CLINICAL REVIEW

Treatment of Acute Bronchitis in Adults Without Underlying Lung Disease

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OBJECTIVE: **To determine whether antibiotic and bronchodilator treatment of acute bronchitis in patients without lung disease is efficacious.**

DESIGN: **A MEDLINE search of the literature from 1966 to 1995 was done, using "Bronchitis" as the key word. Papers addressing acute bronchitis in adults were used as well as several citations emphasizing pediatric infections. A manual search of papers addressing the microorganisms causing acute bronchitis was also done. Data were extracted manually from relevant publications.**

SETTING: **All published reports were reviewed. Papers dealing with exacerbations of chronic bronchitis were excluded in this review.**

RESULTS: **Although acute bronchitis has multiple causes, the large majority of cases are of viral etiology. *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Bordetella pertussis* are the only bacteria identified as contributing to the cause of acute bronchitis in otherwise healthy adults. Nine double-blind, placebo-controlled trials were reviewed. Four studies showed no advantage for doxycycline and one study showed no advantage for erythromycin. One study using erythromycin and one study using trimethoprim and sulfamethoxazole showed that these antibiotics were slightly better than placebo. Two other studies showed an impressive superiority for liquid or inhaled albuterol when compared with erythromycin.**

CONCLUSIONS: **Most studies showed no significant difference between drug and placebo, and the two studies that did showed only small clinical differences. Albuterol had an impressive advantage over erythromycin. Antibiotics should not be used in the treatment of acute bronchitis in healthy persons unless convincing evidence of a bacterial infection is present.**

KEY WORDS: **acute bronchitis, bronchitis; bronchitis treatment.**
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A cute bronchitis is one of the more common conditions seen in ambulatory medicine. In the 1970s a survey of an emergency department in Madison, Wisconsin, including all four seasons, showed that bronchitis, cough, and laryngitis accounted for 12% of visits[1]; and in a 1976 survey of family practitioners, acute bronchitis was the fifth most common cause of office visits.[2] The National Center for Health Statistics found that in 1989 bronchitis (unfortunately, not specified as acute or chronic) was the seventh most common diagnosis for office visits to internists and general and family practitioners, accounting for 2.2% of all visits to internists and 2.3% of all visits to general and family practitioners.[3] This review summarizes what is known about the etiology and clinical management of acute bronchitis, and then focuses on the treatment of acute bronchitis in adults without underlying chronic lung disease. Data regarding the efficacy of specific treatments for patients with acute bronchitis are presented.

METHODS

A MEDLINE search of the English language literature from 1966 to 1995 was done, using "Bronchitis" as the key word. A few more sources were found in the bibliographies of other papers. Nine double-blind studies using antibiotics versus placebo or albuterol in the treatment of acute bronchitis were analyzed and described. All nine studies used cough with sputum (several used purulent sputum) as the major entry criterion. Reports addressing chronic bronchitis were excluded, although several of the nine studies included smokers. Although all the studies stated that chronic obstructive pulmonary disease (COPD) was an exclusion criteria, chest x-rays were used in only three studies to exclude underlying lung disease,[4-6] and two studies used chest x-rays only if fever or signs of consolidation were present, or "at the discretion of the primary provider."[7,8] Pulmonary function tests were not presented in any of the studies in this review.

Reviews describing the epidemiology and clinical course of viral and mycoplasma, chlamydia, and bordetella pertussis respiratory infections were utilized to determine if an etiologic diagnosis could be suspected when the patient was first seen. As most of the treatment studies had relatively few patients, and outcome measures differed between studies, a meta-analysis was not attempted.

