Pathogen-directed Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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Acute exacerbations of chronic obstructive pulmonary disease (COPD) are important events in the natural history of this chronic lung disorder. These events can be caused by a large number of infectious and noninfectious agents and are associated with an increased local and systemic inflammatory response. Their frequency and severity have been linked to progressive deterioration in lung function and health status. Infectious pathogens ranging from viral to atypical and typical bacteria have been implicated in the majority of episodes. Most therapeutic regimens to date have emphasized broad, nonspecific approaches to bronchoconstriction and pulmonary inflammation. Increasingly, therapy that targets specific etiologic pathogens has been advocated. These include clinical and laboratory-based methods to identify bacterial infections. Further additional investigation has suggested specific pathogens within this broad class. As specific antiviral therapies become available, better diagnostic approaches to identify specific pathogens will be required. Furthermore, prophylactic therapy for at-risk individuals during high-risk times may become a standard therapeutic approach. As such, the future will likely include aggressive diagnostic algorithms based on the combination of clinical syndromes and rapid laboratory modalities to identify specific causative bacteria or viruses.

Keywords: chronic obstructive pulmonary disease; acute exacerbations; virus; bacteria; therapy

It has been estimated that approximately 6% of the United States adult population has chronic obstructive pulmonary disease (COPD) (1), whereas the prevalence of chronic bronchitis has been estimated at 3.2% (2). Acute exacerbations of disease (AE-COPDs) in these patients account for about 13 million office visits each year (3, 4). Although the topic remains controversial (5), a generally accepted definition of an AE-COPD is "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD" (6). Exclusion of alternate diagnoses, including congestive heart failure, pneumothorax, and pulmonary emboli, among others, has been considered important (3, 7, 8).

The frequency and severity of exacerbations are quite variable among patients with COPD (9). This variability, in part, reflects the nature of data collection (prospective vs. retrospective), disease severity, medications administered, vaccinations, and smoking status of the population studied (9). Reports that define AE-COPD by use of daily diary cards tend to identify more episodes per year (10, 11). Similarly, studies that include

patients with more severely impaired pulmonary function find a greater number of yearly episodes (12).

Numerous groups have documented the negative effects of AE-COPDs, particularly on health-related quality of life (HRQL) (13, 14). Cross-sectional studies have reported reduced HRQL during an AE-COPD, whereas longitudinal studies have documented that HRQL improves from exacerbation to recovery (13). The greatest improvement in HRQL after a single episode occurs during the first 4 weeks, although HRQL continues to improve over 26 weeks; a recurrence of an AE-COPD results in markedly attenuated improvement (15). A 2-year prospective, longitudinal study of 336 patients with severe COPD confirmed that more frequent exacerbations had a deleterious effect on health status (16).

AE-COPD episodes result in measurable acute deteriorations on pulmonary function (10, 17, 18). Longitudinal effects of repeated AE-COPDs have also been reported. Among continuing smokers, lower respiratory tract infections (LRTIs) have been associated with additional decline in lung function, averaging an additional decline of 7 ml/year in FEV₁ for every one LRTI per year (19). Two separate groups reported decreased lung function in patients with frequent exacerbations compared with those with infrequent exacerbations (20, 21). These data indicate that there are measurable negative short- and long-term impacts on pulmonary function in AE-COPDs.

AE-COPDs are also major source of health care expenditure (22); they were estimated to result in a total treatment cost of \$1.2 billion in patients 65 years and older and \$419 million in those younger than 65 years in the United States in 1995 (4). A prospective Spanish study of 2,414 patients with COPD identified after an acute exacerbation noted that 507 patients (21%) relapsed after therapy (23). Of these, 161 patients required emergency department treatment with 84 requiring hospitalization; these latter patients accounted for 58% of the total cost. Thus, AE-COPD episodes, particularly those that require hospitalization, result in major health care expenditures. Given the totality of these data, it has become increasingly evident that appropriate management of AE-COPDs is of paramount importance.

PATHOGENESIS

An augmented inflammatory response has been shown to be a central event in an AE-COPD (24). Multiple stimuli can acutely increase airway and parenchymal inflammation, leading to increased bronchial tone, bronchial wall edema, and mucous hypersecretion (25). The methodologic approaches to examining the inflammatory response have included sputum analyses, bronchoalveolar lavage, bronchial biopsy, and blood markers. The most robust evidence of an augmented inflammatory response comes from analysis of sputum. Neutrophilic and eosinophilic inflammation has been described. Similarly, a multitude of inflammatory mediators have been implicated. In an elegant prospective study, Fujimoto and colleagues followed 68 patients with emphysematous COPD for 2 to 3 years; 30 patients developed an acute exacerbation and expectorated sputum adequate for analysis (26). During an acute exacerbation total sputum cells,

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lymphocytes, neutrophils, eosinophils, IL-8, neutrophil elastase, eosinophilic cationic protein, and CCL5/RANTES increased compared with the stable state. This inflammatory response is associated with an increased oxidative stress (27, 28).

