Exacerbations of COPD, which include combinations of dyspnea, cough, wheezing, increased sputum production (and a change in its color to green or yellow), are common. The role of bacterial infection in causing these episodes and the value of antibiotic therapy for them are debated. An assessment of the microbiological studies indicates that conventional bacterial respiratory pathogens, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, are absent in about 50% of attacks. The frequency of isolating these organisms, which often colonize the bronchi of patients in stable condition, does not seem to increase during exacerbations, and their density typically remains unchanged. Serologic studies generally fail to show rises in antibody titers to *H influenzae*; the only report available demonstrates none to *Haemophilus parainfluenzae*; and the sole investigation of *S pneumoniae* is inconclusive. Trials with vaccines against *S pneumoniae* and *H influenzae* show no clear benefit in reducing exacerbations. The histologic findings of bronchial biopsies and cytologic studies of sputum show predominantly increased eosinophils, rather than neutrophils, contrary to what is expected with bacterial infections. The randomized, placebo-controlled trials generally show no benefit for antibiotics, but most have studied few patients. A meta-analysis of these demonstrated no clinically significant advantage to antimicrobial therapy. The largest trials suggest that antibiotics confer no advantage for mild episodes; with more severe attacks, in which patients should receive systemic corticosteroids, the addition of antimicrobial therapy is probably not helpful.

Key words: antimicrobial therapy; bacterial infections; COPD exacerbations

Abbreviation: PEFR = peak expiratory flow rate

Exacerbations punctuate the course of COPD in many patients. Although no uniform definition exists for such episodes, they include various combinations of cough, wheezing, worsening dyspnea, and increased sputum production, or a change in its color to yellow or green. Excluded are situations in which these symptoms arise from a distinct disorder requiring specific therapy, such as pneumonia, pneumothorax, or congestive heart failure. Experimental studies and clinical experience implicate diverse provoking factors for COPD exacerbations, including air pollutants, weather changes, and certain microorganisms. Evidence from cultures and antibody tests incriminate viral infections in about 20 to 50% of cases, and serologic studies have identified acute infection with *Mycoplasma pneumoniae* in < 1%. Investigations have implicated *Chlamydia pneumoniae* in about 5 to 20%. *C pneumoniae*, however, is a difficult organism to isolate; indeed, none of these studies identified it on culture in any patient. Instead, diagnosis has rested on serologic tests, but the standards employed varied, and studies that established serologic criteria for diagnosis rarely correlated antibody changes or levels with culture results. Furthermore, asymptomatic acute acquisition and chronic carriage of the organism can occur, sometimes with high levels of antibody titers. These and other factors make the interpretation of
serologic values difficult; the role, if any, of this organism as a cause of exacerbations remains unclear.

A major, therapeutically important issue in the pathogenesis of exacerbations is whether conventional bacteria cause them, and, consequently, the value of antibiotics in their treatment. Establishing that microbes cause a disorder may be difficult. Robert Koch’s famous postulates, developed from studies on tuberculosis and anthrax, state the following: (1) the microorganism must be found in every case of the disease and under circumstances that can account for the clinical and pathologic findings; (2) it occurs in no other illness as a fortuitous and non-pathogenic organism; and (3) after being cultured through many generations, it must produce the condition in experimental animals. These criteria and various modifications of them are too stringent for many conditions, including COPD exacerbations, a situation complicated by the fact that the bacteria primarily incriminated (Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, and Moraxella (Branhamella) catarrhalis) are chronic denizens of both the upper airway and the tracheobronchial tree of many patients with COPD, even during periods of disease quiescence.

Justifiably indicting these organisms as a cause of exacerbations, however, should require evidence supporting at least some of the following microbiological, immunologic, pathologic, and therapeutic criteria: (1) the putative pathogens should be more prevalent in patients suffering an exacerbation than in those in remission; (2) in patients chronically colonized with the bacteria, the density of the microbes should increase during attacks; (3) serologic studies should demonstrate an immunologic response to the organisms during exacerbations; (4) vaccination against the putative pathogens should reduce the frequency of episodes attributed to them; (5) biopsy specimens of affected tissue (bronchi) should demonstrate invasion by the suspected pathogens and the type of inflammatory response that bacterial infection normally elicits; (6) in placebo-controlled trials, antibiotic therapy should clearly decrease the duration and severity of exacerbations; and (7) in trials of antimicrobial agents, symptomatic improvement should coincide with eradicating the putative pathogens, and clinical success should correlate with the antibacterial activity of the medications used. In other words, antibiotics inactive against the incriminated organisms should yield substantially worse results than those to which the microbes are susceptible. None of these criteria provides definitive information, and interpretations of studies investigating them may differ. Immunization may fail, for example, not because the organisms are unimportant in exacerbations, but because the vaccine does not elicit an immunologic response, or because critical host defenses depend on mechanisms other than antibody formation. Nevertheless, the argument that bacteria are important gains force when several of these criteria are met.

