Bacteriological Differences Between COPD Exacerbation and Community-Acquired Pneumonia

Xue-Jun Li MD, Qi Li MD, Liang-Yi Si MD, and Qiao-Ying Yuan MD

OBJECTIVE: To study the differences in pathogen distribution and antibiotic susceptibility between patients with COPD exacerbation and patients with community-acquired pneumonia, and develop guidance for antibiotic treatment of those conditions. METHODS: We retrospectively analyzed the medical records of 586 COPD-exacerbation patients and 345 community-acquired-pneumonia patients from January 2007 to December 2008, including sputum culture results, antibiotic susceptibilities of the microorganisms, and clinical characteristics. RESULTS: 276 (47%) of the COPD-exacerbation patients, and 183 (53%) of the community-acquired-pneumonia patients had a positive sputum culture. In order, the most common pathogens in the COPD-exacerbation patients were *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Acinetobacter baumannii*, and *Haemophilus influenzae*. The most common pathogens in the community-acquired-pneumonia patients were *Streptococcus pneumoniae*, *H. influenzae*, *K. pneumoniae*, *S. aureus*, and *E. coli*. CONCLUSIONS: *P. aeruginosa* was the most common pathogen in our patients with COPD exacerbation, and *S. pneumoniae* was the most common in our patients with community-acquired pneumonia. *P. aeruginosa* is especially common in the patients with serious or extremely serious COPD. *Key words: COPD; exacerbation; community-acquired pneumonia; bacteriology.* [Respir Care 2011;56(11):1818–1824. © 2011 Daedalus Enterprises]

Introduction

Community-acquired pneumonia refers to infected pulmonary parenchymal inflammation that is acquired outside the hospital, has a defined incubation period, and occurs within that average incubation period after entering the hospital. Community-acquired pneumonia is a common and important disease and a threat to human health; it is the first cause of death from infection.[1] Changes in pathogens and increases in the antibiotic-resistance rate have caused many problems in the treatment of community-acquired pneumonia.[2] Therefore, accurate and timely diagnosis and early treatment are key in prognosis.

The authors are affiliated with the Department of Geriatrics, Southwest Hospital, Third Military Medical University, Chongqing, China.

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Correspondence: Xuejun Li MD, Department of Geriatrics, Third Military Medical University, Gao Tanyan Street 30, Sha Pingba District, Chongqing 400038, China. E-mail: lixuejun3@126.com.

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COPD is a global disease with a very high incidence. According to China's epidemiological survey in 2002, the incidence of COPD in people over 40 years of age was 8.2%. Every year millions of patients suffer COPD exacerbation, and more than 1 million people die of COPD.[3] Thus far, the pathogenesis of COPD exacerbation has not been determined; some scholars believe that 80% of COPD exacerbation cases are caused by lower-respiratory-tract infection, and that 50–60% of the pathogens that cause COPD exacerbation are bacteria.[4] Fanny et al found that the most frequent pathogens of COPD exacerbation were *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*.[5]

COPD exacerbation and community-acquired pneumonia usually cause some of the symptoms of respiratory-tract infections, such as fever, purulent sputum, an increase in white blood cells, and an increase in C-reactive protein. Additionally, COPD exacerbation often coexists with community-acquired pneumonia, and several studies have found that early-onset COPD exacerbation and community-acquired pneumonia have similar pathogenic spectrums.[6] Both the American Thoracic Society and European Respiratory Society guidelines for the manage-

ment of community-acquired pneumonia and COPD exacerbation comment on the analogous empirical antibiotic choices in the early stages of these 2 diseases. Therefore, the treatment of these diseases is similar. However, there are some bacteria differences between COPD exacerbation and community-acquired pneumonia when the severity of the diseases differs.[7] We studied the differences in clinical features, etiologies, and antibiotic susceptibilities of the bacteria in patients with community-acquired pneumonia versus patients with COPD exacerbation, and provide a scientific basis for antibiotic selection.

Methods

This study was approved by the research ethics committee of Southwest Hospital, Third Military Medical University, Chongqing, China. The study was retrospective, so the research ethics committee waived the consent requirement.