Bronchoscopic data are more limited, with some investigators confirming increased expression of CCL5/RANTES in both the surface epithelium and subepithelial mononuclear cells during an acute exacerbation of chronic bronchitis (29). Subsequent studies confirmed increased numbers of neutrophils in AE-COPDs, as well as increases in CXCL5 (ENA-87), CXCL8 (IL-8), and CXCR2 (28, 30). These data confirm an inflammatory process involving both neutrophils and eosinophils with an additional imbalance in oxidant status during exacerbations.

A systemic inflammatory response during an AE-COPD has been noted with increases in plasma fibrinogen, IL-6, C-reactive protein (CRP), and endothelin-1, all reported to increase during exacerbations (31–34). Interestingly, one group has confirmed that the degree of systemic inflammation, shown by rising serum IL-6 and CRP levels, correlated with sputum and nasal inflammation (35). In a separate report, only CRP seemed to exhibit reasonable diagnostic accuracy for an AE-COPD, particularly when combined with increased dyspnea, sputum volume, or purulence (34). These data support that the majority of exacerbations are associated with an intensified inflammatory response. The relationship of specific etiologies and the nature of the inflammatory response is a source of intense investigation.

ETIOLOGY

AE-COPDs appear to be triggered by a variety of infectious and noninfectious stimuli. Numerous environmental pollutants can provoke an inflammatory response in patients with COPD (36–38). Importantly, epidemiologic studies have confirmed increased respiratory symptoms and mortality during times of increased air pollution (39–41). Nevertheless, most AE-COPDs are believed to be related to infection, either viral or bacterial (25).

Viruses

Clinical data confirming an important role for viral infection are quite robust (42, 43). Recent studies using advanced methodology have implicated numerous viral pathogens (44). Greenberg documented that 27% of exacerbations in 62 prospectively followed patients with COPD were related to a viral etiology (45); picornaviruses, parainfluenza virus, and coronaviruses accounted for the majority of infections in this study. Other investigators have suggested that up to 60% of exacerbations have been associated with viral infections, including picornaviruses, respiratory syncytial virus (RSV), influenza, and human metapneumoviruses (46–51). One prospective study of hospitalized patients with AE-COPDs found a viral pathogen in more

than 48% of episodes (vs. 6.25% in the stable state), with a similar distribution of viral pathogens as previously noted (52). The most compelling data confirming a role for viruses in the genesis of an AE-COPD come from the experimental model of human rhinovirus (HRV) infection recently published by Mallia and colleagues (53). These investigators administered low doses of rhinovirus 16 (RV16) to four subjects with moderate COPD; all developed symptomatic colds with the lowest dose of virus challenge. Figure 1 illustrates that upper tract symptoms preceded lower tract symptoms by several days. In addition, there were reductions in peak flow and FEV₁ in relation with lower tract symptoms. These data clearly confirm that rhinovirus can precipitate typical symptoms of an AE-COPD; the lag between upper and lower tract symptoms suggests an opportunity for intervention.

Importantly, viral infections have been suggested to augment the inflammatory response in COPD (54). Rhinovirus infection of the bronchial epithelium induces expression of numerous pro-inflammatory genes (55–58). Induction of nuclear factor (NF)- κ B and other transcription factors has been clearly demonstrated with several viruses including HRV, RSV, and influenza (59–64). Rhinovirus and RSV infection of bronchial epithelial cell lines results in the production of eotaxin, eotaxin-2, and RANTES (65, 66). Clinically, the role of RSV infection in COPD has become better defined, with several groups demonstrating that the inflammatory process is augmented in the presence of such infection (67, 68). One of these groups has suggested that persistence of infection may be particularly important in progression of the underlying obstructive process (67), although this remains controversial (69). It is evident that viral infection could account for the inflammatory response previously described as typical of an AE-COPD. In fact, a longitudinal study suggested that virus-associated exacerbations were associated with higher systemic inflammatory marker levels (46).

Bacteria

The role of bacterial infection in individual AE-COPD episodes has been a subject of much controversy (44). Recent comprehensive reviews of this topic suggest that much of this controversy may reflect evolving diagnostic methods (25, 70). These methods have included sputum culture, bronchoscopic sampling, molecular epidemiologic studies of bacterial pathogens, identification of an immune response, and recording a response to antimicrobial therapy. Sputum cultures have been the classic approach to identifying potentially pathogenic bacteria in AE-COPD; the organisms most frequently isolated are nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* (44). However, the relationship between identification of these potentially pathogenic organisms and an etiologic diagnosis in AE-COPD has been questioned (71, 72). Unfortunately, sputum cultures have important limitations—for

Figure 1. Upper (URT) and lower respiratory tract (LRT) symptoms of patients with chronic obstructive pulmonary disease *in vivo* experimentally infected with rhinovirus. A 3- to 4-day gap between the peak of cold symptoms and the peak of lower respiratory symptoms was documented. Reproduced by permission from Reference 54.

example, seriously underestimating colonization with nontypeable *H. influenzae* in comparison to polymerase chain reaction (PCR)-based detection (73).