Perhaps the most important evidence, at least from a therapeutic perspective, is whether antibiotics are beneficial, since experts widely endorse and clinicians commonly prescribe antimicrobials for these episodes. This practice is enormously expensive in aggregate, especially since some pulmonologists advocate and many practitioners employ newer, high-priced agents with a wide spectrum of activity that includes penicillin-resistant S pneumoniae and ampicillin-resistant H influenzae, and M catarrhalis, at least for patients with severe disease. The costs of this approach may be more than financial, since widespread use of such recommended antimicrobials as the newer macrolides (azithromycin and clarithromycin) and the fluoroquinolones (eg, ciprofloxacin and levofloxacin) may contribute to the grave problem of emerging resistance to these valuable antibiotics. Accordingly, a careful examination of the evidence incriminating bacteria is crucial to ensure that exacerbations warrant the costs and risks of antimicrobial therapy.

**Microbiological Studies**

Protected brush samples obtained from the lower respiratory tract by bronchoscopy in both hospitalized and ambulatory patients with exacerbations yield significant growth of potential bacterial pathogens in only about 50% of specimens. In these studies S pneumoniae and H influenzae, alone or together, constitute a large proportion of the isolates, being present in about 30 to 40% of all the patients. Most investigations using cultures of expectorated sputum have also identified these organisms in about 30 to 50% of exacerbations. The frequency of isolating potential pathogens being higher in patients with severe disease and in those who continue to smoke. Studies have not so carefully scrutinized other bacteria in exacerbations, but they account for few isolates. M catarrhalis is present in about 5 to 15% of specimens, commonly in association with H influenzae or S pneumoniae, rather than as the sole organism. In the one prospective study that examined H parainfluenzae, this bacterium grew from the sputum of about 40% of patients during remissions, but the yield decreased during exacerbations. Other organisms cultured in these various studies have included a few of highly questionable pathogenicity, such as corynebacteria.
In some investigations, Gram-negative bacilli that are not ordinarily part of the respiratory flora, such as Escherichia coli, Proteus mirabilis, Serratia marcescens, Pseudomonas aeruginosa, and Stenotrophomonas maltophilia, have been frequent isolates from sputum or protected bronchoscopic specimens in exacerbations that required mechanical ventilation or that occurred in patients with advanced disease, defined by an FEV$_1$ of < 50% of predicted.\textsuperscript{7,21,25,26} A study of 40 patients with stable COPD of various severities suggested that the oropharyngeal carriage rate of Gram-negative bacilli increases with the severity of the underlying respiratory impairment; it was nil in mild disease, 7.7% in moderate disease (FEV$_1$ 50 to 69% of predicted), and 29.4% in severe disease (FEV$_1$ < 50%).\textsuperscript{30} Whether the presence of Gram-negative bacilli is the expected natural history of the bacteriology of chronic bronchitis and its exacerbations, or whether it arises from other factors, such as previous antibiotic treatment, recent hospitalization, prior intubation, or systemic or inhaled corticosteroid therapy\textsuperscript{29} (any of which may change the respiratory tract flora), is unclear. Because these organisms often colonize the respiratory tract during stable periods of severe disease, their presence during exacerbations may not represent a change from baseline and, by itself, does not incriminate them as pathogens.

