SITUATIONS IN WHICH TREATMENT OF ACUTE EXACERBATIONS OF NON-SEVERE COPD WITH ANTIBIOTICS IS NOT NECESSARY

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Doctoral thesis

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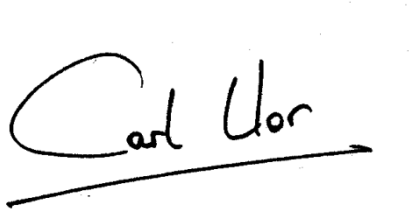
CERTIFICO

Que la doctoranda Ana Moragas Moreno, llicenciada en Medicina i Cirurgia, ha treballat sota la meva direcció, la tesi titlada 'Situations in which treatment of acute exacerbations of non-severe COPD with antibiotics is not necessary', i que pot ser presentada davant el tribunal corresponent per a l'obtenció del grau de Doctor.



A Tarragona, 5 de setembre de 2011

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Dedicated to my father

who died three years ago due to COPD

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SUMMARY

Background. Chronic obstructive pulmonary disease (COPD) constitutes one of the principal demands on healthcare in primary care. Acute exacerbations of COPD are typical events that characterize the course of the disease. Antimicrobial therapy remains a controversial issue, mainly in acute exacerbations of mild-to-moderate COPD. Even though most of the patients attended in the community correspond to mild and moderate COPD, antibiotics are highly prescribed for exacerbations in Spain.

Aims. The main objective was to evaluate the effectiveness of antibiotic therapy compared with placebo at day 9-11 in acute exacerbations of mild-to-moderate COPD. The secondary objectives were to evaluate the rate of clinical success of antibiotic therapy compared with placebo at day 20 and assess the symptom-free interval, i.e. days till next exacerbation in both groups.

Design. Multicentre, parallel, double-blinded placebo-controlled randomized clinical trial carried out from January 2006 to June 2011.

Study setting: Twenty-three primary care centres in Catalonia.

Subjects. Patients aged 40 or older, smokers or ex-smokers of ten packs-year or more, with spirometrically-based diagnosis of mild-to-moderate COPD (forced expiratory volume in one second (FEV_1) > 50% expected and FEV_1/forced vital capacity ratio < 0.7% expected) from a lung function test performed within 24 months prior to inclusion, and the presence of an acute exacerbation defined as the presence of at least one of the following signs and symptoms: increase of dyspnoea, increase in sputum volume and/or increase of sputum purulence. Patients with bronchial asthma, hypersensitivity to β-lactams, bronchiectasis of origin other than COPD, active neoplasm, tracheotomy, presence of radiological signs of pneumonia or hospital admission criteria, and those who refused to participate in the study were all excluded.

Measurements and interventions. The patients were randomised into two treatment groups: amoxicillin and clavulanic acid (500/125 mg three times daily for 8 days) or placebo three times daily for 8 days). The use of antithermics or analgesics was allowed as were short-acting and long-acting β-adrenergics, anticholinergics,

theophyllines, inhaled or oral corticosteroids and any medication that the patient may been have taken for chronic disease and which had been initiated three months prior to inclusion in the study, except for antibiotics. Cure was defined as the disappearance of the acute signs and symptoms related to the infection, improvement, as the non-complete resolution of the symptoms and failure was defined as with an insufficient reduction in the signs and symptoms of infection. Clinical success was considered when either cure or improvement was observed.

Results. A total of 353 subjects were included in the study. Forty-three patients were excluded as they did not fulfil the inclusion criteria. Three hundred ten (158 patients in the amoxicillin and clavulanic acid arm and 152 patients in the placebo arm) fulfilled all the criteria for efficacy analysis. The mean age was 68.1 years (SD: 10.4 years) and the mean FEV_1 was 65% (SD: 11.9%). No differences were found between the two groups regarding the different basal variables analysed. A total of 117 patients assigned to the intervention group (74.1%) and 91 to control group (59.9%) were considered cured at days 9-11 ($p<0.05$). In the multivariate regression analysis failure was associated with C-reactive protein (CRP) concentrations ≥ 40 mg/l (OR: 7.9; 95% CI: 3.9 –16.3), placebo treatment (OR: 2.9; 95% CI: 1.4 – 6) and presence of coronary heart disease (OR: 2.6; 95%CI: 1 – 6.7). Among patients treated with placebo clinical predictors for failure were CRP ≥ 40 mg/l (OR of cure: 0.1; 95% CI: 0 – 0.2) and purulent sputum (OR: 0.2; 95% CI: 0 – 0.7). The predictive value of Anthonisen criteria for clinical outcome in those patients was 0.708 (95% CI: 0.616 – 0.801) and rose to 0.842 (95% CI: 0.76 – 0.924; $p<0.001$) when CRP ≥ 40 mg/l was added. Regardless of the number the Anthonisen criteria, the presence of both CRP low levels and uncoloured sputum was associated with a clinical success of 90% among patients not treated with antibiotics.

Conclusions. Treatment of acute exacerbations of mild-to-moderate COPD with amoxicillin and clavulanic acid is more effective than placebo. Nonetheless, this thesis indicates when antibiotic therapy may be safely withheld in acute exacerbations of mild-to-moderate COPD.

Key words. Acute exacerbations. Mild-to-moderate COPD. Antibiotic. Effectiveness. Randomised clinical trial.

RESUM

Fonament. La malaltia pulmonar obstructiva crònica (MPOC) representa un dels principals motius de salut en atenció primària. Les exacerbacions són events típics que caracteritzen el curs de l'MPOC. El tractament antimicrobià és un tema controvertit, principalment en les exacerbacions de l'MPOC lleu-moderada. Encara que la majoria dels pacients atesos a la comunitat presenten MPOC lleu i moderada, la prescripció antibiòtica en les exacerbacions és molt elevada a Espanya.

Objectius. L'objectiu principal fou avaluar l'efectivitat de l'antibioteràpia en comparació amb el placebo en el dia 9-11 en les exacerbacions de l'MPOC lleu a moderada. Els objectius secundaris foren avaluar la taxa d'èxit clínic de la teràpia antibiòtica en comparació amb el placebo en el dia 20 i avaluar l'interval lliure de símptomes; és a dir, nombre de dies fins a la següent exacerbació, en ambdós grups.

Disseny. Assaig clínic aleatori, controlat amb placebo, doble cec, paral·lel i multicèntric, dut a terme des de gener de 2006 fins a juny de 2011.

Emplaçament. Vint-i-tres centres de salut de Catalunya.

Subjectes. Pacients de 40 o més anys, fumadors o exfumadors de deu paquets-any o més, amb diagnòstic espiromètric d'MPOC lleu-moderada (volum espiratori forçat en un segon (FEV_1) > 50% esperat i raó FEV_1/capacitat vital forçada < 0,7% esperat) basat en una espirometría feta en els 24 mesos previs a la inclusió i presència d'exacerbació definida com la presència d'almenys un dels següents signes i símptomes: augment de la dispnea, augment del volum d'expectoració i/o augment de la purulència de l'esput. Es van excloure als pacients amb asma bronquial, hipersensibilitat als β-lactàmics, bronquièctasis d'origen diferent d'MPOC, neoplàsia, traqueotomia, presència de signes radiològics de pneumònia o criteris d'hospitalització i aquells que van declinar participar.