Bronchoscopically collected samples have confirmed that potentially pathogenic microorganisms are identified in many patients with COPD at baseline and during AE-COPDs (74–78). A recent review pooled data from six published studies suggesting that there was a clear shift to organisms with a higher pathogenic potential (79). A bronchoscopic study has confirmed that patients with COPD colonized with potentially pathogenic bacteria exhibit increased neutrophil counts, IL-8, matrix metalloproteinase-9, and endotoxin (80).

Recent longitudinal cohort studies, using analyses of surface antigen diversity, have demonstrated that acquisition of a bacterial strain with which the patient had not been previously infected was associated with a greater than twofold increase in exacerbation risk (81, 82). Interestingly, new *H. influenzae* strains associated with symptomatic exacerbations resulted in increased neutrophil recruitment in a mouse model of airway bacterial infection as well as greater adherence to epithelial cells and induction of IL-8 release than strains not associated with such a clinical response (82). Similar data have been published regarding *M. catarrhalis* (83). Further support for the importance of bacterial infection in the etiology of AE-COPD comes from recent studies that confirmed a systemic immune response to homologous strains of *H. influenzae* and *M. catarrhalis* isolated simultaneously from sputum of patients during evaluation at time of stability and with symptomatic exacerbations (25, 84–86). Taken together, these data strongly support a pathogenic role for bacterial pathogens in many AE-COPD episodes (70).

Atypical infectious agents, including *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella* species, have also been reported to cause AE-COPD. Based on IgG and IgM antibody titers, *C. pneumoniae* has been reported as an etiologic factor in 4 to 34% of AE-COPDs (87–91). Disparities in reported rates likely relate to differences in serologic methods used to identify *C. pneumoniae* infection and in the prevalence of infection reported in patients with stable COPD disease (92). By contrast, *M. pneumoniae* has been identified in only a minority (<1–14%) of AE-COPDs (71, 89, 93, 94).

A biological interaction between respiratory viruses and bacterial pathogens has been well described. Infection with RSV, human parainfluenza virus, or influenza virus increases bacterial adhesion to epithelial cell lines (95). A similar process has been noted with rhinovirus infection (96). The clinical impact of such interaction has been prospectively examined in 39 patients with COPD during 56 exacerbations; those with both HRV and *H. influenzae* infection exhibited higher bacterial load and serum IL-6 (97). Bandi and colleagues extended these findings by identifying AE-COPDs caused by *H. influenzae* and noting that an acute viral infection was seen in 45.7% of the events (98). The recent prospective study of Papi and colleagues provides important insight (52). Independent of bacterial versus viral infection, sputum neutrophils were increased in AE-COPD compared with baseline, whereas eosinophilic inflammation was seen in patients with viral or mixed viral/bacterial infection. It is evident that the etiology of AE-COPDs likely influences the type and magnitude of the inflammatory response that results.

THERAPEUTIC APPROACHES

General

Optimal therapy for an AE-COPD is multidisciplinary. Inhaled β -agonists and anticholinergic agents have been documented to decrease obstruction during an AE-COPD. Importantly, system-

atic reviews have suggested that both short-acting β -agonists and anticholinergic inhaled bronchodilators have comparable effects on spirometry and a greater effect than parenterally administered bronchodilators (99). Although the combination of an anticholinergic and a β -agonist has the potential for increased therapeutic benefit, studies combining agents from these classes have yielded varying results; on average, these results do not support the routine use of multiple agents for AE-COPDs (99).

The use of systemic corticosteroids for AE-COPD has been studied by numerous investigators (100). A systematic review suggested that systemic steroids result in physiologic improvement over the first 72 hours and reduced the odds of a treatment failure over the subsequent 30 days, although the risk of adverse drug reaction was increased (101). The largest study evaluated 271 patients from 25 Veterans Affairs medical centers (102). Patients were randomized to placebo or one of two steroid treatment arms (Solumedrol 125 mg/d for 3 d followed by either a 15-d or 8-wk taper). Both corticosteroid groups were associated with a faster improvement in FEV₁, a lower number of treatment failures, and a shorter length of hospital stay. Patients in the corticosteroid groups were also more likely to experience complications of treatment; hyperglycemia was the most common.

Subsequently, a separate investigative group randomized patients hospitalized with an AE-COPD to methylprednisolone, 0.5 mg/kg every 6 hours for 3 days followed by either no further steroids or a taper completed on Day 10 (103). Patients treated with a longer course of corticosteroids experienced a greater improvement in FEV₁. A separate study randomized 56 patients admitted with an AE-COPD to a smaller dose of prednisone (30 mg daily for 14 d) versus placebo (104). Patients treated with prednisone had a faster and greater improvement in FEV₁. The median length of stay was also shorter in the steroid-treated group. In a study of 27 outpatients with an AE-COPD, Thompson and colleagues randomized patients to treatment with 9 days of prednisone (60 mg for 3 d, 40 mg for 3 d, and 20 mg for 3 d) or placebo (105). Patients treated with prednisone exhibited a faster and greater improvement in oxygenation and FEV₁, while experiencing fewer treatment failures (0 vs. 57%, $P = 0.002$). An emergency room-based study randomized 147 of 202 eligible patients to prednisone (40 mg daily for 10 d) versus placebo; all patients received an oral antimicrobial agent and inhaled bronchodilators (106). Patients treated with prednisone experienced a reduced rate of relapse at 30 days, as well as a prolonged time to relapse, improved dyspnea, and improved pulmonary function. Recent comprehensive reviews of these data suggest that systemic steroids be used in all AE-COPD patients requiring hospitalization and in those outpatients with “appreciably worse” dyspnea (100, 107).