Study Population

We retrospectively analyzed the medical records of patients with COPD exacerbation and community-acquired-pneumonia, treated at the Southwest Hospital of the Third Military Medical University, from January 2007 to December 2008. We searched our electronic medical records database with key words "exacerbation," "COPD," "chronic bronchitis," and "community acquired pneumonia." We included all patients who had microbiology results from sputum. We excluded patients who did not meet the COPD diagnostic criteria of the 2006 Global Initiative for Chronic Obstructive Lung Disease guidelines (post-bronchodilator $FEV_1/FVC < 0.70$). COPD exacerbation was diagnosed when a patient with background COPD presented with at least 2 of the following major symptoms: increased dyspnea, increased sputum purulence, and increased sputum volume. We excluded patients who were diagnosed with bronchiectasis or apparent consolidation on admission chest radiograph. Community-acquired pneumonia was defined as a new infiltrate on chest radiograph, and at least one major or two minor Fang criteria.[8] Severe community-acquired pneumonia at the time of hospitalization was defined according to then-current American Thoracic Society guidelines.[9] In the community-acquired-pneumonia group we excluded patients who had COPD.

Data Collection

From the medical records we collected data on patient age, sex, smoking history, home oxygen therapy, antibiotic and glucocorticoid use, admission arterial blood gas values, leukocyte count, body temperature, hospital days, and efficacy evaluation. We graded COPD severity according to the 2007 Global Initiative for Chronic Obstructive Lung Disease guidelines.

Microbiological Evaluation

Sputum specimens collected from expectoration, tracheal suctioning, or bronchoalveolar lavage were analyzed with standard procedures within 48 hours of admission. Microscopy was performed on Gram-stained smears. Sputum was cultured on 5% horse blood agar and chocolate agar and incubated in CO_2 for 24–48 hours. The isolates were tested for sensitivity to beta-lactams, a combination of beta-lactam and clavulanic acid, macrolides, and quinolones. Based on microscopy, only specimens representative of the lower respiratory tract were used. A representative lower-respiratory-tract sample was defined as containing < 25 leukocytes and > 10 epithelial cells per low-power field.

Statistical Analysis

Data are expressed as means ± SD. Categorical variables were analyzed with the chi-square test. A P value of $< .05$ was considered significant. The analyses were performed with statistics software (SPSS 10.0, SPSS, Chicago, Illinois).

Results

Clinical Features

There were 875 episodes of COPD exacerbation, in 756 patients, from January 2007 to December 2008. We excluded 170 cases: 123 for pneumonia on initial chest radiograph, and 47 who did not have sputum-culture results. Thus, the COPD group included 586 patients with sputum-culture results and without consolidation on initial chest radiograph. There were 418 men and 168 women, and this group's mean age was 75.3 ± 8.4 years.

In the community-acquired-pneumonia group there were 437 cases, 92 of which were excluded: 59 had been admitted within the previous 15 days, and 33 had severe immunosuppression from conditions such as neutropenia, human immunodeficiency virus infection, or solid-organ or bone-marrow transplant. There were 217 male cases and 128 female cases, and the mean age was 61.3 ± 5.5 years (Table 1).

The average age of the COPD patients was significantly higher than that of the community-acquired-pneumonia patients, and the COPD patients were predominantly male and contained a larger number of ex-smokers. More than

Table 1. Subjects

	COPD Exacerbation (n = 586)	Community-Acquired Pneumonia (n = 345)	P
Age (mean ± SD y)	75.3 ± 8.4	61.3 ± 5.5	< .001
Male, no. (%)	418 (71)	217 (63)	.008
Smoking History, no. (%)			
Current smoker	89 (15)	89 (26)	< .001
Ex-smoker	363 (62)	63 (18)	< .001
Non-smoker	134 (23)	193 (56)	.02
Home oxygen therapy, no. (%)	105 (18)	0	
Corticosteroid use, no. (%)			
Oral	87 (15)	11 (3)	< .001
Inhaled	247 (42)	0	
Antibiotics in the past week, no. (%)	216 (37)	85 (25)	.03
Admission in the past 3 months, no. (%)	160 (27)	23 (13)	<.001