Mesuraments i intervencions. Els pacients s'aleatoritzaren en dos grups: amoxicil·lina i àcid clavulànic (500/125 mg/8 hores, 8 dies) o placebo (cada 8 hores, 8 dies). Es va permetre ús d'antitèrmics, analgèsics, β-adrenèrgics d'acció llarga i curta, anticolinèrgics, teofil·lines, corticoides inhalats o orals i qualsevol altra medicació que

el pacient estigués prenent per a una malaltia crònica i s'hagués iniciat tres mesos abans de la inclusió en l'estudi, menys antibiòtics. Es va definir guariment quan va haver-hi desaparició dels signes aguts i els símptomes relacionats amb la infecció, millora com a falta de resolució completa dels símptomes i fracàs com a reducció insuficient dels signes i símptomes de la infecció. Es va considerar èxit clínic quan es va observar guariment o millora.

Resultats. S'inclogueren en l'estudi un total de 353 subjectes, dels quals 43 es van excloure per no complir els criteris d'inclusió. Un total de 310 (158 pacients en el grup assignat a amoxicil·lina i àcid clavulànic i 152 pacients a placebo) resultaren ser avaluables en l'anàlisi d'eficàcia. L'edat mitjana fou de 68,1 anys (DE: 10,4 anys) i el FEV_1 mig va ser del 65% (DE: 11,9%). No s'observaren diferències entre els dos grups quant a les distintes variables basals analitzades. Es guariren en el dia 9-11 un total de 117 pacients en el grup d'intervenció (74,1%) i 91 del grupo control (59,9%; p<0.05). En l'anàlisi de regressió logística multivariant es va observar una associació entre el fracàs clínic amb les concentracions de proteïna C reactiva (PCR) ≥ 40 mg/l (OR: 7,9; IC 95%: 3,9 –16,3), estar assignat al grup placebo (OR: 2,9; IC 95%: 1,4 – 6) i presència de cardiopatia isquémica (OR: 2,6; IC 95%: 1 – 6,7). Els predictors clínics de fracàs entre els pacients no tractats amb antibiòtics van ser la PCR ≥ 40 mg/l (OR de guariment: 0,1; IC 95%: 0 – 0,2) i la purulència de l'esput (OR: 0,2; IC 95%: 0 – 0,7). El valor dels criteris d'Anthonisen per predir resultat clínic en aquests pacients, amb l'àrea sota la corba ROC, fou de 0,708 (IC 95%: 0,616 – 0,801) i va pujar a 0,842 (IC 95%: 0,76 – 0,924; p<0,001) quan es va afegir la PCR ≥ 40 mg/l. Amb independència del nombre de criteris d'Anthonisen, la presència de valors baixos de PCR i esput no purulent s'associaren amb un percentatge d'èxit del 90% entre els pacients no tractats amb antibiòtics.

Conclusions. El tractament de les exacerbacions de l'MPOC lleu-moderada amb amoxicil·lina i àcid clavulànic és més efectiu que el placebo. No obstant això, aquesta tesi aclareix quan una exacerbació d'MPOC lleu-moderada pot ser tractada sense necessitat de donar antibiòtics.

Paraules clau. Exacerbació aguda. MPOC lleu-moderada. Antibiòtic. Efectivitat. Assaig clínic aleatori.

RESUMEN

Fundamento. La enfermedad pulmonar obstructiva crónica (EPOC) constituye uno de los principales motivos de salud en atención primaria. Las exacerbaciones son eventos típicos que caracterizan el curso de la EPOC. El tratamiento antimicrobiano es un tema controvertido, principalmente en las exacerbaciones de la EPOC leve-moderada. Aunque la mayoría de los pacientes atendidos en la comunidad presentan EPOC leve-moderada, la prescripción antibiótica en las exacerbaciones es muy elevada en España.

Objetivos. El objetivo principal fue evaluar la efectividad de la antibioterapia en comparación con el placebo en el día 9-11 en las exacerbaciones de la EPOC leve a moderada. Los objetivos secundarios fueron evaluar la tasa de éxito clínico de la terapia antibiótica en comparación con el placebo en el día 20 y evaluar el intervalo libre de síntomas, es decir, días hasta la próxima exacerbación, en ambos grupos.

Diseño. Ensayo clínico aleatorio, controlado con placebo, doble ciego, paralelo y multicéntrico, realizado desde enero de 2006 a junio de 2011.

Emplazamiento. Veintitrés centros de salud de Cataluña.

Sujetos. Pacientes de 40 o más años, fumadores o exfumadores de diez paquetes-año o más, con diagnóstico de EPOC leve-moderada (volumen espiratorio forzado en un segundo (FEV_1) > 50% esperado y razón FEV_1/capacidad vital forzada < 0,7% esperado) basado en espirometría realizada en los 24 meses previos a la inclusión y presencia de exacerbación definida como la presencia de al menos uno de los siguientes signos y síntomas: aumento de disnea, aumento del volumen de expectoración y/o aumento de la purulencia del esputo. Se excluyeron a los pacientes con asma bronquial, hipersensibilidad a los β-lactámicos, bronquiectasias de origen distinto de EPOC, neoplasia, traqueotomía, presencia de signos radiológicos de neumonía o criterios de hospitalización y aquellos que declinaron participar.

Medidas e intervenciones. Se aleatorizaron a los pacientes en dos grupos: amoxicilina y ácido clavulánico (500/125 mg/8 horas, 8 días) o placebo (cada 8 horas, 8 días). Se permitió uso de antitérmicos, analgésicos, β-adrenérgicos de acción larga y corta, anticolinérgicos, teofilinas, corticoides inhalados u orales y cualquier otra medicación

que el paciente estuviera tomando para una enfermedad crónica y se hubiera iniciado tres meses antes de la inclusión en el estudio, menos antibióticos. Se definió curación cuando hubo desaparición de los signos agudos y los síntomas relacionados con la infección, mejoría como falta de resolución completa de los síntomas y fracaso como reducción insuficiente de los signos y síntomas de la infección. Se consideró éxito clínico cuando se observó curación o mejoría.

