LIST OF ABBREVIATIONS

3GC	Third Generation Cephalosporin
AE	Acute Exacerbation
AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé
BAP-65	Elevated BUN, Altered mental status, Pulse > 109 beats/min, age > 65 years
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
ED	Emergency Department
FEV1	Forced Expiratory Volume in the first second
FVC	Forced Vital Capacity
Hbg	Hemoglobin
ICD-10	International Statistical Classification of Disease and Related Health Problems 10th Revision
ICU	Intensive Care Unit
PaCO2	Partial pressure of Carbon dioxide in arterial blood
PaO2	Partial pressure of Oxygen in arterial blood
PCT	Procalcitonin
SD	Standard Deviation
SPILF	Société de Pathologie Infectieuse de Langue Française
WHO	World Health Organization

Plan

Antibiotics and oxygen therapy for acute exacerbation of COPD: Are we over-prescribing in the emergency department?

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ABSTRACT

Background: Acute exacerbation of chronic obstructive pulmonary disease is a commonly treated condition in the emergency department. These events are significantly associated with a mortality risk and with a worsening of the lung function. It remains difficult to identify patients with bacterial infection who should benefit from an antibiotic treatment. This can lead to an over-prescription of antibiotics. French guidelines describe antibiotic prescription modalities and are based on GOLD status. In this study, we assessed antibiotics prescriptions adherence to guidelines in a university hospital emergency department. The primary outcome was the concordance rate between prescribed antibiotic and guidelines. Then we identified parameters associated with over-prescription. We also investigated the concordance rate between prescribed oxygen flow-rate and guidelines.

Methods: Retrospective audit of medical records for patients admitted with acute exacerbation of COPD during 2013 and 2014 in a French university hospital emergency department.

Results: Adherence to antibiotic management guidelines was 51% with 43% rate of over-prescription. Patients with over-prescription were more likely to be aged over 75, to have a GOLD status lower than IV, to live in long-stay institutions and to have body temperature over 38°C or high level of CRP or leucocytes count. 58.5% of patients had a guideline-concordant oxygen administration.

Conclusion: We report a medium adherence level to guidelines for antibiotics and oxygen therapy management. Our work highlights that inflammatory markers, which are not recommended for antibiotics management in COPD, remain widely used and may lead to unjustified antibiotics usage. Guidelines including antibiotics management decision tools related to clinical severity may reduce antibiotics over-use.

INTRODUCTION

Chronic pulmonary obstructive disease (COPD) is a major public health issue. World Health Organization (WHO) projections estimate COPD will be the 3rd leading cause of mortality in the world in 2020 (1,2). This condition is common and life threatening complications may occur. Prevalence among adults aged 45 years and older reaches five to ten percent in France (3). COPD is characterized by chronic bronchi and lung parenchyma inflammation. This results in progressive, chronic and not fully reversible airflow limitation (4,5). Initial symptoms include cough and sputum production. Cigarette smoking is the main identified risk factor. Without smoking cessation, the disease progresses toward chronic dyspnea and chronic respiratory failure with long-term oxygen therapy dependency. Spirometry with forced expiratory volume on first second (FEV1) / forced vital capacity (FVC) ratio lower than 0.70 confirms the diagnosis with non-reversible airflow limitation. GOLD classification is based on post-bronchodilator FEV1 measure and is commonly used to assess the severity of the disease (6).

The acute worsening of usual respiratory symptoms results in the clinical syndrome of acute exacerbation (AE) of COPD and can cause death. AE are major events and strongly influence morbidity, mortality and health-related quality of life. In France, hospital admissions for AE increased over the last 10 years and ranged from 69,000 to 112,000 in 2007. In 2010, 51,931 patients were admitted to emergency departments (ED) for AE with 95% of them hospitalized (7). The impact in health is significant and the economic burden of COPD in Europe is estimated at about 50 billion euros a year (3,8,9).

AE are supposedly caused by an exacerbation of bronchi inflammation. The main mechanical consequence is a narrowing of the bronchial tree which abruptly increases the resistance to airflow. This phenomenon leads to thoracic distention by progressive air trapping and alveolar hyperinflation with inefficient respiratory work, hematosis alteration and hypoxemia. Hemodynamic stability may also be compromised by high blood pressure in the

pulmonary arteries leading to acute *cor pulmonale* onset. The main trigger factors identified are lower respiratory tract infections in half of the cases (lungs and/or bronchi infection), acute heart failure and pulmonary embolism. Air pollution may also play a key role as a trigger in AE. Potentially pathogenic bacteria such as *Haemophilus influenzae*, *Streptococcus pneumoniae* or *Moraxella catarrhalis* are identified in about 50% of lower respiratory tract infections (10). The other half of cases are caused by viral or both viral and bacterial infections. However, it is frequent that no trigger factor is identified in clinical practice (11).

Specific bacterial investigations with sputum culture are neither justified nor recommended as first line investigations (12,13). Thus, usually, the pathogen involved in exacerbation remains unknown in ED. Following guidelines, treatment is frequently based on empirical antibiotic choice. International and 2014 updated French guidelines describe antibiotic prescription modalities (6,11,14,15, Supplemental 1). Sputum purulence is the most relevant criteria for determining antibiotic treatment prescription (16,17). Strategy is guided by GOLD status at steady state. GOLD III patients with sputum purulence should receive amoxicillin, oral third generation cephalosporin (3GC) - cefpodoxime or cefuroxime -, pristinamycin, macrolides or telithromycin. GOLD IV patients should receive amoxicillin-clavulanic acid, parenteral 3GC (ceftriaxone or cefotaxime) or levofloxacin (14, Supplemental 1).

The identification of patients requiring an antibiotic treatment and the management of this therapy remain difficult in ED. Furthermore, literature conclusions are contradictory about the place of antibiotics in AE management (18–22).

The emergence of multiple drug resistant bacteria is a major threat to public health leading to increased health costs, therapeutic failures and mortality (23). European Center for Disease Control estimates 25,000 annual deaths could be directly related to bacterial resistances in Europe and 12,000 per year in France according to Carlet report (24). As some

of the recommended antibiotic molecules in AE management such as amoxicillin-clavulanic acid, 3GC and fluoroquinolones are now identified as critical because of their capacity to induce bacterial resistances, this makes the decision of antibiotic drug introduction a delicate problem (25,26). Here, we tried to describe antibiotics prescription practices in AE of COPD in an ED and to assess the rate of guidelines adherence.

Oxygen administration is also major part of AE treatment. Respiratory failure is a life-threatening complication of AE causing hypoxemia and hypercapnia. Deep hypoxemia results in consciousness alteration and anoxic cardiac arrest may occur. As hyperoxia can also induce or increase hypercapnia, oxygen administration needs to be executed carefully. High flow oxygen administration has been shown to enhance mortality in COPD patients (27). Severe hypercapnia will justify noninvasive ventilation use and invasive mechanical ventilation if consciousness alteration appears (27–31). Guidelines suggest oxygen should be supplied with an 88 to 92 % pulse oximetry goal (5). However, the important workload in ED makes this titration difficult. Some studies have shown inappropriate oxygen administration in ED with either episodes of hypoxemia or hyperoxia (32–36). As a secondary outcome, we also investigated the concordance rate between prescribed oxygen flow rate and guidelines.

