Acute exacerbations of chronic obstructive pulmonary disease: etiological bacterial pathogens and antibiotic resistance in Upper Egypt

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Context Previous data on etiologic bacteria in acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in Upper Egypt are limited.

Aim The aim of this study was to identify the causative bacteria in AECOPD and to determine the antibiotic resistance patterns for AECOPD in Upper Egypt.

Settings and design The study design was a prospective one and was conducted in a University Hospital.

Materials and methods Patients who were admitted in Assiut University Hospital with AECOPD were prospectively enrolled. Sputum specimens were investigated using culture. Susceptibilities of the isolated bacterial strains to different antibiotics were determined using the disk diffusion method.

Results During 18 months, 156 patients who experienced 218 AECOPD were enrolled. A significant bacterial growth was found in 77% of patients during 81% of exacerbations. The most commonly detected bacteria were *Haemophilus influenzae* (18%), *Streptococcus pneumoniae* (15%), and *Klebsiella pneumoniae (*14%). The majority of the isolated strains showed high resistance rates to most groups of antibiotics; 63% of the isolated strains were multidrug resistant, 29% were extensively drug resistant, and 5% were pandrug resistant. High resistance rates were observed against penicillins and cephalosporins, moderate rates against fluoroquinolones, and lowest rates against the carbapenems. All gram-positive bacteria were sensitive to linezolid. Increased severity of chronic obstructive pulmonary disease was related to increased prevalence of antibiotic resistance.

Conclusion The predominant bacterial pathogens for AECOPD in Upper Egypt are *H. influenzae, S. pneumoniae*, and *K. pneumoniae*. Bacterial resistance rates were the highest against penicillins and cephalosporins, moderate against fluoroquinolones, and least against carbapenems. Increased severity of chronic obstructive pulmonary disease is related to an increased prevalence of antibiotic resistance.
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Keywords: antibiotic, bacteria, chronic obstructive pulmonary disease, etiology, exacerbation, resistance, Upper Egypt

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory airway disorder characterized by airflow limitation due to a mixture of small airway disease, chronic lung inflammation, parenchymal destruction, and increased airway responsiveness [1]. The chronic course of COPD is often accompanied by acute exacerbations [acute exacerbations of chronic obstructive pulmonary disease (AECOPD)], mainly due to increased inflammation. Patients prone to frequent AECOPD have impaired health status, reduced physical activity levels, increased lower airway bacterial colonization, and accelerated lung function decline [1,2]. Thus, the management of exacerbations with prompt diagnosis and effective treatment should be a major goal in COPD [2].

The majority of COPD exacerbations are caused by infections of the tracheobronchial tree [3]. A key characteristic of airway inflammation in COPD is the persistent presence of bacteria in the lower airways. The most commonly isolated bacteria in the lower respiratory tract of COPD patients were *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*, with growing evidence of the significance of *Pseudomonas aeruginosa* infections in severe COPD disease [4]. Previous data on infection exacerbations of COPD in Upper Egypt are limited [5]. Therefore, the present study was conducted to identify the causative bacteria in AECOPD and to determine the antibiotic susceptibility and resistance patterns among these pathogens at Assiut University Hospital, Upper Egypt.

Patients and methods

Study population

This prospective study aimed to identify the causative bacteria, antibiotic sensitivity, and antibiotic resistance

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in hospitalized patients due to AECOPD in Upper Egypt. All patients previously diagnosed for COPD and admitted with AECOPD in the Department of Chest Diseases, Assiut University Hospital, during the period between September 2014 and March 2016, were candidates for inclusion in the study. COPD diagnosis was based on medical history, clinical presentation, and pulmonary function tests recorded previously to the current admission and was defined according to the Global Initiative for Chronic Obstructive Lung Disease guidelines [2]. AECOPD was defined using the same guidelines. Patients comprised those admitted both at the ward and higher care units (ICU and intermediate care unit), excluding those who underwent invasive mechanical ventilation. Exclusion criteria were diagnosis of another acute respiratory condition (e.g. pneumonia, pneumothorax, or pulmonary embolism), history of respiratory disorders other than COPD (e.g. asthma, bronchiectasis, pulmonary fibrosis, and pulmonary tuberculosis), or inability and/or unwillingness to cooperate for the study.

The study was explained to the participants, and all participants signed an informed consent form that was approved by the Institutional Ethical Committee.