NA = not applicable

Table 2. Admission Clinical Data

	COPD Exacerbation (n = 586)	Community-Acquired Pneumonia (n = 345)	P
Fever (> 38.0°C), no. (%)	158 (27)	120 (35)	.01
Leukocyte count ($\times 10^3$ cells/μL)	12.3 ± 4.1	14.7 ± 5.2	.053
Neutrophils (%)	75 ± 15	82 ± 22	.55
FEV_1 (% predicted)	62 ± 31.8	ND	NA
Comorbidities, no. (%)	317 (54)	95 (28)	< .001
Congestive heart failure	112 (19)	48 (14)	< .001
Coronary artery disease	61 (10)	10 (3)	< .001
Renal disease	71 (12)	19 (6)	.001
Liver disease	18 (3)	17 (5)	.15
Cerebrovascular accident	105 (18)	51 (15)	.22
Diabetes	148 (25)	63 (18)	.01
Others	31 (5)	21 (6)	.61
COPD Severity, no. (%)			
Mild	62 (11)	NA	NA
Moderate	270 (46)	NA	NA
Severe to very severe	254 (43)	NA	NA
Community-Acquired Pneumonia Severity Index, no. (%)			
Class I or II	NA	42 (12)	NA
Class III	NA	210 (61)	NA
Class IV or V	NA	93 (27)	NA
Mortality, no. (%)	57 (10)	23 (7)	.11
Stay (d)	16.7 ± 3.8	10.2 ± 4.5	< .001
Mechanical ventilation, no. (%)	115 (20)	49 (14)	.04
Noninvasive ventilation, no. (%)	110 (19)	39 (9)	.003
Admitted to intensive care unit, no. (%)	20 (3)	14 (4)	.61

± values are mean ± SD.
ND = no data collected
NA = not applicable

70% of the COPD patients had used corticosteroids. Respectively, 37% and 32% of the COPD-exacerbation and community-acquired-pneumonia patients had taken antibiotics within the week before hospitalization (Table 2).

Microbiology

Of the 586 COPD-exacerbation patients, there were 276 cases with positive sputum bacterial culture (47%). We isolated 325 bacterial strains, and the top 5 pathogens were *Klebsiella pneumoniae*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *P. aeruginosa*. More than one bacterial strain was isolated from the sputum of 38 patients (7%).

In the 345 community-acquired-pneumonia patients, there were 183 cases (53%) with a positive sputum bacterial culture. We isolated 214 bacterial strains, and the top 5 pathogens were *S. pneumoniae*, *K. pneumoniae*, *H. influenzae*, *Staphylococcus aureus*, and *P. aeruginosa*. More than one bacterial strain was isolated in 17 patients (5%). Tables 3 and 4 show the relationships between bacteria type and disease severity. Infections in patients with mild or moderate COPD were mainly caused by *S. pneumoniae*, which had an isolation rate of 45%. *P. aeruginosa* played an important role in infections in patients with severe COPD, and had a bacterial isolation rate of 12%. *Acinetobacter baumannii* was found only in patients with extremely severe COPD exacerbation. In the community-acquired-pneumonia patients, the isolation rate of *Pneumococcus* was higher than that of any other bacteria, and accounted for 28%. In patients with severe community-acquired pneumonia the isolation rate of *S. aureus* was the highest (27%) and was significantly higher than that of patients with mild or moderate community-acquired pneumonia.

According to experimental results from the 10 antibiotics, the sensitivity of *P. aeruginosa* to amikacin was greater than 70%, and the sensitivities to meropenem and ceftazidime were approximately 66%; the sensitivities to all the other tested antibiotics were lower. The sensitivity of the *P. aeruginosa* from the community-acquired-pneumonia patients was greater than that from COPD-exacerbation patients, which could be because *P. aeruginosa* is isolated less often from community-acquired-pneumonia patients. In addition, multiple-drug-resistant *P. aeruginosa* accounted for approximately 40% of the community-acquired pneumonia cases (Table 5).

Figures 1 and 2 show the antimicrobial susceptibility of 47 sputum isolates of *P. aeruginosa*, and 90 sputum isolates of *S. pneumoniae*, respectively.

Table 3. Sputum Bacteria Versus COPD Severity

	COPD Severity Stage, no. (%)			
	I or II FEV_1 50–80%* (n = 29)	III FEV_1 30–50%* (n = 143)	IV FEV_1 < 30%* (n = 153)	All (n = 325)
Streptococcus pneumoniae	11 (38)	13 (9)	7 (5)	31 (10)
Staphylococcus aureus	0 (0)	5 (4)	15 (10)	20 (6)
Haemophilus influenzae	7 (24)	37 (26)	27 (18)	71 (22)
Klebsiella pneumoniae	8 (28)	54 (38)	30 (20)	92 (28)
Escherichia coli	0 (0)	5 (4)	6 (4)	11 (3)
Pseudomonas aeruginosa	0 (0)	14 (10)	33 (22)	47 (15)
Acinetobacter baumannii	0 (0)	0 (0)	23 (15)	23 (7)
Moraxella catarrhalis	2 (7)	5 (4)	0 (0)	7 (2)
Other bacteria	1 (4)	10 (7)	12 (8)	23 (7)

* Percent of predicted.