This same issue complicates the interpretation of isolating \textit{H influenzae} and \textit{S pneumoniae}, which have been the focus of most studies evaluating the microbiology of exacerbations. Cultures of sputum\textsuperscript{4,5} and bronchoscopic specimens\textsuperscript{31} have commonly found these two organisms in the respiratory tract of patients with stable chronic bronchitis. In determining if they are pathogens, an important question, then, is whether the frequency of their isolation or the density of their growth increases in the respiratory tract during exacerbations. In one of the investigations using protected brush bronchoscopic specimens, they grew in 17.5% of patients with stable disease, compared to 41% in another group of patients with exacerbations.\textsuperscript{26} Unfortunately, it is uncertain whether the higher isolation rate of organisms in the latter group represents an increase over their baseline carriage rate, which among patients with COPD is higher in those with more severe disease and in those who continue to smoke.\textsuperscript{25,31}

Addressing the issue of whether bacteria increase during exacerbations requires prospective studies that examine the bacteriology of the sputum in the \textit{same} cohort of patients during both remissions and exacerbations. One investigation of 23 patients with chronic bronchitis obtained sputum cultures routinely every 2 months and during exacerbations for 2 years. \textit{S pneumoniae}, \textit{H influenzae}, or both were present in 9% of 233 specimens during remissions, compared to 40% of 56 samples during exacerbations, a significant difference.\textsuperscript{34} Another investigation obtained sputum cultures at least every 2 weeks for 4 years in 25 patients with chronic bronchitis. \textit{H influenzae} was present in 60% of 1,267 cultures during remission, compared to 57% of 86 cultures during exacerbations; the corresponding rates for \textit{S pneumoniae} were 33% and 37%, respectively, an insignificant difference.\textsuperscript{4} In another study, 38 patients with chronic bronchitis had sputum cultures every 4 weeks and during exacerbations for 2 years. \textit{H influenzae} or \textit{S pneumoniae} grew in 22% of routine specimens, compared to 30% of 77 exacerbations, again an insignificant difference.\textsuperscript{5} One investigation examined \textit{H influenzae} and \textit{H parainfluenzae}, but not \textit{S pneumoniae}, in the sputum of 137 patients with COPD seen every 2 months and during acute respiratory illnesses.\textsuperscript{30} \textit{H influenzae} grew in 15.4% of patients during exacerbations, compared to 9.6% during remissions, a significant difference.

The second microbiological issue is whether the concentration of bacteria per milliliter of sputum increases during exacerbations in those chronically colonized with the organisms. To my knowledge, only one study has assessed this issue, finding no difference for \textit{H influenzae}. In samples growing \textit{S pneumoniae}, however, 79% had $>$ 10$^5$ bacteria/mL, compared to 64% during remissions, a significant difference.\textsuperscript{4} A related issue is whether the presence or increased density of these microbes correlates with the sputum purulence typically seen in exacerbations. In the studies examining this question, the results are inconsistent. One found a relationship between purulence and the presence of either \textit{S pneumoniae} or \textit{H influenzae},\textsuperscript{34} one described a correlation with \textit{S pneumoniae} but none for \textit{H influenzae},\textsuperscript{4} and two found no association for either.\textsuperscript{5,35}

**Immunologic Investigations**

**Serologic Studies**

Several studies have examined the immunologic response associated with exacerbations. One investigation employed a RBC agglutination technique with an antigen obtained from a fresh isolate of \textit{H influenzae}.\textsuperscript{36} Antibody titers did not rise during exacerbations, even when \textit{H influenzae} grew from the sputum. Another study employed a complement fixation test using a soluble antigen prepared from a single strain of unencapsulated \textit{H influenzae}.\textsuperscript{37} In a small group of patients with COPD studied during exacerbations, the titers did not rise. Using a complement fixation test with an antigen derived from a
freshly cultured strain of unencapsulated \textit{H influenzae}, an investigation of 74 patients with chronic bronchitis showed no change in antibody levels during exacerbations.\textsuperscript{38} Another study examined 73 patients with chronic bronchitis for 7 months, obtaining sputum cultures and sera at the beginning of each exacerbation and convalescent specimens 3 weeks later.\textsuperscript{39} Titters of IgM and IgG antibody using an indirect fluorescent antibody technique were determined against the potential pathogens isolated from each patient’s sputum; in those without either \textit{H influenzae} or \textit{H parainfluenzae}, the antigen was a single strain of unencapsulated \textit{H influenzae}. Among 43 patients, 56 exacerbations occurred. Various serologic changes occurred, but no consistent patterns emerged, and \textit{H influenzae} was absent from the sputum when most of the antibody changes developed, suggesting that the tests were nonspecific. Serum specimens examined for antibody against antigens obtained from sputum isolates of \textit{S pneumoniae} in 11 exacerbations showed four changes in titters. Unfortunately, no paired sera were obtained in patients during periods of quiescence to determine whether the serologic alterations observed were more frequent in exacerbations than in remissions.