Clinical and functional assessment

All patients underwent thorough clinical examination, pulmonary function testing (spirometry), arterial blood gases evaluation, and radiological evaluation. Chest radiographies were performed for all patients on admission. Computed tomographic scans or computed tomography pulmonary angiography was performed when appropriate or dictated by the clinical condition. Smoking index was calculated as the product of tobacco use (years) and the average number of cigarettes smoked per day/20 (one pack has 20 cigarettes) [6]. Lung volumes (forced expiratory volume in first second, and forced vital capacity) were obtained and calculated during the hospitalization due to the AECOPD. A spirometer (Zan 300; Sensor Medics MGA USB, Oberthulba, Germany) was used. Reversibility was expressed as a percentage of the predicted forced expiratory volume in first second values. Lung volumes were measured before and 10 min after administration of 400 μg of salbutamol. The maneuvers performed and the reference values used were those of the international recommendations [7]. Severity of airway obstruction was defined using Global Initiative for Chronic Obstructive Lung Disease guidelines and criteria as mild, moderate, severe, or very severe disease (stages I–IV, respectively).

Laboratory tests

Venous blood samples were obtained from patients for performing relevant laboratory investigations: complete blood count, blood glucose level, renal function tests, and erythrocyte sedimentation rate.

Bacteriological diagnosis

From each patient, a sputum sample was collected within 24 h of hospital admission, before antimicrobial therapy onset. Valid early morning sputum samples were collected into sterile cups from patients through effective coughing, sometimes assisted by physiotherapy to obtain lung secretions as described previously [8]. Samples were transported directly to the Microbiology and Immunology Department, Faculty of Medicine, Assiut University, where the bacteriological analyses were performed. Sputum samples were considered suitable for culture, with the presence of more than 25 polymorphonuclear leukocytes and less than 10 squamous epithelial cells per magnification field.

Identification of the causative bacterial strains

The samples were examined microscopically after staining with Gram's stain and cultured directly on nutrient, blood, chocolate, mannitol salt, bile esculin, CHROM agar, MacConkey's, and eosin methylene blue agar plates. The cultured plates were incubated aerobically at 37°C for 24–48 h. Blood and chocolate agar plates were incubated at 35–36°C with 5% CO_2 for 48 h for isolation of *S. pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis* strains. Bacterial isolates were identified on the basis of colonial morphology, Gram staining, and standard biochemical reactions according to Bergey's Manual of Systematic Bacteriology [9].

Antibiotic susceptibility testing

Susceptibilities of the isolated bacterial strains were determined to penicillins (amoxicillin and amoxicillin–clavulanic acid), cephalosporins (ceftriaxone, cefepime, ciprofloxacin, and cefotaxime), fluoroquinolones (levofloxacin and ofloxacin) (Bioanalysis, Turkey). In addition, susceptibilities of gram-positive bacterial strains were tested against other penicillins (oxacillin and methicillin), macrolides (erythromycin), glycopeptides (vancomycin and teicoplanin), and oxazolidinones (linezolid). Susceptibilities of gram-negative stains were tested also against aminoglycosides (gentamicin and amikacin) and carbapenems (imipenem and meropenem). The test was performed using the disk diffusion method as recommended by the Clinical and Laboratory Standards Institute guidelines [10]. The results were interpreted as susceptible, intermediate, or resistant.

Multidrug resistance (MDR) was defined as an acquired nonsusceptibility to at least one agent in three or more antimicrobial categories; extensive drug-resistance (XDR) was defined as nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories; and pandrug-resistance (PDR) bacteria was defined as nonsusceptibility to all agents in all antimicrobial categories [11].

Statistical analysis

Statistical analysis was performed using the SPSS 19.0 software for Windows (SPSS Inc., Chicago, Illinois, USA). Data were presented as mean and SD or number and percentage, as appropriate. A *P* value less than 0.05 was considered statistically significant.

Results

Demographic and clinical patients' data

During the study period, 156 patients with a total number of 218 attacks of AECOPD were enrolled prospectively into the current study. There were 144 (92%) male and 12 (8%) female patients, with a mean age of 57.6±8 years (range 40–72 years). Of the 156 patients, 69 (44%) patients had very severe (stage IV) COPD, 45 (29%) had severe (stage III) COPD, 32 (21%) had moderate, and 10 (6%) had mild disease. The duration of hospital stay ranged from 3 to 42 days (mean±SD, 14±9 days). It was significantly longer in patients with very severe versus those with severe, moderate, and mild COPD (analysis of variance, *P*=0.022, 0.001, and 0.000, respectively) and in patients with severe COPD versus moderate and mild COPD (analysis of variance, *P*=0.002 and 0.000, respectively). Table 1 shows the detailed demographic, clinical, and bacteriologic data of the enrolled patients.