Pathogen-specific Therapy

Given the role of infectious pathogens in the genesis of many AE-COPD episodes, pathogen-specific therapy would be ideal. Novel approaches are under active investigation to optimize such a focused approach to therapy.

Antibacterial. Because bacterial infection may be causative in approximately 50% of AE-COPDs, it is not surprising that antimicrobial therapy has been intensively studied in this disease. Numerous placebo-controlled trials of antibiotics in AE-COPDs have been published, with systematic reviews of these trials suggesting a beneficial treatment effect (108–110). Figure 2 illustrates the effect of antimicrobial therapy on short-term mortality (Figure 2A) and treatment failure (Figure 2B) (109). A significant benefit to antimicrobial therapy was suggested. The beneficial effect on reducing treatment failure appears to be better in studies including more severe AE-COPDs (Figure 3) (110). Unfortunately, there has been significant heterogeneity in

A

Review : Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison : 01 Antibiotics versus placebo

Outcome : 01 Mortality (short-term) during study intervention

B

Review : Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison : 01 Antibiotics versus placebo

Outcome : 02 Treatment failure (no resolution or deterioration of symptoms after trial medication of any duration or death)

Figure 2. (A) Effect of antibiotics versus placebo on short-term mortality. (B) Effect of antibiotics versus placebo on treatment failure, defined as no resolution or deterioration of symptoms after trial medication of any duration or death. CI, confidence interval. Reprinted by permission from Reference 109.

the results of the individual studies, with none designed in an optimal fashion (44). Ongoing studies will provide additional data to refine recommendations for antimicrobial therapy, although most international guidelines have interpreted these data to suggest that antimicrobial agents provide additional benefit in selected patients (111).

The role of specific agents remains unclear, with limited data available to allow robust conclusions. Most recent antibiotic trials in AE-COPD have been comparative studies performed to demonstrate equivalence of newer antibiotics with established ones. These studies have generally been designed as noninferiority trials for registration purposes. As such, these studies provide limited information regarding clinical response for various antimicrobial classes. In addition, these studies have involved a wide variety of study designs with response assessed well after therapy

was completed, which limits the ability to interpret differences in efficacy between antimicrobial classes. A recent systematic review of 19 of these trials suggests equivalent clinical outcomes in randomized studies comparing quinolones, macrolides, and amoxicillin-clavulonate tested against each other (112). Interestingly, in microbiologically evaluable patients, macrolides performed worse than quinolones (112).

Recently, studies have been designed that test novel end-points. Some investigators have suggested that a more rapid resolution of symptoms may be seen with quinolones in contrast to comparators (113, 114). Antimicrobial therapy does not necessarily result in complete eradication of the pathogen, a process that has been associated with a persistent inflammatory response (115). As such, antimicrobials that decrease the bacterial load in the lower airways should result in greater symptomatic

Figure 3. Forest plot showing nine studies grouped according to severity of exacerbation. The upper five studies included patients with mild to moderate exacerbations and the four studies below included patients with severe exacerbations. The x axis represents the odds ratio for treatment failure. Reprinted by permission from Reference 110.

resolution and improve the time between exacerbations, the disease free interval (DFI) (116, 117). More recent AE-COPD clinical trials have assessed how different antibiotics affect the DFI (117). Although the data are somewhat conflicting, quinolones seem to be associated with a longer DFI (112, 117). Additional data are required to better establish this novel endpoint as a primary basis for future comparative studies.

Antiviral. Given the important role of viruses, particularly rhinovirus and influenza, in AE-COPDs, it is important to review the potential specific antiviral therapies that are available. Recently, a large number of approaches have been taken, particularly to rhinovirus, which include targeting viral cell susceptibility, viral attachment and receptor blockade, viral uncoating, viral RNA replication, and viral protein synthesis (Table 1) (118, 119). Interferons have protean effects that are mediated through cell receptor signal transduction pathways. Intranasal interferon

TABLE 1. THERAPEUTIC APPROACHES TO RHINOVIRUS INFECTION

Targets	Compounds
Cell susceptibility	Interferons
Viral attachment/binding	Monoclonal antibodies to cellular ICAM-1 Tremacamra (soluble ICAM-1)
RNA inhibition/viral replication	Enviroxime
Viral protein synthesis inhibitors	3C protease inhibitors AG7088
Viral uncoating/capsid function	Capsid-function inhibitors (pleconaril, R61837, pirodavis, SCH48973, SDZ35-682, chalcone compounds)

