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Pseudomonal Infections in Patients with COPD

Epidemiology and Management

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Abstract

COPD is a common disease with increasing prevalence. The chronic course of the disease is characterized by acute exacerbations that cause significant worsening of symptoms. Bacterial infections play a dominant role in approximately half of the episodes of acute exacerbations of COPD. The importance of pseudomonal infection in patients with acute exacerbations of COPD stems from its relatively high prevalence in specific subgroups of these patients, and particularly its unique therapeutic ramifications. The colonization rate of *Pseudomonas aeruginosa* in patients with COPD in a stable condition is low.

A review of a large number of clinical series of unselected outpatients with acute exacerbations of COPD revealed that *P. aeruginosa* was isolated from the patients' sputum at an average rate of 4%. This rate increased significantly in COPD patients with advanced airflow obstruction, in whom the rate of sputum isolates of *P. aeruginosa* reached 8–13% of all episodes of acute exacerbations of COPD. However, the great majority of bacteria isolated in these patients were not *P. aeruginosa*, but the three classic bacteria *Streptococcus*

pneumoniae, *Hemophilus influenzae*, and *Moraxella catarrhalis*. The subgroup of patients, with acute exacerbations of COPD, with the highest rate of *P. aeruginosa* infection, which approaches 18% of the episodes, is mechanically ventilated patients. However, even in this subgroup the great majority of bacteria isolated are the above-mentioned three classic pathogens.

In light of these epidemiologic data and other important considerations, and in order to achieve optimal antibacterial coverage for the common infectious etiologies, empiric antibacterial therapy should be instituted as follows. Patients with acute exacerbations of COPD with advanced airflow obstruction (FEV_1 <50% of predicted under stable conditions) should receive once daily oral therapy with one of the newer fluoroquinolones, i.e. levofloxacin, moxifloxacin, gatifloxacin, or gemifloxacin for 5–10 days. Patients with severe acute exacerbations of COPD who are receiving mechanical ventilation should receive amikacin in addition to one of the intravenous preparations of the newer fluoroquinolones or monotherapy with cefepime, a carbapenem or piperacillin/tazobactam. In both subgroups it is recommended that sputum cultures be performed before initiation of therapy so that the results can guide further therapy.

COPD is a common disease of increasing prevalence primarily caused by smoking. In the setting of the chronic phase of the disease, acute exacerbations often occur in these patients and cause a worsening of symptoms. The mean frequency of these exacerbations in patients with advanced COPD is 1.5–2 episodes per year. The episodes often require assessment and therapeutic intervention and are responsible for a large share of the morbidity and mortality associated with COPD.

In light of evidence that has accumulated over the past decade it is now accepted that bacterial infections play a principal and dominant role in approximately one-half of the episodes of acute exacerbations of COPD. *Pseudomonas* spp. do not appear at or near the top of the list of bacteria commonly found in exacerbations of COPD. However, they are important because of their relatively high prevalence in specific subgroups of patients with COPD and especially in light of the unique therapeutic significance entailed in their treatment.

This review focuses on the epidemiologic and management aspects of pseudomonal infections in patients with COPD. Since this subject cannot be dissociated from its broader context, the main discussion is preceded by a discussion of the problems involved in the diagnosis and treatment of COPD in general, and acute exacerbations in COPD in particular.