Table 1 Demographic and clinical characteristics of patients with AECOPD (*n* = 156)

Characteristic	*n* (%)
Age (years)	
Mean±SD	57.6 ± 8
Range	40–72
Sex	
Male	144 (92)
Female	12 (8)
Admission	
ICU	64 (41)
Intermediate care unit	47 (30)
Ward	45 (29)
COPD stage	
Stage I (mild)	10 (6)
Stage II (moderate)	32 (21)
Stage III (severe)	45 (29)
Stage IV (very severe)	69 (44)
Smoking index	
Nonsmoker	4 (3)
Exsmoker	15 (10)
Mild smoker	13 (8)
Moderate smoker	30 (19)
Heavy smoker	94 (60)
Comorbid pneumonia	
Stage III	4 (3)
Stage IV	15 (10)
Associated cardiopulmonary conditions	
Respiratory failure	77 (49)
DCP	33 (21)
Pulmonary embolism	6 (4)
IHD	41 (26)
Lung cancer	3 (2)
Associated systemic/laboratory abnormalities	
Diabetes mellitus	61 (39)
Impaired renal function	12 (8)
Impaired liver function	23 (15)
Leukocytosis	48 (31)
Hypoalbumenemia	26 (17)
Bacteriologic diagnosis	Number of patients = 156/ number of attacks = 218
Significant bacterial growth	120 patients (77%)/176 attacks (81%)
Single etiologic agent	92 patients (77%)/ 148 attacks (84%)
Mixed infection	28 patients (23%)/ 28 attacks (16%)
No bacterial growth	36 patients (23%)/ 42 attacks (19%)

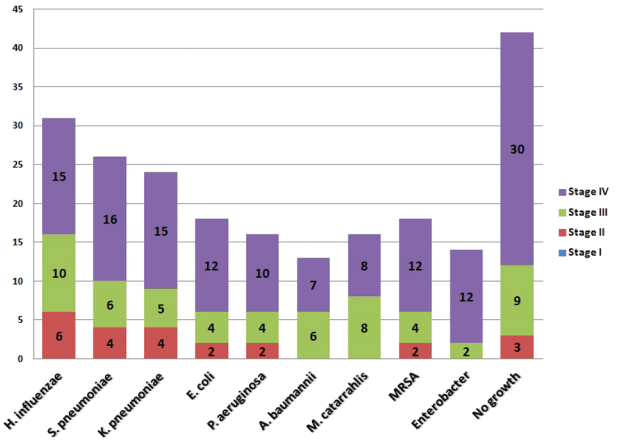
AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; DCP, decompensated cor pulmonale; IHD, ischemic heart disease.

Bacteriological analysis

A significant bacterial growth was found in 120 of 156 (77%) patients during 176 of 218 (81%) exacerbation attacks, whereas no significant bacterial growth was found in 36 of 156 (23%) patients during 42 of 218 (19%) attacks. For those with significant bacterial growth, 92/120 (77%) patients had single etiologic agent in 148/176 (84%) attacks, whereas 28/120 (23%) patients had mixed infection in 28/176 (16%) attacks (Table 1). A total of 176 bacterial strains were isolated in exacerbations of COPD either solely (148, 84%) or mixed (28, 16%).

The most predominant bacterial strains were *H. influenzae*, *S. pneumoniae*, and *Klebsiella pneumoniae*; isolated in 31 (18%), 26 (15%), and 24 (14%) attacks, respectively. The other bacterial strains isolated included, in a decreasing order, *Escherichia coli* (11%), methicillin-resistant *Staphylococcus aureus* (MRSA) (11%), *P. aeruginosa (9%)*, *M. catarrhalis* (9%), *Acinetobacter baumannii* (7%), and *Enterobacter* spp. (7%), respectively. Figure 1 demonstrates the distribution of bacterial isolates in different COPD stages. It was noted that the number of exacerbation

Figure 1



Bacterial strains detected during 218 exacerbation attacks in different COPD stages. Each number of bacterial-positive samples is represented both with a bar and absolute values in the abscissa. No bacterial isolates were detected in 42 attacks. *A. baumannii*, *Acinetobacter baumannii*; *E. coli*, *Escherichia coli*; *H. influenzae*, Haemophilus influenzae; *K. pneumoniae*, Klebsiella pneumoniae; *M. catarrahlis*, *Moraxella catarrhalis*; MRSA, methicillin-resistant *Staphylococcus aureus*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. pneumoniae*, Streptococcus pneumoniae.

attacks, and hence the number of bacterial isolates, was proportionately related to the severity of COPD. Thus, the number of isolates were 107 (61%), 49 (28%), and 20 (11%) in COPD stages IV, III, and II, respectively. No bacterial pathogens were isolated in stage I (Fig. 1).

