Medication Regimens for Managing COPD Exacerbations

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Exacerbations are a hallmark feature of COPD and contribute to morbidity and mortality. There is general agreement that the pharmacotherapy of COPD exacerbations includes bronchodilators, corticosteroids, and antibiotics. Strong evidence exists for the benefit of corticosteroids for exacerbations and of antibiotics in the acute hospital setting. There remains considerable uncertainty, however, in the best drug selection, dose, route, and duration of treatment. This article reviews the evidence base and expert recommendations for drug treatment of COPD exacerbations in the out-patient and in-patient settings. *Key words: COPD; bronchodilators; corticosteroid; antibiotics; pharmacotherapy*. [Respir Care 2018;63(6):773–782. © 2018 Daedalus Enterprises]

Introduction

Exacerbations are an unfortunate and relatively common occurrence among individuals with COPD. Such events are important because they can contribute to progression and worsening of the disease trajectory in COPD and lead to a substantial burden for health care utilization in the United States and worldwide. Exacerbations of COPD are defined as worsening of cardinal respiratory symptoms of cough, phlegm production, and dyspnea that exceed day-to-day variability and last >1–2 d. Some definitions require an event, such as a health care visit or treatment, to occur.[1] With this constellation of symptoms, however, there is a wide range of severity and clinical presentation that make it difficult to assign a single-treatment algorithm for all exacerbations. Many episodes of worsening respiratory symptoms do not come to medical attention and are not treated.[2]

A commonly used classification for severity of exacerbations used in the research setting depends on the treatment that is prescribed. Mild exacerbations are those treated only with intensification of bronchodilators, moderate exacerbations are those treated with antibiotics or corticosteroids or both, and severe exacerbations are those that require hospitalization or emergency department visit. Thus, it is difficult to design recommendations for treatment based on severity because, in this case, it is the treatment that defines the severity of the exacerbation.[3,4] Therefore, treatment decisions are often made based on the severity of associated symptoms and the setting in which treatment is being provided (ie, in-patient vs out-patient setting). In this paper, we attempted to segregate treatment recommendations for either the ambulatory or the hospital set-

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Table 1. GOLD Recommendations for Pharmacotherapy of COPD Exacerbations

Initiate treatment with SABA monotherapy or SABA and short-acting muscarinic antagonist combination therapy
Use one inhalation per hour for 3 initial treatments, then 2 inhalations every 2–4 h as needed
Either nebulizer or pMDI with spacer may be used
Continuous nebulizer treatment not recommended
Maintenance LABA or long-acting muscarinic antagonist treatments may be continued or initiated during hospitalization
Systemic corticosteroids are indicated for both ambulatory and hospitalized patients
Recommended treatment course is prednisone 40 mg/d for 5 d
Oral administration is equally effective as intravenous administration
High-dose nebulized budesonide is an alternative to systemic steroids
Antibiotics are indicated for exacerbations with increase in purulent sputum or that require NIV or mechanical ventilation
Recommended duration of treatment is 5–7 d
Initial treatment with amoxicillin-clavulanate, macrolide, or tetracycline
Antibiotics should be tailored to sputum cultures in patients with severe COPD, frequent exacerbations, or mechanical ventilation
When possible, oral administration of antibiotics is preferred over intravenous administration

Recommendations adapted from Reference 5.
GOLD = Global Initiative for Chronic Obstructive Lung Disease
SABA = short-acting β_2 agonist
pMDI = pressurized metered-dose inhaler
LABA = long-acting adrenergic agonist
NIV = noninvasive ventilation

ting, in accord with the setting where the most convincing evidence was acquired.

Guidelines for the treatment of exacerbations have been promulgated by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[5] (Table 1) as well as by the American Thoracic Society/European Respiratory Society[6] and the European National Institute for Health and Care Excellence.[7] Although adjuncts to drug therapy, such as oxygen or ventilatory support, are important elements of treating a COPD exacerbation, this paper focused on pharmacotherapy. All of the evidence-based guidelines recommend that treatment of exacerbations rely on 3 classes of drugs with the mnemonic ABC: antibiotics, bronchodilators, and corticosteroids. This review discusses recommendations for pharmacotherapy of COPD exacerbations and the evidence that supports these recommendations.