Several publications have highlighted discordances between antibiotic treatments start decision and guidelines with 45 to 79.7% avoidable treatments (37–39). A major source of avoidable prescriptions may be the absence of sputum color identification (40). However, we have not found any study describing the level of adherence in antibiotic molecule prescription. Literature suggests the existence of perfectible use of both antibiotic treatments and oxygen therapy in AE management which could have adverse effect on public health. This work aims to describe antibiotics prescription practices in AE of COPD in the emergency department of the University Hospital of Angers for the years 2013 and 2014 and to confront them to guidelines. Then, we try to identify the contextual, clinical and biological facts which could

explain the discordance between observed practices and guidelines. Finally, in the same way, we describe and analyze oxygen administration practices and its determinants.

METHODS

The study protocol was declared and approved by the ethics committee of the University Hospital of Angers (Angers, France, record 2015/80) and by the French National Commission for Data Processing and Civil Liberties (CNIL, Angers, France, record 2015-013). To collect non-consent advice, an information mail was sent to each patient three weeks before data extractions. Each record was treated anonymously.

Study design

This monocentric, retrospective, descriptive and analytic study was performed at the University Hospital of Angers (Angers, France). This work concerns adult patients with COPD admitted in the emergency department from January 1st of 2013 to December 31st of 2014.

Records selection, inclusions and exclusion criteria

Medical records were identified from the ED database based on the International Statistical Classification of Disease and Related Health Problems 10th Revision (ICD-10). All medical records containing the terms "COPD", "Chronical obstructive bronchopulmonary disease" or "Chronical obstructive pulmonary disease" for the study period were selected for screening. Among selected records, those containing the following terms: "Acute decompensation of COPD", "COPD (infection)", "acute bronchitis" or "exacerbation of COPD" in diagnosis text-field were included and remaining records were screened manually for the same words.

Non-inclusion criteria were patient under 18 years old, non-respiratory final diagnosis, pneumonia diagnosis, no final diagnosis filled. Records without information about previous spirometry, COPD severity, dyspnea base-line status or GOLD classification were excluded. The characteristics of the 451 medical records analyzed were similar to those of the 26 excluded ones [Table 1].

Data collected

Demographic data and baseline status

We collected age, sex, patient provenance (home, retirement home, nursing home, or long-stay hospital unit, other hospital), cigarette smoking status and cardiovascular or respiratory comorbidities. Severity of the COPD and GOLD status were assessed from previous spirometry results (FEV1, FEV1/FVC), hospitalization or consultation reports (5). Every document had to be available at the time of ED admission. Following guidelines, in the absence of functional information on COPD severity, GOLD status was determined using information about baseline status dyspnea, if available (14).

Clinical data and exacerbation severity

We collected the following vital signs: temperature, neurological impairment (Glasgow Coma Scale on admission), blood pressure, heart and respiratory rate. Respiratory failure severity was assessed from the presence of dyspnea, cyanosis, use of accessory inspiratory muscles, asterixis or paradoxical respiratory movements. The presence of purulent sputum in clinical history was also documented. The following laboratory values during the first 6 hours were collected: hemoglobin (Hbg), leucocytes, neutrophils, C-reactive protein (CRP), creatinine, urea, brain natriuretic peptide (BNP), and blood gases values (PaO2, PaCO2 and pH). Then, a BAP-65 risk stratification score for use in AE of COPD to estimate in-hospital mortality was calculated for each patient (41,42).

Exacerbation management in the ED

To describe antibiotic treatment management, we collected previous antibiotics treatment (in the week before admission) and the prescription of an antibiotic in the ED. To describe oxygen administration management, we collected last pulse oximetry value and oxygen flow rate at discharge and the use of non-invasive ventilation. ICD-10 diagnosis code, physician status, time of discharge from the ED and destination were also documented. Time

of discharge was considered as the medical conclusion time. Patients were considered as managed on night or week-end shift schedules when discharged on night or week-end time.

Missing values management

To manage missing values, every patient with no available GOLD status or information about dyspnea baseline status were excluded. Sputum purulence was considered absent if not documented in medical record.

Concordance rate evaluation between prescribed antibiotic and guidelines.

We used AFFSAPS and SPILF 2010 guidelines which recommend a "class I" antibiotic (amoxicillin, pristinamycin, telithromycin, oral 3GC) for GOLD III patients presenting increased purulent sputum and a "class II" antibiotic (ceftriaxone, cefotaxime, amoxicillin-clavulanic acid and levofloxacin) for each GOLD IV exacerbation (14). Following those documents, we determined indication and recommended antibiotic molecule. First, we assessed the adequacy rate of antibiotic indication and molecule choice with comparison between theoretical and clinical practices for each record. Then, adequacy was defined as correct if both indication to an antibiotic treatment and prescribed molecule were similar to guidelines recommendations.

Concordance rate evaluation between oxygen prescription and guidelines.

Oxygen therapy was defined as correct if the last pulse oximetry was between 88 and 92% if oxygen was administered. For patients who did not receive oxygen, oxygen management was defined as correct if the last pulse oximetry was above 88% (5).

Primary and secondary endpoint

The primary endpoint is the rate (in percent) of similarity between prescribed antibiotic and recommended antibiotic prescription. Secondary endpoints were: the rate (in percent) of

similarity between collected pulse oximetry and target pulse oximetry; and significant association of selected parameters with antibiotic and oxygen over-prescription.

Statistical analysis

Data were documented on an Excel file and stored inside ED. Statistical analyses were completed by the Department of methodology and biostatistics using SPSS software. We estimated adequacy rates for antibiotic prescription and oxygen prescription with their 95% confidence intervals. Continuous values were compared using *Student's t test* or *Mann Whitney non-parametrical test* depending on normality and nominal variables with *Pearson's chi-squared test* or *Fisher's exact test*. Statistical significance was denoted by a *P value* < 0.05.

RESULTS

1. Description of the population

1.1. Inclusion of population studied

For this study, we identified 1010 patients with COPD admitted in the ED during years 2013 and 2014. Among them, 477 were admitted for AE. We excluded 26 patients (5.45%) because of missing information about disease steady state severity. The final cohort consisted of 451 patients.