Another investigation used indirect fluorescent antibodies against \textit{H influenzae}, employing as antigen an isolate of an unencapsulated organism from one of the patients.\textsuperscript{40} Paired sera were tested in 22 exacerbations, in 12 of which sputum cultures were positive for \textit{H influenzae}; only one significant rise in titer occurred. One study monitored 137 patients with COPD from 1968 to 1975, including complement fixation tests at bimonthly intervals using antigens from one strain each of unencapsulated \textit{H influenzae} and \textit{H parainfluenzae}.\textsuperscript{28} Among the 2,578 sera collected, fourfold or greater increases in titters to \textit{H influenzae} developed 76 times in 53 patients. About 60% of these serologic changes coincided with acute respiratory illnesses, often with evidence of preceding viral or \textit{M pneumoniae} infection. About 40% of the serologic changes, however, developed in the absence of any interim respiratory illness, indicating that asymptomatic rises in antibody titer to \textit{H influenzae} were common in this patient population. However, only 13 subjects (9.5%) had antibodies to \textit{H parainfluenzae}, titters were low, and no serologic increases developed, even though about 30 to 40% of patients had this organism in their sputum cultures throughout the study period.

In summary, the serologic tests show that antibody titers to pneumococci or \textit{H influenzae} do not change during most exacerbations, even when these organisms are present in the sputum. These negative studies do not exonerate these microbes as causes of exacerbations: for example, the bacterial infection may not have provoked a serologic response or the antigens used may not have been the critical ones. Positive findings, however, would have made the argument favoring a pathogenic role for these two organisms more persuasive.

\textbf{Vaccination Studies}

One small, prospective, double-blind study monitored the incidence of COPD exacerbations in 92 subjects who received a pneumococcal vaccine containing antigens of 14 serotypes and in 97 patients who received a placebo.\textsuperscript{41} Over a 2-year period, no difference emerged between the two groups in hospital admissions or emergency visits for exacerbations. Several randomized, double-blind placebo-controlled trials have assessed an oral vaccine containing \textsuperscript{11} killed organisms per tablet of an unencapsulated strain of \textit{H influenzae}. Subjects received two tablets daily for 3 consecutive days, with this regimen repeated at days 28 and 56. Unfortunately, two of the studies included patient groups that could not illuminate the value of the vaccine in chronic bronchitis in industrialized nations. One involved New Guinea Highlanders,\textsuperscript{42} whose respiratory disease, although labeled chronic bronchitis, differs from that seen in smokers in developed countries. They often reside in poorly ventilated houses with a single living area and a central unvented fireplace and have frequent episodes of pneumonia. Over the 12-month study, 22 cases of pneumonia occurred in the 62 participants, a very much higher incidence than in chronic bronchitis in industrialized nations. Nearly all the patients had \textit{H influenzae} isolated from their sputum during remission, also far in excess of its frequency in industrialized nations. Indeed, the description of their disease suggests that the participants may have had bronchiectasis rather than chronic bronchitis.

A second study, conducted in Australia, included both apparently healthy patients susceptible to recurrent episodes of acute bronchitis and patients with frequent exacerbations of chronic bronchitis (about 60% of the patients), without separately analyzing the results for these very different diseases.\textsuperscript{43} The vaccine did not reduce the frequency of exacerbations accompanied by purulent sputum, although fewer episodes of acute wheezing occurred. The heterogeneity of the population and the small numbers enrolled (only 37 patients) make the results impossible to interpret.

The earliest study of the vaccine included Australian patients with COPD followed over 3 months, and found a remarkable decrease in exacerbations with the vaccine: only 1 episode in 17 patients,
compared with 20 episodes in 32 patients taking placebo. Unfortunately, the microbiological data were incomplete. In the patients from whom such information was available, the development of exacerbations, however, did not clearly correlate with the carriage of *H influenzae*, as assessed by throat cultures (routine sputum cultures were not done). Furthermore, the two groups did not differ in the detection of salivary antibody to *H influenzae*. In another study from Australia, during the winter months, the vaccine was considerably less impressive. Among 64 patients with chronic bronchitis, no statistically significant decrease occurred in either the number of exacerbations among those receiving the vaccine or the rate of carriage of *H influenzae*. The number of patients developing exacerbations was significantly less in the vaccine group. The apparent benefit extended to those not colonized with *H influenzae*, however, suggesting that the effect, if genuine, was nonspecific and cannot help delineate the role of *H influenzae* in causing exacerbations. Unless a large, well-conducted trial with good microbiological data confirms a genuine benefit for the vaccine, its efficacy remains unclear. Most importantly, however, even if it proved efficacious, before the information could be used to support a role for *H influenzae* as a cause of exacerbations, it would be necessary to show that the benefit arose from an immunologic effect directly related to *H influenzae*, rather than a nonspecific immune stimulation that affects many organisms, possibly including viruses.