Treatments

Antibiotics

Approximately 50% of COPD exacerbation events are associated with a new bacterial infection, typically non-typable *Haemophilus influenzae*.[8] Many exacerbations, however, are preceded by viral infections, particularly rhinovirus or respiratory syncytial virus.[9] Accordingly, this provides a strong rationale for the use of antibiotics in some settings for the treatment of COPD exacerbations. The GOLD strategy, based on a literature review and expert opinion concludes that antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospital length of stay. The duration of therapy should be 5–7 d.[5]

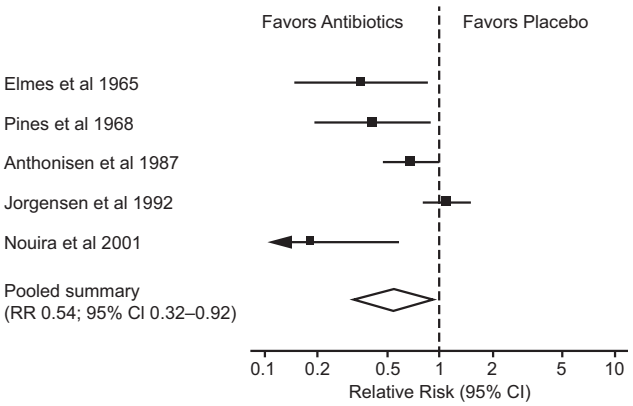


Fig. 1. Forest plot of effects of antibiotic therapy on risk of COPD exacerbation treatment failure. From Reference 10, with permission.

Two systematic reviews with a meta-analysis of antibiotic use for exacerbations of COPD provided support for the recommendations in the GOLD strategy.[5,10,11] A review of the results from 5 clinical trials concluded that the efficacy of antibiotics was most convincingly demonstrated in subjects who were hospitalized[10] in whom antibiotic use was associated with a 66% reduction in a risk for treatment failure and a 78% reduction in in-hospital mortality, although such strong associations were not demonstrated for studies in the out-patient setting (Fig. 1).[10] Another meta-analysis, conducted by Vollenweider et al,[11] analyzed data from 16 trials and found that, although high-quality evidence existed that showed non-ICU hospitalized subjects had a 23% reduction in the risk of treatment failure with antibiotic use, the evidence was low quality for the use in out-patients (although the estimated effect size was 25% for reduction in risk of treatment failure in this group). This study found no significant mortality benefit for the use of antibiotics overall.[11]

However, in the single placebo-controlled trial of antibiotics in an ICU population ($N = 93$), there was an 80% reduction in the rate of treatment failure and an 80% reduction in the odds of death.[12] In a retrospective analysis of 53,900 subjects hospitalized for COPD and treated with corticosteroids in 410 hospitals in the United States, the use of antibiotics was associated with a 40% reduction in death and a 13% reduction in the risk of readmission to the hospital within 30 days. Ad-

verse events were reported 53% more frequently in subjects treated with antibiotics versus placebo, with the most common adverse reaction being diarrhea.[13] Based on the summarized evidence, it is a strong recommendation that antibiotics should be prescribed for patients hospitalized for a COPD exacerbation. The population for which the evidence base affords a less-clear recommendation is among ambulatory patients.

The American Thoracic Society/European Respiratory Society evidence review focused on whether antibiotics were recommended for ambulatory patients,[6] an important population, given that out-patient exacerbations comprise >75% of all COPD exacerbations. The American Thoracic Society/European Respiratory Society evidence-based guidelines conclude "The use of antibiotics in ambulatory patients with exacerbations of COPD reduces the treatment failure rate and increases the time to the next exacerbation. However, the majority of subjects avoided treatment failure even in the placebo group (58%), suggesting that not all exacerbations require treatment with antibiotics."