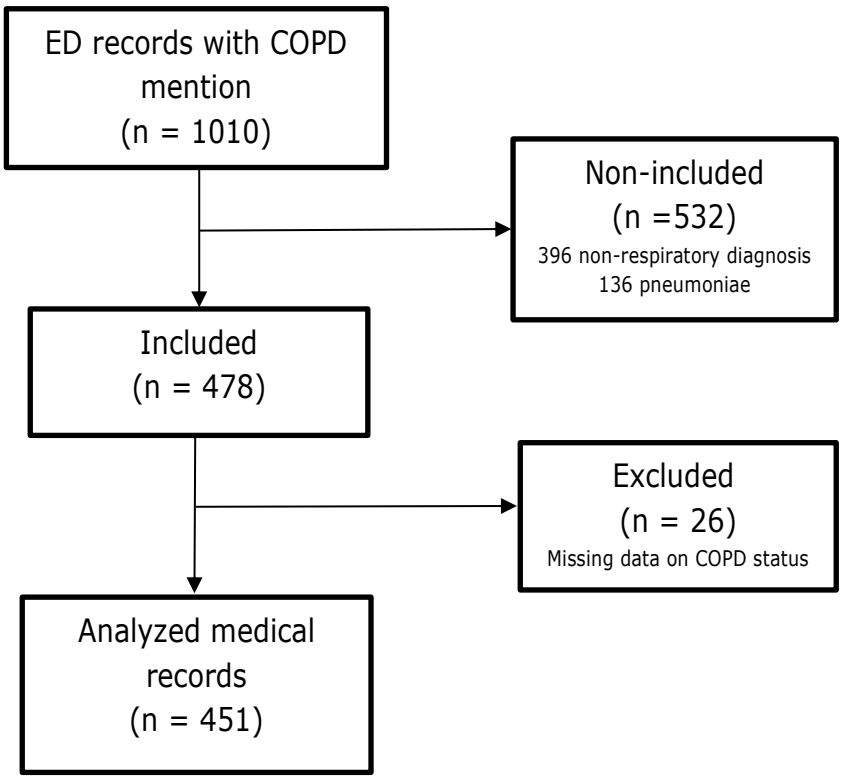

Figure 1 : Flowchart: inclusion of the study population

1.2. Demographic characteristics of included and excluded patients

The mean age was 74 years old, 66% were men and 57% were admitted during week end or night shift schedule. We didn't notice significant differences between analyzed and excluded medical records main characteristics (p value > 0.05) [Table 1].

Table I: Demographic characteristics of included and excluded patients. Data are n (%) unless otherwise specified.

Demographic characteristics (n = 477)	Included (n = 451)	Excluded (n = 26)	*P* value
Age, mean ± SD, y	74 ± 14.1	78 ± 14.1	0.12
Sex Male (n = 315)	298 (66.2)	17 (68)	0.86
On-call team (%)	257 (57)	15 (57.7)	0.94

2. Disease history and severity of the exacerbation episode

2.1. COPD severity status and previous therapeutics

About a quarter of included patients (23.9%) received an antibiotic treatment in the week before ED admission. Aminopenicillin were the most prescribed antibiotics before ED admission with amoxicillin-clavulanate (39.81%) and amoxicillin (12.96%). The mean FEV1 value was 51.62 liters with 67 (14.9%) GOLD IV patients, 148 (32.8%) GOLD III patients, 117 (25.9%) GOLD II patients and 69 (15.3%) GOLD I patients. A total of 50 (11.1%) patients had available spirometry results showing no bronchial obstruction but were considered as an AE of COPD on the ED discharge. A major proportion had a past cardiovascular history (64.1%), about one quarter had pre-existing respiratory condition (24.6%) other than COPD and 18.8% were smokers. Purulent sputum was found in 118 patients (26.2%)

2.2. Exacerbation characteristics and severity

Most patients experienced shortness of breath on ED admission (86%) with high respiratory rate (mean 26 movements / minute, SD 7). Use of accessory respiratory muscles was the most frequent clinical signs of severity with 46.8% patients presenting intercostal recession, 14.6% presenting paradoxical abdominal respiratory movements. Three and one half percent had hypercapnia symptoms and three percent had cyanosis. Mean pulse oximetry on admission was 94.6%. Temperature was mostly in the normal range with only 10.2% of

patients over 38.5°C. To assess global severity, we used the BAP-65 score. Following this score, 84 (18.6%) patients were class I and considered as low severity exacerbation, 358 (79.4%) had a mild severity exacerbation and nine (2%) had a severe exacerbation [Table II].

Table II: Clinical parameters and BAP-65 class on admission.

Characteristic	**Value: n (%)**
Presence of purulent sputum	118 (26.2)
Body temperature, mean ± SD, °C	37.31 ± 0.85
Heart rate, mean ± SD, beats per minute	92.45 ± 18.64
Systolic blood pressure, mean ± SD, mmHg	138.53 ± 22.76
Diastolic blood pressure, mean ± SD, mmHg	82.38 ± 16.22
Pulse oximetry, mean ± SD, %	94.56 ± 3.97
Respiratory rate, mean ± SD, movements per minute	26.09 ± 6.96
Breathlessness	388 (86)
Cyanosis	14 (3.1)
Paradoxical abdominal movements	66 (14.6)
Use of accessory inspiratory muscles	211 (46.8)
Asterixis	16 (3.5)
BAP 65 score (n = 451)	
BAP65 - 1	84 (18.6)
BAP65 - 2	249 (55.2)
BAP65 - 3	109 (24.2)
BAP65 - 4	8 (1.8)
BAP65 - 5	1 (0.2)

Data are n (%) unless otherwise specified.

Regarding inflammatory markers, the mean neutrophils count was 8.15 G/L and 134 patients (35.4%) had CRP over 50 ng/ml. Blood gas analysis was performed in 374 (82.9%) patients [Table III].

Table III: Biological parameters on admission

Value	Hbg (g/dl)	Leucocytes (G/L)	Neutrophils (G/L)	CRP (mg/L)	Urea (mmol/L)	BNP (ng/L)	PaO2 (mmHg)	PaCO2 (mmHg)
n	436	435	432	379	436	246	373	374
Mean	13.54	10.74	8.15	57.67	8.54	252.66	71.92	48.98
SD	1.85	4.72	4.47	71.54	34.95	401.27	28.86	15.69
Median	13.6	9.85	7.16	28	5.85	116.5	66	45

Hbg = hemoglobin, CRP = C reactive protein, BNP = Brain Natriuretic Peptide, PaO2 = partial pressure of oxygen in arterial blood, PaCO2 = partial pressure of carbon dioxide in arterial blood. Data are n.

3. Exacerbation management in the ED: care track

Most of the patients came from home (82.9%) and 257 (57%) on night or week end shift time. The physician in charge was mostly an emergency physician (68.9%) or a resident (22.6%). 73.2% of admitted patients were hospitalized and 20.8% were discharged to home. The most frequent hospitalization units were respiratory unit (38.18%), general medicine unit (25.15%) and infectious diseases unit (10%). Others were admitted in medical or surgical specialty units. 28 (8.48%) inpatients were admitted in intensive care unit.

4. Exacerbation management in the ED: antibiotics

4.1. Antibiotic treatment management description

About half of the patients (57%) received an antibiotic treatment in the emergency department. Among them, only 36 (14%) were prescribed a class I molecule and 216 (84%) a class II molecule. Amoxicillin-clavulanic acid was the most prescribed molecule (71%) followed by amoxicillin (7.4%). [Table IV]

Table IV: Antibiotic molecules prescribed in the emergency department for acute exacerbation of COPD

Molecule	Value
Class 1	36 (14.01)
Amoxicillin	19 (7.39)
Macrolide	1(0.39)
Pristinamycin	16 (6.23)
Class 2	216 (84.05)
Amoxicillin - clavulanate	184 (71.60)
Ceftriaxone	17 (6.61)
Levofloxacin	15 (5.84)
Others	4 (1.56)
Bi-antibiotic treatment	7 (2.72)
Penicillin	220 (85.6)

Data are n (%).