**Pathologic Investigations**

To determine the bronchial histology of exacerbations compared to baseline conditions, biopsy specimens obtained with fiberoptic bronchoscopy of a total of 24 subjects with stable chronic bronchitis were compared to those of 20 patients during an exacerbation. The most prominent inflammatory cells in the bronchial submucosa were lymphocytes, but their numbers changed little during exacerbations. The greatest difference was in eosinophils, which increased 30- to 37-fold. Neutrophils had a substantially less impressive change, increasing 2 to 3.7 times. No special stains were performed to detect bacteria. The histologic findings, however, are not those expected for tissue infection with bacteria like *H influenzae*, *S pneumoniae*, or *M catarrhalis*, which should provoke intense neutrophilic inflammation and markedly reduce the number of eosinophils. The expectorated sputum of these patients during exacerbations, when compared to stable disease, also showed an increase in the proportion of eosinophils, but not in neutrophils, again contrary to the expected change with a bacterial infection.

**Antibiotic Trials**

**Placebo-Controlled Studies**

An ideal study of antibiotic efficacy in exacerbations should be prospective, randomized, double-blind, and placebo-controlled. It should enroll numerous patients to ensure a representative population sample and to avoid missing an effect because of inadequate numbers of participants. Using chest radiographs, it should exempt patients with parenchymal opacities consistent with pneumonia, since the inclusion of participants with that infection would, of course, favor antibiotics. The trial should employ microbiological studies to help define the cause of the exacerbation and to permit scrutiny of the correlation between the identity of the organisms isolated and the clinical response to therapy. It should ensure that, aside from the trial medication, the patients' treatment should be one of the following: (1) all patients receive identical therapy; (2) patients have different baseline regimens, but either no other changes be made during the trial or the alterations be uniform throughout the subjects (eg, all participants increase their inhaled bronchodilators to specified doses and frequencies of administration); and (3) the study has a standardized approach to systemic corticosteroid therapy, since controlled trials demonstrate that it is effective in ameliorating exacerbations. The options for steroids are as follows: (1) everyone receives them in an identical regimen; (2) no one receives them; or (3) some receive them, in a uniform dose and duration, but these patients should be randomized and analyzed separately from those not given steroids. Since the patients' most common and significant complaint is dyspnea, the outcome criteria, assessed at several points during and after treatment, should include both subjective assessment of breathlessness, and objective measurements, such as a standard protocol to assess exercise tolerance. Other features to examine should include the following: (1) duration of the exacerbation as determined by the time that elapses before patients return to baseline symptoms and activities; (2) frequency of hospitalization; and (3) development of pneumonia. None of the 11 published randomized, double-blind, placebo-controlled trials satisfies all, or even most, of these criteria; consequently, they do not fully answer the question of the benefit for antibiotics in exacerbations.

Of these 11 studies, 8 show no statistically significant benefit for the recipients of antibiotic ther-
It is important to try to explain the reasons for the disparate results. One positive study, a pilot trial conducted in the 1960s among hospitalized patients with “severe” disease, ended prematurely after only 30 patients participated, because those in the placebo group did significantly worse than the antibiotic recipients.58 The details of the study are too sparse to allow any assessment of its quality or the validity of its conclusions. The same group published results from a second trial, which investigated 259 “moderately ill” hospitalized patients randomized to treatment with chloramphenicol, tetracycline, or placebo.22 The study included an undisclosed number of patients with radiographic pulmonary consolidation and fever. When assessed at day 7, patients receiving antibiotics had significantly better improvement in general condition as determined by their clinicians, a more rapid change in sputum from purulent to mucoid, and a higher success in abating fever and leukocytosis, but no difference in sputum quantity, improvement in peak flow rate, or change in Pco2. Patients receiving antibiotics had a higher rate of eradication of H influenzae and S pneumoniae, found in 31% and 17%, respectively, of the initial cultures from their sputum. The benefits were short-lived in the participants, however, for about 50% had purulent sputum again only 7 days after treatment ended, and about 60% had an exacerbation within the next 2 to 4 weeks. Several aspects of this study are disturbing. It included an unknown, but apparently small, number of patients with pneumonia. The rapid recurrence of sputum purulence is uncommon in most people with chronic bronchitis, who have only one to two exacerbations annually,60 suggesting that this group is unrepresentative or possibly contained patients with bronchiectasis. Although the authors stated that they excluded subjects with that disease, they did not divulge their criteria.