Resultados. Se incluyeron en el estudio un total de 353 sujetos, de los cuales 43 se excluyeron por no cumplir los criterios de inclusión. Un total de 310 (158 pacientes en el grupo asignado a antibiótico y 152 pacientes a placebo) resultaron ser evaluables en el análisis de eficacia. La edad media fue de 68,1 años (DE: 10,4 años) y el FEV_1 medio fue 65% (DE: 11,9%). No se observaron diferencias entre los dos grupos en cuanto a las distintas variables basales analizadas. Se curaron en el día 9-11 un total de 117 pacientes en el grupo de intervención (74,1%) y 91 del grupo control (59,9%; p<0.05). En el análisis de regresión logística multivariante se observó una asociación entre el fracaso clínico con las concentraciones de proteína C reactiva (PCR) ≥ 40 mg/l (OR: 7,9; IC 95%: 3,9 –16,3), tomar placebo (OR: 2,9; IC95%: 1,4 – 6) y presencia de cardiopatía isquémica (OR: 2,6; IC95%: 1 – 6,7). Los predictores clínicos de fracaso entre los tratados con placebo fueron PCR ≥ 40 mg/l (OR de curación: 0,1; IC 95%: 0 – 0,2) y esputo purulento (OR: 0,2; IC 95%: 0 – 0,7). El valor de los criterios de Anthonisen para predecir resultado clínico en estos pacientes, con el área bajo la curva ROC, fue de 0,708 (IC 95%: 0,616 – 0,801) y ascendió a 0,842 (IC 95%: 0,76 – 0,924; p<0,001) cuando se añadió la PCR ≥ 40 mg/l. Con independencia del número de criterios de Anthonisen, la presencia de valores bajos de PCR y esputo no purulento se asociaron con un porcentaje de éxito del 90% entre los pacientes no tratados con antibióticos.

Conclusiones. El tratamiento de las exacerbaciones de la EPOC leve-moderada con amoxicilina y ácido clavulánico es más efectivo que el placebo. Sin embargo, esta tesis clarifica cuando una exacerbación de EPOC leve-moderada puede ser tratada sin necesidad de dar antibióticos.

Palabras clave. Exacerbación aguda. EPOC leve-moderada. Antibiótico. Efectividad. Ensayo clínico aleatorio.

ABBREVIATIONS

AUC	Area under the curve
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner
HRQL	Health-related quality of life
IQR	Interquartiile range
ITT	Intention to treat
l/min	Litres/minute
mg/l	Milligrams/litre
NS	Non-significant
OR	Odds ratio
PCR	Polymerase chain reaction
PP	Per protocol
ROC	Receiver operating characteristic
SD	Standard deviation
SGRQ	St George's respiratory questionnaire

INTRODUCTION

Definitions

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. The main component affects the lungs and is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases (*Global Initiative for Chronic Obstructive Lung Disease, 2010*). This definition does not use the terms chronic bronchitis and emphysema and definitely excludes asthma which is a reversible airflow limitation. Symptoms of COPD mainly include cough, sputum production and dyspnoea. Chronic bronchitis, defined as the presence of cough and sputum production for at least 3 months in each 2 consecutive years, is not necessarily associated with airflow limitation. Worldwide, the most commonly encountered risk factor for COPD is cigarette smoking. It means therefore that a diagnosis of COPD should be considered in any patient who has dyspnoea, chronic cough or sputum production and a history of exposure to risk factors for the disease, especially cigarette smoking (*Global Initiative for Chronic Obstructive Lung Disease, 2010*). Other aetiologies different from smoking are actually uncommon in our country.

The diagnosis of COPD should be based on a spirometric study, with the measurement of the forced vital capacity (FVC), defined as the maximum volume of air that can be exhaled during a forced manoeuvre, and the forced expiratory volume in one second (FEV_1), which can be defined as the volume expired in the first second of maximal expiration after a maximal inspiration. In other words, this is a measure of how quickly the lungs can be emptied. With the former two measurements, the rate FEV_1/FVC can be calculated, expressing the FEV_1 as a percentage of the FVC, giving a clinical useful index of airflow limitation. The ratio FEV_1/FVC is between 70% and 80% in normal adults; a value less than 70% indicates airflow limitation and the possibility of COPD. Postbronchodilator FEV_1 is recommended for the diagnosis and assessment of severity of COPD (*Global Initiative for Chronic Obstructive Lung Disease, 2010*). Patients with COPD typically show a decrease in both FEV_1 and FEV_1/FVC. FEV_1 is influenced by the age, sex, height and ethnicity, and is best considered as a percentage of the predicted

normal value. The degree of spirometric abnormality generally reflects the severity of COPD. According the update guidelines of Global Initiative for Chronic Obstructive Lung Disease (GOLD), stage I or mild COPD is defined as a mild airflow limitation ($FEV_1/FVC < 70\%$ and $FEV_1 \geq 80\%$ predicted) and sometimes, but not always, chronic cough and sputum production. Not all the guidelines define this stage similarly and it depends on which classification system is used (*Celli BR et al, 2004a; Global Initiative for Chronic Obstructive Lung Disease, 2010; Institute for Clinical Systems Improvement, 2009*). However, mild COPD is consistently defined as a $FEV_1 \geq 80\%$ (*Celli BR et al, 2004a; Global Initiative for Chronic Obstructive Lung Disease, 2010; Institute for Clinical Systems Improvement, 2009*). At this stage most individuals may not be aware that his or her lung function is abnormal.

Stage II or moderate COPD is defined as the worsening airflow limitation ($FEV_1/FVC < 70\%$ and a FEV_1 ranged from 50% to 80%), with shortness of breath typically developing on exertion. This is the stage at which patients typically seek medical attention because of chronic respiratory symptoms or an exacerbation of their disease. There are two other stages: stage III or severe COPD with further worsening of airflow limitation ($FEV_1/FVC < 70\%$ and FEV_1 between 30% and 50%), and stage IV or very severe COPD, with severe airflow limitation $FEV_1/FVC < 70\%$ and $FEV_1 < 30\%$ predicted, but these stages are not being treated in this thesis. A fifth category, stage 0 or at-risk, appeared in the 2001 report but it is no longer included as a stage of COPD, as there is incomplete evidence that the individuals who meet the definition of at-risk (chronic cough and sputum production, and normal spirometry) necessarily progress on to stage I or mild COPD (*Global Initiative for Chronic Obstructive Lung Disease, 2010*). Nevertheless, the importance of the public health message that chronic cough and sputum are not normal is unchanged and their presence should trigger a search for underlying causes. The goals of COPD management include the relief of symptoms, the prevention of disease progression, the improvement of the exercise tolerance, the improvement of health status, the prevention and treatment of complications, the prevention and treatment of exacerbations, the reduction of mortality and the prevention or minimization of side effects from treatment. Table 1 describes the updated definitions of non-severe COPD in the most important classifications in the

world. The GOLD classification will be used hereafter in this thesis, since it is widely use (*Global Initiative for Chronic Obstructive Lung Disease, 2010*).