4.2. Antibiotic treatment management concordance with guidelines

A total of 51% of patients (n = 230, 95% CI: 46.4-55.6) received guideline-concordant antimicrobial therapy regarding indication and molecule choice [Figure 2]. According to guidelines, 110 (24.4%) patients should have been prescribed an antibiotic treatment with 43 (9.53%) prescriptions of class I molecules for GOLD III patients and 67 (14.9%) prescriptions of class II molecules for GOLD IV patients. In clinical practices, 196 (43%) of patients received an over-prescribed antibiotic including 167 (37%) patients who should not have received any antibiotics and 29 (6.4%) patients who received a class II instead of a class I molecule. Regarding guidelines-concordant management, 174 (38.6%) patients without antibiotic treatment indication did not receive any and 56 (12.4%) received the appropriate molecule. If we focus on antibiotic treatment indication, 263 (58.3%) antibiotic prescriptions were appropriate.

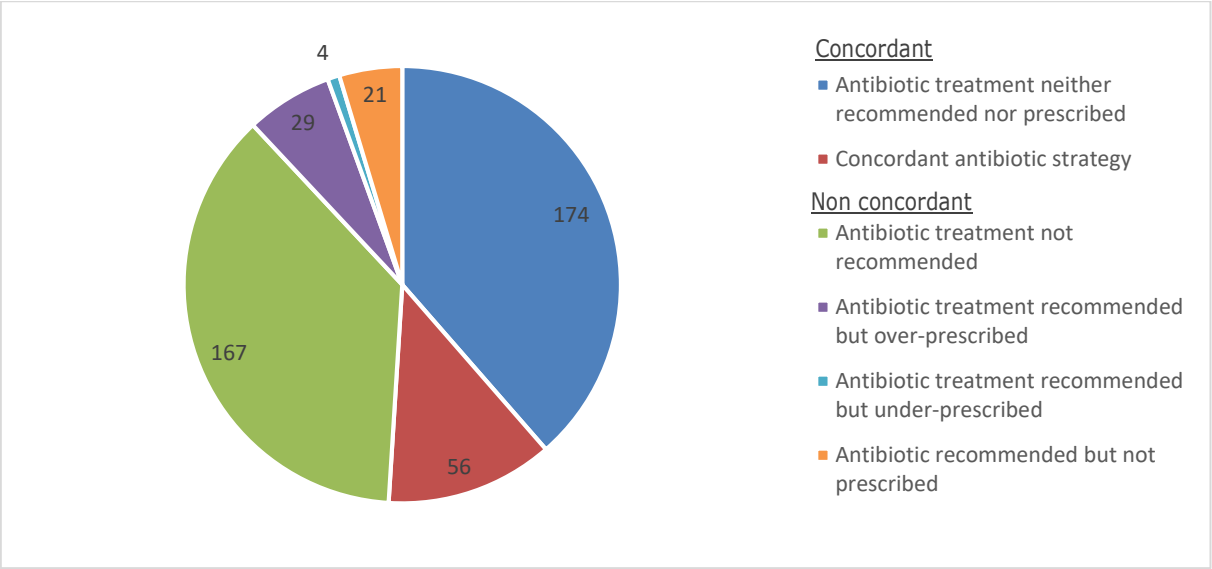

Figure 2: Concordance of antibiotic treatment strategy with guidelines. The rate of agreement between practices and guidelines for indication and molecule choice was 51%. Data are (n).

4.3. Antibiotic treatment management: parameters associated with over-prescription.

The same demographic, clinical and biological characteristics were associated with antibiotic indication and molecule choice over evaluation. Patients aged over 75 years old, coming from home and with a non-severe COPD (GOLD status between 0 and II) were significantly more likely to be prescribed an antibiotic treatment that was not recommended [Table 5]. Also, temperature over 38.5°C on admission was associated with guidelines-discordance. Concerning biological parameters, high levels of inflammatory biomarkers (leucocytes count, neutrophils count and CRP over 50 ng/ml), pCO2 arterial lower than 45 mmHg and pH over 7.35 were risks factors for antibiotic over-prescription. Severity of EACOPD episode, assessed on BAP-65 prognostic score was not significantly correlated with antibiotics over-prescription [Table 6].

Table V: Global antibiotic treatment management: demographic characteristics associated with over-prescription

Characteristics	Patients with antibiotic treatment over-prescription (n=196)	Patients with concordant antibiotic management (n=230)	*P*
Age, mean ± SD, y	76.52 ± 13.74	72.27 ± 13.98	**0.002**
< 75 years old	68 (34.7)	117 (50.9)	**0.001**
> 75 years old	128 (65.3)	113 (49.1)	
Provenance			**0.003**
Home	141 (76.2)	194 (87.4)	
Nursing home / long-stay institution	44 (23.8)	28 (12.6)	
Antibiotic treatment on admission			0.653
Absence	146 (74.5)	178 (77.7)	
Class 1 molecule	24 (12.2)	22 (9.6)	
Class 2 molecule	26 (13.3)	29 (12.7)	
Severity of COPD			**< 0.001**
Gold stage 0	26 (13.3)	24 (10.4)	
Gold stage 1	35 (17.9)	34 (14.8)	
Gold stage 2	62 (31.6)	55 (23.9)	
Gold stage 3	73 (37.2)	69 (30)	
Gold stage 4	0 (0)	48 (20.9)	
Severity of COPD			**0.005**
Gold stage 0 to 2	123 (62.8)	113 (49.1)	
Gold stage 3 to 4	73 (37.2)	117 (50.9)	
Cardio-vascular comorbidities			0.608
Absence	72 (36.7)	79 (34.3)	
Presence	124 (63.3)	151 (65.7)	
Respiratory comorbidities			0.648
Absence	148 (75.5)	178 (77.4)	
Presence	48 (24.5)	52 (22.6)	

Data are n (%) unless otherwise specified. Comparisons between concordant and discordant groups were performed Student's t test or Pearson's Khi² test. Statistical significance is denoted by a P value < 0.05

Table VI: Global antibiotic treatment management: clinical and biological parameters associated with over-prescription