1. Diagnostic Issues

1.1 Bronchial Colonization in Stable COPD

In contrast with healthy individuals, in whom sterility of the respiratory tract is maintained, in most patients with COPD there is an intermittent presence of pathogens, a condition known as bronchial colonization. This condition, which was considered in the past to be benign and inconsequential in terms of its pathophysiologic significance, is now looked upon totally differently. *In vitro* studies have shown that this condition can cause mucosal hypersecretion, impair mucociliary clearance, destroy epithelial cells, and induce a cytokine reaction in which neutrophils are mobilized to the respiratory tract.[1,2] The characteristics of this induced inflammatory response to colonization depends on the type of bacteria and the bacterial load.[3] From the clinical perspective, bacterial colonization of the lower respiratory tract when the patient is in a stable condition can affect the nature and frequency of acute exacerbations of COPD.[4] A comparison of various quantitative parameters of lower respiratory tract bacteria in patients with stable COPD compared with patients with acute exacerbations of COPD found that during acute exacerbations there is a significant increase in the percentage of patients with pathogenic bacteria in their respiratory tract and a corresponding increase in the mean concentration of those bacteria.[5] Based on molecular typing it has recently been suggested that the development of a new strain of bacterial pathogen in colonized flora is associated with an increased risk of exacerbation.[6] Despite the above, there is no doubt that in a significant number of COPD patients in stable condition there is a constant state of colonization of the respiratory tract with a significant concentration of bacteria. When these patients are in a state of exacerbation bacterial pathogens can be isolated from their sputum that would appear to be associated with or to cause the exacerbation, but in actual fact only represent the bacterial flora of colonization. This possibility should be considered when addressing the data that will be presented in section 4.2 on the percentage of isolates of the various bacteria in studies that based the etiologic diagnosis of acute exacerbations of COPD or acute exacerbations of chronic bronchitis on sputum cultures.

1.2 Microbiologic Sampling of the Respiratory Tract During Acute Exacerbations of COPD

The simple and trivial way to obtain microbiologic samples from the lower respiratory tract in acute exacerbations of COPD and chronic bronchitis is by culturing expectorated sputum. Indeed, most early studies were based on this method as the diagnostic technique. The major problem with the use of this diagnostic method is the difficulty in distinguishing between bronchial colonization and bronchial infection, a problem that was discussed in section 1.1. In addition, the fact that expectorated sputum, in its path from the respiratory tract to the culture plate, passes through the oropharynx, which often contains respiratory pathogens in large quantities, cannot be ignored. A quantitative assay of expectorated sputum provides a partial answer, at best, to these two issues, and is technically complicated and expensive. Some investigators tried to deal with this problem by using an invasive method of fiberoptic bronchoscopy to obtain sterile samples from the distal respiratory tract with a protected specimen brush (PSB). These studies are discussed in detail in section 4.4. In our best assessment of the relevant literature, we feel that there is no absolute certainty that bacteria isolated from expectorated sputum are representative of the bacteria that cause acute exacerbations of COPD, although it is highly likely that they are.

1.3 Bronchiectases and COPD

Bronchiectasis is a disease entity with similar clinical manifestations to chronic bronchitis and is characterized with recurrent episodes of cough with purulent sputum. In light of this overlap of symptoms between bronchiectasis, chronic bronchitis, and COPD, the latter two entities require exclusion of bronchiectasis if the patient is to be diagnosed as having chronic bronchitis or COPD. In routine clinical work the diagnosis of bronchiectasis is ruled out on clinical grounds and routine chest x-rays only. The spectrum of bacteria that participate in colonization and exacerbation in patients with bronchiectasis is significantly different from that in patients with COPD and there is a particularly high rate of infection with *Pseudomonas aeruginosa*.[7] In an important and original study[8] that tested the various characteristics of patients diagnosed with COPD in primary care, evidence of bronchiectasis was found in 29% of the patients using high-resolution computerized tomography. Although tubular bronchiectasis in a small area of the lung may be looked upon as a part of the course of severe COPD, this finding, if confirmed in other studies, may be significant in terms of the types of bacteria identified in patients who are allegedly COPD patients, but in actuality also have areas of bronchiectasis. This fact should also be taken into account when evaluating the epidemiologic data on pseudomonal infection in patients with COPD.

2. Management Issues

2.1 Antibacterial Treatment of Acute Exacerbations of COPD

In episodes of acute exacerbations of COPD, infection is only one aspect of the clinical complex. The worsening of airflow obstruction that stems from the exacerbation is another important aspect predominant in most patients. Thus, in addition to the classic objectives of antibacterial therapy there are three other goals in the treatment of acute exacerbations of COPD with antibacterials. These include acceleration of clinical recovery and a quick return to the baseline respiratory state, prevention of deterioration in the clinical condition, which in turn eliminates the need for hospitalization or mechanical ventilation because of respiratory insufficiency, and prolongation of the exacerbation-free interval. The primary significance of these objectives is that any cost/benefit analysis of antibacterial therapy for acute exacerbations of COPD has to take all these factors into account. Indeed, a study that examined this question concluded that treatment with an antibacterial that cost more to purchase could be less expensive in the final cost analysis.[9]