TABLE 1. Definitions of mild to moderate COPD in current classification systems

	Mild	Moderate
GOLD	Stage I: • $FEV_1/FVC < 0.70$ • $FEV_1 \geq 80\%$ predicted	Stage II: • $FEV_1/FVC < 0.70$ • $50\% \leq FEV_1 < 80\%$ predicted
ATS/ERS	• $FEV_1/FVC \leq 0.70$ • $FEV_1 \geq 80\%$ predicted	• $FEV_1/FVC \leq 0.70$ • FEV_1 50–80% predicted
ICSI	• $FEV_1 \geq 80\%$ predicted • No abnormal signs • Cough (± sputum) • Little or no dyspnoea	• FEV_1 50–79% predicted • Breathlessness (± wheeze on moderate exertion) • Cough (± sputum) • Variable abnormal signs (general reduction in breath sounds, presence of wheezes) • Hypoxaemia may be present

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ATS/ERS: American Thoracic Society/European Respiratory Society; ICSI: Institute for Clinical Systems Improvement

According to GOLD guidelines, an exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum production that is beyond normal day-to-day

variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD (*Global Initiative for Chronic Obstructive Lung Disease, 2010*). These episodes may be accompanied with systemic symptoms such as fatigue, sleep disturbances and low-grade fever (*Anzueto A et al, 2007*).

Impact of exacerbations on COPD

COPD affects a large number of patients and is associated with significant morbidity, disability and mortality (*Global Initiative for Chronic Obstructive Lung Disease, 2010; Mannino DM et al, 2002; Rabe KF et al, 2007*). In fact, COPD is one of the main causes of morbidity and mortality in developed countries (*Anzueto A et al, 2008*). The prevalence of spirometrically-confirmed COPD in England was estimated at 1.4%, compared with 3.6% for coronary heart disease, 1.5% for stroke, 3.3% for diabetes, 0.5% for cancer, and 5.8% for asthma (*Health and Social Care Information Centre, 2005*). The BOLD study, in which nearly ten thousand individuals from twelve countries completed postbronchodilator spirometry testing plus questionnaires on respiratory symptoms, health status, and exposure to COPD risk factors revealed that the prevalence of GOLD stage II or higher COPD was 10.1% overall, 11.8% in men and 8.5% in women (*Buist AS et al, 2007*). The overall pooled estimate of the adjusted OR for COPD was 1.94 per 10-year age increment (*Buist AS et al, 2007*). The prevalence of non-severe COPD among patients with COPD is high and varies significantly between countries (*Buist AS et al, 2007*). In the BOLD study, the prevalence of GOLD stage I COPD ranged from 1% in the Philippines to 16% in Austria, while that of GOLD stage II COPD ranged from 5% in Germany to 12% in South Africa (*Buist AS et al, 2007*). Miravitlles et al has recently reported a prevalence of 56% of mild COPD and 38% of moderate COPD (*Miravitlles M et al, 2009*).

Exacerbations of COPD are of major global importance. Yet controversies remain over the definition of exacerbations, how they should be monitored and their underlying mechanisms. Exacerbations of COPD are now recognised as important events in the natural course of COPD and this fact is underlined in major international guidelines (*Global Initiative for Chronic Obstructive Lung Disease, 2010; Celli BR et al 2004a*).

Exacerbations are an important outcome, not only because they pose a considerable economic burden but more importantly because repeated exacerbations of COPD lead to deteriorating health-related quality of life (HRQL) (*Seemungal TA et al, 1988; Donaldson GC et al, 2002*) and, when associated with ventilatory failure, to premature death (*Connors AF Jr et al, 1996*).

Although poorly characterized in the past, recent investigations have clarified the significance, aetiology, and pathogenesis of exacerbations (*Sethi S et al, 2008a*). In a landmark longitudinal study in the 1960s, no relationship was found between loss of lung function and frequency of COPD exacerbation (*Fletcher F et al, 1977*). Recent studies dispute the earlier result (*Donaldson GC et al, 2002; Kanner R et al, 2001*). Exacerbations are the leading cause of death in advanced COPD, are associated with a more rapid decline in the HRQL of patients with COPD, and as a result of hospitalization, account for 40% – 50% of the costs of care of COPD (*Andersson F et al, 2002; Calverley PM et al, 2007; Spencer S et al, 2001*). Exacerbations of COPD are estimated to result in approximately 110,000 deaths in United States and more than 500,000 hospitalisations per year, with over $18 billion spent in direct costs annually *(National Institutes of Health. National Heart, Lung, and Blood Institute, 2002: Mannino DM et al, 2002*). In addition to the financial burden required to care for these patients, other costs, such as days missed from work and severe limitations in HRQL, are important features of this condition (*Miravitlles M* et al, 2002a; *Miravitlles M et al, 2004a*).

Exacerbations are a significant component of the clinical course in COPD (*Halpern MT et al, 2003*). Furthermore, as COPD progresses, exacerbations become more frequent (*Burge PS et al, 2000; Donaldson GC et al, 2002*; *Global Initiative for Chronic Obstructive Lung Disease, 2010; Gompertz S et al, 2001a; Greenberg SB et al, 2000; Miravitlles M et al, 1999a; Miravitlles M et al, 2000; Paggiaro PL et al, 1998*). Donaldson et al (*Donaldson GC et al, 2002*) reported that patients with severe COPD (GOLD stage III) had an annual exacerbation frequency of 3.4 events per year compared with 2.7 per year for those with moderate COPD (GOLD stage II; $p < 0.05$). Paggiaro et al (*Paggiaro PL et al, 1998*) reported, in patients with forced expiratory volume (FEV_1) > 60% predicted, 1.6 exacerbations per year compared with 1.9

exacerbations in patients with FEV_1 59%–40% predicted, and 2.3 exacerbations in patients with FEV_1 < 40% predicted (*Donaldson GC et al, 2002; Paggiaro PL et al, 1998*). Other studies showed that patients who suffer a high number of exacerbations will continue to have frequent episodes (*Gompertz S et al, 2001a*). Recent large prospective clinical studies have shown that COPD patients in GOLD category II (FEV_1 50–80% predicted) also have a significant number of exacerbations that can be reduced with pharmacotherapy (*Decramer M et al, 2009; Jenkins CR et al, 2009*). Thus, patients with more severe COPD are going to have frequent exacerbations, but it is also important to point out that patients with more moderate disease also develop a significant number of these events.

