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The use of the Prospector calculator reduces antibiotic therapy in exacerbations of chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) exacerbations frequently cause patient consultations in both out- and inpatient settings. Recent data suggest that only 40–60% of exacerbations are of bacterial origin and mandate antibiotic treatment. However, a reliable tool to justify prescribing antibiotics for COPD exacerbation is still lacking. This study was designed to explore the hypothesis that utilization of a novel decision-making tool called Prospector would lead to lower consumption of antibiotics and provide a more rational approach to managing COPD exacerbations versus standard therapy in patients with COPD. The study included 77 COPD patients who experienced a COPD exacerbation and were treated in outpatient settings. The Prospector group (PG) ($n = 40$) were treated by the study author using the Prospector calculator (a tool designed by the first author that translates: patient symptoms, exacerbation, and medical history of COPD into a decision on the use of antibiotics in COPD exacerbation treatment). Other primary care specialists treated the control group (CG) ($n = 37$) in the same outpatient clinic; antibiotic therapies were implemented at the physician's discretion, most often using Anthonisen's criteria. All other medications were administered at the physician's discretion. Safety endpoints were set as: death, hospitalization, and number of exacerbations. Antibiotics were administered in 32.8% and 81.2% of exacerbations in the PG and CG, respectively ($p < 0.0001$). A comparable percentage was verified positively in both PG patient subsets: those that did and did not receive antibiotics at visit 1 (94.7% and 94.9%, respectively). Twenty-eight patients in the PG and 37 in the CG were followed for up to 35 months. Failure to recover (defined as deterioration or lack of improvement) in 30 days following exacerbation was 10.7% in the PG and 47.2% in the CG. In the CG, the failure rate was significantly higher ($p = 0.0043$). Hospitalization rates in the PG and the CG were 42.9% and 94.4%, respectively. In the CG, the hospitalization rate was significantly higher ($p < 0.0001$). COPD hospitalization rates in the PG and the CG were 17.9% and 33.3%, respectively ($p = 0.1643$). This preliminary study suggests that using the Prospector calculator results in markedly reduced antibiotic prescription for COPD exacerbations. No new safety signals have been identified for the method.

Keywords COPD exacerbation, Antibiotics, Calculator, C-reactive protein, Eosinophil blood count, Oral glucocorticosteroids

Abbreviations

CBC	Complete blood count
CG	Control group
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
EBC	Eosinophil blood count
GP	General practitioner
ICS	Inhaled corticosteroids
LABA	Long-acting beta2-agonists
LLN	Lower limit of normal
OCS	Oral corticosteroids

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PG	Prospector group
RR	Relative risk
SABDs	Short-acting bronchodilators
SD	Standard deviation

Chronic obstructive pulmonary disease (COPD) exacerbations are often addressed in consultation with a general practitioner (GP). About 4% of all GP encounters during the year are due to problems associated with respiratory tract infection; among them, about 20% for COPD exacerbation[1]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) currently defines COPD exacerbation as an event characterized by dyspnea and/or cough and sputum that worsen over ⩽14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways"[2]. The goal of COPD exacerbation treatment is to minimize the negative impact of the current exacerbation and to prevent subsequent events[3]. Yet, there is no clear consensus when to use antibiotics or OCS in specific clinical scenarios. Currently, there is no proven method that indicates in which exacerbation cases initiation of antibiotics would bring clinical benefit[4].

Antibiotic use, regardless of whether warranted, is a primary factor in developing anibiotic-resistant bacteria. Much of this prescribing is inappropriate, with research showing that at least 30% of antibiotic use in outpatient settings is unnecessary[5]. In the United States alone, 2 million people yearly develop hospital-acquired infections that lead to 99,000 deaths, mostly due to antibiotic-resistant bacteria[6]. The total annual economic cost associated with antibiotic resistant bacteria is estimated to be $20 billion in healthcare costs and $35 billion in lost productivity[6]. In 2018, Europe reported deaths from treatment-resistant bacterial infections of 33,000 patients yearly[7]. The increasing resistance of bacteria to antibiotics is undoubtedly associated with their abuse. Reducing the misuse of antibiotics has been a high priority in many developed countries, and several initiatives have been implemented that led to some decrease in antibiotic use, especially in outpatient settings[5,8,9]. Yet many countries are failing in this regard: Greece, Italy, Romania, and Portugal are among the countries with the highest antibiotic consumption and bacteria-resistant ratio. Outpatient antibiotic consumption has grown significantly (by 50%) in Poland between 2004 and 2017[10].

COPD exacerbations are the most common reason for medical appointments and hospital admissions and generate significant costs in healthcare. Evidence indicates that each exacerbation is associated with a deterioration of lung function[11]. Vollenweider et al. have shown that using antibiotics in intensive care units is associated with an indisputable benefit in COPD exacerbations, but similar benefits in outpatients have not been demonstrated[12].

In outpatient settings matter is complicated by the fact that factors that cause COPD exacerbations are not limited to bacterial pathogens, which cause about 40–60% of all exacerbations. It is estimated that viral infections can lead to about 23–50% of all COPD exacerbations[13]. Other factors include atypical bacteria (5–10%) and inhalation of harmful air pollutants such as ozone, nitrogen dioxide, and sulfur dioxide (10%)[14]. Additionally, the profile of granulocytes involved differs in each case. Most of them are neutrophilic, but 10–40% of cases are eosinophilic exacerbations. It has also been proven that eosinophil levels above 340/μL are associated with a higher frequency of exacerbations in COPD patients[15].

Currently, there is no consensus on when and to whom clinicians should prescribe antibiotics during an exacerbation of COPD. Some providers consider historical Anthonisen criteria[16], while others use arbitrary criteria based on experience rather than guidelines. There have also been reports of using Anthonisen criteria with C-Reactive protein (CRP) cut-off point[17]. However, to the best of our knowledge, an easy and simple tool that would facilitate decision making is not yet available.