Recommendations for specific antibiotics depend on the severity of the exacerbation and the local antibiotic sensitivities. Physicians are encouraged to consult their local antibiotic recommendation guidelines. At one institution, for ambulatory patients who are unlikely to have infection with *Enterobacteriaceae* or *Pseudomonas*, first-line empiric antibiotics include the following: doxycycline 100 mg orally twice a day for 5 d, azithromycin 500 mg orally daily for 3 d, amoxicillin-clavulanate 875 mg orally twice a day for 5 d, cefpodoxime 200 mg orally twice a day for 5 d, or cefdinir 300 mg orally twice a day for 5 d, with keeping in mind that individuals on chronic azithromycin therapy for frequent exacerbations should be given an antibiotic regimen that does not include azithromycin. The oral route is preferred if the patient can take oral medications. Empiric use of fluoroquinolones are discouraged unless there is culture evidence of resistant Gram-negative organisms or *Pseudomonas*.[14] If there are risk factors for *Pseudomonas,* such as repeated courses of antibiotics, bronchiectasis on lung imaging,[15] or previous cultures positive for *Pseudomonas*, then treatment may include levofloxacin 750 mg orally or intravenously once daily or intravenous administration of cefepime, ceftazidime, or piperacillin-tazobactam.

Excessive use of antibiotics may lead to the development of resistant organisms in the individual patient or in the community. Because many ambulatory patients with exacerbations may not have bacterial infections as a cause of the exacerbation, investigators have been interested in various biomarkers that might indicate the necessity for antibiotics. A common disease marker that has been used to aid in decision-making for the use of antimicrobials is sputum color and quantity. Some investigators recommend that antibiotics should not be used in ambulatory patients unless there is purulent sputum. The color of sputum that ranges from white to yellow to green is a reliable indicator of neutrophil density in expectorated phlegm because of the greenish color of myeloperoxidase, which is stored in the azurophilic granules of neutrophils.[16,17]

In one study, of 123 subjects with exacerbations, the presence of green sputum was 94% sensitive and 77% specific for the presence of a high bacterial load, which indicated a greater likelihood of response to antibiotics.[16] However, in a study that used a combination of sputum color and inflammatory biomarkers to guide the use of antibiotics in hospitalized subjects, there did not seem to be better outcomes in the sputum color biomarker-guided therapy.[18] Another trial, which used procalcitonin, a biomarker of bacterial infection to tailor antibiotic therapy, demonstrated that a shorter course of antibiotics (3 vs 10 d) was feasible in hospitalized subjects who were not in respiratory failure. Although the trial was underpowered for non-inferiority, there was no significant increase in exacerbation rates over the 6 months after the initial exacerbation.[19]

Bronchodilators

Intensification of bronchodilator use is often an initial sign of an impending exacerbation because patients self-medicate to relieve symptoms of dyspnea, chest tightness, or wheeze. Most clinicians treat exacerbations with increased frequency of short-acting bronchodilators: albuterol a short-acting β_2 adrenergic agonist (SABA) and/or ipratropium, a short-acting muscarinic antagonist. Although both bronchodilators are well established compared with placebo in patients with stable COPD, there are no placebo-controlled trials to establish their use during exacerbations. Nonetheless, short-acting bronchodilators that provide symptom relief for patients with exacerbations have become a cornerstone of treatment for COPD exacerbations. GOLD guidelines specifically recommend that "short-acting inhaled β_2-agonists, with or without short-acting anticholinergics are recommended as the initial bronchodilators to treat an exacerbation."[5]

As suggested by the GOLD strategy, recommendations differ among experts about whether to use SABA monotherapy or SABA and short-acting muscarinic antagonist combination therapy. In patients with stable COPD, there is abundant evidence that combination SABA and short-acting muscarinic antagonist administered either by a pressurized metered-dose inhaler (pMDI) or a nebulizer provides superior bronchodilation to either agent alone.[20–22] However, in the setting of exacerbations, a meta-analysis that compared SABA

with combination therapy found no difference between a single agent and the combination.[23]