Definition of abbreviations: ICAM-1=intercellular adhesion molecule 1.
Adapted from References 118 and 119.

alpha 2b has been demonstrated to be effective in both experimental and natural colds when provided prophylactically; it has little effect on the development of infection or symptoms when administered after infection (119). In addition, the presence of numerous local side effects, including nasal mucosal bleeding, has limited its clinical utility. Because 90% of HRV serotypes use the intercellular adhesion molecule 1 (ICAM-1) receptor for attachment to cells, preventing binding to this receptor has been explored therapeutically (119). Tremacamra, a soluble ICAM-1, was studied in a series of double-blinded studies where the agent was administered as a nasal spray solution or inhaled powder (120). It reduced the severity of experimental colds when administered less than 12 hours after HRV challenge. Dosing six times daily and its poor tolerability limited clinical development.

The most promising of the agents developed to date have targeted the HRV capsid. Numerous agents from diverse molecular classes exhibit antiviral activity by preventing viral attachment and/or uncoating. The agent that came furthest in clinical development was pleconaril. In two large phase II, placebo-controlled, natural cold trials, pleconaril was demonstrated to reduce the time to alleviation of illness in patients with an onset of a typical cold within 36 hours of respiratory symptoms during the months between July and December; this clinical response was noted in subjects who were HRV positive (121). Furthermore, subsequent analyses confirmed that clinical response to pleconaril was limited to those infected with pleconaril-sensitive HRV strains (122). Induction of reduced pleconaril susceptibility in HRV isolates was seen in greater than 10% of patients, although the clinical course of illness in these subjects was less protracted than in the overall group. A subsequent 6-week prophylaxis study documented that pleconaril induced CYP3A4, which led to intermenstrual bleeding

and related menstrual abnormalities in women taking estrogen-based oral contraceptives (121, 123). In March 2002, a U.S. Food and Drug Administration Antiviral Drugs Advisory Committee voted to not recommend pleconaril approval based on these drug interactions and possible transmission of resistance isolates. Given the potential advantage of pleconaril treatment in patients with underlying lung disease, a nasal preparation is currently under development. The ability of this agent to decrease disease duration in conjunction with the data suggesting a delayed onset of lower respiratory tract symptoms following upper tract symptoms after experimental HRV infection suggests that pleconaril may be promising in patients with COPD as a prophylactic agent.

The HRV 3C protease is an enzyme responsible for post-translational cleavage of viral precursor polyproteins (124). Several different compounds have been developed targeting this enzyme. Ruprintivir is an agent that has been developed as a nasal spray. In experimentally induced HRV colds in healthy volunteers, it was able to moderate disease severity and reduce viral load (125). Unfortunately, a subsequent natural infection study was not able to reproduce these findings (126).

Influenza has major repercussions in patients with underlying lung disease (127). A number of agents with activity against this pathogen are licensed for use. Inhibitors of M2, a membrane protein in influenza A, are available for clinical use (amantidine and rimantidine). They reduce duration of fever and symptoms in patients by approximately 24 hours. Their high incidence of side effects in elderly patients and the rapid development of resistance during treatment have limited their use (127). Neuraminidase inhibitors, zanamivir and oseltamivir, are also available for clinical use. Clinical trials have confirmed that these agents reduce symptoms and speed disease resolution (128). Data in patients with chronic lung disease have confirmed these findings. Murphy and colleagues reported a randomized, placebo-controlled study of zanamivir in 525 patients 12 years or older with asthma or COPD (~21–24% with asthma/COPD or COPD alone) (129). Zanamivir reduced the median time to alleviation of symptoms (5.5 vs. 7.0 d; difference, 1.5 d; 95% confidence interval, 0.5–3.25; $P = 0.009$), overall symptom scores, nights of sleep disturbance, and total incidence of complications. No adverse effect on pulmonary function was noted. A retrospective analysis of high-risk patients (COPD, asthma, cardiovascular disease, age ≥ 65) in several zanamivir, placebo-controlled trials confirmed a 2.5-day reduction in median time to alleviation of clinical symptoms and a 3-day reduction in time to return to normal activities (130). A similar analysis in 10 placebo-controlled studies of oseltamivir has been reported (131). In at-risk patients (age ≥ 65 , COPD/asthma, or cardiovascular disease), oseltamivir reduced antibiotic use by 34% and hospitalizations by 50% in influenza-infected patients. These data confirm that neuraminidase inhibitors can be beneficial in patients with chronic respiratory disease who are infected with influenza and present within 36 hours of the onset of symptoms.

The therapy for RSV is largely supportive, although aerosolized ribavirin has been licensed for use in infants (69). This agent is a guanosine analog with broad antiviral properties (69). Experience with this agent in adults is limited, although it has been administered safely to elderly patients (132). Several other anti-RSV agents interfere with RNA, and small-molecule fusion inhibitors are under active development (69). As better therapeutic options become available, it will likely become feasible to give high-risk individuals prophylactic agents during at-risk times to prevent AE-COPDs.