This study was designed to explore the hypothesis that utilization of a novel decision-making tool called Prospector will lead to lower consumption of antibiotics and provide a more rational approach to managing COPD exacerbations versus standard therapy in patients with COPD while maintaining patient safety and health outcomes.

Methods

Study design

This is preexperimental study with a static group comparison. A prospective analysis was performed on COPD patients who reported to a single outpatient clinic, Suchanino in Poland, with a COPD exacerbation and whose treatment decision was guided by the Prospector method between 01/OCT/2015 and 04/JAN/2019. For comparison, a retrospective analysis was performed on patients who reported to the same clinic at the same time period but whose decision was guided by the treating physician's best knowledge. Informed consent to participate in the study was obtained from all patients. The authors confirm that all research was performed in accordance with relevant guidelines/regulations. Approval for this study was received from the Bioethics Committee of District Medical Chamber in Gdańsk, Poland (consent number for the study nr KB 14/2/15).

Settings and participants

Inclusion criteria for both groups were: previous COPD diagnosis (ICD-10 code J44 and J44 /45, J44/J20) International Statistical Classification of Diseases and Related Health Problems 10th Revision, age > 40 years, COPD exacerbation, post 400 μg salbutamol $FEV_1/FVC < 0.7$ and/or the lower limit of normal values (LLN) adjusted for age, and availability of medical records[2]. Patients in the Prospector group (PG) ($n = 40$, 12 lost to follow-up) were treated by the first study author using the Prospector calculator. The control group (CG) ($n = 37$) were treated by physicians other than the first author, according to their best knowledge, where Anthonisen's criteria were used[16]. Patients were tracked for exacerbations, hospitalizations, failure to recover,

and death. Primary endpoints was: Prospector is better or similar to conservative treatment in terms of antibiotic consumption .

Secondary endpoints: Prospector is better or similar to conservative treatment in terms of safety: death reate, hospitalization rates, exacerbation recurrence.

The characteristics of both groups are presented in Table 1.

The Prospector method

Prospector was created based on available data from the publications included in the article and the GOLD guidelines - regarding the diagnosis of COPD exacerbation and clinical experience in the management of patients with COPD exacerbation. Individual parameter was implemented based on COPD exacerbation definition, variables which are determinants of bacterial exacerbation like change in colour sputum, number of exacerbations of previous year, FEV_1% previously used in COPD classification severity, this variables correlates strong with bacterial exacerbation and strong correlation was address as point 2, 3 and 4 in scale ranking. Lower FEV_1% better correlation with bacterial exacerbation prediction and higher point in ranking scale Variables like temperature above 38 Celsius degrees, $Sa0_2$ below 95%, feeling of illness have mild correlation and are scored 1, as single variables but with combination with above mentioned predicting probability for bacterial exacerbation rise substantially. In the publications, the authors validated the variables in terms of their usefulness in diagnosing bacterial exacerbation of COPD, but in none of these studies did they combine them. The simple design of the calculator was necessitated by clinical experience and taking into account the above-mentioned variables, which had already been validated in previous studies for their usefulness in diagnosing bacterial exacerbation of COPD. Simple scoring also forced a cutoff point, arbitrarily set at 10 - antibiotic administration, < 10, i.e. 9 or less against antibiotic administration. Stat analysis showed that a more precise cut-off point could be 8, which is covered in the text. From original cut off point was 10 and whole trial was set on 10 points as discrimination point for antibiotic treatment. Statistician was proposed 8 as for better AUC curve but is subject for further evaluation.

The patient qualification scheme according to the Prospector calculator during the first and second visit is shown in two figures (Figs. 1 and 2).

Prospector is a novel clinical calculator developed by the study authors where information on patient symptoms, exacerbation, and medical history of COPD is translated into a score (Table 2). The score is compared against a cutoff point. A cutoff point was set arbitrarily as ≥ 10 for the recommendation of antibiotics treatment and ≤ 9 for recommendation against antibiotics treatment. Upon scoring ≥ 10, the patient was prescribed an antibiotic on visit (1). Upon scoring ≤ 9, the decision on antibiotic therapy was deferred to visit (2). In cases of suspected pneumonia, the investigator ordered a chest X-ray. Patients with ≤ 9 points were collected C-reactive protein (CRP) and complete blood count (CBC) tests to recognize markers of bacterial infection, which were set based on the literature on CRP ≥ 40, neutrophils ≥ 7500/µl with leukocytes ≥ 10,000/µl and phenotyping based on eosinophils ≥ 200/µl as a candidate for OCS treatment[3,18,19]. A follow-up visit (visit 2) was recommended 2 to 3 days later to assess eosinophil count and verify intervention efficacy.

Visit 1

During the first visit, exacerbation history (past 12 months), medical examination, and history related to concomitant diseases were collected from the study group. Based on these data, patients were assessed using the Prospector method.

For enrollment into the Prospector group, patients needed to meet 2 criteria from points 1–5 (Table 2). To manage their exacerbation, patients were given bronchodilators for nebulization (0.5 mg fenoterol and 0.25 mg/ml ipratropium bromide or 0.25 mg/ml ipratropium bromide) and OCS (30 mg prednisone or equivalent if in the source documentation, the historical value of eosinophils was ≥ 200/µl). If eosinophil blood count (EBC) was unknown, patients were ordered CRP and CBC tests.