Several studies compared the efficacy of bronchodilators delivered by a pMDI with a spacer to delivery by a nebulizer during COPD exacerbations. A systematic review of these studies concluded that methodological flaws in many of these studies led to an inability to draw a firm conclusion of whether one approach was better than another. In one of the secondary outcomes, 1-h FEV_1, there was an 83-mL advantage of the nebulizer over the pMDI, but the nebulizer was also associated with more adverse effects.[24] Accordingly, selection of a delivery device for short-acting bronchodilators during an exacerbation should be based on factors such as the ability to use the device correctly, cost, convenience, and patient preference.

Initial dosing of short-acting bronchodilators in patients who are acutely ill has not been systematically studied. In acute episodes of asthma, it is recommended, with strong evidence, that albuterol be inhaled every 20 min for 3 doses and then repeated every 1–4 h as needed.[25,26] Albuterol inhalation of 4–10 puffs by using pMDI with a spacer is recommended in asthma for rapid bronchodilation. Evidence supporting a similar approach in COPD is lacking, and GOLD recommends that patients initiate treatment with one puff of albuterol every hour for 2 or 3 doses and then every 2–4 h based on the patient's response.[5] The use of continuous versus intermittent nebulization of bronchodilators is controversial in asthma, but systematic reviews have found it to be effective and safe in severe asthma exacerbation.[27] GOLD expert opinion does not recommend continuous nebulizer treatment for initial bronchodilator therapy in COPD, given the lack of evidence for this option in COPD exacerbations.[5]

In theory, the use of long-acting bronchodilators that have a high affinity for the adrenergic or muscarinic receptors may prevent the effectiveness of short-acting bronchodilators; however, this does not seem to be a problem in routine practice.[28,29] On the contrary, GOLD recommends that long-acting maintenance bronchodilators should be continued during the period of an exacerbation or be initiated before hospital discharge to avoid a gap in maintenance treatment.[5]

Some nebulized long-acting bronchodilators, such as arformoterol or formoterol, have an onset of action similar to albuterol but have a longer duration of action. It is logical, therefore, that these agents, available in nebulizer solutions, might be effective bronchodilators during exacerbations and could reduce the required frequency of treatments. However, there have not been any trials to compare nebulized long-acting β_2 agonist with nebulized SABA for COPD exacerbations, although this approach has been used in some hospital settings. One recent retrospective case-control study that compared hospitalized subjects treated with an long-acting β_2 agonist versus an SABA found that there was a reduction in 30-d readmissions with the long-acting β_2 agonist.[30] Methylxanthine bronchodilators, such as theophylline or aminophylline, are not recommended for treatment of exacerbations because of their minimal efficacy in this setting and high prevalence of adverse effects.[31]

Corticosteroids

Corticosteroids are well studied in placebo-controlled studies of hospitalized subjects with exacerbations and are established for their utility in the hospital setting to speed the recovery of lung function, reduce the risk of treatment failure, and shorten hospitalization.[10,32–34] There is less certainty about the utility of systemic corticosteroids in ambulatory patients. The limited data that are available tend to show the benefit of a course of corticosteroids in terms of recovery of lung function and possibly hospitalizations.[35] With respect to ambulatory patients, the American Thoracic Society/European Respiratory Society task force concluded that the benefits of oral corticosteroids probably outweigh adverse effects, burdens, and costs but is uncertain due to very-low confidence in the accuracy of the estimated effects.[6] Nonetheless, a conditional recommendation was given that ambulatory patients with COPD exacerbations should receive a course of oral corticosteroids that lasts for $\leq$14 d.[6]