Table 4. Sputum Bacteria Versus Community-Acquired Pneumonia Severity

	Community-Acquired Pneumonia Severity Stage, no. (%)			
	I or II (n = 25)	III (n = 125)	IV or V (n = 64)	All (n = 214)
Streptococcus pneumoniae	12 (48)	35 (28)	6 (9)	53 (25)
Staphylococcus aureus	0 (0)	10 (8)	17 (27)	27 (13)
Haemophilus influenzae	4 (16)	32 (26)	12 (19)	48 (22)
Klebsiella pneumoniae	7 (28)	33 (26)	11 (17)	51 (24)
Escherichia coli	1 (4)	7 (6)	5 (8)	13 (6)
Pseudomonas aeruginosa	0 (0)	1 (1)	6 (9)	7 (3)
Acinetobacter baumannii	0 (0)	0 (0)	2 (3.1)	2 (1)
Moraxella catarrhalis	1 (4)	5 (4)	1 (2)	7 (3)
Other bacteria	0	2 (2)	4 (6)	6 (3)

Table 5. Antibiotic Resistance of Bacteria in Our Subjects

	Community-Acquired Pneumonia no. (%)	COPD Exacerbation no. (%)	Total no. (%)	P
Multiple Drug Resistance				
Staphylococcus aureus	14/21 (67)	19/27 (70)	33/48 (69)	.78
Pseudomonas aeruginosa	6/15 (40)	18/40 (45)	24/55 (44)	.74
Resistance to Extended-Spectrum Beta Lactamase				
Escherichia coli	8/13 (62)	7/11 (64)	15/24 (63)	.63
Klebsiella pneumoniae	21/58 (36)	29/78 (37)	50/136 (37)	.91

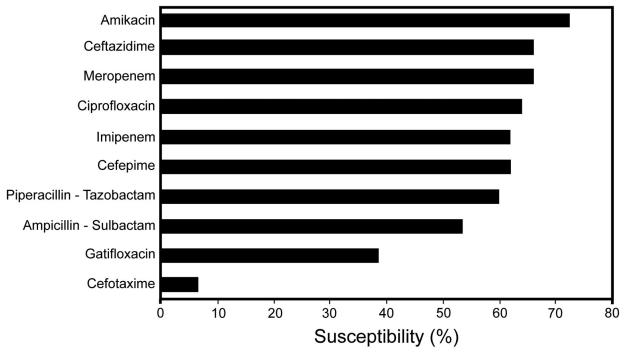

Fig. 1. Antimicrobial susceptibility of 47 sputum isolates of *Pseudomonas aeruginosa*.

Treatments and Outcomes

The average hospitalization was 17.8 ± 5.5 days for the COPD-exacerbation patients and 13.3 ± 6.1 days for the community-acquired-pneumonia patients. The number and percentage of patients who needed mechanical ventilation in the COPD-exacerbation and community-acquired-pneumonia groups were 115/586 (20%) and 49/345 (14%), respectively, and that difference was significant. The death rates of the COPD-exacerbation and community-acquired-pneumonia groups were 10% and 7%, respectively ($P < .01$).

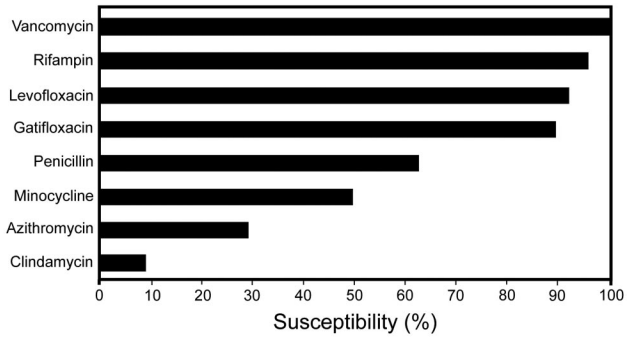

Fig. 2. Antimicrobial susceptibility of 90 sputum isolates of *Streptococcus pneumoniae*.

Table 6. Antibiotic Therapy

	COPD Exacerbation (n = 586) no. (%)	Community-Acquired Pneumonia (n = 345) no. (%)	P
Respiratory fluoroquinolone	189 (32)	151 (41)	< .001
Macrolides	61 (10)	48 (13)	.11
Third-generation cephalosporin	205 (35)	101 (27)	.07
Semisynthetic penicillin	131 (22)	49 (13)	.002
Carbapenems	89 (15)	42 (11)	.20
Other*	48 (8)	28 (8)	.97
Combination therapy	124 (21)	51 (14)	.03

* The other drugs included clindamycin, first-generation cephalosporins, second-generation cephalosporins, and aminoglycosides.