	Prospector Group	**Control Group**
	***n* = 28**	***n* = 37**
Sex		
Female	10 (32%)	17 (46%)
Male	18 (64%)	20 (54%)
Age (mean)	66,6 years	70,7 years
COPD severity		
Mild + moderate ($FEV_1 > 50$)	13 (46%)	31 (84%)
Severe + very severe ($FEV_1 < 50$)	14 (54%)	6 (16%)
Concomitant disease ICD-10	I50 2[7%], I25 4[14%], E11 6[21%], I10 18[64%], I48 3[11%]	I50 3[8%], I25 5[14%], E11 10[27%], I10[24]64%, I48 8[22%]
Number of chronic diseases other than COPD		
0–1	9[32%]	7[19%]
2	7[25%]	8[22%]
3+	12[43%]	22[59%]

Table 1. Patient characteristics of the Prospector and control group.

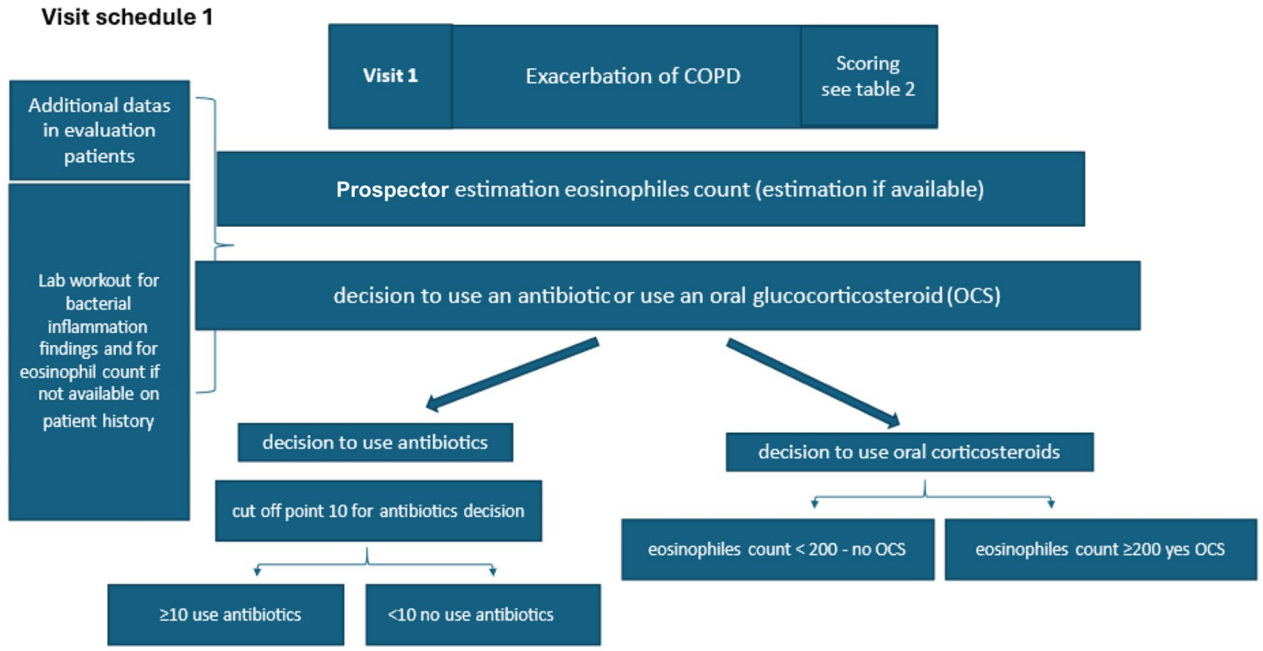

Fig. 1. First visit qualification for treatment with antibiotics and oral glucocorticoid according to Prospector.

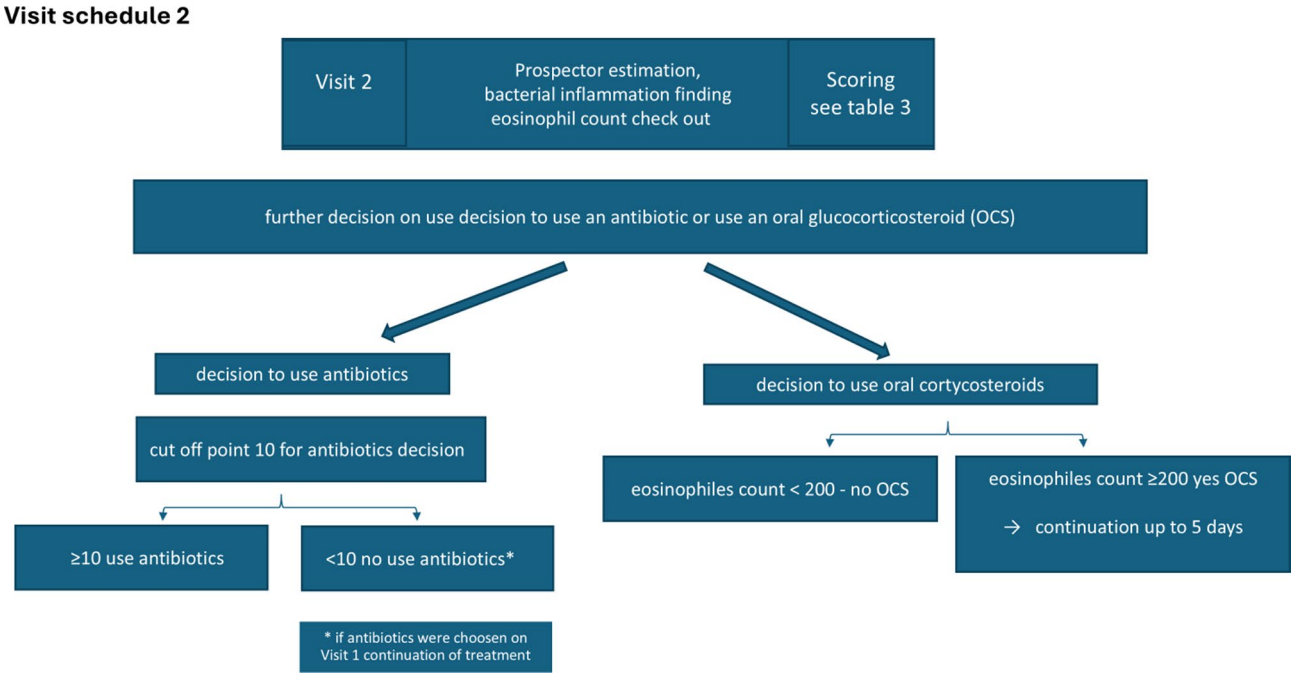

Fig. 2. Second visit qualification for treatment with antibiotics and oral glucocorticoid according to Prospector.