There remains uncertainty about the duration and dose of corticosteroids that should be used in both in-patient and out-patient settings. In a systematic review of trials that used different doses of corticosteroids, there did not seem to be a substantial difference in the risk for treatment failure or improvement in FEV_1 in trials that used lower ($<$80 mg prednisone or equivalent) compared with trials that used a higher ($>$80 mg prednisone or equivalent) initial dose, although there was no statistical test that substantiated to this comparison (Fig. 2).[36] In a retrospective pharmacoepidemiologic analysis of 79,985 patients, the risk for treatment failure in hospitalized subjects was not different when treatment was initiated with high-dose intravenous therapy compared with lower-dose oral treatment.[37]

With regard to the time course of the treatment, most of the trials that showed benefit of corticosteroids used treatment courses that lasted 10–14 d. A Department of Veterans Affairs cooperative study showed that extending the treatment period beyond 2 weeks did not reduce treatment failures or hospital readmissions (Fig. 3).[33] A pivotal trial of emergency department subjects in Switzerland compared 40 mg prednisone for 5 d versus 14 d in 314 subjects and found no difference in survival or time to re-exacerbation.[38]

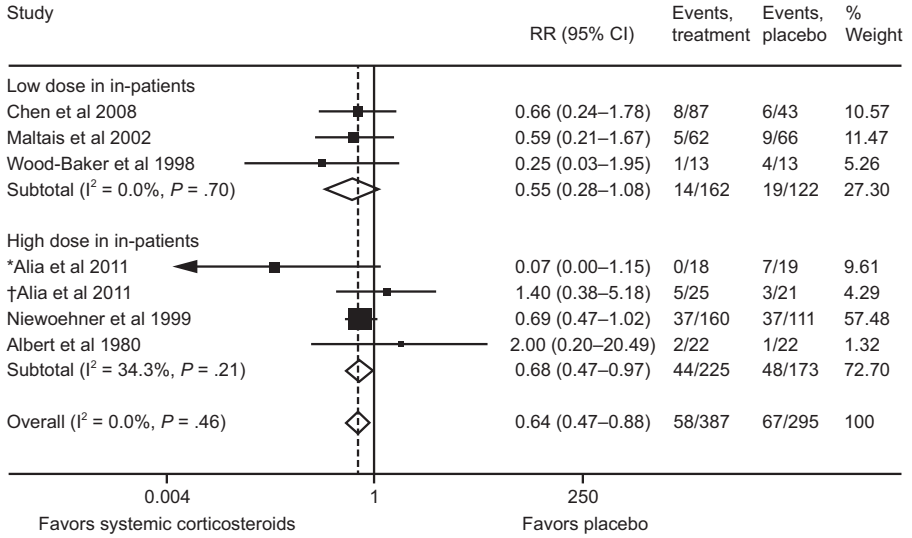
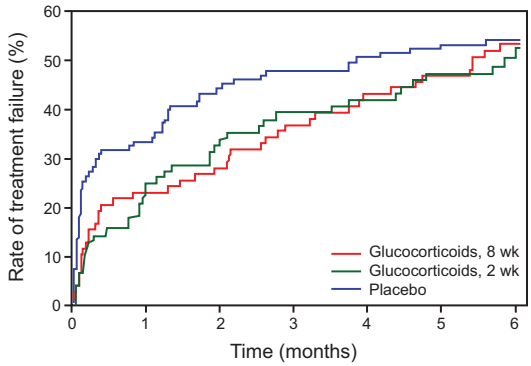


Fig. 2. Forest plot of corticosteroid dosing on risk for COPD exacerbation treatment failure. * Subjects who failed noninvasive ventilation. † Subjects who died. From Reference 36, with permission.



Subjects at risk, *n*

Glucocorticoids, 8 wk	80	61	50	21
Glucocorticoids, 2 wk	80	59	46	20
Placebo	111	74	58	39

Fig. 3. Kaplan-Meier curves of risk for COPD exacerbation treatment failure by duration of steroid dose. From Reference 33, with permission.