ETIOLOGY

Acute bronchitis, characterized by inflammation of the trachea and bronchi, can be caused by microbial in-

fection or noninfectious assaults on the bronchial tree such as allergy or air pollution.[9] The presence of a cough, with or without fever, cold symptoms, or sputum production is the symptom that usually leads to a diagnosis of acute infectious bronchitis, after other causes of cough such as bacterial sinusitis, allergies, atmospheric pollution, or other lung diseases have been reasonably excluded. Viral infections are thought to be the predominant cause of acute bronchitis in otherwise healthy adults, but the precise ratio of viral causes to bacterial causes is not known. Numerous viruses have been implicated as causing acute bronchitis, including influenza viruses and adenoviruses,[10,11] respiratory syncytial virus (RSV),[11,12] and the common cold viruses such as rhinoviruses,[11] and (less frequently) coronaviruses.[13] Measles[14] and herpes simplex virus[15] may also cause bronchitis, and are associated with particularly severe cases.

The only bacteria known to contribute significantly to the etiology of acute bronchitis are *Mycoplasma pneumoniae*,[10] *Chlamydia pneumoniae* (formerly known as TWAR),[16] and *Bordetella pertussis*.[17] Other bacteria, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, have been suggested as etiologic agents in acute bronchitis in otherwise healthy patients, but there is little evidence to support this contention, as these bacteria are part of the usual upper respiratory tract flora in many patients.

EPIDEMIOLOGY

Enteroviruses such as coxsackieviruses and echoviruses may cause acute bronchitis during the summer months, rhinovirus is present during all seasons, but most other viruses cause bronchitis between early fall and spring.[18] Influenza generally occurs from late November through March, and measles bronchitis can be seen during a measles outbreak. RSV may cause bronchitis (and pneumonia) in elderly adults,[12] as well as in younger adults having frequent contact with young children, such as pediatric hospital personnel and parents or other caregivers of young children.[19] Almost all the viral causes of acute bronchitis have relatively brief incubation periods, from 1 day (influenza) to 5–7 days (RSV).

M pneumoniae infections occur throughout the year with occasional epidemics occurring every 4 to 7 years.[20] *C pneumoniae* infections appear to have a higher incidence every 4 years.[21] Both *M pneumoniae* and *C pneumoniae* infections have relatively long incubation periods, averaging 3 weeks (16–35 days) for *M pneumoniae*,[22] and 30 days for *C pneumoniae*.[21] *B pertussis*, the agent causing whooping cough, may have a long incubation period, which can vary from several days to over 3 weeks,[23,24] with epidemics occurring every 3 to 5 years. Pertussis has been increasing in incidence since 1981,[25] and is becoming a more important cause of acute bronchitis in adults who have never had a natural infection because of the pertussis immunizations received in childhood.[24] Most of the adult population is left without antibody to *B pertussis*, as the protection of childhood immunization wanes by 4 to 12 years.[24,25]

In an epidemic situation, pertussis has an attack rate of 23% to 100% if 12 or more years has passed since the last pertussis immunization and an adult is exposed to a family member with whooping cough.[24,26] In one epidemic in rural Wisconsin, young children were more likely to acquire whooping cough from teenagers or adults, rather than the converse.[24] The cough is usually preceded by rhinorrhea, conjuctivitis, and a low-grade fever. Unfortunately, the characteristic "whoop" is usually lacking in adults,[17] so pertussis is rarely considered as causing bronchitis unless the patient gives a history of contact with a known case of pertussis. It is probable that pertussis is a more common cause of bronchitis than is currently realized. In children, treatment with erythromycin in the catarrhal stage, and sometimes in the paroxysmal stage, may be of benefit.[27] However, as adults do not have the usual whoop, it would be difficult to determine if they had pertussis unless there was contact with a known case. The author is unaware of studies of antibiotic use in adults with pertussis, but it might be reasonable to use erythromycin in adults if there is recent contact (within less than 2 weeks) with a person known to have pertussis.