Characteristics	Patients with antibiotic treatment over-prescription (n=196)	Patients with concordant antibiotic management (n=230)	*P*
Vital signs			
Temperature, mean ± SD, °C	37.57 ± 0.94	37.14 ± 0.72±	< **0.001**
< 38.5 °C	161 (82.1)	218 (95.2)	< **0.001**
> 38.5 °C	35 (17.9)	11 (4.8)	
Heart rate, mean ± SD, pulse	92.45 ± 19.07	92.23 ± 18.67	0.902
Respiratory rate, mean ± SD	26.3 ± 7.17	26.06 ± 6.77	0.72
Pulse oximetry on admission, mean ± SD	94.64 ± 3.36	94.48 ± 4.45	0.681
Respiratory severity signs			
Dyspnea			0.074
Absence	34 (17.3)	26 (11.3)	
Presence	162 (82.7)	204 (88.7)	
Cyanosis			0.565
Absence	189 (96.4)	224 (97.4)	
Presence	7 (3.6)	6 (2.6)	
Paradoxical respiration			0.291
Absence	170 (86.7)	191 (83)	
Presence	26 (13.3)	39 (17)	
Use of accessory inspiratory muscles			0.118
Absence	112 (57.1)	114 (49.6)	
Presence	84 (42.9)	116 (50.4)	
AECOPD severity assessment			0.383
BAP 65 score 1-2	135 (68.9)	179 (77.8)	
BAP 65 score 3-5	61 (31.1)	51 (22.2)	
Biological parameters			
Leucocytes, mean ± SD, Giga/liters	11.46 ± 4.54	10.24 ± 4.84	**0.009**
Neutrophils, mean ± SD, Giga/liters	8.93 ± 4.25	7.56 ± 4.59	**0.002**
CRP, mean ± SD, ng/ml	81.83 ± 84.39	38.04 ± 49.78	< **0.001**
CRP < 50 ng/ml	86 (50.9)	140 (74.9)	< **0.001**
CRP > 50 ng/ml	83 (49.1)	47 (25.1)	
BNP, mean ± SD, pg/ml	236.26 ± 391.14	274.39 ± 420.89	0.476
PO2 arterial, mean ± SD, mmHg	71.55 ± 27.73	72.72 ± 30.66	0.711
PCO2 arterial, mean ± SD, mmHg	45.16 ± 12.69	51.29 ± 16.7	< **0.001**
PCO2 > 45 mmHg	61 (37.9)	114 (59.1)	< **0.001**
PCO2 < 45 mmHg	100 (62.1)	79 (40.9)	
pH arterial	7.40 ± 0.06	7.38 ± 0.07	< **0.001**
pH > 7.35	140 (87)	140 (72.5)	**0.001**
pH < 7.35	21 (13)	53 (27.5)	

Hbg = hemoglobin, CRP = C reactive protein, BNP = Brain Natriuretic Peptide, PaO2 = partial pressure of oxygen in arterial blood, PaCO2 = partial pressure of carbon dioxide in arterial blood. Data are n (%) unless otherwise specified. Comparisons between concordant and discordant groups were performed Student's t test or Pearson's Khi² test. Statistical significance is denoted by a P value < 0.05

5. Exacerbation management in the ED: Oxygen administration

5.1. Oxygen management description

On ED admission, 243 (53.9%) patients were already receiving oxygen at a mean flow rate of 2.2 liter/minute (SD 2.8) and a mean pulse oximetry of 95% (SD 4.3). Only three patients (0.7%) were treated with noninvasive ventilation on admission. After medical examination, 266 (59%) patients were prescribed oxygen therapy at a 1.5 liter / minute (SD 1.7) mean flow rate. On ED discharge, mean pulse oximetry value was 93.8% (SD 3.4). A total of 39 (8.6%) patients were treated with noninvasive ventilation on ED discharge with 92.3% (SD 4.1) mean pulse oximetry.

5.2. Oxygen management concordance with guidelines

Guidelines recommend oxygen flow rate administration should be adapted on pulse oximetry values with a target between 88% and 92% (5). We therefore considered that 264 (58.5%) patients had a guideline-concordant oxygen administration [Figure 3]. Oxygen flow was too high in 176 (39%) patients and 11 (2.4%) had an oxygen flow too low.

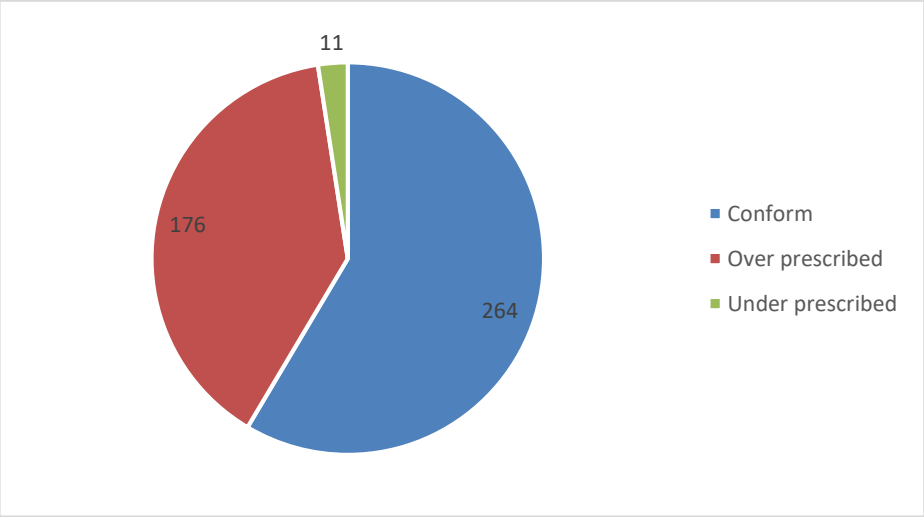

Figure 3: Concordance of oxygen administration management with guidelines. The rate of agreement between practices and guidelines was 58.5%. Data are (n).

5.3. Oxygen administration management: parameters associated with oxygen over-prescription.

As observed in antibiotic treatment management, patients over 75 years old were more likely to receive inappropriate oxygen flow rate. Also, patients who already received oxygen before ED admission had an over-prescribed oxygen flow rate. COPD baseline severity was not significantly associated with concordance [Table 7]. Respiratory failure signs such as high respiratory rate, chest recession or presence of dyspnea, hospitalization and high in-hospital mortality score (BAP 65 3-4) were associated with oxygen over-prescription. PO2 arterial was higher in patients with over-prescribed oxygen flow rate [Table 8].

Table VII : Oxygen administration management: demographic characteristics associated with oxygen over-prescription.

Characteristics	**Discordance between guidelines and practices (n=176)**	**Concordance between guidelines and practices (n=264)**	***P***
Age, mean ± SD, y	76.18 ± 12.59	72.61 ± 14.75	**0,007**
< 75 years old	60 (34.1)	132 (50)	**0,001**
> 75 years old	116 (65.9)	132 (50)	
Female sex	61 (34.7)	88 (33.5)	0.795
Male sex	115 (65.3)	175 (66.5)	
Physician status			0.473
Emergency physician	123 (70.7)	176 (67.4)	
Non-emergency physician	16 (9.2)	20 (7.7)	
Resident	35 (20.1)	65 (24.9)	
On-call schedule	106 (60.2)	143 (54.2)	0.209
Orientation			< **0.001**
Hospitalization	167 (95.4)	165 (62.7)	
ED discharge to previous structure/home	8 (4.6)	98 (37.3)	
Provenance			0.387
Home	134 (807)	215 (84)	
Nursing home / long-stay institution	32 (19.3)	41 (16)	
Severity of COPD			**0.039**
Gold stage 0	12 (6.8)	38 (14.4)	
Gold stage 1	25 (14.2)	42 (15.9)	
Gold stage 2	53 (30.1)	63 (23.9)	
Gold stage 3	54 (30.7)	89 (33.7)	
Gold stage 4	32 (18.2)	32 (12.1)	
Severity of COPD			0.533
Gold stage 0 to 2	90 (51.1)	143 (54.2)	
Gold stage 3 to 4	86 (48.9)	121 (45.8)	
Cardio-vascular comorbidities			0.839
Absence	61 (34.7)	94 (35.6)	
Presence	115 (65.3)	170 (64.4)	
Respiratory comorbidities			0.5
Absence	135 (76.7)	195 (73.9)	
Presence	41 (23.3)	69 (26.1)	