Based on this study and a systematic literature review, it was concluded that a 5-d course of steroids is likely to be sufficient in patients with mild-to-moderate exacerbations, with the recognition that the quality of the evidence behind this recommendation is moderate.[39] Thus, the GOLD experts recommend treatment of exacerbations with 40 mg prednisone for 5 d and do not distinguish between exacerbation care setting (hospitalized vs ambulatory).[5] However, there remains uncertainty whether patients who have severe exacerbations with respiratory failure should be started on higher doses of corticosteroids. In a recent survey of critical care experts, the median reported initial dose for patients receiving ventilatory support was 120 mg prednisone daily, with a range of 40–500 mg/d, which suggests significant variation in practice for treatment in this most severely ill group of patients with COPD exacerbations.[40]

As an alternative to systemic corticosteroid therapy, nebulized corticosteroids have been considered for treatment. Nebulized budesonide has been shown to be more effective than placebo in hospitalized subjects with COPD exacerbations in improving FEV_1 and had slightly less efficacy than prednisolone but caused less hyperglycemia.[41] Therefore, nebulized budesonide might be an alternative for hospitalized patients who cannot tolerate the adverse effects of systemic corticosteroids. In a non-inferiority trial of high-dose inhaled budesonide-formoterol via pMDI versus oral prednisolone with formoterol, there was no difference in improvement of FEV_1 and no difference in symptom outcomes and re-exacerbation, which suggests that this might be an option for patients with milder exacerbations or who do not have access to oral steroids or who cannot tolerate the adverse effects.[42]

In recent years, there has been increasing recognition that eosinophilia is an important biomarker in patients with COPD as well as a suggestion that eosinophilia is associated with better efficacy of maintenance therapy with inhaled corticosteroids.[43,44] Accordingly, eosinophilia has been studied as a biomarker for initiation and continuation of corticosteroid treatment in COPD exacerbations. In one trial of eosinophil-guided corticosteroid therapy, there did not seem to be any advantage to using such an algorithm compared with standard treatment. However, subjects who did not have eosinophilia tended to recover faster after an exacerbation than those

who received corticosteroids.[45] Therefore, it remains for further research to determine whether eosinophilia will be a useful guide for initiation of corticosteroid therapy.

Future Treatments

Several other treatments for the prevention of COPD exacerbations are under investigation, and some of these may ultimately prove helpful for treating exacerbations. These include monoclonal antibodies to a variety of inflammatory cytokines, p38 mitogen activated protein kinase inhibitors, phosphoinositide-3 kinase inhibitors, and a single-molecule muscarinic antagonist and adrenergic agonist.[46] There continues to be interest in cysteine-containing anti-oxidant mucolytic agents, for example, N-acetylcysteine. These agents are now recommended by the American College of Chest Physicians and Canadian Thoracic Society guidelines for prevention of COPD exacerbations if other treatments are not effective.[47] Trials have shown that N-acetylcysteine is not effective in improving recovery of FEV_1, N-acetylcysteine has been shown to reduce symptoms of cough and phlegm, and to reduce inflammatory biomarkers during exacerbations.[48–50] Thus, N-acetylcysteine may be a useful adjunct to drug therapy in patients with difficulty clearing airway secretions.

Summary

There is a general consensus based on clinical trial evidence and expert opinion that the mainstays of pharmacotherapy for COPD exacerbations include antibiotics, bronchodilators, and corticosteroids. There is some uncertainty about whether all of these treatments are indicated in patients, based on their severity of disease and treatment setting (in-patient, out-patient, intensive care), and the best route of administration and dose or duration of treatment, particularly for systemic corticosteroids. In addition, further study is needed to examine the role of biomarkers in assisting clinicians in deciding on the optimal treatment for COPD exacerbations. This is an important field of study given the burden of COPD exacerbations on health care systems and highlights the importance of adequate treatment in preventing further exacerbation events, health-care utilization, and adverse outcomes in COPD.