Impact of exacerbations on systemic inflammation and comorbidities

COPD is a condition that becomes clinically apparent in mid-to-late life. Comorbidity is relatively common in patients with COPD and this raises the issue as to whether such a comorbidity is age-related, related to a common factor, such as smoking and cardiovascular disease, due to the effect of drugs like corticosteroids and the development of diabetes, or a reflection of the increase in systemic inflammatory cytokine concentrations, which are a feature of COPD with systemic involvement. Data are emerging that the same inflammatory mediators are central to the pathogenesis of other diseases and, to illustrate this, focus was directed towards type 2 diabetes and cardiovascular diseases. Coexistent cardiac disease has been shown to be a risk factor for increased hospital admission (*Adams SG et al, 2000; Dewan NA et al, 2000*) and mortality in patients with COPD exacerbation (*Antonelli Incalzi R et al, 1997; Murata GH et al, 1992*). Recent studies have shown that there is a 3.1 and 2.6 incidence ratio of myocardial infarction or first stroke during the first 3 days after a systemic respiratory infection, suggesting a close association (*Smeeth L et al, 2004*). Furthermore, ischaemic heart disease and/or congestive heart failure were reported to increase the rate of treatment failure, thus contributing to the worsening of the patients' condition (*Adams SG et al, 2000; Dewan NA et al, 2000*). However, in a hospital-based study, very severe COPD patients (FEV_1 < 35% predicted and use of

supplemental oxygen therapy) no association between cardiac comorbidity and outcome was found (*Antonelli Incalzi R et al, 1997*). The results suggest that cardiac comorbidity is a risk factor of poor outcome, particularly in moderate–severe COPD patients; however, when lung disease is severe, impairment in pulmonary function prevails over cardiac disease. Additionally, older patients who also have more severe comorbid conditions appear to be at risk for severe life-threatening exacerbations that may result in hospital admission and even death (*Antonelli Incalzi R et al, 1997*, *Miravitlles M* et al, 2000; *Vilkman S* et al, 1997).

Several studies have shown that COPD patients have higher levels of some inflammatory markers in blood, mainly CRP (*Pinto-Plata VM et al, 2006*), fibrinogen (*Dahl M et al, 2001*) and inflammatory cytokines (*Piehl-Aulin K et al, 2009*). A study indicated that the concentrations of interleukin 6 and CRP in plasma were significantly related to an increased risk of coronary heart disease in males and females (*Pai JK et al, 2004*). Cardiac troponin-1 is often raised during acute exacerbations that require hospitalisation but are without other evidence of an acute coronary syndrome, indicating that an acute exacerbation has detrimental effects on cardiac muscle (*Harvey MG et al, 2004*). Elevation of the CRP is as well an independent predictor of myocardial infarction. Eagan et al (*Eagan TM et al, 2010*) assessed the systemic levels of six inflammatory mediators in a large cohort of COPD patients and controls. These investigators confirmed that certain circulating inflammatory mediators are affected in COPD. COPD confounded variables, such as sex, age, smoking status, disease severity, comorbid conditions, *etc*., were controlled. These investigators demonstrated that COPD patients were more likely to have significantly decreased blood levels of osteoprotegrin and higher levels of CRP. They were also able to identify that soluble tumour necrosis factor receptor-1 and osteoprotegrin changes were related to disease severity, based on GOLD stage and frequency of exacerbations. Furthermore, recent reports have shown that using anti-inflammatory medications, such as statins, significantly impact the rate of lung function decline, and their use prior to exacerbations is associated with significant decreases in mortality (*Mortensen EM et al, 2009*). Therefore, exacerbations are likely to be present in patients with comorbid conditions and result in a significant inflammatory burden.

The interaction between comorbidities and COPD is only just beginning to be explored but it is clear that survival in COPD is better predicted by variables other than simply the degree of airflow limitation (*Celli BR et al, 2004b*). How these factors relate to the development and perpetuation of exacerbations remains to be elucidated but they are likely to be very important in patients with COPD.

Impact of exacerbations on lung function

Some investigators believe that more frequent exacerbations are associated with more rapid decline of FEV_1 (*Anzueto A et al, 2009a*). Donaldson et al (*Donaldson GC et al, 2002*) reported a mean of 2.9 exacerbations per year in COPD patients with moderate to very severe disease (mean FEV_1 38% predicted). The mean rate of decline in FEV_1 in the total cohort was 36 ml per year but was greater in patients with more exacerbations (40.1 ml per year versus 32.1 ml per year, respectively). Frequent exacerbations (more than two per year) have been associated with increased dyspnoea and reduced exercise capacity (*Donaldson GC et al, 2002; Jenkins CR et al, 2009*), greater decline in health status (*Spencer S et al, 2001; Spencer S et al, 2003*) and increased likelihood of becoming housebound (*Donaldson GC et al, 2002; Donaldson GC et al, 2005*). More recently, Celli et al (*Celli BR et al, 2008*) reported the impact of frequent exacerbations on the decline in FEV_1 in data from the TORCH study, in which patients experiencing greater frequency of exacerbations during the 3-yr study period had a faster decline in FEV_1.

It seems logical that repeated episodes of COPD exacerbations may potentially impair lung tissues and lead to an accelerated rate of decline in pulmonary function. This concept is supported by a number of experimental observations. First, exacerbations are associated with transient decreases in pulmonary function that, in some cases, take weeks to return to baseline levels (*Connors AF Jr. et al, 1996; Seemungal TA et al, 2000a*). Second, patients suffering from recurrent exacerbations have been shown to have increased concentrations of inflammatory markers in sputum, even in stable phase, which suggests persistent inflammation and potential lung damage (*Crooks SW et al, 2000*). Third, neutrophils are attracted into the airway lumen during

exacerbations (*Ras G et al, 1990*). In fact, increased levels of neutrophils in sputum correlated with rapid decline in FEV_1 in a 15-yr follow-up study (*Stanescu D et al, 1996*). There are recent reports that have identified a significantly increased number of eosinophils in patients with COPD exacerbation (*Papi A et al, 2006; Zhu J et al, 2001*). The significance of these findings is not fully understood. Fourth, in cross-sectional studies, higher bacterial load in respiratory secretions have been associated with increased inflammation and decreased lung function (*Sethi S et al, 2000*). Fifth, the urinary excretion of desmosine and isodesmosine, products of degradation of lung elastine, are significantly increased during exacerbations of COPD compared with stable phase (*Viglio S et al, 2000*), coinciding with an increase in free elastase during exacerbations (*Crooks SW et al, 2000; Gompertz S et al, 2001b*); furthermore, higher urinary concentrations of desmosine have been associated with faster decline in FEV_1 in COPD (*Gottlieb DJ et al, 1996*). Finally, a correlation has been found between the number of previous exacerbations and the extent of emphysematous changes seen by computed tomography scan (*Kosmas EN et al, 1997*).

Impact of exacerbations on health-related quality of life

Although it is recognised that exacerbations are associated with considerable symptomatic and physiological deterioration, the burden imposed on patients may be underestimated. Interestingly, patients are not familiar with the term exacerbation as used by healthcare professionals and, if given a choice, they may use their own words to describe the worsening of symptoms. The terminology used by patients is extremely varied but consistent for each patient. The way in which patients perceive exacerbations and how exacerbations affect patients have been greatly helped by the systematic scoring of health status questionnaires. The application of such tools to study exacerbations has provided major new insights, although it still remains a hypothesis-generating exercise. Exacerbations have been shown to dramatically impair the feeling of wellbeing in COPD patients. Differences in scores in HRQL questionnaires between the stable phase and the exacerbation are very important in magnitude. A group of patients with COPD exacerbation showed a moderate-to-large improvement

in all four domains of the Chronic Respiratory Disease Questionnaire after 10 days of treatment (*Aaron SD et al, 2002*). This improvement was not observed in patients who relapsed after treatment of exacerbation.