Data are n (%) unless otherwise specified. Comparisons between concordant and discordant groups were performed Student's t test or Pearson's Khi² test. Statistical significance is denoted by a P value < 0.05

Table VIII : Oxygen administration management: clinical and biological characteristics associated with oxygen over-prescription

Characteristics	Discordance between guidelines and practices (n=176)	Concordance between guidelines and practices (n=264)	*P*
Vital signs			
Temperature, mean ± SD, °C	37.37 ± 0.95	37.27 ± 0.77	0.202
< 38.5 °C	152 (86.4)	242 (92)	0.056
> 38.5 °C	24 (13.6)	21 (8)	
Heart rate, mean ± SD, pulse	94.67 ± 18.04	90.86 ± 18.98	**0.036**
Respiratory rate, mean ± SD	27.01 ± 7.22	25.46 ± 6.71	**0.022**
Pulse oximetry on admission, mean ± SD	94.79 ± 3.61	94.57 ± 3.87	0.546
Oxygen administration on admission			**< 0.001**
Absence	56 (31.8)	150 (56.8)	
Presence	120 (68.2)	114 (43.2)	
Respiratory severity signs			
Dyspnea			**0.023**
Absence	17 (9.7)	46 (17.4)	
Presence	159 (90.3)	218 (82.6)	
Cyanosis			0.066
Absence	174 (98.9)	253 (95.8)	
Presence	2 (1.1)	11 (4.2)	
Paradoxical respiration			0.136
Absence	145 (82.4)	231 (87.5)	
Presence	31 (17.6)	33 (12.5)	
Use of accessory inspiratory muscles			**0.004**
Absence	79 (44.9)	155 (58.7)	
Presence	97 (55.1)	109 (41.3)	
AECOPD severity assessment			**< 0.001**
BAP 65 score 1-2	113 (64.2)	212 (80.3)	
BAP 65 score 3-5	63 (35.8)	52 (19.7)	
Biological parameters			
Leucocytes, mean ± SD, Giga/liters	10.93 ± 4.5	10.55 ± 4.9	0.414
CRP, mean ± SD, ng/ml	64.36 ± 71.26	51.66 ± 69.86	0.087
CRP < 50 ng/ml	93 (59.2)	148 (69.2)	**0.048**
CRP > 50 ng/ml	64 (40.8)	66 (30.8)	
BNP, mean ± SD, pg/ml	287.39 ± 374.85	221.77 ± 420.96	0.21
PO2 arterial, mean ± SD, mmHg	75.96 ± 31.72	68.67 ± 25.15	**0.018**
PCO2 arterial, mean ± SD, mmHg	48.95 ± 13.55	48.31 ± 16.65	0.693
PCO2 > 45 mmHg	87 (53.7)	92 (45.5)	0.122
PCO2 < 45 mmHg	75 (46.3)	110 (54.5)	
pH arterial	7.38 ± 0.06	7.39 ± 0.07	0.404
pH > 7.35	127 (78.4)	162 (80.2)	0.673
pH < 7.35	35 (21.6)	40 (19.8)	

Hbg = hemoglobin, CRP = C reactive protein, BNP = Brain Natriuretic Peptide, PaO2 = partial pressure of oxygen in arterial blood, PaCO2 = partial pressure of carbon dioxide in arterial blood. Data are n (%) unless otherwise specified. Comparisons between concordant and discordant groups were performed Student's t test or Pearson's Khi² test. Statistical significance is denoted by a P value < 0.05

DISCUSSION AND CONCLUSION

1. Main findings and strengths

This work focuses on two major parts of AE of COPD therapeutic management in the ED. Adherence to antibiotic management guidelines was 51% with 43% rate of over-prescription. Patients with over-prescription were more likely to be aged over 75, to live in nursing home or long-stay institutions, to have higher inflammatory markers (temperature over 38.5°C, CRP, leucocytes and neutrophils counts) and a less severe COPD status and respiratory failure. This audit confirms that oxygen administration is a major part of emergency treatment of COPD exacerbation with 59 % of patients receiving oxygen on ED discharge. But it is not controlled enough as we observed only a moderate proportion (58.5%) of patients receiving oxygen with a pulse oximetry value within the recommended range of 88-92% target values. Oxygen administration was more likely to be inappropriate with elderly patients (age above 75), with GOLD II or IV patients and with patients who were already receiving oxygen during prehospital transport.

An original aspect of our study is that we analyzed both antibiotic treatment indication and choice of antibiotic molecule to describe antibiotic management practices more precisely. To the best of our knowledge there was no existent work describing guidelines adherence following those two modalities and investigating parameters associated with over-prescription. We only collected data available at ED admission so they reflect the parameters that the physician may have considered in deciding whether or not to start an antibiotic treatment. Another original aspect of our study is that as we analyzed the last oxygen flowrate and the last pulse oximetry value before ED discharge so that our results reflect medical management of oxygen therapy. Studies available in literature about oxygen therapy in ED focus on pre-

hospital care, are not specific to COPD patients or evaluate oxygen administration flow rate without considering pulse oximetry target values as outcome.

Our study population was similar to previous studies in terms of age, sex ratio and vital signs (38,43,44).

2. Interpretation of findings in relation to previously published work

2.1. Antibiotics management in AE

Regarding adherence to antibiotic management guidelines, our findings are similar to other studies despite heterogeneity of results. In literature, global adherence range from 10% to 64%, depending on more or less restrictive evaluation criteria (38,42,44). For instance, a 2014 retrospective study in an Australian regional university hospital found 36% over-prescription in the ED in terms of antibiotics indication and treatment length. Another recent Australian retrospective study from February 2017, reported an adherence rate of 10% with most of the patients receiving broad spectrum antibiotics (ceftriaxone) instead of recommended narrow spectrum (amoxicillin) (42). Interestingly broad spectrum regimen did not reduce the length of stay, but broad spectrum treated patients appeared to suffer from a more severe exacerbation. The risk factors for over-prescription we identified were the same that were reported in this study except for the prognostic score we used (BAP-65) that was not significant in our work. We report that antibiotic over-prescription concerned both indication and molecule spectrum choice. Patients with a mild to severe COPD (GOLD I, II and III) and with suspected but non-documented COPD were more susceptible to be prescribed antibiotics while it was not recommended. According to current guidelines, patients with GOLD status I to II should not receive any antibiotic treatment except in case of documented pneumonia (14). A narrow spectrum antibiotic such as amoxicillin should be prescribed to GOLD III patients with increased purulent sputum. Over-prescription in these patients could

be caused by a lack of attention to the sputum color criterion. Because amoxicillin-clavulanate was the most prescribed molecule, we can suppose that GOLD III patients frequently received it instead of recommended narrow spectrum amoxicillin. As expected, GOLD IV patients were less susceptible to receive a non-indicated antibiotic because broad spectrum molecules are recommended in every AE episodes. Those fragile patients are at risk of severe exacerbations with blood gas values disruption. This could explain why normal blood gas values are associated in our work with over-prescription.