The most extensive study supporting antibiotics investigated 362 exacerbations in 173 Canadian outpatients.60 Exacerbations were defined by the presence of increased dyspnea, sputum volume, and sputum purulence, and were classified into three types: type 1 had all three features, type 2 had two features, while type 3 had one of the three features accompanied by another finding: sore throat or nasal discharge within the previous 5 days, otherwise unexplained fever, worsening wheezing, increased cough, or an increment of at least 20% in heart or respiratory rates. Success, defined as resolution of symptoms within 21 days of therapy, was 65% in the antibiotic recipients and 55% in the placebo group, a significant difference. Deterioration, defined as the need for hospitalization (which was infrequent63) or treatment with antibiotics in an unblinded fashion, occurred in 19% of the placebo recipients vs 10% in the antibiotic group, also a significant difference. When analyzed by subcategories, antibiotics conferred no advantage in type 3 exacerbations (which constituted about 18% of the attacks) and little benefit for type 2 (about 40% of the attacks); but in type 1 (about 40% of attacks), success was greater (63%) in the antibiotic group than in the placebo recipients (43%), although the authors provide no statistical analysis of this difference. Peak flow rates increased significantly faster in antibiotic recipients, but the maximum difference between the two groups, whose average value was approximately 200 L/min, was only about 10 L/min (5%). This was an admirable study, but it has several deficiencies. Pneumonia was not excluded by radiographic studies, even though nearly 30% of patients were febrile. Sputum microbiology was not reported, and no stratification was made for systemic corticosteroid administration, which occurred in about 40% of patients, but in no standard regimen. In those receiving corticosteroids, however, antibiotics provided no statistically significant improvement in success rate when compared to placebo.

A major problem with the eight studies that show no significant benefit for antibiotic therapy is the small number of subjects: only one study61 had > 100 participants. That investigation randomized 278 patients to placebo treatment or amoxicillin for 7 days, with exacerbations defined as subjective worsening of at least 3 days due to change in sputum volume, viscosity, or color, possibly accompanied by cough or dyspnea. No significant difference emerged between the two groups in symptoms, peak flow rate, or the doctors’ overall evaluation of the patients’ health. The incidence of diarrhea, however, was significantly greater in the amoxicillin group. This study differs from the Canadian trial60 in several respects: entry criteria, definition of exacerbations, time of outcome evaluation (day 8 vs day 21), criteria used for assessing improvement, and severity of illness, which may have been less than in the Canadian study, as indicated by a higher average peak flow rate. This investigation, however, eliminated two weaknesses of the other trial by excluding patients with pneumonia and those receiving systemic corticosteroids.

Several prospective, double-blind, controlled studies have demonstrated that systemic corticosteroids relieve the symptoms of exacerbations more rapidly than placebo.56–58 Since these trials prescribed antibiotics for the participants in both arms of the investigations, they did not assess the independent effect of antimicrobial therapy in those receiving corticosteroids. Another study, however, did examine this issue.62 Among 71 patients with exacerbations,
defined as increased dyspnea with or without sputum production, all received oral corticosteroids and were randomly given placebo, amoxicillin, or sulfamethoxazole-trimethoprim. No difference emerged among the three groups in the rapidity of resolution of the exacerbation. Weaknesses of the study, however, are the small number of participants, the inclusion of 10 patients with asthma, and the mild disease and short smoking history (average, 16 pack-years) in those with chronic bronchitis.