Antibiotic susceptibility patterns

High resistance rates were observed among the isolated bacterial strains against most groups of antibiotics; 115 (65%) of the isolated strains were MDR, 52 (29%) were XDR, and nine (5%) were PDR (Table 2). Most isolates were resistant to amoxicillin, amoxicillin/clavulanic acid, cephalosporins (except ciprofloxacin), and ofloxacin. About half the isolates were resistant to ciprofloxacin and levofloxacin. Among the gram-positive bacteria, resistance rates were high against the penicillin group and erythromycin, whereas resistance to vancomycin, and teicoplanin ranged from 54 to 61%. All isolated gram-positive bacteria were sensitive to linezolid. For gram-negative isolates, the resistance rates to the aminoglycosides group ranged from high level to gentamicin to a slightly lower level to amikacin. Only few isolates showed resistance to the carbapenem group that belonged to *H. influenzae* (13%) and *E. coli* (11%), whereas *K. pneumoniae, P. aeruginosa*, and *M. catarrahlis* were completely susceptible to the carbapenem group (Table 2).

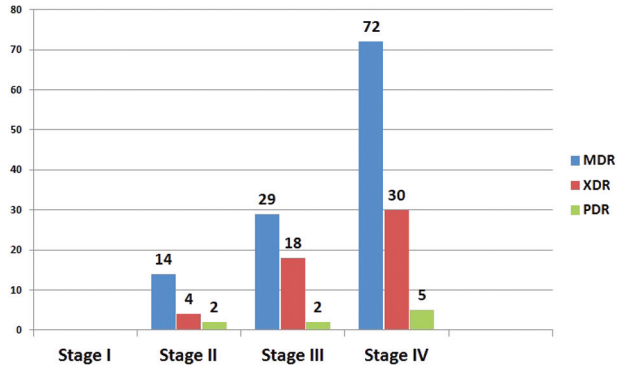
Most of the *H. influenzae* strains (77%) were MDR, 3 (10%) strains were XDR, and another 3 (10%) strains were PDR. For *S. pneumoniae*, 73% of the

Table 2 Resistance patterns of isolated bacterial strains to antimicrobial agents

Bacterial isolates	Total *n* (%)	1			2				3		4	5		6	7		8		MDR	XDR	PDR
		Amoxicillin	Amoxicillin/ Clavulinate	Oxacillin	Methicillin	Ceftriaxone	Cefepime	Ciprofloxacin	Cefotaxime	Levofloxacin	Ofloxacin	Erythromycin	Vancomycin	Teicoplanin	Linezolid	Amikacin	Gentamicin	Meropenem	Imipenem			
H. influenzae	31 (18)	31(100)	20 (65)	ND	ND	14 (45)	26 (84)	11 (35)	23 (74)	10 (32)	12 (39)	ND	ND	ND	ND	8 (26)	25 (81)	3 (10)	4 (13)	24 (77)	3 (10)	3 (10)
S. pneumoniae	26 (15)	23 (88)	21(81)	23 (88)	24 (92)	20 (77)	20 (77)	15 (57)	17 (65)	15 (57)	18 (69)	16 (61)	14 (54)	16 (61)	0 (0)	ND	ND	ND	ND	19 (73)	9 (35)	2 (7)
K. pneumoniae	24 (14)	24 (100)	20 (83)	ND	ND	18 (75)	20 (83)	14 (58)	18 (75)	15 (62)	13 (54)	ND	ND	ND	ND	10 (42)	14 (58)	0 (0)	0 (0)	15 (62)	8 (33)	0 (0)
E. coli	18 (11)	18 (100)	12 (67)	ND	ND	14 (78)	15 (83)	14 (78)	18 (100)	12 (67)	12 (67)	ND	ND	ND	ND	9 (50)	12 (67)	2 (11)	2 (11)	12 (67)	11 (61)	4 (22)
P. aeruginosa	16 (9)	16 (100)	16 (100)	ND	ND	16 (100)	16 (100)	0 (0)	12 (75)	0 (0)	3 (19)	ND	ND	ND	ND	10 (62)	12 (75)	0 (0)	0 (0)	12 (75)	4 (25)	0 (0)
A. baumannii	13 (7)	13 (100)	13 (100)	ND	ND	13 (100)	13 (100)	13 (100)	13 (100)	13 (100)	13 (100)	ND	ND	ND	ND	4 (30)	4 (30)	0 (0)	0 (0)	12 (92)	5 (38)	0 (0)
M. catarrahlis	16 (9)	16 (100)	14 (88)	ND	ND	14 (88)	14 (88)	8 (50)	7 (44)	0 (0)	12 (75)	ND	ND	ND	ND	16 (100)	16 (100)	0 (0)	0 (0)	10 (62)	0 (0)	0 (0)
MRSA	18 (11)	18 (100)	10 (55)	18 (100)	18 (100)	18 (100)	18 (100)	17 (94)	17 (94)	16 (89)	18 (100)	18 (100)	9 (50)	8 (44)	0 (0)	ND	ND	ND	ND	9 (50)	4 (22)	0 (0)
Enterobacter spp.	14 (7)	14 (100)	14 (100)	ND	ND	14 (100)	14 (100)	14 (100)	14 (100)	14 (100)	14 (100)	ND	ND	ND	ND	14 (100)	14 (100)	7 (50)	14 (100)	2 (14)	8 (57)	0 (0)
Total	176 (100)	173 (98)	140 (80)	41 (23)	42 (24)	141 (80)	156 (89)	106 (60)	139 (79)	95 (54)	115 (65)	34 (19)	23 (13)	24 (14)	0 (0)	71 (40)	97 (55)	14 (8)	20 (11)	115 (65)	52 (29)	9 (5)