COPD patients are frequently exposed to antibiotics during AE in primary care or hospital. The same tendencies were observed in an ambulatory treated patients survey concluding that guidelines regarding the prescription of antibiotics are poorly followed (45). Those repeated expositions could be pejorative leading to acquisition of bacterial resistances. Specific recommendations have been made about antibiotic consumption in French hospitals. Specifically, healthcare authorities encourage to save molecules with a high risk of bacterial resistance development such as amoxicillin-clavulanate or 3GC which are recommended and the mostly used molecules in AE (26).

Actually, the position of antibiotics in the treatment of AE of COPD remains unclear and controversial (17,21,46). The main difficulty is probably to stratify and identify patients who could benefit from such treatments (47). Data supporting the benefits of antibiotic treatment in AE have a low level of evidence in inhospital patients. They are provided by studies which did not differentiate COPD exacerbation from bronchitis in non-COPD patients, studies without placebo-control or without X-ray to exclude underlying pneumonia (5).This lack of evidence in available literature appears to be caused by the heterogeneity of patients and exacerbations included in these studies. The clinical presentations vary and range from episodic symptomatic deterioration that is poorly responsive to usual treatment to life threatening respiratory distress (48). A 2006 Cochrane systematic review of placebo controlled studies has shown that

antibiotics reduced the risk of short-term mortality, treatment failure and sputum purulence in patients experiencing moderate to severe exacerbation with increased cough and purulence (20). In the same way, latest 2012 Cochrane review concludes there is strong evidence that antibiotics have a beneficial effect on mortality and hospital length of stay only in patients admitted to ICU (21). However, according to this recent meta-analysis, the benefits in mild to moderate exacerbations are questionable with no reduction in length of hospital stay or mortality (21). Finally, this suggests that antibiotics may be effective in selected patients with severe exacerbations requiring treatment in ICU. As our work reports that most of the patients admitted in ED are hospitalized in conventional units, further randomized and placebo control studies are needed to assess the benefits of antibiotics in an homogenic group of moderate exacerbations.

Our work shows that high values of leucocytes and neutrophils count, CRP or elevated body temperature were significantly associated with antibiotic over-prescription. The latest GOLD guidelines do not recommend stratification strategies using inflammatory biomarkers. It recommends to select patients who could experience bacterial respiratory tract infection by identifying those "*who have three cardinal symptoms: increase in dyspnea, sputum volume and sputum purulence or two of the cardinal symptoms if increased purulence of sputum is one of the two symptoms"* (5). Today, sputum color is the strongest predictor of respiratory tract bacterial infection in AE of COPD (46). Sputum purulence appeared documented in most of the records we reviewed and 84% (n=379) of the patients we analyzed were tested for CRP. This suggests physicians do not consider only sputum purulence to start antibiotics but probably pay more attention to inflammatory markers. CRP appears to be a factor leading physicians to antibiotic over-prescription. Several biomarkers have been tested to identify patients with bacterial exacerbations. The gold standard to identify patients with bacterial exacerbations is cytobacteriological analysis of expectorated sputum (5). Sputum samplings

are delicate to execute, frequently do not provide reliable results and require too much time for bacterial cultures. These difficulties make this procedure clearly impractical to achieve routinely in the ED so it is only used for hospital inpatients with treatment failure or multidrug resistant bacteria colonization. Evaluations of CRP to identify bacterial infections have reported contradictory findings. Some works report that high concentration of CRP are associated with bacterial infections and purulent sputum (49,50). Other works report neither CRP nor PCT can differentiate bacterial or viral infections (51,52). Interestingly some studies report that bacterial infections are associated with low CRP values and normal body temperature (52). Thus, the use of CRP in the ED to state bacterial origin of infection is not recommended in the latest GOLD guidelines (5). PCT is supposed to be a more specific marker for detection of bacterial infections and is another routine inflammatory biomarker available in our unit. A recent meta-analysis concludes that PCT-guided treatment could safely reduce antibiotic overuse in patients with AE of COPD (53,54). Those data are not sufficient to conclude that PCT is a good marker to detect bacterial exacerbations and it should rather be considered as a *rule out* tool. The outstanding issue then is the cut-off value to exclude antibiotic treatment. Available studies used different thresholds but a commonly accepted value to start an antibiotic treatment appears to be 0.25 µg/L (55–57).

National guidelines do not consider any severity parameters suggesting physicians should not consider respiratory failure signs to decide whether an antibiotic treatment should be delivered or not. Recent French academic documents suggest any patient with respiratory failure signs should be prescribed an antibiotic treatment without considering presence of purulent sputum (58). The GOLD guidelines recommend in the same way the use of antibiotic *"if the patient requires mechanical ventilation (invasive or noninvasive)"* (5). This means respiratory failure, ie mechanical ventilation requirement, should make physicians consider antibiotic treatment whatever the GOLD status and even if there is no increased sputum

purulence. Today, clinical severity of AE appears to have a high correlation with antibiotics treatment benefits. Next national guidelines should consider clinical presentation and respiratory failure severity evaluation in the management of antibiotic treatments.

2.2. Oxygen administration in AE

Oxygen administration was lower than in previous French studies which reported 95% treated patients (40). An ED Australian study shows oxygen flow rate was inappropriately administered to about 45% of patients (59). Several prehospital studies report too important airflow are frequent on ED admission, are associated with increased length of stay and cause serious clinical adverse events such as respiratory acidosis (32,60,61). We observe here that oxygen administration on ED admission, and supposedly during prehospital transport, is associated with over-prescription on ED discharge suggesting a lack of revaluation of oxygen flow. In our work, oxygen overprescribed flow rate was also associated with vital signs traducing respiratory distress: tachycardia, high respiratory rate, dyspnea or use of accessory inspiratory muscles. As might be expected, oxygen over-prescription was associated with significant hyperoxia and with a higher mortality BAP-65 score. It is acceptable to consider that patients presenting with acute respiratory distress need transient high flow oxygen administration because this short-term administration will not lead to carbon dioxide retention and acidosis. In this study, we carried out long term oxygen over-prescription because oxygen flow rate prescriptions on ED discharge are supposed to be applied by nurses in hospitalization units. This may not have consequences during day time as ward physicians can adjust the flow rate prescription but it could lead to deleterious clinical outcome during night time while there is no medical presence in conventional hospital wards. Oxygen flow adjustment remains tough in the ED because it is time consuming. Also, physicians or nurses probably pay more attention to hypoxemia than hyperoxia. Hyperoxia in COPD is particularly problematic because it might be associated with hypercapnia and adverse clinical outcomes such as respiratory acidosis and

increased mortality (27,28,62). To offset this problem automated oxygen titration devices have been proposed (36). Oxygen administration should more simply be prescribed with target pulse-oximetry values instead of flow rate. Altogether, these results underline a lack of attention in oxygen flow repeated adjustment in the ED.