The most commonly used antibiotic among the community-acquired-pneumonia patients was respiratory quinolone, followed by third-generation cephalosporins (Table 6). The most commonly used antibiotic among the COPD-exacerbation patients was the third-generation cephalosporins, then respiratory quinolone. The use of carbapenem in the COPD-exacerbation group was significantly higher than that in the community-acquired-pneumonia group, and the COPD-exacerbation group received more combined antibiotic therapy than the community-acquired-pneumonia group ($P < .01$).

Discussion

Both community-acquired pneumonia and COPD exacerbation have high morbidity and mortality and are caused by bacterial infections. Community-acquired pneumonia is the most common complication of COPD exacerbation.[10] Some studies have carefully examined whether patients with community-acquired pneumonia and COPD present differences in clinical manifestations, etiology, or outcome, with special emphasis on mortality compared to those that do not have COPD.[11,12] To our knowledge, the present study is the first to compare the clinical features, etiological distribution, and treatment outcomes of patients with COPD exacerbation versus patients with community-acquired pneumonia.

The COPD-exacerbation group was significantly older than the community-acquired-pneumonia group (64.7 ± 8.4 y vs 61.3 ± 5.5 y), and there were significant differences in the ratios of sex, smoking, use of glucocorticoids (inhaled or oral), and antibiotics use before hospitalization between the 2 groups. Furthermore, the COPD-exacerbation patients had a higher ratio of mechanical ventilation than the community-acquired-pneumonia patients, the majority of whom needed noninvasive ventilation. All these clinical differences are in agreement with the clinical features of the two diseases.[13]

The rate of positive sputum culture in the COPD-exacerbation patients was significantly lower than that in the community-acquired-pneumonia patients. This result might be explained by the fact that the ratio of viruses and atypical pathogens in COPD-exacerbation pathogens is higher than in community-acquired-pneumonia pathogens, and that the ratio of COPD-exacerbation patients who received antibiotics before hospitalization was significantly higher than in the community-acquired-pneumonia patients.[14] The top 5 bacteria in the COPD-exacerbation patients were *K. pneumoniae, H. influenzae, P. aeruginosa, S. pneumoniae*, and *A. baumannii*.[15] The top 5 bacteria in the community-acquired-pneumonia patients were *S. pneumoniae*, *K. pneumoniae, H. influenzae, S. aureus*, and *Escherichia coli*.[16]

Due to differences in disease severity, the bacterial distribution was significantly different between the 2 groups. *S. pneumoniae*, *K. pneumoniae*, and *H. influenzae* were the major bacteria in patients with mild COPD exacerbation, and each of those bacteria accounted for approximately 25%. In the patients with severe COPD exacerbation the percentages of some non-fermenting bacteria (eg, *P. aeruginosa* and *A. baumannii*) were quite high (22% and 15%, respectively), whereas the percentage of *S. pneumoniae* was only 5%. The etiological distribution in the community-acquired-pneumonia patients was different. *S. pneumoniae* was the most common species in all severity levels in the community-acquired pneumonia patients, and the total percentage was 28%. The isolation rates of *K. pneumoniae* and *H. influenzae* in the level I–III community-acquired-pneumonia patients were both more than 25% of the isolation rate. *S. aureus* was the most common bacteria in the patients with level IV or greater community-acquired pneumonia, and accounted for about 25%.[17] The percentage of mixed infections that were caused by COPD exacerbation was slightly higher than those caused by community-acquired pneumonia.

S. pneumoniae was the main pathogen in community-acquired pneumonia patients, and its isolation rate in the COPD-exacerbation patients was close to 10%. The drug-resistance rates of *S. pneumoniae* to penicillin and macrolide antibiotics could reach 42% and 90%, respectively.

The isolation rate of *S. aureus* in patients with severe community-acquired pneumonia was the highest (about 25%). The percentage of isolated methicillin-resistant *S. aureus* was 69%. Therefore, the antibiotics used to treat severe community-acquired pneumonia should be effective against methicillin-resistant *S. aureus*.