Verification (visit 2)

During the second visit, laboratory results were evaluated, the history of the last 2–3 days was collected, the patient was examined, and the Prospector method verified intervention efficacy. Patients scoring ≥ 10 points (Table 3) did not pass the verification and antibiotics were introduced. If the patient had antibiotics introduced at visit 1 and the verification was still negative, treatment was adjusted at the physician's discretion. OCS were continued for 5–7 days if the new EBC was ≥ 200/µl; if not, OCS were discontinued.

Manifestation	Scoring	Reference
1. Cough greater than usual	1 point	16
2. Increased amount of sputum	1 point	4 16
3. Increased sputum purulence (change of sputum color to purulent-green, brown)	2 points	20 21 16
4. Increased dyspnea	1 point	22 14 16
5. Feeling of illness, symptoms of infection	1 point	23
6. Exacerbations in the last 12 months: 2 treated on an outpatient basis or 1 or more hospitalizations due to exacerbation of COPD	1 point	18 4 24
7. Airflow limitation severity (COPD grade)	Very severe, 3 points; severe, 2 points; medium, 1 point; mild, 0 points	3
8. Concomitant diseases: cardiovascular, rheumatological, renal failure, chronic liver disease, cancer, metabolic and endocrine	1 point	25
9. Temperature > 38^{0}C	1 point	23
10. Saturation (SaO_2) < 95%	1 point	26
11. Auscultatory changes other than ordinary daily wheezing and crackles	4 points	23

Table 2. Scoring system visit 1.

Manifestation	Scoring	Reference
1. Leukocytosis 10,000/µl with neutrophils 7500/µl	4 points	19
2. CRP ≥ 40	4 points	18
3. Chest X-rays confirm pneumonia	4 points	19
4. Deterioration during treatment	5 points	27
5. Improvement during treatment	−5 points	28
6. Auscultatory changes	Increased, 2 points; same as on visit 1, 1 point; no change, 0 points	28

Table 3. Scoring system on visit 2.

In the control group, antibiotic therapies were implemented at the physician's discretion, often using Anthonisen's criteria. A second visit, if applicable, was set up at the physician's discretion.

Data collection

Patient demographics, exacerbation history in the previous 12 months, hospitalizations, symptoms of exacerbations, concomitant diseases, airflow limitation severity (COPD grade: 1,2,3,4), temperature, saturation, and physical examination findings were collected according to available electronic data retrieved from Serum system version 4.5.8.26 Kamsoft S.A. (Poland) and from the Prospector database. All laboratory tests were retrieved from a local authorized laboratory, Bruss (Poland).

Statistical analysis

The statistical analyses have been performed using the statistical suite TIBCO Software Inc. (2017) and Statistica data analysis software system, version 13 (http://statistica.io). The quantitative variables were characterized by the arithmetic mean of standard deviation or median or max/min (range) and a 95% confidence interval. The qualitative variables were presented with the use of count and percentage. The statistical significance of differences between the two groups was processed with the student T-test or Mann-Whitney u-test. Chi-squared tests for independence were used for qualitative variables. In all the calculations, the statistical significance level of $p = 0.05$ has been used. ROC (receiver operating characteristic curve) and AUC (area under curve) was implemented to verify accuracy of arbitrary set cut-off point. Value of $P < 0.05$was considered statistically significant.

Results

There were two groups of patients: the PG and the CG. The mean age was 66.6 and 70.7 years in PG and CG, respectively. The populations differed in COPD severity: 54% and 16% of the patients had severe or very severe disease ($FEV_1 < 50$) in PG and CG, respectively. It has to be noted that demographics data was only available for 28 out of 40 PG patients. The PG reported a total of 58 exacerbations from 01/10/2015 until 04/01/2019. At visit 1, 19 (32.8%) patients were assessed by the Prospector calculator as requiring antibiotics (score ≥ 10). After 2–3 days of preliminary treatment, the treatment decision was verified and 94.7% of the patients were verified positively. A comparable percentage was verified positively in both patient subsets: those that did and did not receive antibiotics at visit 1 (94.7% and 94.9%, respectively, Table 4) (relative risk [RR] is 0.999 [95%

	Indicated	Not indicated
	(% of all exacerbations)	(% of all exacerbations)
All Prospector exacerbations	19 (32.8)	39 (67.2)
Verification: Positive	18 (94.7)	37 (94.9)
Verification: Negative	1 (5.3)	2 (5.1)

Table 4. Antibiotic therapy decisions and treatment effectiveness compared with 2–3 day rating.

CI 0.878–1.136]). This means that the effectiveness of the Prospector tool in the use and non-use of antibiotic therapy was at a similar level. In a total of 3 cases (5.2%), verification was negative. In one case, antibiotics were given (Prospector score ≥ 10), but no improvement was achieved. In the remaining two (Prospector score ≤ 9), antibiotics were not initiated and the patients did not experience symptom improvement; those patients scored 9 points on visit 1, meaning they were right below the antibiotic threshold. Therapeutic failures means in this study that initial determination to treat with or without antibiotics didn`t match determination of subsequent visit (visit2) and or failure of treatment causes change of primary treatment.