CLINICAL FINDINGS

The usual presenting symptoms of bronchitis are cough, frequently accompanied by rhinitis or other cold symptoms such as pharyngitis and laryngitis. Fever may or may not be present. Infection with the three bacteria, influenza viruses, and adenoviruses generally cause fever, while rhinovirus infection usually does not. The patient may or may not give a history of producing sputum, which if present can be clear or colored. The presence of colored sputum is due to release of peroxidases by neutrophilic or eosinophilic leukocytes or both and should not be considered definite evidence of bacterial infection.[28]

The initial physical examination may reveal nothing more than a low-grade fever, rhinitis, and pharyngitis. Usually the lung examination is normal, although rales and ronchi may be present in influenza, adenoviral, and *C pneumoniae* infections, and occasionally with *M pneumoniae* bronchitis. Wheezing may be present, as viruses and the three bacteria that cause bronchitis are the only known microbial pathogens (other than parasites) that may produce bronchospasm, although this is more common in children.[24,29-33] With the exception of differences in incubation periods between the bacterial and viral causes of acute bronchitis, their symptoms are often nearly identical. Some distinguishing features that may be helpful in diagnosis are various rashes in mycoplasma infections, which occur in up to 25% of cases[34]; laryngitis, which was more common in *C pneumoniae* than mycoplasma or viral infections in one series[35]; and laryngitis

and pharyngitis, which often precede the cough by several days to a week in *C pneumoniae* infections.[21] The presence of sinusitis or otitis is of no help as either may occur in viral, *M pneumoniae*, and *C pneumoniae* infections.[35,36]

Pulmonary infiltrates characteristic of the atypical pneumonia syndrome may be present in 3% to 10% of cases of *M pneumoniae* infections,[32,33] and about 10% of *C pneumoniae* infections.[35] The majority of pneumonia cases due to *M pneumoniae* occur in older children and young adults, while the bulk of *C pneumoniae* cases are found in the elderly.[21] Elevation of the white blood cell count occurs in 27% or less of acute bronchitis cases.[10,35]

TREATMENT

Many physicians use antibiotics to treat acute bronchitis in patients without underlying disease such as COPD. This practice is often deplored in journal articles and textbooks written by infectious disease specialists.[14,37–39] As most cases of acute bronchitis are due to a viral infection, antimicrobial treatment should be ineffective in this group, save for influenza A, which responds to amantadine or rimantadine with a 33% to 50% shortening of the duration of the illness when given in the first 48 hours of the illness.[40–42] Aerosolized ribavirin has been shown to have a modest beneficial effect in adults with bronchitis due to RSV.[43] In a study of 98 patients, tetracycline therapy did not shorten the duration of cough in patients with *M pneumoniae* infections compared with nonrandomized control patients.[22]

To date, nine clinical trials have compared the use of antimicrobial agents and placebo or albuterol in patients with acute bronchitis (Table 1). Four of these trials used doxycycline as the antibiotic.[7,8,44,45] Two of the studies had small numbers of patients. Both studies were randomized double-blind prospective trials. The smaller study had only 39 patients enrolled with 31 completing the study, and the larger study enrolled 74 patients with 69 completing the study. Neither study showed an advantage for doxycycline, but the larger trial showed an advantage for the placebo, although only fewer days missed from work was statistically significant.[7]

The largest of the four studies enrolled 212 patients from three group practices in Wales, with 207 completing the trial.[44] This prospective double-blind randomized controlled trial used doxycycline 100 mg twice the first day and 100 mg per day for the next 9 days, with 104 patients receiving doxycycline and 103 receiving placebo. In this study there was also no difference between doxycycline and placebo.

The most recent study using doxycycline in the same dose as the previous study enrolled 158 patients randomized to doxycycline or placebo. The authors found "no clinically relevent effect in all patients who have an acute cough with purulent sputum." There was a minimal beneficial effect of doxyclycline in those aged over 54 years.[45]

There has been one prospective randomized double-blind placebo-controlled trial using trimethoprim and sulfamethoxazole (160/80 mg in a fixed-dose combination) twice daily for 7 days, versus a placebo.[46] In this trial 67 patients were studied, 34 receiving trimethoprim and sulfamethoxazole and 33 receiving placebo. Patients kept a daily record of symptoms for the 7 days of the study. Trimethoprim and sulfamethoxazole had a statistically significant advantage compared with placebo after 7 days, but only for less cough and lower temperature (93% on trimethoprim and sulfamethoxazole were still coughing vs 99% on placebo, and average temperature was 36.9°C for trimethoprim and sulfamethoxazole vs 37.3°C for patients on placebo). Nocturnal cough was also less common on the active drug. Other end points, such as activity level, return to work, cough frequency and amount, showed no significant differences between trimethoprim with sulfamethoxazole and placebo.