1, penicillins and penicillin combinations; 2, cephalosporines; 3, fluoroquinolones; 4, macrolides; 5, glycopeptides; 6, oxazolidinones; 7, aminoglycosides; 8, carbapenems; *A. baumannii*, *Acinetobacter baumannii*; *E. coli*, *Escherichia coli*; *H. influenzae*, Haemophilus influenzae; *K. pneumoniae*, Klebsiella pneumoniae; *M. catarrahlis*, *Moraxella catarrhalis*; MDR, multidrug resistance; MRSA, methicillin-resistant *Staphylococcus aureus*; ND, not determined; *P. aeruginosa*, *Pseudomonas aeruginosa*; PDR, pandrug-resistance; *S. pneumoniae*, Streptococcus pneumoniae; XDR, extensive drug-resistance.

Figure 2



Antibiotic resistance patterns in relation to different COPD stages. Significant bacterial growth was detected in 176 exacerbation attacks. MDR, multidrug resistance; PDR, pandrug-resistance; XDR, extensive drug-resistance.

strains were MDR, 35% were XDR, and 7% were PDR. For *K. pneumoniae*, 62% were MDR, 33% were XDR, and no isolates were PDR. All *Staphylococcus aureus* strains were methicillin and oxacillin-resistant (Table 2).

The patterns of antibiotic resistance in different COPD stages are shown in Fig. 2. The advancements in COPD stage was related to the increased prevalence of antibiotic-resistant bacterial strains. Patients with stage IV disease had 72, 30, and 5 exacerbation attacks with MDR, XDR, and PDR organisms, respectively. However, patients with stage II disease had 14, 4, and 2 exacerbation attacks with MDR, XDR, and PDR organisms, respectively (Fig. 2).

Discussion

This prospective study aimed to identify the causative bacteria, antibiotic sensitivity, and antibiotic resistance in hospitalized patients due to AECOPD in Upper Egypt. The chronic course of COPD is often accompanied by acute exacerbations (AECOPD), mainly due to increased inflammation. Morbidity and mortality in COPD patients are, for the most part, related to those acute exacerbations [2]. Published data had shown that the majority of AECOPD (50–60%) are due to respiratory tract infection, the minority (10%) are due to environmental factors, whereas in nearly 30% of cases, the etiology remains unclear [12]. COPD exacerbations are frequently triggered by upper respiratory tract infections, and these are more common in the winter months, when there are more respiratory viral infections in the community [13]. It is also possible that patients are more susceptible to exacerbations in the winter months, as lung function in COPD patients shows small but significant decreases with reduction in outdoor temperature during the winter months [13]. However, data from previous studies showed that between 25 and 50% of COPD patients have lower airway colonization by bacteria, especially noncapsulated *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*. This colonization has been related to the severity of COPD and cigarette smoking [14].

The presence of bacteria in the lower airways of COPD patients implies a breach of host defense mechanisms, which sets up a vicious cycle of epithelial cell damage, impaired mucociliary clearance, mucus hypersecretion, increased submucosal vascular leakage, and inflammatory cell infiltration. The airway bacterial load in the stable state is associated with airway inflammatory markers, and thus increased bacterial colonization is associated with greater airway inflammation [15]. The presence of bacterial colonization in COPD patients may have an influence both on the exacerbation frequency and on the character and severity of exacerbations [13,16]. Fortunately, at AECOPD, there is an increased chance of detecting bacteria, especially if the exacerbation is associated with the presence of purulent sputum. With antibiotic therapy, bacterial load and airway inflammation decreases, and the rate of resolution of the airway inflammatory changes is related to the clearance of bacteria from the sputum [17].

In the current study, most of the participated patients were old aged, suffering from severe (29% of patients) or very severe (44%) COPD, had associated cardiopulmonary or systemic comorbidities, and were critically ill and required admission in the ICU (41%) or the intermediate care unit (30%). Moreover, our data showed that 87% of the enrolled patients were smokers, which reflected the effect of current smoking as a risk factor for severe exacerbations. Smoking perpetuates an ongoing inflammatory response that leads to airway narrowing and hyperactivity, and hence patients become more prone to infection exacerbation attacks [18]. Moreover, we found that exsmokers (10% of patients) had experienced exacerbation attacks, which imply that smoking cessation was too late and the disease progression continued even after smoking cessation. The duration of hospital stay was significantly longer in patients with severe and very severe COPD versus those with mild or moderate disease, which corresponds to previous reports [19]. Shorter durations of exacerbations were a predictor of success of treatment, whereas longer durations were a predictor of need for ventilatory support and poor outcome of the disease [20].