One approach for assessing the conflicting findings among the studies is to perform a meta-analysis. Such an effort found that six of the published trials, including two of the three trials supporting antibiotic use, had peak expiratory flow rate (PEFR) as an outcome criterion. Analyzing the combined results, the authors found that those receiving antibiotics had a 10.75 L/min greater improvement in PEFR. Since the average PEFR in patients before treatment was about 200 L/min, this finding represents a 5% difference, the same as seen in the Canadian study. Interpreting these findings requires an understanding of the limitations of the test and the clinical significance of changes in it. The PEFR varies during the day, especially in asthma and COPD, meaning that the examinations need to be done at the same time of the day when comparing changes over time. More importantly, the test is effort dependent, and has a coefficient of variation of $\geq 10\%$. This finding means that the results of the test, whether performed at the same session or over several days to weeks, vary $\geq 10\%$ in asymptomatic people, smokers or not. The 5% difference seen in the Canadian study and the meta-analysis, therefore, could easily be attributed to the expected variation in testing, rather than a genuine change due to antibiotic therapy. Most importantly, clinicians familiar with using the PEFR to assess patients realize that a difference so slight as 10 L/min in people whose average PEFR is 200 L/min simply does not produce either symptomatic or objective improvement in dyspnea or exercise tolerance.

**Trials Comparing Antibiotics**

Studies comparing one antibiotic to another in treating COPD exacerbations cannot determine whether prescribing these agents is better than withholding them. Such trials could indirectly support the use of antimicrobials, however, if they showed that those with activity against certain organisms were clearly more effective than those lacking it, or if the clinical efficacy of the antimicrobial agents consistently correlated with the susceptibility of the bacteria isolated.

A plethora of such studies exists. Unfortunately, they generally suffer from such debilitating deficiencies that they are nearly uninterpretable, as a review of some relatively recent, but representative, trials reveals. They typically define the cause of an exacerbation by the presence, in any amount, of a potential “pathogen” in sputum cultures, rather than demanding that it achieve a certain concentration or predominance as assessed by quantitative (eg, colonies per milliliter of sputum) or semiquantitative (eg, heavy, medium, or light growth) criteria. Accordingly, a bacterium could be considered the “cause” of an exacerbation even if only a single colony of it grew. Secondly, these studies include as potential “pathogens” a wide variety of bacteria, including enteric Gram-negative bacilli, whose capacity to cause purulent sputum in the absence of pneumonia is unknown. Third, they usually allow participation of patients who have recently taken antibiotics (the typical criteria exclude antimicrobial use only in the preceding 2 to 7 days rather than a longer period, and some fail to specify any exclusion at all for recent antibiotics), meaning that the organisms isolated could be colonizing, nonpathogenic bacteria recently acquired because prior therapy had eradicated the flora previously present in the respiratory tract. Fourth, the studies almost never ensure that the patients in the groups being compared receive identical treatment (other than the antibiotics being tested), such as bronchodilators, corticosteroids, and theophylline. Fifth, the outcome criteria are variable, and the studies often evaluate subjects several weeks after therapy has ended. Since, as the placebo-controlled trials indicate, most exacerbations are short-lived and self-limited or, at least, respond to treatment other than antibiotics, a late assessment usually guarantees a high clinical response to all interventions. Since the purpose of many of these trials, predominantly sponsored by pharmaceutical companies, is to demonstrate that a new product is equivalent to an older one that had previously received approval for treating exacerbations, this timing of the evaluation virtually ensures success.

The outcome measures typically include both a clinical assessment, often with ill-defined or unstated criteria, and a repeat sputum culture to determine whether the putative pathogens remain. One finding in some of these studies that undermines the role of bacteria in causing exacerbations is the discrepancy between clinical and microbiological response. The bacteria purportedly causing the episodes often remain present in the sputum despite clinical improvement. In one study, for example, the clinical success for both ciprofloxacin and sulfamethoxazole-trimethoprim recipients was 96% at day 14, while the bacterial eradication rate was only 87% and 84%, respectively. Similarly, the antimicrobial suscepti-
bility may correlate poorly with the clinical outcome. In one trial, clinical success was 92% for both levofloxacin and cefaclor, microbial eradication rates were 94% and 87%, respectively, but 23% of the isolates were resistant to cefaclor, compared to 1.9% to levofloxacin. In another investigation, the clinical response to both grepafloxacin and amoxicillin was 85%, but 98% of the pathogens in the grepafloxacin group were sensitive to that agent, while only 69% of the isolates from the amoxicillin-treated patients were susceptible to that antibiotic. Even though some have argued that clinicians should use antimicrobials effective against β-lactamase-producing *H influenzae* or *M catarrhalis* for exacerbations, this and another study fail to demonstrate any superiority of quinolones to amoxicillin. The numerous problems with these studies make any results difficult to assess, but the discrepancies between clinical outcome and microbiological findings certainly vitiate the concept that the bacterial isolates caused the exacerbations.