There have been two studies that used erythromycin base (333 mg 3 times a day) for 7 or 10 days.[4,47] These studies were prospective, and the patients were randomized to erythromycin or placebo. Both studies used patient diaries to record various symptoms. The smaller of the two studies (50 of 52 patients completed the study) used 7 days of treatment, and showed a nonsignificant trend favoring erythromycin among nonsmokers, but there was no difference between erythromycin and placebo among those who smoked.[4] The larger study enrolled 63 patients and used 10 days of erythromycin treatment; 6 patients did not return for follow-up, and 9 (7 of whom were given erythromycin) stopped their study drug because of gastrointestinal side effects or because they "forgot" or "it didn't help." The authors analyzed the results with and without these 9 patients (i.e., 57 or 48 total patients). This study found a statistically significant advantage for erythromycin in terms of fewer symptoms between day 6 and day 10 of the study. However, on day 10 (the last day of the study), only reduction in "congestion" in the erythromycin group showed a statistically significant advantage over placebo. The authors found no difference between smokers and nonsmokers, or between the group of 57 versus the group containing 49 patients.[47]

The eighth study compared liquid erythromycin ethylsuccinate 400 mg, with liquid albuterol 2 mg, every 6 hours for 7 days. This study was also prospective and double blind with the patients completing symptom diaries every day. Forty-five patients were enrolled, and 42 began the study. Two of 22 patients receiving erythromycin and 2 of the patients receiving albuterol withdrew because of medication side effects. Two more patients taking erythromycin and one patient taking albuterol failed to return for follow-up after 7 days of treatment, and one patient was dropped because of a cough lasting over 30 days (an exclusion criterion). Therefore, 34 patients completed this study with 17 in each group. Interestingly, 65% of the albuterol group were smokers versus 35% of the erythromycin group. After 7 days, only 41% of the albuterol group were still coughing compared with 88% of the