A significant bacterial growth was found in 77% of patients during 176 of 218 (81%) exacerbation attacks, and a total of 176 bacterial strains were isolated. The most predominantly encountered strains were *H. influenzae*, *S. pneumoniae*, and *K. pneumoniae* isolated in 31 (18%), 26 (15%), and 24 (14%) attacks, respectively. *H. influenzae* was the most common bacteria detected in our study. This is in accordance with previous works in Egypt [5] and other countries [21,22]. Strains of *H. influenzae* stimulate mucus hypersecretion and inhibit ciliary beat frequency. Furthermore, they can cause direct epithelial damage and their endotoxin increase epithelial expression of the proinflammatory cytokines, thus providing potential mechanisms to upregulate the process of inflammation in COPD [12]. *S. pneumoniae* strains were detected in 15% of AECOPD in this work. A previous documentation has shown that airway colonization with *S. pneumoniae* increases the risk for a first COPD exacerbation [23]. A substantial number (9%) of our patients had *P. aeruginosa* that was lower than that reported previously (15%) by other studies [24]. COPD was considered as an independent factor in the isolation of MRSA in the ICU [25]. MRSA were detected in 11% of our participated patients. Although *A. baumannii* is a major pathogen in nosocomial infections, community-acquired acinetobacter infections are of an increasing concern because they mainly affect patients with certain comorbidities such as COPD [26]. *A. baumannii* strains were found in 7% of AECOPD in our work.

In disagreement with previously reported data, [27] found a relationship between the severity of COPD and the type of isolated bacterial strains. Our results found no significant association between the type of bacterial isolates and severity of COPD. This difference may be due to different demographic data and the small sample size of our study. A larger sample size is required to prove these findings. However, we observed that the number of exacerbation attacks, and hence the number of bacterial isolates, was proportionately related to the severity of COPD. Thus, the number of isolates were 107 (61%), 49 (28%), and 20 (11%), in COPD stages IV, III, and II, respectively. No bacterial pathogens were isolated in stage I.

To obtain high susceptibilities to antimicrobial agents, we tested the susceptibilities of the isolated bacterial strains to major groups of antibiotics that have effect against both gram-negative and gram-positive bacteria. Our findings demonstrated high resistance rates among the isolated bacterial strains to different groups of antibiotics; 115 (65%) of the isolated strains were MDR, 52 (29%) were XDR, and 9 (5%) were PDR. Most isolates were resistant to amoxicillin, amoxicillin/clavulanic acid, cephalosporins (except ciprofloxacin), and ofloxacin. This finding is similar to that obtained previously in Upper Egypt [5]. About half the isolates in the current study were resistant to ciprofloxacin, and levofloxacin. A similar rate of sensitivity to ciprofloxacin was also observed in a previous data from India [28]. Previous studies evidenced the high bacteriological eradication rate in AECOPD patients when treated with levofloxacin [29].

All *S. aureus* strains in our COPD patients were oxacillin and methicillin resistant, which was similar to that reported in previous reports [27,30]. This high prevalence of MRSA in the current study should be an alarm for the increasing prevalence of MRSA among hospitalized patients in our locality. This coincides with the recent report by Borg *et al.* [31], who observed that the prevalence of MRSA in invasive isolates from blood cultures from nine hospitals in Egypt was 52%. This should alarm the local health authorities to take the proper infection control measures against increasing prevalence of MRSA. All isolated gram-positive bacteria in this work were sensitive to linezolid, the first commercially available oxazolidinone antibiotic. Similarly, linezolid was active against gram-positive isolates in previous studies in the UK [32].

In comparison with other members of the aminoglycoside group used in this study, resistance rate to amikacin was slightly lower among the gram-negative isolates. This is similar to previous reports from Egypt [5,33]. Sensitivity of our gram-negative bacteria was at the highest level to the carbapenem group, which was similar to previous studies from Egypt [33] and China [34]. Again, our data revealed that MDR bacteria were isolated at a rate of 65%, which is higher than that reported in previous reports [33,35]. Emergence of resistance to multiple antimicrobial agents in pathogenic bacteria has become a significant public health threat as there are fewer, or even sometimes no, effective antimicrobial agents available for infections caused by these bacteria. Gram-positive and gram-negative bacteria are both affected by the emergence and rise of antimicrobial resistance [11]. The situation is compounded by cross-resistance within and between classes of antibacterial agents, which further limits treatment options [36]. Our data showed that the advancements in COPD stage was related to the increased prevalence of antibiotic-resistant bacterial strains. This finding

highlights the importance of smoking cessation as an effective measure for preventing progression of the disease.