**Conclusion**

Assessing the available studies with the criteria delineated earlier fails to provide compelling evidence that bacteria cause COPD exacerbations:

**Microbiological Studies on Frequency of Isolating Putative Pathogens**

Careful investigations find potential bacterial pathogens in only about 50% of exacerbations, even with attacks severe enough to require hospitalization. Three of the four prospective studies following a cohort of patients demonstrate either no increase in the number of subjects with these organisms during exacerbations or just a slight increment that, even if valid, could explain only a small fraction of attacks.

**Microbiological Studies Evaluating the Density of Bacteria**

The concentration of *H influenzae* per milliliter of sputum does not change during exacerbations, while the observed increase in *S pneumoniae* could account for only a few percent of exacerbations. Sputum purulence does not consistently correlate with the presence or density of the putative pathogens.

**Serologic Studies**

The lack of standardized serologic tests for assessing an immunologic response to *H influenzae* hampers studies investigating the role of this organism in exacerbations. Some reports reveal no serologic change with exacerbations, and in the two reports that do, the specificity of this finding is dubious, since in one report, *H influenzae* was often absent from the patients' sputum cultures at the time of the exacerbations, and in the other, antibody changes were nearly as frequent in patients during remissions. Thus, the serologic tests fail to provide convincing evidence of an immunologic response to *H influenzae* during exacerbations that would strongly incriminate it as a cause. The single study examining *H parainfluenzae* showed that few patients had detectable antibody to the organism at all, and, in them, rises during exacerbations did not occur. The sole investigation evaluating *S pneumoniae* was inconclusive.

**Vaccine Studies**

The single, albeit small, trial of pneumococcal vaccine showed no benefit in decreasing exacerbations. The studies of oral *H influenzae* vaccine have several defects, yield discrepant results, and, even in those studies that suggest some efficacy, do not show convincingly that the benefit derives from a specific immunologic response to the organism that could implicate it as a cause of exacerbations.

**Histologic Findings**

Neither bronchial biopsy specimens nor sputum cytology results display the expected findings of bacterial infections, a major increase in neutrophils; instead, they reveal a rise in eosinophils, which ordinarily markedly diminish in bacterial infections.

**Randomized, Placebo-Controlled Studies**

These trials of antibiotic therapy for COPD exacerbations have several weaknesses and do not definitively demonstrate whether antimicrobials are useful. The best investigation supporting antibiotics suggests that, at most, only 40% of exacerbations might benefit, and even in those the results are not dramatic. Although it did not separately randomize patients with corticosteroid use, *post hoc* analysis of this group showed no advantage to antimicrobials in those receiving corticosteroids, a point supported by another study. The largest study, which had few defects but included many patients with mild exacerbations, showed no benefit for antibiotic therapy. A meta-analysis of the trials demonstrated a clinically unimportant improvement in patients receiving antibiotics.

**Studies Comparing One Antibiotic to Another**

These trials have such severe deficiencies that any interpretation of the results is hazardous. Some,
however, show disparities between the clinical and microbiological outcomes that make the role of the cultured bacteria dubious.

None of these points, singly or in aggregate, definitively disproves the concept that bacteria cause, or that antibiotic therapy benefits exacerbations. Resolving this issue would require new randomized, double-blind, placebo-controlled antimicrobial trials that employ detailed microbiological studies, provide contemporary therapy with systemic corticosteroids and bronchodilators, and stratify patients according to the severity of both their underlying disease and their exacerbations. Such investigations are certainly warranted. In the meantime, a thoughtful decision about whether to use antibiotics must rest on the available information. Certainly, both large trials\(^{60,62}\) agree that antimicrobial agents are not helpful in mild attacks. For more severe episodes, patients should clearly receive systemic corticosteroids\(^{50-53}\); a reasonable interpretation of the data is that, with such therapy, antibiotics provide no additional benefit.\(^{60,62}\)

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