Pathogen-directed approaches. Given the various etiologies for AE-COPDs, clinical guidelines have struggled with the optimal approach to treating specific etiologies, whether bacte-

rial or viral. The majority of recent international guidelines have provided recommendations on which patients with an AE-COPD are more likely to have bacterial infection and are, therefore, more likely to benefit from an antimicrobial agent. Most have heavily relied on the sentinel study of Anthonisen and colleagues (133). These investigators randomized 173 patients during 362 episodes of AE-COPDs to an antibiotic (trimethoprim-sulfamethoxazole, amoxicillin, or doxycycline), stratifying the results based on the number of symptoms at presentation (133). Patients with at least two cardinal symptoms (increase in dyspnea, increase in sputum production, and/or change in sputum color) experienced a benefit with antibiotic therapy. Importantly, recent data using bronchoscopic sampling in hospitalized patients stratified by the Anthonisen criteria confirmed a greater likelihood of bacterial infection in patients with multisymptom AE-COPDs (134). Thus, antibiotic therapy is more likely to be advantageous in patients with AE-COPDs suffering from multiple symptoms.

An exacerbation associated with sputum purulence has been suggested to be more likely to benefit from antibiotic treatment. Stockley and colleagues noted that 32 of 34 patients with an exacerbation and mucoid sputum, as defined by a semiquantitative scoring system, resolved their exacerbation without antibiotic therapy; patients with purulent sputum were more likely to have polymorphonuclear cells and organisms in sputum, with 77 of 87 patients resolving their AE-COPDs with antibiotic therapy (135). A multicenter Italian study expanded these findings by noting that increasing sputum purulence, as defined by a semiquantitative colorimetric scale, was associated with bacterial growth (136). In addition, deepening sputum color was associated with increased yield of gram-negative bacteria, including *P. aeruginosa*/Enterobacteriaceae. Importantly, the definition of color by subjects and investigators was concordant in only 68% of cases without the aid of an objective color stick. These data suggest that new purulent sputum may identify a patient more likely to benefit from antibiotic therapy, although additional data defining how this concept can be incorporated in daily decision making are required. Despite these uncertainties, numerous major multispecialty societies have incorporated these concepts into the identification of patients who should be treated with antimicrobial therapy (Table 2).

Biomarkers have been highly sought after to complement or replace symptom-based methods to identify patients in whom bacteria are pathogenic during an AE-COPD. As such, an evolving role for procalcitonin level to define AE-COPD patients with a higher likelihood of bacterial infection has been suggested (137). This small protein (116 amino acid, 13 kD) is normally undetectable in plasma (138), but increases in bacterial infections. Data from single-center, cluster-randomized, single-blinded studies suggest that procalcitonin-guided therapy can be used safely to reduce antibiotic use in patients with LRTI at low likelihood of bacterial infection (137, 139). Stolz and coworkers randomized 208 consecutive patients admitted to the hospital with an AE-COPD to usual care (management based on standard criteria without access to procalcitonin levels) or to a procalcitonin-guided group where antibiotic use was based on procalcitonin level at time of admission (140). In the procalcitonin-guided therapy group, a level of less than 0.1 $\mu\text{g/L}$ was considered to be nonbacterial, and antimicrobial use was discouraged. In those with a procalcitonin level greater than 0.25 $\mu\text{g/L}$, bacterial infection was believed to be present and antimicrobial therapy was encouraged. For patients with levels between 0.1 and 0.25 $\mu\text{g/L}$, the use of antimicrobial agents was based on the clinical situation at admission and during early follow-up. Total antimicrobial use was decreased during the hospitalization (72% in usual-care group compared with 40% in

TABLE 2. RECOMMENDATIONS REGARDING TIMING OF ANTIMICROBIAL THERAPY IN RECENT SPECIALTY-SOCIETY RECOMMENDATIONS

Guideline Source, Year (Reference)	Recommendation*
Canadian Thoracic Society, 2003 (143)	"The Panel proposes that antibiotics should only be considered for use in patients with <i>purulent exacerbations</i> ."
American Thoracic Society/European Respiratory Society, 2004 (169)	"[Antibiotics] may be initiated in patients with <i>altered sputum characteristics</i> ."
National Institute for Clinical Excellence, 2004 (107)	"Antibiotics should be used to treat exacerbations of COPD associated with a history of <i>more purulent sputum</i> ."
European Respiratory Society, 2005 (170)	"[Hospitalized patients with COPD exacerbations should receive antibiotics if] I. Patients with all three of the following symptoms: <i>increased</i> dyspnea, sputum volume and <i>sputum purulence</i> (a type I Anthonisen exacerbation). II. Patients with only two of the above three symptoms (a type II Anthonisen exacerbation) when <i>increased purulence of sputum</i> is one of the two cardinal symptoms. III. Patients with a severe exacerbation that requires invasive or non-invasive mechanical ventilation. IV. Antibiotics are generally not recommended in Anthonisen type II without purulence and type III patients (one or less of the above symptoms)."
GOLD, 2006 (144)	"Antibiotics are only effective when patients with worsening dyspnea and cough also have <i>increased sputum volume and purulence</i> ."