Table 1. Published Studies on Antibiotic Treatment in Acute Bronchitis

Study	Study Design	Result
Stott and West[44]	Patients (212) with cough and purulent sputum from 3 group practices were randomized to placebo or doxycycline 100 mg: 2 tabs on day 1 and 1 tab qd thereafter for 9 days. Symptoms were reviewed by their physicians. Five patients did not complete trial. The study was double blind.	By day 7 of trial, 94 of 104 patients on doxycycline were well, compared with 86 of 103 on placebo. No significant difference between groups was found.
Williamson[7]	Patients (74) were randomized to doxycycline 100 mg or placebo: 3 capsules in the first 24 hours and 1 capsule qd for 5 more days. Patients completed a symptoms diary daily for 7 days. This study was double blind.	No significant difference between active drug and placebo groups was found for cough duration (20.1 and 18.2 days, respectively), work absence (1.5 and 0.6 days), or days of fever (1.4 and 1.2 days).
Scherl et al.[8]	Of 39 patients randomized to doxycycline 100 mg or placebo, only 31 completed the study. Patients took 1 pill bid on day 1 and 1 pill qd for the next 6 days. Patients kept a symptoms diary. This study was double blind.	No significant difference between groups was found. At 2-week follow-up active drug group had had 9.4 ± 1.3 days of cough compared with 10.8 ± 1.2 days of cough in the placebo group.
Verheij et al.[45]	Of 158 patients randomized to doxycycline 100 mg or placebo, 140 completed the trial. Patients took 1 tab bid on day 1 and 1 tab qd for 9 more days. Patients kept a daily diary of symptoms. This study was double blind.	No significant difference was found in patients under age 55. Patients over 55 had 4.1 fewer days of cough on doxycycline and recorded 2.8 fewer days of feeling ill. Active drug group had 1.5 fewer days of cough than placebo group (4.7 vs 6.2 days), $p < .01$. By day 11, 87% of doxycycline group were improved vs 78% of placebo.
Franks and Gleiner[46]	Patients (67) were randomized to trimethoprim & sulfamethoxazole (160/800 mg) bid for 7 days. Patients kept a daily record of symptoms. The study was double blind.	Cough, night cough, and temperature were reduced, but the difference was small, i.e., 99% of placebo group were still coughing at 7 days vs 93% of treatment group, and 74% of active drug group were back to work vs 60% in placebo group.
Brickfield et al.[4]	Of 52 patients randomized to placebo or erythromycin 333 mg for 7 days, 50 patients completed the study. This study was double blind.	Cough and sputum production resolved more rapidly in the erythromycin group, but differences were not statistically significant for nonsmokers. In smokers, no difference between drug and placebo was found.
Hueston[5]	Patients (42), some of whom were smokers, were randomized to liquid erythromycin ethylsuccinate 400 mg or liquid albuterol 2 mg qid for 7 days. Data from the 34 patients who completed the study were analyzed. This study was double blind.	After 7 days, 59% of albuterol patients were free of cough compared with 12% in the erythromycin group. Of the smokers, 45% of the albuterol group and 100% of the erythromycin group were still coughing after 7 days of treatment ($p = .03$). There was no difference in groups in return to work.
Hueston[6]	Patients (46), some of whom were smokers, were randomized to albuterol inhaler or placebo inhaler and erythromycin 250 mg or placebo capsule qid. There were 4 patient treatment groups: albuterol and erythromycin, albuterol and placebo, erythromycin and placebo, and 2 placebos. This study was double blind.	After 7 days, a statistically significant increase in percentage of patients not coughing was noted in the albuterol group, compared with the control group (39% vs 9%, $p = .02$) and patients treated with albuterol were more likely to return to work by day 4 (78% vs 52%, $p = .05$). There was no difference between smokers and nonsmokers (69% vs 50%, still coughing).
Dunlay et al.[47]	Patients (63) were randomized to enteric coated erythromycin base 333 mg tid or placebo for 10 days. Data were based on 45 patients completing the trial. Patients kept a symptoms diary daily. This study was double blind.	By day 10, 38% of active drug patients had no cough vs 33% on placebo; 14% of active drug patients felt "poor" vs 30% of placebo patients. Congestion was the only symptom for which improvement by the active drug was statistically significant ($p < .05$).

erythromycin group (the report states that p = .002), and there was a nonsignificant trend for the albuterol group "feeling better quicker."[5]

The author of the above paper, performed a second study (the ninth overall) using inhaled albuterol from metered-dose inhalers instead of liquid albuterol. Forty-six patients were in the study, and randomized to four groups: albuterol plus a placebo capsule, albuterol plus erythromycin, erythromycin plus a placebo inhaler or a placebo capsule, and a placebo inhaler. Again, albuterol was superior to either placebo or erythromycin.[6]