The CG reported a total of 74 exacerbations within the same timeframe as the PG.

In general, the more points scored at visit 1, the likelihood of using antibiotics and the chance of negative verification after 2–3 days increases. Therefore, if the number of points were linked to the verification after 2–3 days, the following ROC curve was obtained (Fig. 3). For 7 points or less, negative verification after 2–3 days was observed in all cases (AUC = 0.666, 95% CI 0.529–0.804, $p = 0.0180$). The default cutoff point was 10 points or more for antibiotic treatment. Statistical analysis found that 8 points would be a more reliable cutoff point. Based on ROC curve analysis, sensitivity was 82.8% and specificity was 53.1%.

Safety. The PG and CG failure rates were 10.7% and 47.2%, respectively. In the CG, the failure rate was significantly higher ($p = 0.0043$). Hospitalization rates in the PG and CG were 42.9% and 94.4%, respectively. In the CG, the hospitalization rate was significantly higher ($p < 0.0001$). On the other hand, the COPD hospitalization rates in the PG and CG were 17.9% and 33.3%, respectively ($p = 0.1643$). Because exacerbations, OCS, and nebulization occurred more than once for a single patient, the analyses were performed comparing the average values of these parameters in the groups.

There were no significant differences in exacerbation rates between the groups related to nebulization and OCS treatment ($p = 0.4526$) (Table 5). On the other hand, OCS and nebulization were significantly more frequent in the PG ($p < 0.0001$).

In the univariate model, two variables, increased amount of sputum and airflow limitation severity (COPD grade), were statistically significant regarding antibiotic treatment. In the multivariate model, only one variable, airflow limitation severity (COPD grade), was statistically significant regarding antibiotic treatment (Table 6).

Discussion

The goals of treatment for COPD exacerbations are to minimize the negative impact of the current exacerbation and prevent development of subsequent events[3]. Thus, a rapid and precise clinical assessment is crucial for proper exacerbation management.

Prospector calculator use

In this pilot study, we describe the Prospector calculator method that has the potential to: (1) rapidly determine the right therapeutic decision, (2) reduce antibiotic prescription to necessary COPD exacerbation events, and (3) maintain safety and efficacy of COPD exacerbation treatment. Furthermore, it helps the physician to collect a more structured and complete medical history leading to categorizing of COPD exacerbation, future exacerbation risk assessment, and initiation or cessation of OCS, inhaled corticosteroids, or long agonists combination treatment.

The results of this pilot study are in accordance with the results of a large study of more than 1,000 patients[17] where physicians using the Anthonisen criteria prescribed antibiotics on average for 80.6% of exacerbations, while physicians using an additional CRP examination prescribed them in approximately 54.3% of cases. Furthermore, authors disclosed several predictors for antibiotic prescription in COPD exacerbations using multivariate regression analysis. Still, only a few of them (e.g., age, fever, increase in cough intensity, purulent sputum, chest x-ray, and patient request) reach statistical significance and were incorporated into the calculator[1,17,29,30]. Statistical analysis in our study confirms two variables, increased amount of sputum and airflow limitation severity (COPD grade), were statistically significant with regard to antibiotic treatment (Table 6) and were in accordance with similar findings from other studies.

Antibiotic use

In our study, antibiotic use in the PG was 32.8% and in the CG, 81.2%. It is thus tempting to speculate that the addition of exacerbation predictors on top of a CRP cutoff allowed us to further reduce antibiotic usage. High antibiotic consumption is common. Llor C[17] recorded 1,222 exacerbations, where about ¾ of patients were given antibiotics. Van der Valk[28] and Krahnke and colleagues[27] tried to determine what factors could most likely indicate the need for antibiotics to be used in the exacerbation of COPD. The study was conducted on 116 patients, 19% of whom had antibiotic therapy, and found that if the patient meets all the indications (no bacteria