A study by Connors JR et al (*Connors AF Jr. et al, 1996*) reported the quality of life outcomes in patients hospitalised with acute exacerbations of COPD. At 6 months, 54% of patients required assistance with at least one activity of daily living and 49% considered their health status to be fair or poor. No analysis was conducted on the relationship between readmissions and perceived quality of life. The recovery of HRQL parameters after an acute COPD exacerbation may be determined by several factors. Spencer et al (*Spencer S et al, 2001*) in exacerbated patients who did not relapse during follow-up experienced an improvement in the St George's Respiratory Questionnaire (SGRQ) of 11.8 units at 1 month and 17 units after 5 months of the onset of the exacerbation. These results indicate that the recovery of health status after an exacerbation may take longer than previously expected. In contrast, median recovery time for lung function after an exacerbation is 6 days and for symptoms is 7 days (*Spencer S et al, 2001*). However, this recovery may be influenced by the severity of the exacerbation. The more severe the exacerbation, the longer it takes to recover. Seemungal et al (*Seemungal TA et al, 2000a*) showed that only 75% of patients return to their baseline peak flow values 35 days after the episode. The SGRQ and Medical Research Council questionnaire were completed by patients at the end of the study. Exacerbations were more frequent in patients with frequent previous exacerbations with an odds ratio (OR) of 5.5. Using the median number of exacerbations, patients were classified as infrequent exacerbators (0–2) or frequent exacerbators (3–8). SGRQ total score was significantly worse in frequent exacerbators, with a mean difference of 14.8.

In multiple regression analyses, exacerbation frequency was strongly correlated with SGRQ total score and component scores. Miravitlles et al (*Miravitlles M et al, 2004a*) confirmed the impact of exacerbations on health status. Thus, these studies showed that patients who suffered more exacerbations had significantly worse SGRQ scores compared with infrequent exacerbators, and HRQL-related questionnaires offer complementary information to lung function and respiratory symptoms to monitor the

course of recovery of an exacerbation. The slow recovery of HRQL after an exacerbation suggests that these patients will not return to their baseline condition and will experience further deterioration of their HRQL over time. Furthermore, a patient's therapy during the exacerbation may influence outcome. Andersson et al (*Andersson I et al, 2002*) showed that patients who received long-term oxygen therapy had an improvement of the SGRQ scores by a mean of 14 units after 3 months; in contrast, those who did not receive oxygen showed a change of 9 units.

Unreported exacerbations are common and their long-term impact on HRQL has been identified. Previous studies have shown that at least half of all COPD exacerbations identified by symptom worsening were not medically reported and therefore left untreated. Seemungal et al (*Seemungal TA et al, 1998*) demonstrated that unreported exacerbations had similar characteristics to the reported ones. These exacerbations are associated with worsening symptoms when they remain untreated. The short- and long-term impacts of unreported exacerbations on HRLQ were recently reported by Xu et al (*Xu W et al, 2010*). In a multicentre prospective cohort of 491 COPD patients, these investigators demonstrated that more than one unreported exacerbation was associated with significant worsening of the SGRQ score, and HRQL at 1 year after adjusting for known confounders. These data suggest that unreported exacerbations may have important long-term impact on patients, and there is an urgent need to develop tools that emphasise early recognition of exacerbations.

Symptomatic GOLD stage I COPD patients have shown to increase respiratory care utilisation, including inhaler use, emergency room visits, hospitalisation due to respiratory problems and ambulatory visits, and lower HRQL than asymptomatic GOLD stage I patients. These latter are similar to individuals with normal lung function (*Bridevaux PO et al, 2008*). Even symptomatic mild COPD patients with relatively preserved FEV_1, FVC and resting inspiratory capacity have extensive small airway dysfunction that results in troublesome exertional symptoms (*Ofir D et al, 2008*). Furthermore, GOLD stages I and II patients also have an approximately 3-fold increased risk of depressive symptoms than healthy individuals (*Omachi TA et al, 2009*).

Impact of exacerbations on exercise performance

COPD exacerbations not only impair both the short- and long-term quality of life, but also produce significant reduction in physical activity (*García-Aymerich J et al, 2006*). In order to understand how exacerbations actual impaired patients, Haughney et al (*Haughney J et al, 2005*) reported a study that used actual patients' relative value judgment with discrete choice modelling techniques. These investigators demonstrated that exacerbations significant impact daily activities and level of medical care. For patients, the main impact of exacerbation on daily life is being housebound, more so than the actual symptoms. Other studies have also shown that exacerbations will not only impact physical activity but also physiological wellbeing (*Kessler R et al, 2006*). These and future studies are needed to develop strategies in the prevention and management of COPD.

Loss of skeletal muscle has long been established as a feature of stable COPD. COPD patients have decreased quadriceps strength and fat-free mass (*Hopkinson NS et al, 2007*). These effects are worse after acute exacerbations. These effects may be more pronounced if we take into consideration that these patients received high doses of corticosteroids during an exacerbation. Further data related to the impact of exacerbation on exercise activity is the work by Donaldson et al (*Donaldson GC et al, 2005*). In a longitudinal study, these investigators quantified time spent outdoors, and found that frequent exacerbators had spent less time. These investigators identified decreased activity a few days prior to exacerbations, which remained decreased for up to 5 weeks. More recent studies have utilised ambulatory activity monitoring. Pitta et al (*Pitta F et al, 2006*) confirmed prior reports, and also described decreased activity level in patients that have exacerbations compared with those who did not. Furthermore, a decreased activity level 1 month after an exacerbation was associated with increased risk for hospitalisation. Thus, the investigators concluded that exacerbations decreased the overall exercise tolerance. More recently, the effect of exacerbations on the Body mass, Obstruction, Dyspnoea and Exercise capacity (BODE) index were reported (*Cote C et al, 2007*). The BODE index significantly decreases with

an exacerbation and these effects remain over time. Most of the effect is due to significantly decreased exercise tolerance, manifested as decreased distance in 6-minute walk test. Thus, exacerbations also impact upon exercise tolerance.

Economic impact of exacerbations

Some studies have determined that hospitalisation costs represent 40–57% of total direct costs generated by patients with COPD, and this percentage may be as high as 63% in severe patients (*Hilleman DE et al, 2000*). Since acute exacerbations are the main cause of hospitalisation among COPD patients, it is evident that the economic burden of acute exacerbations is considerable. Observational studies performed in primary care centres observed that 16–22% of patients having exacerbations were admitted during 1 year (*Pena VS et al, 2000*). The costs of exacerbations that require hospitalisation increase dramatically compared with those that can be treated in an ambulatory setting. An analysis derived from a clinical trial in patients with COPD demonstrated that the 15% of exacerbations requiring hospital admission generated 90% of the costs associated with exacerbations (*Miravitlles M et al, 2002*). In a recent study in primary care in Spain, the mean total cost of an acute exacerbation of COPD was estimated to be US$159, with the main part being due to hospitalisations, which represented 58% of the total cost, followed by the drug costs amounting to 32% of the total (*Miravitlles M et al, 2005*). Failure implies a cost that is three times higher than the cost of management of the exacerbation, particularly due to the high cost of hospitalisation. If the percentage of relapses could be reduced, especially in severe cases, or if switching a patient from parenteral to oral therapy could reduce the length of hospital stay, valuable resources could be saved. The costs of managing acute exacerbations of chronic bronchitis are high, particularly because of the high costs associated with relapse (*Feenstra TL et al, 2001; Jacobson L et al, 2000).* Strategies to improve the outcome of ambulatory treatment of exacerbations should be very cost-effective, especially in more severe patients who are at increased risk of being admitted to hospital as a consequence of therapeutic failure.