2.2 Choice of Specific Antibacterial Therapy

The factors that have to be considered when deciding on specific antibacterial therapy are the pathogen on the one hand and the host on the other. Similar to most respiratory infections, the therapeutic decision in the first phase is empiric and based on the need to cover the pathogens that are most common in these episodes. In terms of the host it is important to consider the clinical risk factors that could lead to treatment failure and also to provide antibacterial cover for less common pathogens in patients at risk.[10] These risk factors include: moderate or severe airflow obstruction; four or more episodes of exacerbation in the preceding year; frequent antibacterial therapy; and chronic comorbidity (congestive heart failure, diabetes, chronic renal failure, and chronic liver disease). From the pharmacologic point of view, it is desirable to treat with an oral preparation that is well absorbed and administered once or, at most, twice daily with few adverse effects and a minimal risk of development of drug resistance.

3. Microbiology of *Pseudomonas* spp.

Pseudomonas spp. are aerobic, nonspore-forming, Gram-negative rods which are straight or slightly curved. They are 1.5–5μm long and 0.5–1.0μm wide and possess a strictly respiratory meta-

bolism with oxygen as a terminal electron acceptor. *P. aeruginosa* is the most important human pathogen in the genus *Pseudomonas* with respect to both the number and types of infections caused and their associated morbidity and mortality. *Pseudomonas* spp. other than *P. aeruginosa* infrequently cause infection. Because of their low virulence, infections due to these species are often iatrogenic and are associated with the administration of contaminated solutions, medicines, and blood products or the presence of indwelling catheters. *P. aeruginosa* have a predilection for moist environments. Because of their ability to survive in aqueous environments, these organisms have become problematic in the hospital environment and have been found in a variety of aqueous solutions and frequently in equipment used for respiratory disorders. *P. aeruginosa* is found infrequently as part of the microbial flora of healthy individuals. In these persons, the gastrointestinal tract is the most frequent site of colonization, but other moist body sites including the throat and nasal mucosa may become colonized.[11]

An unusual 'mucoid' phenotype of *P. aeruginosa* chronically infects approximately 70–80% of adolescents and adults with cystic fibrosis.[12] The high levels of elastase produced by this pathogen damage the lungs and have a cumulative, deleterious effect on pulmonary function over a period of years or even decades, eventually resulting in death.[13] Mucoid phenotypes of *P. aeruginosa* are occasionally seen causing pulmonary infections in individuals with other chronic lung disease.[14]

Community-acquired isolates of *P. aeruginosa* are usually susceptible to antipseudomonal penicillins (ticarcillin and piperacillin), the aminoglycosides (gentamicin, tobramycin, and amikacin), ciprofloxacin, cefoperazone, ceftazidime, meropenem, and imipenem. Susceptibility is less predicable for other broad-spectrum cephalosporins (ceftriaxone and cefotaxime) and the monobactam aztreonam.[11]

Nosocomially-acquired isolates of *P. aeruginosa* tend to be more resistant to antimicrobial agents than the community-acquired strains and frequently display resistance to multiple classes of antimicrobial agents.[11]

4. Epidemiology of Pseudomonal Infection in COPD

4.1 Colonization with *P. Aeruginosa* in COPD Patients

The rate of colonization with *P. aeruginosa* in patients with COPD is low. In a bronchoscopic study,[15] there was no evidence of colonization with this bacterium in any of 18 stable patients. In another bronchoscopic study, colonization with this bacterium was identified in only 1 of 40 patients studied.[5] However, these two bronchoscopic studies included patients with moderate COPD. In another study, which included COPD patients with more advanced airway obstruction and was based on expectorated sputum, the rate of *P. aeruginosa* colonization in stable patients was 3.6%.[6] In a separate study that was based on expectorated sputum[3] and included other patient groups besides COPD (all in stable condition), colonization with *P. aeruginosa* was identified in 9% of the patients studied. These colonized patients had particularly high levels of myeloperoxidase in their sputum as an expression of the high level of respiratory tract inflammation induced by that bacterium.