Finally, it would be appropriate if 'follow-up' sputum cultures are carried out before discharging the patient, to get an idea about possible resistant organisms, keeping these data in the patient's file for future use. However, in the current study we could not perform that due to financial concerns.

At the end, our results have many similarities to and differences from other studies. Continued surveillance, particularly based on local data, is obviously needed to clarify the problems of antimicrobial resistance and to prevent further spread of such resistance. Data from this study can be very useful. A master antibiogram for our region would allow tertiary care institutions to consider resistance patterns in hospitals referring patients and to select appropriate antimicrobial therapy or change drugs in nonresponding patients. Implementing continued local surveillance programs for antibiotic resistance is essentially important. Moreover, further local studies should be carried out to elucidate the mechanisms of resistance of different pathogens in AECOPD. Judicious use of antimicrobials is essential to prevent the emergence of resistant and/or MDR bacteria in AECOPD.

Conclusion

H. influenzae, *S. pneumoniae*, and *K. pneumoniae* are the leading bacterial pathogens in patients with AECOPD in Upper Egypt. Our bacteriological profiles highlighted the role of other pathogens, including *E. coli* and MRSA, in AECOPD. The isolated bacterial strains were characterized by high resistance rates to most groups of antimicrobials. Sensitivity was high to linezolid and the carbapenem group. More advanced COPD stage is related to increased prevalence of antibiotic-resistant bacterial strains. Further local studies are warranted.

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Nil.

Conflicts of interest

There was no conflicts of interest.

References

1 Perera WR, Hurst JR, Wilkinson TM, Sapsford RJ, Müllerova H, Donaldson GC, Wedzicha JA. Inflammatory changes, recovery and recurrence at COPD exacerbation. *Eur Respir J* 2007; **29**:527–534.

2 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of COPD, updated 2015. Available at: http://www.goldcopd.org

3 Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; **57**:847–852.

4 Kyd JM, McGrath J, Krishnamurthy A. Mechanisms of bacterial resistance to antibiotics in infections of COPD patients. *Curr Drug Targets* 2011; **12**:521–530.

5 Agmy G, Mohamed S, Gad Y, Farghally E, Mohammedin H, Rashed H. Bacterial profile, antibiotic sensitivity and resistance of lower respiratory tract infections in Upper Egypt. *Mediterr J Hematol Infect Dis* 2013; **5**: e2013056.

6 Indrayan A, Kumar R, Dwivedi S. "A simple index of smoking" (November 2008). COBRA Preprint Series. Working Paper 40. Available at: http://biostats.bepress.com/cobra/ps/art40

7 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, *et al.* ATS/ERS Task Force General considerations for lung function testing. *Eur Respir J* 2005; **26**:153–161.

8 Henig NR, Tonelli MR, Pier MV, Burns JL, Aitken ML. Sputum induction as a research tool for sampling the airways of subjects with cystic fibrosis. *Thorax* 2001; **56**:306–311.

9 Holt JG, Krieg NR, Sneath PHA, Staley H, Williams ST. *Bergey's manual of determinative bacteriology*. 9th ed. Baltimore, MD: Lippincott Williams and Wilkins; 1994.

10 Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial disk susceptibility tests*. 9th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2006.

11 Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME Giske CG, *et al.* Multidrug-resistant, extensively drug-resistant and pan drug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18**:268–281.

12 White AJ, Gompertz S, Stockley RA. Chronic obstructive pulmonary disease. 6: the aetiology of exacerbations of chronic obstructive pulmonary disease. *Thorax* 2003; **58**:73–80.

13 Wedzicha JA, Donaldson GC. Exacerbations of chronic obstructive pulmonary disease. *Respir Care* 2003; **48**:1204–1213 discussion 1213–1215.

14 Zalacain R, Sobradillo V, Amilibia J, Barrón J, Achótegui V, Pijoan JI, Llorente JL. Predisposing factors to bacterial colonization in chronic obstructive pulmonary disease. *Eur Respir J* 1999; **13**:343–348.

15 Hill AT, Campbell EJ, Hill SL, Bayley DL, Stockley RA. Association between airway bacterial load and markers of airway inflammation in patients with stable chronic bronchitis. *Am J Med* 2000; **109**:288–295.

16 Nakou A, Papaparaskevas J, Diamantea F, Skarmoutsou N, Polychronopoulos V, Tsakris A. A prospective study on bacterial and atypical etiology of acute exacerbation in chronic obstructive pulmonary disease. *Future Microbiol* 2014; **9**:1251–1260.

17 White AJ, Gompertz S, Bayley DL, Hill SL, O'Brien C, Unsal I, Stockley RA. Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis. *Thorax* 2003; **58**:680–685.