P. aeruginosa was the common bacteria in severe and extremely severe COPD exacerbation and was especially common in older patients who had used antibiotics before hospitalization and needed a respirator. *P. aeruginosa* has also been found in some patients with severe community-acquired pneumonia. *P. aeruginosa* is more susceptible to amikacin than to any other drug, and hydrocarbon mold vinyl antibiotics are the next most effective. However, the susceptibilities are both less than 80%. Because amikacin has a weaker sterilization effect in an acidic and hypoxic environment and could easily induce drug resistance if used alone,[18] we used it with other drugs. The percentage of multiple-drug-resistant *P. aeruginosa* was relatively high, which might be due to the patients' advanced ages, comorbidities, long-term use of inhaled corticosteroids, a long hospitalization period, and the use of a respirator.

A. baumannii was found only in patients with extremely severe COPD exacerbation. Carbapenem antibiotics have the strongest effect in inhibiting *A. baumannii*'s in vitro activity, but its sensitivity rate has decreased to 75%. Of course, the sensitivity to any other antibiotic is even lower. We also found 2 pan-resistant strains of *A. baumannii*. The relevant percentages of extended-spectrum beta-lactamases produced by *E. coli* and *K. pneumoniae* were 63% and 37%, respectively, which are significantly higher than the 35% reported by Qiu et al.[19] Our extended-spectrum beta-lactamases produced by *E. coli* and *K. pneumoniae* were mainly the TEM-X-type beta-lactamases, which is in agreement with a previous report.[20] Presently, carbapenems are the most effective drugs for the treatment of *E. coli* and *K. pneumoniae*.

The mortalities of the COPD-exacerbation and community-acquired-pneumonia groups were 12% and 9%, respectively. That difference is statistically significant and might be due to the advanced age, comorbidities, poor nutrition, and immunization conditions of the COPD-exacerbation patients. The use of inhaled corticosteroid was not significantly associated with mortality in the COPD-exacerbation patients.[21,22]

Respiratory quinolone was the common antibiotic in both groups, used in more than a third of the cases. In recent years the drug resistance of *S. pneumoniae* has been rising, and the isolation rate of atypical pathogens in COPD-exacerbation patients and community-acquired pneumonia patients has increased.[23] Additionally, with its good pharmacokinetic performance, high drug concentration in the lung tissue, long half-life, highly efficient bactericidal effect, broad antibiotic spectrum, low drug-resistance rate, safety, convenience, and good tolerance in patients, respiratory quinolone is being used more and more frequently.[24] In contrast, because of problems such as inducing drug resistance and cross-resistance, third-generation cephalosporins are gradually being eliminated. The use of carbapenem in the COPD-exacerbation group was significantly higher than in the community-acquired-pneumonia group, and the COPD-exacerbation group received more combined antibiotic treatment than the community-acquired-pneumonia group ($P < .01$). This might be because the COPD-exacerbation patients had a higher isolation rate of *P. aeruginosa*, *A. baumannii*, and other nonfermenting bacteria, a higher incidence of respirator use, and poorer basic patient conditions.

Limitations

The most important limitation was that the study population was in only one hospital and the cohort was primarily elderly and male, which may affect the representation of our findings. In addition, bacteria were identified with only one sputum culture, and there are more sensitive techniques we did not use. Because of the study's retrospective design, we may not have had the optimal clinical or laboratory data needed to evaluate clinical results. Further, multicenter prospective studies are needed to disclose the host-pathogen interaction that leads to COPD exacerbation and community-acquired pneumonia, to develop novel preventive and therapeutic approaches.

Conclusions

Bacteria was found in the sputum of more than half of the community-acquired-pneumonia patients and the COPD-exacerbation patients, but the bacterial isolation rate was lower in the patients who had used antibiotics before hospitalization. There were significant differences in the spectrum of bacteria in the community-acquired-pneumonia patients and the COPD-exacerbation patients with different disease severities. *S. pneumoniae* is the major pathogen of community-acquired pneumonia, whereas almost all COPD-exacerbation patients suffer from infections caused by Gram-negative bacilli. Respiratory quinolone can serve as the first-line drug for the empirical treatment of community-acquired pneumonia and COPD exacerbation, without the risk of infections from nonfermentative bacteria.[25] Carbapenems are the most effective at inhibiting Gram-negative bacilli, but their sensitivity to carbapenems is decreasing, so carbapenem use should

be strictly controlled. Combined antibiotic therapy might enhance the effect of treatment in patients with severe COPD exacerbation. These findings may influence the choice of empirical antibiotics in patients with COPD exacerbation or community-acquired pneumonia, according to disease severity. Multicenter prospective clinical research is required to determine reasonable treatment programs, improve prognosis, and develop novel preventive and therapeutic approaches for COPD exacerbation and community-acquired pneumonia.

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