overusing antibiotics

The societal cost of inappropriate antibiotic use is the rapid emergence of antibiotic resistance among bacterial pathogens [130–132]. Resistance is rising among common community-acquired pathogens, including *S pneumoniae* (DRSP) [133–135]. This pathogen is a leading cause of ear and sinus infections, pneumonia, sepsis, and meningitis in the United States. At the community level, the mean increase in DRSP prevalence is directly proportional to the amount of antibiotics consumed [136]. On an individual level, a person's risk for carriage, transmission, and invasive infection with antibiotic-resistant bacteria is associated strongly with prior antibiotic use [137–140].

Finally, the sheer magnitude of antibiotic prescriptions dispensed each year for ARIs requires that excess health care costs also be considered. In 1998, 41 million antibiotic prescriptions were written for ARIs, 55% of

which were likely unnecessary [141]. The cost of these excess prescriptions was estimated at \$726 million. Similar high rates of inappropriate antibiotic use are seen in Europe [142]. In addition, the result of antibiotic resistance on antibiotic selection and clinical outcomes further increases health care costs [143].

If they don't work, why are antibiotics so frequently prescribed for acute bronchitis?

Physician education likely reflects a small component of inappropriate antibiotic use. Evidence suggests that physicians and patients are more likely to believe that antibiotics are appropriate if purulent secretions are present [144,145], despite significant evidence to the contrary. Physician specialty and level of training also are associated with antibiotic prescriptions for ARIs. Family medicine physicians are more likely to prescribe antibiotics to children with ARIs than pediatricians [146]. Also, providers that are further from medical school graduation and practicing in rural areas are more likely to prescribe antibiotics [147].

Antibiotic prescribing behavior is associated poorly with clinicians' subjective norms and intentions, which suggests that external forces such as patient-specific beliefs and health plan factors play a greater role [148] than physician knowledge. Patients frequently expect to receive antibiotics for uncomplicated acute bronchitis [149,150] and patients or parents who expect antibiotics are more likely to receive them [150,151]. Communication elements associated with antibiotic prescriptions for ARIs include patient appeals to specific life circumstances (eg, a pressing social engagement), identification of a previous positive experience with antibiotic use [81], or being labeled as having "acute bronchitis" rather than a "chest cold" [149].

Not surprisingly, clinicians with greater patient workloads prescribe antibiotics for ARIs more frequently, likely reflecting the perceived time it would take to discuss the inappropriateness of antibiotic use in ARIs [152]. Other health plan factors that may contribute to prescribing behavior include restricting formularies and practice characteristics such as payment structure. A recent survey of physicians' attitudes regarding the role of societal risks in making antibiotic treatment decisions for individual patients found that societal concerns about promoting antibiotic resistance ranked below patient-centered factors such as ease of use and cost to the patient [153].

Despite physician concerns about patient expectations, most studies find that satisfaction with care for ARIs is tied more closely to how much time the physician spent explaining the illness, rather than receipt of antibiotics [150,151,154]. Communication elements associated with high patient satisfaction include positive responses to the following statements: "the doctor spent enough time with me"; "the doctor explained the illness to me"; and "the doctor treated me with respect" [147]. An intervention

strategy consisting of patient and clinician education reduced antibiotic prescription rates for acute bronchitis in adults [155], but did not decrease patient satisfaction [147]. Furthermore, antibiotic prescribing does not seem to reduce additional care seeking in adult patients [156].

Nonantibiotic treatment of acute bronchitis

Anti-influenzal therapy

Influenza is the most common cause of acute bronchitis, and influenza vaccination is the most effective strategy for preventing influenzal illness. Treatment for high-risk exposed individuals and those who present within 48 hours of symptom onset is also possible. Amantadine, rimantidine, zanamivir, and oseltamivir decrease illness duration by approximately 1 day and lead to a 0.5-day quicker return to normal activities [157]. The primary difference between the agents is that the neuraminidase inhibitors are effective against influenza A and B, whereas amantadine and rimantidine are effective only against influenza A. The relative proportion of cases caused by each type of influenza virus varies from year to year, and is determined best through consultation with local public health agencies. Adverse events are modestly more common with rimantidine (32% of patients, most commonly central nervous system) than with the neuraminidase inhibitors (24% of patients, mostly gastrointestinal) [157]. Because each of these therapies is only effective if initiated within the first 48 hours, and preferably 30 hours, of symptom onset, rapid diagnosis is key. During documented influenza outbreaks, the positive predictive value of clinical diagnosis based on clinician judgment is good (correct approximately 70% of the time) [158], and compares favorably with rapid diagnostic tests for influenza (sensitivities of 63%–81%) [158–160]. Diagnosis of influenza in a nonoutbreak period is more difficult and diagnostic testing should be considered.

Antiviral treatment for other viral illness either have been studied inadequately, carry inappropriately high side-effect profiles, or are ineffective in otherwise healthy individuals [161]. Ribavirin is indicated in bone marrow transplant patients who have RSV, and in this population reduces morbidity and mortality [162].