4.2 Pseudomonal Infection in Outpatients with Acute Exacerbations of COPD

The vast majority of data on the prevalence of infections caused by *P. aeruginosa* in patients with acute exacerbations of COPD and chronic bronchitis come from studies that were conducted to assess or compare the effectiveness of various antibacterial therapies in those episodes. Another source of epidemiological data included the relatively few studies that were conducted to investigate the inflammatory aspects of these episodes. In all of these studies the source for isolation of *P. aeruginosa* was expectorated sputum from patients in the exacerbation phase of their chronic disease. Table I presents data on the percentage of isolates of *P. aeruginosa* in acute exacerbations of COPD or chronic bronchitis derived from 16 studies that were published between 1996 and 2002. In all of these studies the participating patients were outpatients. The percentage of isolates of *P. aeruginosa* ranged from 1% to 13% of the total bacterial isolates. The percentage of COPD exacerbations in which *P. aeruginosa* was isolated ranged from 1% to 8%. An averaging of the percentages presented in table I showed that the mean percentage of exacerbations in which *P. aeruginosa* was isolated was 3.9% and that 6.6% of all bacterial isolates were *P. aeruginosa*. A unique bronchoscopic study[5] of the prevalence of various bacteria in the lower respiratory tract in 29 outpatients with acute exacerbations of COPD reported higher rates of pseudomonal infection. In that study there were 17 bacterial isolates, of which two were *P. aeruginosa*, representing 7% of all exacerbations and 12% of all bacterial isolates. In none of these reports were there any details of the clinical or spirometric characteristics concerning the patients in whom *P. aeruginosa* was identified in the sputum. Due to this lack of data it is impossible to attribute specific characteristics or risk factors to the isolation of *P. aeruginosa* from sputum during exacerbations. It is impossible to rule out the possibility that the difference in results of the various studies stems from differences in the technique of sputum sampling, handling, or culturing. However, in light of other data in the literature that will be discussed subsequently, it is reasonable to assume that the main reason for the differences in the rate of pseudomonal infections in exacerbations of COPD lies in the

Table I. Rates of *Pseudomonas aeruginosa* infection in outpatients with acute exacerbations of COPD and chronic bronchitis

Study	Year of publication	Exacerbations (n)	Bacterial isolates (n)	*P. aeruginosa* isolates (% of total)	Exacerbations with *P. aeruginosa* (% of total)
Allegra et al.[16]	1994	728	375	11	6
Langan et al.[17]	1997	656	542	3	2
Anzueto et al.[18]	1998	2180	673	4	1
Chodosh et al.[19]	1998	307	208	3	2
Chodosh et al.[20]	1998	376	234	5	3
Langan et al.[21]	1998	684	211	5	2
Habib et al.[22]	1998	373	181	13	6
DeAbate et al.[23]	1998	798	835	4	4
Pryka et al.[24]	1998	228	191	6	5
Wilson et al.[25]	1999	750	342	1	1
Shah et al.[26]	1999	832	577	8	6
Read et al.[27]	1999	364	128	5	2
Davies and Maesen[28]	1999	140	146	8	8
Casellas et al.[29]	1999	154	112	10	7
Sethi et al.[6]	2002	363	142	10	4
Grassi et al.[30]	2002	235	103	9	4

distribution of clinical characteristics, especially the severity of airflow obstruction in the patients included in the studies. Therefore, it is noteworthy that all rates cited express the rates of isolation of *P. aeruginosa* in acute exacerbations of COPD without proof of a causal association between the bacterium and the exacerbation. In one of those studies,[6] the rate of isolation of *P. aeruginosa* was compared in COPD patients with and without exacerbation; infection with *P. aeruginosa* was not associated with an increased frequency of exacerbations.