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Discussion

Donohue: Bob, that was great. In the follow-up that Bruce [Rubin] was talking about yesterday, Rand Sutherland, when he was still at National Jewish, wrote that, in the BRONCUS (Bronchitis Randomized on NAC Cost-Utility Study),[1] those subjects who were not on inhaled corticosteroids did well. How did that resolve, do you know?

Wise: Yes, that was true, if subjects did not have inhaled corticosteroids, they did do better. But because they didn't meet their primary outcome, that was a post hoc subgroup. The PEACE study,[2] which was a carbocysteine study in China, found a very significant benefit of carbocysteine, a similar compound to N-acetylcysteine, but only 17% of the subjects were on inhaled corticosteroids, and a lot of them were on theophylline. There was another N-acetylcysteine study from China, the PANTHEON study,[3] in which 44% of the subjects were on inhaled corticosteroids, and they did show a benefit in reducing the exacerbation rate with N-acetylcysteine. Dennis Niewoehner believed that the dose of N-acetylcysteine was very important, so he initiated a Veterans Affairs study,[4] in the United States, of 1,800 mg N-acetylcysteine daily to test this, but the data-monitoring committee stopped it prematurely because a study in mice with N-acetylcysteine as well as vitamin E allowed tumors to progress faster in susceptible mice because oxidants are important in preventing tumor progression. So, they had to stop the study, but he published the partial results and they were negative. I think this is an unfortunate mistake by the committee because it tends to close the door on the definitive trials that we really need, and, of course, N-acetylcysteine and vitamin E are still widely available over the counter without government regulation.

Rubin: Zambon was the sponsor of the BRONCUS trial.[1] It's a privately held company, and they make Fluimucil, which is the largest-selling N-acetylcysteine in Europe. They were convinced that BRONCUS would be a positive study, but it was absolutely clear that, over a several-year period, it made no difference in outcomes in subjects with COPD.[1] They did a variety of exploratory analyses, some of them clearly showing benefit for placebo, some suggesting benefit for N-acetylcysteine. What was reported in the paper was the non-steroid group subgroup analysis.[1] They followed on because they couldn't believe the results with an exacerbation and follow-up study that showed more benefit to the placebo group than N-acetylcysteine.

Wise: Zambon also did a follow-up primary care study[5] that compared N-acetylcysteine to inhaled corticosteroids. In that study, the N-acetylcysteine group had significantly more exacerbations than did placebo, but, strangely, so did the inhaled corticosteroid group.

Pleasants: Honestly, I think N-acetylcysteine is a moot point because nobody here in the United States uses it. Does anybody here use it in their patients with COPD? However, in other parts of the world, it is widely used.

Wise: N-Acetylcysteine is recommended, with evidence grade 2B, by the American College of Chest Physicians guidelines for prevention of exacerbations in those with severe COPD and $\geq$2 exacerbations in 2 y.[6] But still, it is not widely used in the United States. I have used it from time to time in some patients who have cough with difficulty expectorating, and every so often patients will report considerable relief.

***Newhouse:** The effects of anticholinergics would only occur if you are using wet nebulization, small-volume nebulization because it's positive pressure. The masks usually don't fit very well, so you end up getting a lot around your eyes. With a pMDI, or, in this case, it would be the Boehringer Ingelheim soft mist, you have to draw the aerosol out of the chamber. So it doesn't end up going around your eyes.

MacIntyre: That sounds perfectly reasonable.

Wise: It's something that we don't often think about. Mydriasis is common in patients who use nebulized ipratropium with a poor-fitting face mask. It can lead to narrow-angle glaucoma, in that there is a narrow anterior chamber. I think the most-striking consequence of this effect is when there is unilateral fixed dilation of a pupil that can trigger an extensive neurologic evaluation.[7]

Peters: It's kind of sad to say, but when you push the button on the Respimat, it does come out with force because it's spring-loaded. We had one patient who pushed it, dilated his eye, and even though he was wide awake they took him for an emergency computed tomography of the head to make sure he wasn't herniating because of the unilateral dilation of his pupil.