Bronchodilator therapy

Three randomized, controlled trials have demonstrated a consistent benefit to bronchodilator treatment [163–165]. Approximately 50% fewer patients report the presence of cough after 7 days of treatment. This benefit seems to be greatest in the subset of patients who had bronchial hyperresponsiveness. A large trial of patients who had URI-associated cough, but not clearly acute bronchitis, reported no benefit of bronchodilator treatment [166]. A meta-analysis of these studies showed no significant

benefit from β_2 -agonists [167], but is limited by the addition of the Littenberg study, which enrolled patients who had acute, nonspecific cough.

Whether anticholinergic bronchodilator therapy is effective in patients who have uncomplicated acute bronchitis is not known. Similarly, no studies have examined the effect of inhaled corticosteroid therapy, although the delay in onset of action for this type of therapy (1–2 weeks) may preclude finding a major benefit.

Antitussive therapy

The effectiveness of antitussive therapy seems to depend on the cause of cough illness. Acute or early cough caused by colds and other upper respiratory tract infections does not seem to respond to dextromethorphan or codeine. Cough of greater than 3 weeks' duration, cough associated with underlying lung disease, and experimentally induced cough seem to respond to these agents. Given that the cough of acute bronchitis often lasts for 2 to 3 weeks, these agents likely have a modest impact on cough severity and duration.

Immunomodulating therapies

Most trials of immunomodulatory (alternative) therapies have been conducted on patients who have early symptoms of colds and nonspecific ARIs. As a result, these data are difficult to extrapolate to patients who have acute bronchitis, who generally present later and with more severe illness. Vitamin C at doses exceeding 1 g/d seems to offer small but significant reduction in illness duration of about 0.5 day per cold episode [168]. Well-performed clinical trials comprising mostly small studies of zinc gluconate and zinc acetate lozenges have had mixed results [169] and their benefit is unclear. Echinacea seems to be of benefit in some preparations [170], but there is significant heterogeneity of study design, as well as preparations tested. Also, quality control of echinacea preparations sold to the community is poor, with one study demonstrating that 10% of single-herb echinacea preparations in one metropolitan area had no active ingredient, and less than half met the quality standards described on the label [171].

A recent randomized, double-blind, placebo-controlled trial has shown the benefit of an extract of *Pelargonium sidoides* roots in acute bronchitis [172]. This plant extract is used commonly in Europe and Mexico. Its mechanism of action is poorly understood, but is believed to be immunomodulatory in nature, having been used first in the early 1900s as a treatment for tuberculosis. In the recent study, adult patients who had acute bronchitis of greater than 48 hours' duration and a bronchial severity score (BSS) of at least 5 points were enrolled. Patients were excluded if they were to receive or recently had received antibiotics or had other serious illnesses. Patients were randomized to receive active ingredient or color-, smell-, viscosity-, and taste-matched placebo. Among patients receiving pelargonium, decrease in BSS on

day 7 was 5.9 points compared with 3.2 points for placebo ($P < .0001$). Duration of illness ($P < .001$) and inability to work (16% versus 43%, $P < .0001$) were significantly less in the pelargonium group compared with placebo. Further studies are necessary to confirm these interesting results. In the United States, *Pelargonium sidoides* is marketed under the trade name Umcka (Nature's Way, Springville, Utah).

Approach to the patient with acute bronchitis

The approach to the otherwise healthy patient with acute cough illness first should be to assess his or her likelihood of pneumonia. In the nonelderly patient without abnormal vital signs or consolidative lung findings, the likelihood of pneumonia is less than 1% in the ambulatory care setting [99,101]. When these abnormalities are present, a chest radiograph should be considered, depending on overall clinical impression and likelihood of influenza. For patients who present with prolonged cough (longer than 1 week), pertussis should be considered, along with bronchial hyperresponsiveness.

Once a diagnosis of acute bronchitis has been made, providers should address symptomatic treatment and patient expectations for the visit. Physicians should validate the severity of the patient's illness (because it has affected the patient's activities enough to seek care and acute bronchitis significantly decreases quality of life) [173]. Treatment discussions should focus on alleviating symptoms and providing realistic expectations for the duration of symptoms. Patients should be informed that they should expect their cough to last 10 to 14 days after the office visit. Providers should also inform patients of which symptoms should prompt a return to the clinic or office.

For patients who request antibiotics for clear viral infections, providers should discuss the lack of benefit and the risks of inappropriate antibiotic use. These risks should be personalized as much as possible, informing them that previous antibiotic use increases their personal risk of carriage and infection with antibiotic-resistant infections. In addition, antibiotics cause frequent side effects, especially of the gastrointestinal tract.

Symptomatic treatment will depend on severity of illness and time at presentation. Alternative and over-the-counter preparations may be most effective in the early stages of illness. For those with prolonged or severe cough or clear bronchial hyperresponsiveness, bronchodilator treatment and antitussives should be considered. Further studies are necessary on the plant extract *Pelargonium sidoides* to assess further its benefit in this setting.

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