The direct health costs of COPD are substantial, even in non-severe COPD. A Spanish 1-year follow-up study estimated that mild COPD incurred a cost of $1,484 per patient (versus $2,911 for severe COPD), with hospitalisations accounting for 41.2%, drug acquisition accounting for 42.5% and clinic visits and laboratory/diagnostic accounting for 16.2% of the costs (*Miravitlles M et al, 2003a; Miravitlles M et al, 2003b*). In an Italian study, the mean annual direct healthcare cost per patient was approximately €755 for GOLD stage 0, €1,000 for GOLD stage I and €2,000 for GOLD stage III COPD (*Dal Negro RW et al, 2008*).

Impact of exacerbations on mortality

Clinical studies have reported a high mortality rate in patients admitted to the hospital with an acute exacerbation of COPD (*Almagro P et al, 2002; Connors AF Jr et al, 1996; Fuso L et al, 1995; Groenewegen KH et al, 2003; Soler-Cataluña JJ et al, 2005*). Soler-Cataluña et al (*Soler-Cataluña JJ et al, 2005*) were the first to report that severe exacerbations of COPD have an independent negative prognostic impact, with mortality increasing with the frequency of severe exacerbations and those requiring hospitalisation. Patients with frequent exacerbations had the highest mortality rate with a risk of death 4.3 times greater than for patients requiring no hospital management. Thus, exacerbation itself may be a significant factor associated with increased mortality in COPD, but the severity of the underlying disease may influence patient's outcome. No studies on non-severe COPD have been carried out so far.

Impact of treatment on reduction of exacerbations among patients with non-severe COPD

The two most important preventive measures of COPD exacerbation are active immunisations, including influenza and pneumococcal vaccinations, and chronic maintenance pharmacotherapy (*Global Initiative for Chronic Obstructive Lung Disease, 2010; Rabe KF et al, 2007*).

The 2010 updated GOLD report states that, alongside active reduction of risk factors and influenza vaccination, patients with GOLD stage I mild COPD should receive symptomatic treatment with short-acting bronchodilators, while those in stage II should also have regular treatment with one or more long-acting bronchodilators, plus rehabilitation *(Global Initiative for Chronic Obstructive Lung Disease, 2010*). Furthermore, the GOLD report emphasises that the underrecognition and underdiagnosis of COPD can lead to significant underreporting and, crucially, that early diagnosis and implementation of treatment, including smoking cessation, can prevent or delay the course of airflow obstruction or reduce its expression. The American College of Physicians concludes that there is evidence to support inhaled treatment in symptomatic patients with an FEV_1 < 60% predicted and perform a spirometry in symptomatic adults with an FEV_1 > 60% predicted for determining when to initiate therapy (*Qaseem A et al, 2007*). This has recently been challenged by the findings in TORCH and UPLIFT (*Decramer M et al, 2009; Jenkins CR et al, 2009*).

The principle that patients with non-severe COPD could benefit significantly from intervention was established in 1994 by the Lung Health Study (*Anthonisen NR et al, 1994*) in which 5,887 patients with moderate airway obstruction (FEV_1 50% –90% predicted and FEV_1/FVC ≤ 70%) who were otherwise healthy were randomised to an intensive, long-term smoking cessation program or usual care for 5 years. Sustained smoking cessation was associated with significantly lower declines in FEV_1 than continued smoking, at 31 ml/year and 62 ml/year respectively, and a significant difference in change in FEV_1 % predicted compared with intermittent smoking, at 1.98% and - 0.74% respectively (*Scanlon PD et al, 2000*).

Recent clinical studies have demonstrated that chronic maintenance therapy in patients with COPD can significantly decrease the frequency of exacerbations. These studies show that long-active bronchodilators, including long-acting β-agonists (*Mahler DA et al, 1999*); and long-acting anticholinergics, such as tiotropium, reduce the mean rate of COPD exacerbation (*Decramer M et al, 2009; Dusser D et al, 2006; Niewoehner DE et al, 2005; Tashkin DP et al, 2008*). These effects have also been reported with combination therapy of inhaled corticosteroids and long-acting β-adrenergics (*Anzueto A et al, 2009b; Calverley PM et al, 2007; Ferguson GT et al, 2008; Hanania NA et al,*

2003). Furthermore, these studies have demonstrated that the reduction in exacerbations results in a significant decrease in hospitalisations and healthcare utilisation (*Anzueto A et al, 2009b; Calverley PM et al, 2007; Dusser D et al, 2006; Ferguson GT et al, 2008; Hanania NA et al, 2003; Niewoehner DE et al, 2005; Tashkin DP et al, 2008*). However, these studies have been carried with patients with also severe and very severe COPD. Among patients with non-severe COPD only some studies analysing tiotropium and inhaled corticosteroids have shown some positive results but clinically not relevant.

TORCH study, which compared salmeterol plus fluticasone versus single substances and placebo, included 2,156 patients with GOLD stage II disease, who had a mean baseline FEV_1 of 58.8% predicted (*Jenkins CR et al, 2009*). Post-hoc analysis showed that, compared with placebo, salmeterol plus fluticasone was associated with an increase in FEV_1 of 101 ml and a decrease in the decline of FEV_1 of 16 ml/year. This compared with an increase in FEV_1 of 46 ml and a decrease in the decline of FEV_1 of 14 ml/year with fluticasone alone, and with an increase in FEV_1 of 67 ml and a decrease in the decline of FEV_1 of 20 ml/year with salmeterol alone. Furthermore, combination therapy significantly reduced the number of exacerbations per patient per year compared with placebo.

In UPLIFT study, which compared tiotropium bromide versus placebo, 2,739 (46%) patients were in GOLD stage II (*Decramer M et al, 2009; Tashkin DP et al, 2008*). Post hoc analysis demonstrated that treatment with tiotropium in these patients significantly reduced rates of decline in post-bronchodilator FEV_1 compared with placebo, with improvements in lung function sustained over 4 years. Tiotropium also, compared with placebo, significantly slightly reduced the number of exacerbations per patient per year and significantly increased the median time to the first exacerbation, at 23.1 months versus 17.5 months. Active treatment significantly improved SGRQ scores at all-time points during follow-up (*Decramer M et al, 2009*). Importantly, the benefits of tiotropium observed in the MISTRAL and UPLIFT studies occurred despite patients being allowed to receive other drugs, such as inhaled corticosteroids (61%–74%, respectively) and/or long-acting β-adrenergics (32%–72%, respectively) (*Dusser D et al, 2006; Tashkin DP et al, 2008*). Crucially, a further post-hoc analysis of the UPLIFT

data in 810 treatment naïve patients, 60% of whom were in GOLD stage II, showed that tiotropium, compared with placebo, was associated with a significantly lower rate of post-bronchodilator decline in FEV_1, a significantly higher morning pre-dose FEV_1 at 48 months and a significantly slower decline in SGRQ total score (*Troosters T et al, 2010*).