Definition of abbreviation: GOLD = Global Initiative for Chronic Obstructive Lung Disease.
* Italics added for emphasis.

procalcitonin-guided therapy), at short-term follow-up and through 6 months. No difference was noted in clinical success rate during the index hospitalization, antimicrobial use during the subsequent 6 months, or in time to the next exacerbation. Additional investigation is required to assess if patients with low procalcitonin levels require antimicrobial therapy or if similar results can be achieved in a properly designed multicenter trial (141).

The choice of antimicrobial agent remains nebulous. Increasingly, guidelines have suggested stratifying patients according to the risk of treatment failure (142–144). These stratification schemes have generally suggested features for a high likelihood of infection with organisms that are not covered with standard antibiotic regimens (e.g., *P. aeruginosa*, drug-resistant bacteria) or host factors that predict treatment failure. The latter include worse lung function, increased frequency of exacerbation/office visits, ischemic heart disease, and other comorbid conditions (145, 146). Prospective data supporting such an approach are quite limited, however. A recent study prospectively confirmed that patients with a complicated AE-COPD experienced inferior clinical response rate compared with those with an uncomplicated AE-COPD (114). A tailored approach for the initial antimicrobial regimen selection in individuals at increased risk for treatment failure requires additional prospective validation.

As a clearer picture develops of which patients are infected with viral pathogens, effective antiviral agents can be considered. The benefit of such a targeted approach will depend on the ability to rapidly identify the causative viral pathogen. The science behind this endeavor has been evolving rapidly, with approaches to diagnosis that range from an appreciation of seasonal distribution of specific viridae, clinical syndromes, and rapid diagnostic laboratory testing. It is well known that many common respiratory viruses associated with respiratory illnesses are most evident during specific times of the year (Figure 4) (147, 148). The combination of these seasonal patterns with clinical syndromes has been used in clinical trials and advocated for clinical use (148). Influenza serves as a prototypical agent for this approach. A retrospective, pooled analysis of phase II and III clinical trials that enrolled mainly adults (mean age, 35 yr) with an “influenza-like illness” (defined as fever or feverishness and at least 2 of the following symptoms: headache, myalgia, cough, or sore throat) has been published (149). Of the 3,744 subjects enrolled, 2,470 (66%) were confirmed to have influenza infection. Infected subjects were more likely to have fever, cough, and nasal congestion but less likely to have sore throat. In multivariate modeling, the best positive predictive value (PPV) was seen with the combination of fever and cough: the higher the temperature, the higher the PPV. A smaller

Figure 4. Proportion for each of four viral pathogens isolated during each calendar month over a 6-month period of study in Tecumseh, Michigan. Reprinted by permission from Reference 147.

TABLE 3. SENSITIVITY AND SPECIFICITY OF INDIVIDUAL AND COMBINED CLINICAL CHARACTERISTICS BETWEEN RESPIRATORY SYNCYTIAL VIRUS- AND INFLUENZA-INFECTED ELDERLY OR HIGH-RISK PATIENTS ADMITTED WITH RESPIRATORY ILLNESS DURING FOUR CONSECUTIVE WINTERS

Clinical Characteristic	Sensitivity %	Specificity %
Nasal congestion	63	55
Sputum production	79	32
Wheezing by history	68	43
Feverishness	46	56
Rhinorrhea on examination	11	93
Wheezing on examination	75	38
Temperature > 37.9° C	60	30
Combined nasal congestion, wheezing on examination and temperature > 37.9° C	13	91

Adapted from Reference 153.

prospective study yielded similar results (150). Unfortunately, the PPV of cough and fever seems to be lower in elderly hospitalized patients (151), a problem that could be particularly problematic in patients with COPD.

HRV infection also presents with a well-described symptom complex. Unfortunately, significant overlap with other infectious agents is present. Two large studies recruited adults (age > 18 yr) with self-diagnosed colds including moderate-severe rhinorrhea and more than one other respiratory symptom (nasal congestion, cough, sore throat) that was moderate or greater in severity (121). Importantly, subjects were excluded if they had a fever (oral temperature > 37.8°C). Of the 2,096 enrolled subjects, 1,363 (65%) were reverse transcriptase-PCR (RT-PCR) positive for a picornavirus infection. Clearly, a clinical definition is not foolproof in diagnosing rhinovirus infection. In a well-defined cohort of patients with COPD followed prospectively, 10 of 43 exacerbations were associated with rhinovirus isolation in either induced sputum or nasopharyngeal cultures (152). Increased nasal discharge/nasal congestion ("colds") was present in 26 (61%), sore throat in 13 (30%), and increased sputum volume in 21 (49%) of all exacerbations. The simultaneous presence of cold and increased sputum volume was the symptom combination most strongly associated with the isolation of rhinovirus (odds ratio, 6.15; $P = 0.036$); importantly, however, two of the rhinovirus exacerbations (20%) were not associated with colds.