3. Limitations

The main limitations of this study are its retrospective and monocentric design so it only reflects local practices. Inaccuracies in diagnosis input may have made our selection partial. To limit this bias, we firstly extended our selection to all COPD patients consulting in the ED. We then identified manually records for inclusion. Patients who are neither identified as COPD nor previously diagnosed as COPD may then have been omitted. Also, as we did not analyze chest X-ray to confirm or infirm presence of a pneumonia we could also have included pneumonia.

4. Conclusion

In conclusion, our study highlights the fact that management of COPD exacerbation remains challenging. We observed a medium rate of adherence to guidelines in terms of antibiotic prescribing and a high rate of overprescribed treatments. French guidelines present probably an insufficient level of precision about antibiotic indications and management. As in pneumonia treatment guidelines, an antibiotic management strategy based on clinical severity could be considered. But because literature contains conflicting results about the benefits of antibiotics, further placebo-controlled studies are necessary. Such trials could help physicians in limiting the antibiotic exposure of those patients who are likely to receive frequent antibiotic treatments. We should use decision support tools to enhance adherence rate to guidelines and to limit over-prescription of antibiotics and subsequent bacterial resistance acquisition. Furthermore, our results show that oxygen therapy, despite the risks of complications, remains

widely over-prescribed and not enough adapted in the ED. This could adversely affect mortality by increasing hypercapnia. In consequence, oxygen should be prescribed with appropriate pulse oximetry target values and we should focus on a formalized evaluation rhythm of pulse oximetry in order to avoid hyperoxia.

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Supplemental 1: Acute exacerbation of COPD, antibiotics indications and choice. From "SPILF, AFSSAPS. Antibiothérapie par voie générale dans les infections respiratoires basses de l'adulte. Pneumonie aigue communautaire, exacerbations de bronchopneumopathie chronique obstructive. 2010."

COPD clinical severity status on basic status		**Indications for antibiotic use**	**Antibiotic choice**
Without spirometry values	Known spirometry values		
No shortness of breath	FEV1 > 50%	No antibiotic treatment	
Dyspnea on exertion	FEV1 < 50%	Greenish purulent sputum	**amoxicillin**, cefuroxime-axetil, or cefpodoxime-proxetil or macrolide or pristinamycin or telithromycin
Dyspnea on mild exertion or at rest	FEV1 < 30%	Antibiotic systematically recommended	amoxicillin/clavulanic acid or parenteral 3GC or levofloxacin

In view of literature, no hierarchy could be proposed between recommended molecules. FEV1 = Forced expiratory volume in the first second.

Supplemental 2: BAP-65 score definition and class-associated mortality. From "Tabak YP, Sun X, Johannes RS, Gupta V, Shorr AF. Mortality and need for mechanical ventilation in acute exacerbations of chronic obstructive pulmonary disease: development and validation of a simple risk score. Arch Intern Med. 2009 Sep 28;169(17):1595–602."

BAP-65 score	**Score**
Urea > 9 mmol/l	+1
Altered mental status, GCS < 14	+1
Heart rate > 109 beats / min	+1
Age > 65 years	+1

BAP-65 scoring and mortality rates		
Class	**Score**	**Mortality**
1	0	0.5%
2	1	1.4%
3	2	3.7%
4	3	12.7%
5	4	26.2%

LE BASTARD Quentin

Antibiotiques et oxygénothérapie dans les exacerbations de BPCO : surprescrivons nous aux urgences ?

RÉSUMÉ

Contexte : L'exacerbation aigue de bronchopneumopathie chronique obstructive est un motif fréquent de consultations aux urgences. Ces évènements sont associées à un risque de décès et de détérioration de la fonction pulmonaire. La difficulté réside dans l'identification des patients présentant une surinfection bactérienne e nécessitant une antibiothérapie. Cette difficulté expose au risque de sur-prescription d'antibiothérapie. Les recommandations françaises d'introduction d'une antibiothérapie sont basées sur le statut GOLD. Nous avons évalué le taux d'adhérence aux recommandations de prescription d'une antibiothérapie dans un service d'urgences adultes. Le critère de jugement principal était le taux d'adéquation entre les recommandations et la pratique clinique. Les critères de jugement secondaires étaient l'identification des paramètres associés à une sur-prescription d'antibiotiques ainsi que le taux de concordance avec les recommandations en termes de prescription d'oxygénothérapie.

Méthode : Audit rétrospectif des dossiers des patients admis aux urgences d'un centre hospitalier universitaire français pour exacerbation aigue de BPCO durant les années 2013 et 2014.

Résultats : 51% des antibiothérapies prescrites étaient conformes aux recommandations avec 43% de sur-prescription. Les facteurs de sur-prescription identifiés étaient un âge supérieur à 75 ans, la vie en institution, une température supérieure à 38,5°C, une hyperleucocytose et une élévation de la CRP ainsi qu'un statut GOLD inférieur à III. 58,5% des patients recevaient une oxygénothérapie adaptée.

Conclusion : Cet audit retrouve un niveau moyen d'adhérence aux recommandations de prescription d'antibiothérapie et d'oxygénothérapie. Il met en évidence que les marqueurs inflammatoires, non recommandés dans l'indication d'une antibiothérapie, sont largement utilisés et facteurs de sur-prescription. Des recommandations incluant des critères de décision tenant compte de la sévérité clinique de l'exacerbation pour la prescription d'une antibiothérapie pourraient limiter le risque de surprescription.

Mots-clés : antibiotiques, bon usage des antibiotiques, bronchopneumopathie chronique obstructive, respect des recommandations

Antibiotics and oxygen therapy for acute exacerbation of COPD: Are we over-prescribing in the emergency department?

ABSTRACT

Background: Acute exacerbation of chronic obstructive pulmonary disease is a commonly treated condition in the emergency department. These events are significantly associated with a mortality risk and with a worsening of the lung function. It remains difficult to identify patients with bacterial infection who should benefit from an antibiotic treatment. This can lead to an over-prescription of antibiotics. French guidelines describes antibiotic prescription modalities and are based on GOLD status. In this study, we assessed antibiotics prescriptions adherence to guidelines in a university hospital emergency department. The primary outcome was the concordance rate between prescribed antibiotic and guidelines. Then we identified parameters associated with over-prescription. We also investigated the concordance rate between prescribed oxygen flow rate and guidelines.

Methods: Retrospective audit of medical records for patients admitted with acute exacerbation of COPD during 2013 and 2014 in a French university hospital emergency department.

Results: Adherence to antibiotic management guidelines was 51% with 43% rate of over-prescription. Patients with over-prescription were more likely to be aged over 75, to have a GOLD status lower than IV, to live in long-stay institutions and to have body temperature over 38°C or high level of CRP or leucocytes count. 58.5% of patients had a guideline-concordant oxygen administration.

Conclusion: We report a medium adherence level to guidelines for antibiotics and oxygen therapy management. Our work highlight that inflammatory markers, which are not recommended for antibiotics management in COPD, remains widely used and leads to unjustified antibiotics usage. Guidelines including antibiotics management decision tools related to clinical severity may reduce antibiotics over-use

Keywords: antibiotics, antimicrobial stewardship, chronic obstructive pulmonary disease, guidelines adherence

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