DISCUSSION

How should one interpret the results of the above studies, given that only one study with erythromycin and the only study with cotrimoxazole showed a statistically significant advantage over placebo, and even these advantages were minimal? As the vast majority of acute bronchitis cases are thought to be caused by viruses, it seems that antibiotic administration should have little effect, if any. With the exception of amantadine and rimantadine in influenza virus infections, there is a lack of evidence for the efficacy of antimicrobial agents in acute bronchitis, save for the two studies mentioned above that reached statistical significance for a minority of the end points of each study. As these statistical differences were small, they may not be clinically significant. Although the three bacteria involved in acute bronchitis have in vitro sensitivity to erythromycin and tetracycline, neither drug has been shown to shorten the course of mycoplasma or chlamydia bronchitis, because neither drug has been tested in patients with documented bronchitis from mycoplasma or chlamydia bronchitis. Patients with pneumonia due to *M pneumoniae*, however, respond to either tetracycline or erythromycin. Grayston feels that both tetracycline and erythromycin are effective in *C pneumoniae* infections, but points out that no treatment studies have been reported.[21] Erythromycin shortened the course of whooping cough in children in an uncontrolled open trial,[27] but no studies have been done in adults; although one could justify its use in adults on public health grounds, as it should reduce the spread of *B pertussis*.

How should the above studies influence treatment of acute bronchitis? In view of the minimal advantage for either trimethoprim with sulfamethoxazole or erythromycin in only two of the seven studies comparing antibiotics with placebo, the finding in the two small studies showing an advantage for either oral or inhaled albuterol over erythromycin should be pursued, by replicating these studies with a larger number of patients. If used in clinical practice, inhaled albuterol would probably be a better way to deliver the drug. Relief of bronchospasm by albuterol is probably the mechanism for shortening the duration of the cough in acute bronchitis.

Another possible strategy is to take advantage of the difference between the incubation times of acute bronchitis of viral and bacterial etiology. Because of the long incubation time characteristic of the three bacteria that have been implicated in acute bronchitis, it is often possible to predict that the infecting microbe is one of these bacteria, all of which have in vitro sensitivity to erythromycin. For example, if there is an outbreak of bronchitis in a family or work situation in which the time between new cases is over a week, the chance is fairly high that the microbial cause is not viral, and erythromycin may be used (with or without albuterol), even though no study has been done to demonstrate antibiotic effectiveness in acute bronchitis for either mycoplasma or chlamydia pneumoniae. The fact that pneumonia may be present in 3% to 20% of *M pneumoniae* infections[20,32] adds some support to this, as *M pneumonia*, in which both erythromycin and tetracycline have a modest effect, may masquerade as bronchitis unless an x-ray is obtained. Conversely, if the incubation period seems to be under a week, the likelihood that the microbial cause is viral seems overwhelming, and no antimicrobial drug should be used. Rather, use of albuterol may shorten the course of the bronchitis.

Finally, we are in an era of rapid development of bacterial resistance to antibiotics.[48] Although there are several reasons for this phenomenon, one of the important factors is the inappropriate prescribing of antibiotics by physicians. Treating a condition that is largely viral in origin with antibiotics whose sole effect is to kill or inhibit the growth of bacteria can only do harm, unless there is reasonable evidence that the patient being treated is one of the few with a bacterial infection.

CONCLUSIONS

Acute bronchitis is one of the most common conditions seen in ambulatory medical practice. Many physicians treat this condition with antibiotics in spite of exhortations from the infectious diseases community that antimicrobial treatment is unjustified for a condition that is usually viral in origin, and will only lead to an increase in bacterial resistance to the antibiotics used. In fact, seven of the nine studies comparing antibiotics to placebo showed either no statistical difference between groups or, in one study, an advantage for the placebo. One of two studies showed a slight advantage for erythromycin compared with placebo, and one study showed a slight advantage for trimethoprim with sulfamethoxazole over placebo. Two small studies showed a statistical advantage for albuterol over erythromycin, presumably because of the effectiveness of albuterol in relieving bronchospasm. At present, inhaled albuterol may be the preferred treatment for acute bronchitis, although a larger study comparing albuterol versus erythromycin and a placebo needs to be done.

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REFERENCES

1. Moffet HL. Common infections in ambulatory patients. Ann Intern Med. 1978;89(pt 2):743–5.

2. Marsland DW, Wood M, Mayo F. Content of family practice. J Fam Pract. 1976;3:37–8.

3. National Ambulatory Care Survey: 1989 Summary. Vital Health Stat [13]. 110:12–45.

4. Brickfield FX, Carter WH, Johnson RE. Erythromycin in the treatment of acute bronchitis in a community practice. J Fam Pract. 1986;23:119–22.