Clinical features of RSV infection overlap significantly with those of other winter respiratory viruses (69). One group contrasted clinical syndromes for elderly or otherwise high-risk adults admitted to hospital with respiratory illness during four consecutive winters (153). A total of 118 RSV and 133 influenza-infected patients were available; they were generally elderly (mean age, 76), female (~60%), with 49 to 54% having underlying heart disease and 55 to 58% chronic lung disease. Subtle differences were noted in clinical characteristics (Table 3). Unfortunately, even the combination of these features did not markedly improve operating characteristics. Additional diagnostic modalities, as described below, will be required to improve RSV detection.

Although not strictly a pathogen-directed therapeutic approach, vaccination has assumed an important role in the patient with COPD. The most promising data to date are those surrounding influenza vaccination. Large population-based studies have suggested that influenza vaccination improves COPD mortality (154). Six placebo-controlled trials in patients with COPD have been reviewed; a reduction in the total number of exacerbations was described, particularly in AE-COPDs occur-

ring after 3 or 4 weeks (155). Although data are limited, the clinical effect does not appear to vary by spirometric disease severity (156), nor does the immune response vary by the concomitant use of corticosteroids (157). As such, influenza vaccination has been strongly recommended in the latest international guideline (144). Data regarding the effect of pneumococcal vaccination are more limited. Retrospective studies have suggested decreased risk of pneumonia hospitalization and death in elderly patients with chronic lung disease, an effect that was additive to that of influenza vaccination (158) or in veterans with asthma or COPD (159). Very little information is available from randomized, controlled trials. A recent Cochrane review identified a paucity of such studies, with no convincing evidence of clinical benefit (160). The largest available study suggested that benefit may be most likely in those younger than 65 years or with in those with more severe spirometric disease ($FEV_1 < 40\%$ predicted) (161), a recommendation that has been incorporated with more modest enthusiasm in the latest international guideline (144). Oral bacterial vaccines for the prevention of AE-COPDs are under intensive study (162).

Novel Approaches

Given the limitations of seasonal variation and syndrome definitions, specific diagnostic strategies continue to evolve, including the use of inflammatory markers, viral cultures, antigen identification, and molecular assays (including RT-PCR) (69, 118). The recent identification of differing inflammatory patterns in the sputum samples of hospitalized patients with an exacerbation suggests a possible additional approach to identify viral versus bacterial etiology; sputum eosinophil values greater than $1.68 \times 10^6/g$ exhibited a sensitivity of 0.82 and specificity of 0.77 for a viral etiology (52). An extension of this approach has been proposed by the incorporation of sputum inflammatory markers (tumor necrosis factor- α and IL-8) in segregating exacerbations caused by "common bacteria" compared with *Pseudomonas* or nonbacterial etiologies (163).

For the identification of specific viral pathogens, viral cultures remain the "gold standard" but exhibit limited sensitivity and take days to return, limiting the practical value in direct clinical care. Improved diagnostic approaches have been best developed for influenza infection. Numerous laboratory approaches have been advocated with rapid antigen diagnostic studies available on the market (164); unfortunately, their sensitivity varies. Despite this limitation, one group has suggested that rapid antigen test results can aid in decision making in hospitalized adults (165). One group has compared multiple diagnostic modalities in 1,033 patients enrolled in clinical trials of zanamivir (166); in 692 patients, the results of viral culture, hemagglutinin inhibition serology, or RT-PCR agreed. In 791 (77%) of the patients, a positive result for one of the three tests was identified. It was evident that diagnostic accuracy of the tests varied, although RT-PCR exhibited 92% sensitivity and 84% specificity compared with the other two diagnostic modalities. The value of RT-PCR in the diagnosis of picornavirus (167) and RSV (69) infection has increasingly been recognized. In fact, advanced, comprehensive microarray systems have been developed that can detect the majority of respiratory viruses in clinical samples (168). It is likely that straightforward, relatively inexpensive, and accurate diagnostic modalities for specific viral pathogens will be developed in the near future.

CONCLUSIONS

Acute exacerbations of COPD are important events in the natural history of this disease. These events can be caused by a large number of infectious and noninfectious agents. Infectious

pathogens range from viral to atypical to typical bacterial pathogens. Increasingly, approaches targeting pathogen-specific etiologies have been developed. These include clinical and laboratory-based methods to identify bacterial versus viral infections. Further additional investigation has suggested specific pathogens within these broad classes. The goal should be to better target specific antibacterial or antiviral therapies to individual episodes.

Conflict of Interest Statement: F.J.M. is a consultant for Altana Pharma and has received compensation greater than \$10K. He has been a member of several advisory boards, CME committees, and the speaker's bureau for Boehringer Ingelheim, Pfizer, and GlaxoSmithKline. His total compensation per company is greater than \$10K. In addition, he is on an advisory board for Novartis and speaker's bureau for Sepracor and AstraZeneca, receiving less than \$10K per company. He has been an investigator for industry-sponsored studies for GlaxoSmithKline, Boehringer Ingelheim, and Actelion.

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