4.3 Pseudomonal Infection in COPD Patients with Severe Airflow Obstruction

The association between bacterial etiology and the severity of airway obstruction, as measured by pulmonary function tests, has been investigated in only a few studies. Although these studies had limitations of sample size, selection bias, and antibacterial intake that limited the validity of their conclusions, they were the only studies available in the literature on this issue. In a retrospective study of 112 patients hospitalized with infective exacerbation of chronic bronchitis,[31] 82 had sputum cultures that were positive for bacteria and FEV_1 values <50% of predicted. *P. aeruginosa* was isolated in 13 of these patients (16%). In contrast, in patients with FEV_1 >50% of predicted, *P. aeruginosa* was isolated in only one patient. In this study, among patients with FEV_1 <50% of expected, the following rates of infection with other bacteria were noted; *Streptococcus pneumoniae* in 12 patients (15%), *Hemophilus influenzae* in 10 (12%), and *Moraxella catarrhalis* in 7 (9%). It was impossible to determine from the published data the exact percentage of all the patients included in the study, with FEV_1 <50% of expected, who had positive sputum cultures for these bacteria. However, positive cultures were noted in 53% of all participants who were hospitalized and met the inclusion criteria. Thus, it can be approximated that among all the patients with acute exacerbations of COPD and FEV_1 <50% of expected, *P. aeruginosa* can be isolated in about 8% of the patients. Confirmation for this trend of an association between the isolation of *P. aeruginosa* and low FEV_1 values was also reported in another group of patients with acute exacerbation of COPD.[32] In a separate multicenter study,[33] quantitative cultures of expectorated sputum were carried out in 91 ambulatory patients with acute exacerbations of COPD. *P. aeruginosa* was isolated in 13 (20%) of 64 patients with FEV_1 <50% of expected, compared with only one of 27 patients with FEV_1 values >50% of expected. Again, in this study it was impossible to determine the exact percentage of participating patients with FEV_1 <50% from whom the bacteria were isolated, but the authors did state that the data related to 65% of the patients who met the inclusion criteria. This fact enables us to estimate that, in this study, among all patients with acute exacerbations of COPD and FEV_1 <50% of expected, *P. aeruginosa* was isolated in approximately 13%. Further analysis of the results of this study showed that all patients with *P. aeruginosa* in their sputum had FEV_1 values <1700mL, and that FEV_1 <50% of expected was a risk factor for isolation of *P. aeruginosa* with an odds ratio (OR) of 6.62. Another noteworthy finding was the prevalence of *H. in-*

fluenzae in 28% isolates (OR 6.85) with 9% of the isolates positive for *S. pneumoniae* and 8% for *M. catarrhalis*. A group of pathogens that has been recently added to the list of causative agents of acute exacerbations of COPD are the atypical bacteria. They were also identified at significant rates in the group of patients with severe airway obstruction.[34]

In summary, these data indicate that FEV_1 <50% of expected in patients with stable disease is a risk factor for the isolation of *P. aeruginosa* from sputum during an acute exacerbation of COPD. In these patients the rate of isolation of this bacterium reaches 8–13%, but the prevalence of the classic bacteria associated with acute exacerbations of COPD such as *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* is much higher.

4.4 Pseudomonal Infection in Mechanically Ventilated Patients with Acute Exacerbations of COPD

In terms of clinical severity of exacerbations, patients with COPD who develop serious respiratory deterioration with respiratory insufficiency and mechanical ventilation are at the far end of the spectrum. This group of patients are also unique in terms of the microbiologic etiology of the exacerbation. In 54 patients with acute exacerbation of chronic bronchitis who required mechanical ventilation, the lower respiratory tract was evaluated within 24 hours of hospitalization by flexible bronchoscopy with PSB and quantitative cultures.[35] *P. aeruginosa* was isolated in three patients (6%). In contrast, in that same series *S. pneumoniae*, *H. influenzae*, *H. parainfluenzae* and *M. catarrhalis* were identified in 27 isolates. In a more recent study,[36] the microbiology of the upper and lower respiratory tract was analyzed in 50 patients with severe acute exacerbations of COPD who were hospitalized from the community and required mechanical ventilation. In this study all patients underwent tracheobronchial suction, fiberoptic bronchoscopy with PSB and bronchoalveolar lavage. *P. aeruginosa* was identified in significant concentrations in nine patients (18%) and *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* were found in significant concentrations in 19 of 34 (56%) isolates. Clinical parameters did not predict the presence of *Pseudomonas* spp. and these bacteria were not identified in patients with lower FEV_1. The authors[36] suggested that in this population of patients with acute exacerbations of COPD antibacterial therapy should be based on the results of bacteriologic samples from the respiratory tract.