5. Hueston WJ. A comparison of albuterol and erythromycin for the treatment of acute bronchitis. J Fam Pract. 1991;33:476–80.

6. Hueston WJ. Albuterol delivered by metered-dose inhaler to treat acute bronchitis. J Fam Pract. 1994;39:437–40.

7. Williamson HA Jr. A randomized, controlled trial of doxycycline in acute bronchitis. J Fam Pract. 1984;19:481–8.

8. Scherl ER, Riegler SL, Cooper JK. Doxycycline in acute bronchitis: a randomized double-blind trial. J Ky Med Assoc. Sept 1987:539–41.

9. Baxter PJ, Ing R, Falk H, Plikaytis B. Mount St. Helens eruptions: the acute respiratory effects of volcanic ash in a North American community. Arch Environ Health. 1983;38:138–43.

10. Mogabgab WJ. Mycoplasma pneumoniae and adenovirus respiratory illness in military and university personnel, 1959–1966. Am Rev Respir Dis. 1968;97:345–57.

11. Mogabgab WJ. Acute respiratory illness in university (1962–1966), military and industrial (1962–1963) populations. Am Rev Respir Dis. 1968;98:359–77.

12. Franson H, Sterner G, Forsgren M, et al. Acute lower respiratory illness in elderly patients with respiratory syncytial virus infection. Acta Med Scand. 1967;182:323–9.

13. Higgins PG. Viruses associated with acute respiratory infections 1961–71. J Hyg, Camb. 1974;72:425–32.

14. Gwaltney JM. Pleuropulmonary and bronchial infections. In: Mandell GL, Douglas RG, Bennett JE, eds. Principles and Practice of Infectious Diseases. 3rd ed. New York, NY: Churchill Livingstone; 1990:529–31.

15. Sherry MK, Klainer AS, Wolff M, Gerhard H. Herpetic tracheobronchitis. Ann Intern Med. 1988;109:229–33.

16. Grayston JT, Aldous MB, Easton A, et al. Evidence that Clamydia pneumonia causes pneumonia and bronchitis. J Infect Dis. 1993; 168:1231–5.

17. MacLean DW. Adults with pertussis. J R Coll Gen Pract. 1982; 32:298–300.

18. A collaborative study of the aetiology of acute respiratory infections in Britain 1961-4. A report of the Medical Research Council Working Party on Acute Respiratory Virus Infections. BMJ. 1965;2:319–26.

19. Hall WJ, Hall CB, Speers DM. Respiratory syncytial virus infection in adults: clinical, virologic, and serial pulmonary function studies. Ann Intern Med. 1978;88:203–5.

20. Foy HM. Infections caused by Mycoplasma pneumoniae and possible carrier state in different populations of patients. Clin Infect Dis. 1993;17 (suppl 1):37S–46S.

21. Grayston JT. Infections caused by Chlamydia pneumoniae strain TWAR. Clin Infect Dis. 1992;15:757–63.

22. Foy HM, Grayston JT, Kenny GE, Alexander ER, McMahan R. Epidemiology of Mycoplasma pneumonia infection in families. JAMA. 1966;197:137–44.

23. Lapin JH. Whooping Cough. Springfield, Ill: Charles C. Thomas; 1943:112–22.

24. Biellik RJ, Patriarca PA, Mullen JR, et al. Risk factors for community- and household-acquired pertussis during a large-scale outbreak in central Wisconsin. J Infect Dis. 1988;157:1134–41.

25. MMWR. Dec 17, 1993;952–60.

26. Lambert HJ. Epidemiology of a small pertussis outbreak in Kent County, Michigan. Public Health Rep. 1965;80:365–9.

27. Bergquist S, Sverker B, Dahnsjo H, Sundelof B. Erythromycin in the treatment of pertussis: a study of bacteriologic and clinical effects. Pediatr Infect Dis J. 1987;6:458–61.