***Newhouse:** That's why you need the chamber to put it into.

Peters: Let me ask a question, when we are looking at the sputum of patients with COPD, is it really like cystic fibrosis, when it doesn't matter which antibiotics we give, or do we really need to target the sensitivities of these organisms? Even though the GOLD guidelines[8] recommend antibiotics based on sensitivities in severe COPD or in patients with frequent exacerbations, I believe that the data that support these specific recommendations are not very strong.

***Newhouse:** I would like to add that Israel Amirov and I published a study[9] a few years ago on the use of the Respimat with our InspiraChamber on infants who were asleep. We used our Soother mask in which you put their pacifier through a slot in the mask, the kids stayed asleep, and we had scintigraphy to show that the aerosol was getting into the lungs extremely well.

Giordano: I want to ask Bob [Wise], we are reliably informed that there are folks who prescribe SABA 4 times a day or on another regularly scheduled basis. We have looked in the literature, and we know it's not the right thing to do for stable patients. It's inferred in the GOLD guidelines.[8] Are there any circumstances beyond initialization and symptom relief for bronchodilator therapy when it would be justified to prescribe on a regular scheduled basis and not as needed?

Wise: I can say that 50% of the patients at our hospital who are discharged, mostly by hospitalists, are sent home on maintenance therapy with 4 times a day nebulized albuterol and ipratropium. So I think it's widely used; the main reason not to do it as opposed to a once or twice daily maintenance therapy is the complexity of the regimen, which may lead to worse adherence. In terms of pharmacology, I think it's OK to use nebulized treatment 4 times daily, but we should not forget that there are also nebulized twice-daily treatments that are helpful for patients who cannot manipulate other devices. We also need to understand that nebulized medications may be covered by insurance in patients who cannot afford hand-held inhalation devices.

Donohue: Sam, I think you raise a great point. In the guidelines now, like in GOLD, you don't see much talk about it.[8] But I did, and you remember those days. All the pivotal studies that we did, I did the original ipratropium curves with the late Tom Petty, and they were all regularly scheduled maintenance studies. They were given 3–4 times/d. The downside in asthma is that it has been shown that regular use is probably not a good thing, but certainly in COPD that was just the tradition and how we grew up. The therapies are so much better today that you really shouldn't do that. I like that you bring that up because it allows us to refocus.

Mann: It might help to provide some labeling perspective on this. Albuterol is cleared for the treatment or prevention of bronchospasm in patients with reversible obstructive airway disease. These agents are not limited to asthma or COPD but have that broader indication. The dosage and administration for an albuterol pMDI is 2 inhalations every 4–6 h, and I think the label says that sometimes one inhalation may also be sufficient. Clinically, regarding the question of regular use or as needed use, the label doesn't really comment on that, it just says every 4–6 h, but, importantly, it does not say "maintenance," so that sort of implies it's not for chronic and/or maintenance use. Ipratropium labeling is different. Atrovent HFA is indicated as a bronchodilator for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. So, ipratropium is just for COPD and clearly is labeled as a maintenance therapy. Finally, Combivent, which contains both albuterol and ipratropium, has an even more-specific COPD indication. Combivent is for use in patients with COPD on a regular aerosol bronchodilator who continue to have bronchospasm and require a second bronchodilator.

Rubin: Sam, although we're talking about asthma and COPD, cystic fibrosis is a chronic disease and the cystic fibrosis guidelines[10] do recommend regularly scheduled albuterol before airway clearance maneuvers, which are also regularly scheduled. As well as hyperosmolar solutions, for example, hyperosmolar saline solution, can produce bronchospasm in as many as one quarter of patients with cystic fibrosis. So albuterol pretreatment is recommended. Under those circumstances, when you do airway clearance, it is a recommendation. Weak evidence, but a recommendation.

Pleasants: It's all about Medicare Part B, and, for some people, it's the only way they can get bronchodilators that they can afford.

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