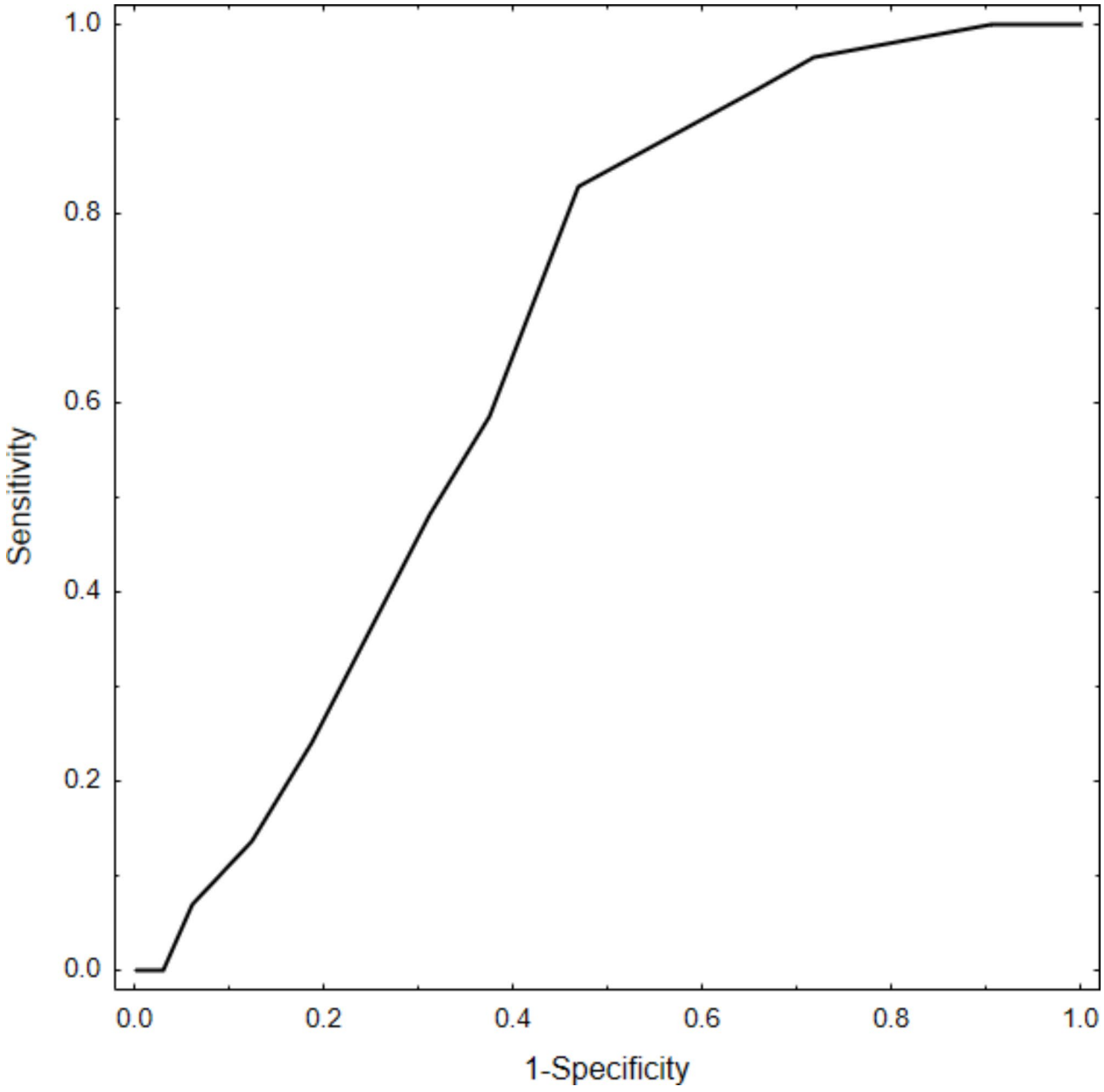

Fig. 3. ROC Curve and proposed cutoff point for antibiotic treatment.

in sputum, no deterioration in the spirometric values, and < 2 exacerbations within last 12 months), 100% are not a candidate for antibiotic therapy. However, if all 3 characteristics were met, the probability of bacterial exacerbation requiring antibiotic therapy is 67%. Here, we provide a different approach, implementing Evidence Based Medicine predictors into the Prospector calculator, but splitting exacerbation and treatment assessment into two visits. The statistical analysis performed here suggests that the decision efficacy for prescribing or not prescribing the antibiotics was 94.7 for positive verification and 94.9 for negative verification decision.

Two patients who did not receive antibiotics were verified negatively at visit 2. They scored 9 points, where antibiotics were initiated from 10. However, a total of 5 patients scored 9 in the PG, the remaining 3 passing the verification. The author therefore believes that sensitivity should not be increased at the cost of specificity.

Decision in favor of antibiotic treatment based solely upon a specific cutoff point for CRP may be misleading, as shown in the Llor C[17,31]. It can therefore be seen that in the CRP ranges from 0 to 10, the use of antibiotic therapy is 1 in 5 or 20%, and in the range of > 50 non-use of antibiotic therapy is 1 in 7 or 14%. When CRP was between 11 and 50, physicians were uncertain whether or not to prescribe antibiotics compared to a CRP value below 11 and above 50. Here, a CRP = 40 cutoff was implemented, as Higdon et al. used, achieving a sensitivity of 77% for bacterial infections that mandated antibiotic treatment versus viral infections[32].

	PG ($n=28$)	CG ($n=36$)	*P*-value
Antibiotics administered	19 (32.8%)	62(81.2%)	< 0.0001
Failure	3 (10.7%)	17 (47.2%)	0.0043
Hospitalizations	12 (42.9%)	34 (94.4%)	< 0.0001
COPD hospitalizations	5 (17.9%)	12 (33.3%)	0.1643
Exacerbations			
Mean (SD)	1.7 (0.8)	2.1 (1.2)	0.4526
Range	1.0–3.0	1.0–5.0	
Median	1.5	2.0	
95%CI	[1.4;2.0]	[1.6;2.5]	
OCS			
Mean (SD)	1.5 (0.9)	0.2 (0.4)	< 0.0001
Range	0.0–3.0	0.0–1.0	
Median	1.0	0.0	
95%CI	[1.1;1.8]	[0.1;0.4]	
Nebulization			
Mean (SD)	1.7 (0.8)	0.4 (0.7)	< 0.0001
Range	1.0–3.0	0.0–2.0	
Median	1.5	0.0	
95%CI	[1.4;2.0]	[0.2;0.6]	

Table 5. PG vs. CG with and without antibiotic treatment and main safety points.

	Univariate		Multivariate	
Predictor variable	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Cough greater than usual	0.44 (0.04;5.07)	0.5069	0.93 (0.03;32.49)	0.9657
Increased amount of sputum	**5.28 (1.04;26.96)**	**0.0454**	4.11 (0.58;29.09)	0.1570
Increased sputum purulence	1.60 (0.82;3.10)	0.1679	1.40 (0.58;3.41)	0.4529
Increased dyspnea	$>10^6$ (na)	na	$>10^4$(na)	na
Feeling of illness, symptoms of infection	3.78 (0.72;19.94)	0.1171	5.74 (0.90;36.80)	0.0653
Exacerbations in the last 12 months	3.03 (0.77;11.96)	0.1134	1.66 (0.30;9.25)	0.5610
Airflow limitation severity (COPD grade)	**3.12 (1.42;6.87)**	**0.0047**	**3.27 (1.07;9.97)**	**0.0376**
Concomitant diseases	0.89 (0.23;3.45)	0.8648	2.83 (0.35;22.76)	0.3290
Temperature > 38°C	1.11 (0.15;8.44)	0.9189	0.36 (0.01;12.81)	0.5722
Saturation (SaO2) < 95%	0.64 (0.22;1.88)	0.4115	0.31 (0.07;1.44)	0.1335
Auscultatory changes other than ordinary daily wheezing and crackles	0.97 (0.75;1.26)	0.8297	0.90 (0.62;1.30)	0.5590

Table 6. Univariate and multivariate regression analysis of variables associated with antibiotic treatment. na - non applicable. Significant values are in [bold].