5. Recommendations for Antibacterial Therapy

Not a single study has shown failure of treatment of acute exacerbations of COPD to be linked with isolation of *P. aeruginosa* and ineffective antibacterial treatment. However, in light of the methodologic difficulties involved in conducting studies of this type it is not surprising that, to date, there has been no studies designed to specifically address this issue. Under these circumstances, infection with *P. aeruginosa* has to be taken into account in some COPD patients experiencing acute exacerbations. It is critical to remember that in the vast majority of cases initial antibacterial therapy is empiric and based in the absence of diagnostic certainty as to the precise bacterial etiology. Under these conditions, infection with *P. aeruginosa* has to be considered, particularly in the subgroups of patients with a higher risk for this pathogen. In those cases it is reasonable that the therapeutic spectrum of the empirically chosen initial antibacterial drug should include *P. aeruginosa*.

We propose that sputum samples be cultured in patients with frequent episodes of acute exacerbations of COPD or patients who have received antibacterial therapy frequently at the time of initiation of empiric therapy. Treatment failure with one of the preparations, together with a sputum culture in which a bacterium resistant to the empiric therapy is identified, will then lead to discontinuation of the initial empiric therapy and its substitution with another antibacterial.

As described in section 2.2, the two risk factors for *P. aeruginosa* infection in patients with COPD are advanced obstructive airflow impairment and mechanical ventilation. The prevalence of pseudomonal infection in these two groups was 8–13%[33] and 6–18%[36], respectively, of all study episodes of acute exacerbations of COPD. Rates of this magnitude could lead to controversy as to the justification for including *P. aeruginosa* in the list of pathogens that should be covered by initial empiric therapy. Our inclination to answer this question affirmatively stems from the fact that in those studies other pathogens that are microbiologically close to *P. aeruginosa* were also identified and they responded to the same antipseudomonal antibacterial therapy. In addition, it should be noted that there were a significant number of episodes in those studies in which the true bacterial etiology was not identified. The possibility that in some of those cases *P. aeruginosa* or a related bacterium was the causative agent cannot be ruled out. These two findings can potentially increase the stated prevalence rates.

The discussion on recommendations for specific antibacterial treatment will be divided into: (i) the subgroup of patients with acute exacerbations of COPD with advanced obstructive airflow impairment who are treated as outpatients or hospitalized in stable respiratory condition; and (ii) the subgroup of patients with severe acute exacerbations of COPD who are hospitalized in an internal medicine ward or an intensive care unit with respiratory insufficiency and are either undergoing mechanical ventilation or are on the verge of requiring it.

6. Antibacterial of Choice for Acute Exacerbations in COPD Patients with Stable Respiratory Condition

6.1 The Need for an Oral Preparation

Therapy for all outpatients should be oral. Most hospitalized patients can and should receive oral antibacterial therapy. The recommendation for oral therapy, together with the need to cover *P. aeruginosa,* reduces the choices of a specific preparation to the fluoroquinolones.

6.2 Bacteriologic Considerations

Among the fluoroquinolones, ciprofloxacin still maintains the best *in vitro* activity against *P. aeruginosa*.[37] Despite this, the possibility of recommending ciprofloxacin as monotherapy for this group of patients is problematic primarily because this preparation demonstrates poor activity against *S. pneumoniae*, a bacterium that is very prevalent in these patients.

There are two possible solutions to this problem. First, to offer combination therapy with ciprofloxacin and another preparation that has good antistreptococcal activity, such as amoxicillin, amoxicillin/clavulanic acid, or trimethoprim/sulfamethoxazole (co-trimoxazole). This solution, like all combination therapies, is not optimal because the rate of adverse events is, at the least, additive for the two preparations, patient adherence is reduced due to the need to take more pills several times a day, and the increased cost. Combination therapy also does not provide a solution to the problem of penicillin-resistant *S. pneumoniae*. The other possible solution is monotherapy with one of the new fluoroquinolones that are now available i.e. levofloxacin, moxifloxacin, gemifloxacin, or gatifloxacin.