18 Hunter MH, King DE. COPD: management of acute exacerbations and chronic stable disease. *Am Fam Physician* 2001; **64**:603–612.

19 Nowiński A, Kamiński D, Korzybski D, Stokłosa A, Górecka D. The impact of comorbidities on the length of hospital treatment in patients with chronic obstructive pulmonary disease. *Pneumonol Alergol Pol* 2011; **79**:388–396.

20 Mohan A, Premanand R, Reddy LN, Rao MH, Sharma SK, Kamity R, Bollineni S. Clinical presentation and predictors of outcome in patients with severe acute exacerbation of chronic obstructive pulmonary disease requiring admission to intensive care unit. *BMC Pulm Med* 2006; **6**:27.

21 Ko FW, Ng TK, Li TS, Fok JP, Chan MC, Wu AK, Hui DS. Sputum bacteriology in patients with acute exacerbations of COPD in Hong Kong. *Respir Med* 2005; **99**:454–460.

22 Molyneaux PL, Mallia P, Cox MJ, Footitt J, Willis-Owen SA, Homola D, *et al.* Outgrowth of the bacterial airway microbiome after rhinovirus exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; **188**:1224–1231.

23 Bogaert D, van der Valk P, Ramdin R, Sluijter M, Monninkhof E, Hendrix R, *et al.* Host-pathogen interaction during pneumococcal infection in patients with chronic obstructive pulmonary disease. *Infect Immun* 2004; **72**:818–823.

24 Groenewegen KH, Wouters EF. Bacterial infections in patients requiring admission for an acute exacerbation of COPD: a 1-year prospective study. *Respir Med* 2003; **97**:770–777.

25 González-Castillo J, Cenci C, Rodriguez-Adrada E, Candel FJ, de la Torre-Misiego F, Fernández C, Martín-Sánchez FJ. *Staphylococcus aureus* infections and factors associated with resistance to methicillin in a hospital emergency department. *Rev Esp Quimioter* 2013; **26**:337–345.

26 Falagas ME, Karveli EA, Kelesidis I, Kelesidis T. Community-acquired *Acinetobacter* infections. *Eur J Clin Microbiol Infect Dis* 2007; **26**:857–868.

27 Li XJ, Li Q, Si LY, Yuan QY. Bacteriological differences between COPD exacerbation and community-acquired pneumonia. *Respir Care* 2011; **56**:1818–1824.

28 Madhavi S, Rama Rao MV, Janardhan Rao R. Bacterial etiology of acute exacerbations of chronic obstructive pulmonary disease. *J Microbiol Biotech Res* 2012; **2**:440–444.

29 Lode H, Eller J, Linnhoff A, Ioanas M, Evaluation of Therapy-Free Interval in COPD Patients Study Group. Levofloxacin versus clarithromycin in COPD exacerbation: focus on exacerbation-free interval. *Eur Respir J* 2004; **24**:947–953.

30 Thwaites GE. The management of *Staphylococcus aureus* bacteremia in the United Kingdom and Vietnam: a multicentre evaluation. *PLoS One* 2010; **5**:14170.

31 Borg MA, de Kraker M, Scicluna E, van de Sande-Bruinsma N, Tiemersma E, Monen J, Grundmann H, ARMed Project Members and Collaborators. Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in invasive isolates from southern and eastern Mediterranean countries. *J Antimicrob Chemother* 2007; **60**:1310–1315.

32 Johnson AP, Warner M, Livermore DM. Activity of linezolid against multi-resistant gram-positive bacteria from diverse hospitals in the United Kingdom. *J Antimicrob Chemother* 2000; **45**:225–230.

33 El-Korashy RI, El-Sherif RH. Gram negative organisms as a cause of acute exacerbation of COPD. *EJCDT* 2014; **63**:345–349.

34 Ye F, He LX, Cai BQ, Wen FQ, Chen BY, Hadiarto M, *et al.* Spectrum and antimicrobial resistance of common pathogenic bacteria isolated from patients with acute exacerbation of chronic obstructive pulmonary disease in mainland of China. *Chin Med J (Engl)* 2013; **126**:2207–2214.

35 Nseir S, Di Pompeo C, Cavestri B, Jozefowicz E, Nyunga M, Soubrier S, *et al.* Multiple-drug-resistant bacteria in patients with severe acute exacerbation of chronic obstructive pulmonary disease: prevalence, risk factors, and outcome. *Crit Care Med* 2006; **34**:2959–2966.

36 Fogarty CM, Kohno S, Buchanan P, Aubier M, Baz M. Community-acquired respiratory tract infections caused by resistant pneumococci: clinical and bacteriological efficacy of the ketolide telithromycin. *J Antimicrob Chemother* 2003; **51**:947–955.