Eosinophil blood count

The presence of elevated EBC in COPD patients is a biomarker of eosinophilic respiratory tract disease in COPD patients and a risk factor for future exacerbations[15]. Patients with elevated EBC were shown to benefit from LABA/ICS treatment and have fewer exacerbations when compared to LABA alone[33]. In the general COPD population, EBC above 340/µL is associated with a higher risk of exacerbation (risk ratio: 1.76)[15]. Exacerbation management with OCS was demonstrated to bring clinical benefits to patients with EBC > 200/µL (failure to recover was 15% vs. 2%, respectively)[19]. In the PG, all patients without evidence for EBC ˂200/µL received OCS at visit 1. OCS were withdrawn at visit 2 if the ordered laboratory test produced a result below 200/µL. The authors are aware that even short bursts of OCS result in an increased risk of adverse events[34], yet in COPD exacerbation, they shorten recovery time, improve lung function, oxygenation, the risk of early relapse, treatment failure, and hospitalization length[3,35]. Prolonged exacerbation duration is associated with poorer health status and a greater risk of future exacerbations[36]. In our study, we disclosed that the failure rates in the PG and the CG were 10.7% and 47.2%, respectively. In the CG, the failure rate was significantly higher ($p=0.0043$).

Hospitalizations

Hospitalization rates in the PG and CG were 42.9% and 94.4%, respectively. In the CG, the hospitalization rate was significantly higher ($p < 0.0001$). On the other hand, the COPD hospitalization rates in the PG and CG were 17.9% and 33.3%, respectively ($p = 0.1643$). An almost four-fold higher incidence of failure to recover in the CG vs. the PG may be the result of a higher tailored OCS utilization in the PG.

Breaking down the exacerbation into two visits makes practical sense. Firstly, we monitor the change in symptoms, secondly, we have an insight into laboratory tests, and thirdly we see the patient's response to preliminary treatment. Therefore, we can more consciously determine the optimal treatment for a given exacerbation. That transforms into better outcomes for exacerbation treatment in outpatient settings. Failure to recover in 30 days following the exacerbation in the PG was 10.7% and 47.2% in the CG, and would possibly lower the costs of exacerbation treatment and further hospital admissions.

The statistical analysis of this Prospector pilot study support the hypothesis that it can be effective in reducing the amount of antibiotics used in COPD exacerbations and is safe as a best practice based on classical standards of diagnosis and treatment of these exacerbations in the sense of hospitalization and death and recovery or health status before exacerbation of COPD, thus fulfilling the principal main goals of COPD exacerbation management.

Limitations

The presented findings must be interpreted with caution because of some methodological limitations. The limitations come from its design (it is not a case-control study) and proposed methodology. First of all, this is a preliminary, single center study and the two patient groups were treated by different physicians from the center. Another significant limitation is the limited sample size. Other limitations are: no randomized allocations, limited patient demographics, differences in COPD severity between groups, demographics not available for some patients and not enough data to compare treatment effectiveness in various COPD severity scales. The authors believe that a larger study can overcome the above limitations.

Conclusions

The Prospector calculator allows the clinician to take a tailored approach towards managing a COPD exacerbation. It allows for a rapid decision on antibiotic use, limiting it only to cases where it brings clinical benefit, but at the same time maintaining safety and efficacy. It also helps them to collect a more structured and complete medical history, contributing to better future COPD management.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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References

1. Chan, Y. L. et al. C-Reactive protein as an indicator of bacterial infection of adult patients in the emergency department. *Chang. Gung Med. J.* **25** (7), 437–445 (2002).
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global strategy for the diagnosis & management, and prevention of chronic obstructive pulmonary disease. (2023 REPORT) https://goldcopd.org/. Accessed 10 November 2023.
3. Singh, D. et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: The GOLD science committee report 2019. *Eur. Respir J.* **53** (5), 1900164 (2019).
4. Sohy, C., Pilette, C., Niederman, M. S. & Sibille, Y. Acute exacerbation of chronic obstructive pulmonary disease and antibiotics: What studies are still needed? *Eur. Respir J.* **19** (5), 966–975 (2002).
5. Zetts, R. M., Stoesz, A., Smith, B. A. & Hyun, D. Y. Outpatient Antibiotic Use and the need for increased antibiotic stewardship efforts. *Pediatrics* **141** (6), e20174124 (2018).
6. Golkar, Z., Bagasra, O. & Pace, D. G. Bacteriophage therapy: A potential solution for the antibiotic resistance crisis. *J. Infect. Dev. Ctries.* **8** (2), 129–136 (2014).
7. Cassini, A. et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: A population-level modelling analysis. *Lancet Infect. Dis.* **19** (1), 56–66 (2019).
8. Dobson, E. L. et al. SIDP Community Pharmacy Antimicrobial Stewardship Task Force. Outpatient antibiotic stewardship: Interventions and opportunities. *J. Am. Pharm. Assoc.* **57** (4), 464–473. (2003).
9. Holstiege, J. et al. The decline in Outpatient Antibiotic Use. *Dtsch. Arztebl Int.* **117** (41), 679–686 (2020).
10. Bezpieczeństwo pacjentów przy stosowaniu antybiotykoterapii w szpitalach. KZD.430.001.2019. Nr ewid. 40/2019/P/18/058/KZD. March (2022). https://www.nik.gov.pl/plik/id,20833,v,artykul_19634.pdf. Accessed: 30.
11. Puhan, M. A., Vollenweider, D., Latshang, T., Steurer, J. & Steurer-Stey, C. Exacerbations of chronic obstructive pulmonary disease: When are antibiotics indicated? A systematic review. *Respir Res.* **8** (1), 30 (2007).
12. Vollenweider, D. J., Frei, A., Steurer-Stey, C. A., Garcia-Aymerich, J. & Puhan, M. A. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* **10** (10), CD010257 (2018).
13. Kwak, H. J. et al. The role of viral infection in COPD exacerbation. B47. COPD EXACERBATIONS: MISCELLANEOUS. *Am. J. Respir Crit. Care Med.* **183**, A3118 (2011).
14. Siddiqi, A. & Sethi, S. Optimizing antibiotic selection in treating COPD exacerbations. *Int. J. Chron. Obstruct Pulmon Dis.* **3**(1), 31–44 (2008).
15. Vedel-Krogh, S., Nielsen, S. F., Lange, P., Vestbo, J. & Nordestgaard, B. G. Blood eosinophils and exacerbations in chronic obstructive pulmonary disease. The copenhagen general population study. *Am. J. Respir Crit. Care Med.* **193** (9), 965–974 (2016).
16. Anthonisen, N. R. et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann. Intern. Med.* **106** (2), 196–204 (1987).
17. Llor, C. et al. Predictors for antibiotic prescribing in patients with exacerbations of COPD in general practice. *Ther. Adv. Respir Dis.* **7** (3), 131–137 (2013).