6.3 New Fluoroquinolones as Drugs of Choice

In comparison with ciprofloxacin the newer fluoroquinolone preparations including levofloxacin, moxifloxacin, gemifloxacin, and gatifloxacin have several significant advantages. Their improved pharmacokinetic and pharmacodynamic properties are manifested by excellent bioavailability and longer serum half-life, allowing for once-daily oral administration. The broad range of activity of these preparations provides excellent coverage of *S. pneumoniae* strains, including those that are resistant to penicillin and macrolides, making them ideal for the patient population under consideration. An additional advantage of these preparations is that their range of activity also includes the atypical pathogens. The major problem with these preparations in relation to the patient population discussed here is their limited activity against *P. aeruginosa*.[37] The significance of this limitation depends on how one looks at the relevant data. *In vitro* data show that for all four antibacterial preparations the minimum inhibitory concentration at which 90% of bacteria are inhibited are above the accepted breakpoints for the determination of resistance of this bacterium to the agent. In contrast, results from a global antibacterial resistance surveillance program showed that of 1135 isolates of *P. aeruginosa*, 69% were sensitive to gatifloxacin *in vitro* compared with 80% sensitivity to ciprofloxacin,[38] a difference that was not impressive. In addition, most *P. aeruginosa* isolates in the *in vitro* studies are from nosocomial infections in which the breakpoints for resistance for the bacterium is significantly higher than isolates from community-acquired respiratory infections.[39] Also, in some cases an isolate is resistant to a specific antibacterial preparation *in vitro*, but is actually sensitive to the same preparation *in vivo*.

In light of this, we believe that the best way to approach the limitations of the range of activity of the four new fluoroquinolone preparations against community-acquired respiratory infections is that they reduce by an uncritical degree the number of *P. aeruginosa* isolates sensitive to these preparations compared with ciprofloxacin, which is considered the optimal oral therapy in these infections. This situation should be considered together with the important data that in the population under discussion the overall rate of *P. aeruginosa* infections is about 10%, and the fact that these preparations provide excellent coverage against other common pathogens. The obvious conclusion, in our opinion, when all of this information is integrated, is that these preparations can definitely be suggested as drugs of choice for the initial empiric therapy in the subgroup of patients with acute exacerbations of COPD and advanced baseline airflow impairment under stable respiratory conditions.

6.3.1 Bacterial Resistance

In order to complete the discussion of the various bacteriologic considerations for the new fluoroquinolones, it should be noted that in a recent study[40] the resistance rates of *P. aeruginosa* to levofloxacin were similar to those of ciprofloxacin at around 16% in North America, 25% in Europe, and 33% in South America. The isolates tested in this study also included nosocomial infections, so it is reasonable to assume that community-acquired isolates would have even lower rates of resistance. There are unproven theoretical contentions that the mechanisms that lead to resistance to various bacteria are more likely to apply to levofloxacin than to moxifloxacin, gatifloxacin, or gemifloxacin.[41] Thus, at least to a certain degree, the latter three preparations are preferred over levofloxacin.

6.3.2 Cost Considerations

In an age in which all medical decisions are scrutinized from an economic perspective we should also take into account cost considerations relating to the suggested drugs of choice. The cost of purchase of the new fluoroquinolones is higher than any other oral monotherapy and even some of the combination therapies that could be considered for this group of patients. However, we believe that in the final analysis the higher purchase cost of these preparations will lead to a considerable reduction in the overall total cost of treatment of patients with COPD. The vast majority of these patients are at risk for treatment failure with initial empiric therapy with first-line drugs.[42] Treatment failure entails a significant risk for hospitalization and, in some patients, mechanical ventilation. The costs of hospitalization and mechanical ventilation, even in a small percentage of these patients, will lead to a much higher overall treatment cost than the total purchase cost of new fluoroquinolones. In addition to their high bacteriologic effectiveness, these preparations can be administered in a single daily oral dose, a property that increases patient adherence to the treatment and reduces the risk of treatment failure.