28. Chodosh S. Acute bacterial exacerbations in bronchitis and asthma. Am J Med. 1987;82(suppl 4A):154–63.

29. Beasley R, Coleman ED, Hermon Y, Holst PE, O'Donnell TV, Tobias M. Viral respiratory tract infection and exacerbations of asthma in adult patients. Thorax. 1988;43:679–83.

30. Williamson HA, Schultz P. An association between acute bronchitis and asthma. J Fam Pract. 1987;24:35–8.

31. O'Connor SA, Jones DP, Collins JV, Heath RB, Campbell MJ, Leighton MH. Changes in pulmonary function after naturally acquired respiratory infection in normal persons. Am Rev Respir Dis. 1979;120:1087–93.

32. Clyde WA Jr. Clinical overview of typical Mycoplasma pneumoniae infections. Clin Infect Dis. 1993;17(Suppl 1):32S–6S.

33. Hahn DL, Dodge RW, Golubjatnikov R. Association of Chlamydia pneumoniae (strain TWAR) infection with wheezing, asthmatic bronchitis, and adult-onset asthma. JAMA. 1991;266:225–30.

34. Murray HW, Masur H, Senterfit LB, Roberts RB. The protean manifestations of Mycoplasma pneumoniae infection in adults. Am J Med 1975;58:229–42.

35. Grayston JT, Campbell LA, Kuo CC, et al. A new respiratory tract pathogen: Chylamydia pneumonia strain TWAR. J Infect Dis. 1990;161:618–25.

36. Griffen JP, Klien EW. Role of sinusitis in primary atypical pneumonia. Clin Med. April 1971:23–7.

37. Gleckman RA. Bronchial infections: acute bronchitis and acute exacerbations of chronic bronchitis. Compr Ther. 1987;13(2):44–8.

38. Rodnick JE, Gude JK. The use of antibiotics in acute bronchitis and acute exacerbations of chronic bronchitis. West J Med. 1988;149:347–51.

39. Gonzales R, Sande M. What will it take to stop physicians from prescribing antibiotics in acute bronchitis? Lancet. 1995;345: 665–6.

40. Hayden FG, Monto AS. Oral rimantadine hydrochloride therapy of influenza A virus H3N2 subtype infection in adults. Antimicrob Agents Chemother. 1986;29:339–41.

41. Younkin SW, Betts RF, Roth FA, Douglas RG Jr. Reduction in fever and symptoms in young adults with influenza A/Brazil/78 H1N1 infection after treatment with aspirin or amantidine. Antimicrob Agents Chemother. 1983;23:577–82.

42. Wingfield WL, Pollack MD, Grunert RR. Therapeutic efficacy of amantadine HCl and rimantadine HCl in naturally occurring influenza A2 respiratory illness in man. N Engl J Med. 1969;281: 579–84.

43. Hall CB, Walsh EE, Hruska JF, Betts RF, Hall WJ. Ribavirin treatment of experimental respiratory syncytial viral infection. JAMA. 1983;249:2666–70.

44. Stott NCH, West RR. Randomised controlled trial of antibiotics in patients with cough and purulent sputum. BMJ. 1976;2:556–9.

45. Verheij TJM, Hermans J, Mulder JD. Effects of doxycycline in patients with acute cough and purulent sputum: a double blind placebo controlled trial. Br J Gen Pract. 1994;44:400–4.

46. Franks P, Gleiner JA. The treatment of actue bronchitis with trimethoprim and sulfamethoxazole. J Fam Pract. 1984;19:185–90.

47. Dunlay J, Reinhardt R, Roi LD. A placebo-controlled, double-blind trial of erythromycin in adults with acute bronchitis. J Fam Pract. 1987;25:137–41.

48. Murray ME. New aspects of antimicrobial resistance and the resulting therapeutic dilemmas. J Infect Dis. 1991;163:1185–94.