18. Hurst, J. R. et al. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. *Am. J. Respir Crit. Care Med.* **174** (8), 867–874 (2006).
19. Bafadhel, M. et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease. *Am. J. Respir Crit. Care Med.* **186** (1), 48–55 (2012).
20. Soler, N. et al. Sputum purulence-guided antibiotic use in hospitalised patients with exacerbations of COPD. *Eur. Respir J.* **40** (6), 1344–1353 (2012).
21. Stockley, R. et al. Assessment of airway neutrophils by sputum colour: Correlation with airways inflammation. *Thorax* **56** (5), 366–372 (2001).
22. Calverley, P. et al. Relationship between respiratory symptoms and medical treatment in exacerbations of COPD. *Eur. Respir J.* **26** (3), 406–413 (2005).
23. Ball, P., Harris, J. M., Lowson, D., Tillotson, G. & Wilson, R. Acute infective exacerbations of chronic bronchitis. *QJM* **88** (1), 61–68 (1995).
24. Vestbo, J. et al. ECLIPSE investigators. Evaluation of COPD longitudinally to identify predictive surrogate end-points (ECLIPSE). *Eur. Respir J.* **31** (4), 869–873 (2008).
25. Wilson, R. et al. Antibiotic treatment and factors influencing short and long term outcomes of acute exacerbations of chronic bronchitis. *Thorax* **61** (4), 337–342 (2006).
26. Kent, B. D., Mitchell, P. D. & McNicholas, W. T. Hypoxemia in patients with COPD: Cause, effects, and disease progression. *Int. J. Chron. Obstruct Pulmon Dis.* **6**, 199–208 (2011).
27. Krahnke, J. S. et al. COPD patients with chronic purulent Sputum have more frequent COPD exacerbations and require more frequent treatment with antibiotics. B93. COPD EXACERBATIONS: IMPACT OF BACTERIAL AND VIRAL INFECTIONS. Am. *J. Respir Crit. Care Med.* **183**, A3732 (2011).
28. van der Valk, P. et al. Clinical predictors of bacterial involvement in exacerbations of chronic obstructive pulmonary disease. *Clin. Infect. Dis.* **39** (7), 980–986 (2004).
29. Póvoa, P. C-reactive protein: A valuable marker of sepsis. *Intensive Care Med.* **28** (3), 235–243 (2002).
30. Cals, J. W. L. C-reactive protein point-of-care testing for respiratory-tract infections in primary care. (2012). https://acutecaretesting.org/-/media/acutecaretesting/files/pdf/creactive-protein-pointofcare-testing-for-respiratorytract-infections-in-primary-care.pdf Accessed: 30 March 2022.
31. Llor, C. et al. Effectiveness of two types of intervention on antibiotic prescribing in respiratory tract infections in primary care in Spain. *Happy Audit Study Atención Primaria*. **46** (9), 492–500. https://doi.org/10.1016/j.aprim.2014.02.006 (2014).
32. Higdon, M. M. et al. Association of C-reactive protein with bacterial and respiratory syncytial virus–associated pneumonia among children aged < 5 years in the PERCH study *Clin. Infect. Dis.* **64** (suppl_3), S378–S386 (2017).
33. Villalobos, R. E., Magallanes, J. & David-Wang, A. P143 blood eosinophilia as predictor for patient outcomes in COPD exacerbations: A systematic review and meta-analysis. *Thorax* **71** (Suppl 3), A1–A288 (2016).
34. Waljee, A. K. et al. Short term use of oral corticosteroids and related harms among adults in the United States: Population based cohort study. *BMJ* **357**, j1415 (2017).
35. Aaron, S. D. et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl. J. Med.* **348** (26), 2618–2625 (2003).
36. Donaldson, G. C. et al. Impact of prolonged exacerbation recovery in chronic obstructive pulmonary disease. *Am. J. Respir Crit. Care Med.* **192** (8), 943–950 (2015).

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M.P. devised the PROSPECTOR calculator and treated the M.P., K.K. and S.Z. analyzed the data and wrote the manuscript.

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Declarations

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Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Additional information

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