6.3.3 Practical Issues Relating to Treatment with the Newer Fluoroquinolones

The once-daily oral dosages and the duration of therapy successfully evaluated in clinical trials of acute exacerbation of chronic bronchitis for the four new fluoroquinolone preparations are as follows: levofloxacin 250–500mg for 5–7 days; moxifloxacin 400mg for 5 days; gatifloxacin 400mg for 7–10 days; and gemifloxacin 320mg for 5 days. The most common adverse effects of these preparations, that occur in low percentages of patients, include gastrointestinal tract symptoms (nausea, vomiting, diarrhea), central nervous system symptoms (dizziness, headaches), allergic reactions (rash, pruritus), phototoxicity, taste perversion, and vaginitis. The following more specific associations should be noted: nausea and diarrhea with moxifloxacin; nausea and vaginitis with gatifloxacin; and headaches with gemifloxacin.[37] The risk of a prolonged corrected QT interval (QTc) is considered a class effect of all fluoroquinolones and several preparations were removed from the market for this reason. Although a significant rate of cardiac abnormalities have not been reported with levofloxacin, moxifloxacin, gatifloxacin and gemifloxacin, its occurrence should be closely monitored. These drugs should be avoided in patients with significant cardiovascular disease, a history of a dangerous arrhythmia, or who are receiving other drugs that could potentially prolong the QTc interval. In general, drug interactions with new fluoroquinolones are limited, but all fluoroquinolones interact with metal ion-containing drugs such as antacids.[37]

7. Antibacterial of Choice for Mechanically Ventilated COPD Patients with Acute Exacerbations

The serious clinical condition of this group of patients stems primarily from ventilatory aspects of the episode. However, in light of the patient's critical clinical condition the infectious/bacterial aspects, which may make a significant contribution to the condition, cannot be ignored and require uncompromising attention when deciding on treatment. It should be noted that this section of our review deals only with community-acquired infections in mechanically ventilated patients with acute exacerbations of COPD and not with ventilator-associated pneumonia. The latter, different entity is not unique to this category of patients and is beyond the scope of the present review.

Pseudomonal infection as well as infection with other Gram-negative rods can be identified close to the time of hospitalization in up to one-fifth of the mechanically ventilated patients with acute exacerbations of COPD. The need for uncompromising antibacterial therapy means that the initial empiric therapy in these patients should include an antibacterial preparation that has maximal activity but minimal potential for resistance against *P. aeruginosa*. This is in addition to the requirement that all patients with acute exacerbation of COPD should receive initial empiric therapy that covers *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. The serious condition of these patients necessitates intravenous treatment in all cases, so the recommended therapy must also be available by this route.

The *in vitro* results of the worldwide SENTRY Antimicrobial Surveillance Program (1997–2000)[40] that were published recently provided important data obtained in recent years on resistance to *P. aeruginosa*, but without separate data on nosocomial and community-acquired isolates. In the light of these data the initial empiric treatment of choice in the specific patient populations alluded to, could include several treatment alternatives. One is to add amikacin to one of the intravenous preparations of the newer fluoroquinolones. Other options include monotherapy with cefepime or carbapenems or piperacillin/tazobactam. The choice among these alternatives should be made in accordance with the clinical condition of each specific patient, the resistance data for the specific geographic region, and the local purchase costs of each of the antibacterials.

Although each of these treatment alternatives provides highly effective antibacterial coverage for the bacteria involved in acute exacerbations of COPD, treatment failure can occur. Therefore, it is recommended that in patients with acute exacerbations of COPD who are mechanically ventilated a sample of respiratory tract secretions be drawn for culture through the tracheal tube before empiric antibacterial therapy is initiated.[36] The results of

the cultures, when available, should guide the decision to reduce the spectrum of antibacterial coverage for the duration of hospitalization in cases of treatment success, or to change the treatment in cases of treatment failure.

8. Conclusions

The rate of *P. aeruginosa* infections in all patients with acute exacerbations of COPD is very low, but it reaches significant proportions in two subpopulations. In patients with advanced airflow obstruction, as determined by lung function testing, the rate of infection is about 10%. In these patients, it is recommended that initial empiric therapy be one of the newer fluoroquinolone preparations such as levofloxacin, moxifloxacin, gemifloxacin or gatifloxacin. The rate of infection with *P. aeruginosa* is about 20% in patients with severe acute exacerbations of COPD who are mechanically ventilated. In these patients the recommended initial empiric therapy is intravenous treatment with classic antipseudomonal preparations. In both of these patient populations cultures of respiratory tract secretions should be used to guide and adjust antibacterial therapy following the initial phase.

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