Early treatment may also have an impact on exercise capacity. A preliminary study by O'Donnell et al demonstrated that, in 16 patients with symptomatic GOLD stage I COPD, nebulised ipratropium bromide 500 µg significantly increased pulmonary function, as measured by FEV_1, residual volume and specific airway resistance within 2 hours. Furthermore, during constant-load exercise, active treatment was associated with a significant reduction in dyspnoea per minute ventilation and a significant increase in tidal volume (*O'Donnell DE et al, 2009*). Other chronic therapies, such as carbocisteine and *N*-acetylcysteine, showed a decrease in COPD exacerbations (*Gramdjean EM et al, 2000; Poole B et al, 2010; Stey C et al, 2000; Zheng JP et al, 2008*), while other studies failed to show these effects (*Decramer M et al, 2005*). These findings could also be explained by the severity of patients enrolled in these studies and the use of concomitant medications.

All these trials, overall, demonstrate that, in the early studies, inhaled corticosteroids did not benefit lung function and improvements with salmeterol/fluticasone in the TORCH study were restricted to patients with an FEV_1 between 50% and 60%. All other interventions were associated with negative results, aside from intensive smoking intervention.

Aetiology of COPD exacerbations

Under normal conditions, the healthy human tracheobronchial tree and lung parenchyma have a remarkable ability to maintain sterility, in spite of repetitive exposure to microbial inocula from micro-aspiration and inhalation. In the setting of COPD, however, this innate lung defence appears to be disrupted as a result of exposure to smoke and other environmental irritants. The impairment in lung defence results in two distinct infection cycles in COPD that could contribute to progressive loss

of lung function (*Sethi S, 2010*). The acute cycle is well recognised. The lung in COPD becomes susceptible to repeated acute airway mucosal infections with viruses and bacterial pathogens, leading to episodes of increased inflammation and worsened symptoms, which are clinically diagnosed as exacerbations of COPD. The viral and bacterial pathogens associated with exacerbations share several common characteristics. All have tropism for the upper airway in the healthy human host. The primary mode of transmission is human to human. They usually asymptomatically colonize the upper airway, above the glottis, or cause mild infections. In the patient without COPD, the innate defence mechanisms keep the lower airway sterile in spite of repeated inhalation and micro-aspiration of bacteria and viruses (*Sethi S et al, 2008a*). In the context of COPD, the innate lung defence system is damaged, with subsequent increased risk of microbial colonization that extends into the lower (subglottic) airway. Pathogen presence in the lower airway stimulates a host immune-inflammatory response in an attempt to eradicate the pathogens.

COPD is now recognized as an inflammatory disease of the airways and the parenchyma of the lung (*Hogg JC et al, 2004*). Exacerbations have been characterized as acute inflammatory events superimposed on this background of chronic inflammation (*Sethi S et al, 2008a; Sethi S et al, 2008b*). This excess inflammation increases airway obstruction by inducing bronchoconstriction, excess mucus production, and airway oedema, which translates to the cardinal clinical symptoms of dyspnoea, cough, and sputum production. Many patients with COPD have these symptoms when they are at their stable baseline status; in such patients, an increase in symptoms that are beyond their usual day to day variability defines an exacerbation, as before mentioned. The typical course of an exacerbation, with a sub-acute onset over days to a peak, followed by gradual resolution over days, is suggestive of an infectious process. With use of modern diagnostic techniques, it is clear that the majority of exacerbations are of infectious origin (*Sethi S et al, 2008a*). Viruses, bacteria and environmental agents account for the vast majority of episodes of exacerbation (*Rohde GG, 2010*). In a study of patients admitted to hospital with severe exacerbations, 78% of patients had evidence of viral or bacterial infection (*Papi A et al, 2006*).

The less well-recognised infection cycle in COPD is the chronic cycle, whereby microbial colonisation results in chronic inflammation and lung destruction, conceptualised as the called 'vicious circle hypothesis' (*Sethi S et al, 2001; Sethi S, 2010*). This hypothesis posits that once impaired innate lung defence due to tobacco smoking allows microbial pathogens to become established in the lower respiratory tract, the microbial pathogens further impair mucociliary clearance and lung defence due to increased mucus secretion, disrupted ciliary activity and airway epithelial injury (*Sethi S et al, 2001*). Thus, microbial colonisation of the lower airways in patients with COPD can perpetuate itself. There is evidence to suggest a defect in macrophage phagocytosis in COPD patients that may result in defective clearance of infectious agents from the lower respiratory tract (*Hodge S et al, 2003*). Furthermore, this chronic presence of bacteria in the lower airways is not innocuous; rather, it induces inflammation and can contribute to progressive airflow obstruction and lung damage characteristic of this disease (*Sethi S, 2010*).

Role of viruses

There is considerable evidence that upper respiratory tract viruses may precipitate exacerbations of COPD. Approximately 50% of exacerbations are associated with upper respiratory tract virus infections and infection with rhinovirus, respiratory syncytial virus and influenza has been associated with exacerbations (*Papi A et al, 2006; Wedzicha JA et al, 2004*). The presence of an upper respiratory tract infection leads to a more severe exacerbation and a longer symptom recovery time at exacerbation (*Seemungal TA et al, 2000a*). Increased symptoms induced by virus-associated exacerbations appear to last longer than bacterial exacerbations (*Seemungal T et al, 2001*). More than 60% of exacerbations in COPD are associated with the symptoms of a common cold (*Seemungal TA et al, 2000b*).

Several studies carried out during the 1950s–1970s report a viral aetiology of COPD exacerbations. These studies relied on viral culture and serologic findings (*Murphy TF et al, 1992*). With these techniques, the presence of at least one respiratory virus was associated with approximately 30% of exacerbations. In contrast, when the same

patients with COPD were studied in stable periods, viral isolation or serologic conversion was found in less than 1% of the cases. A major drawback in these older studies and several recent studies is the reliance on nasopharyngeal samples for viral culture. There may be discordance between the presence of virus in the nasopharyngeal samples and virus in the lower respiratory tract. The presence of virus and a specific 4-fold increase in antibody titre in convalescent serum samples is supportive evidence of infection. A positive serologic response could occur in a viral upper airway infection. Therefore, although earlier studies are supportive of a viral causation of exacerbations, it was presumed that the nasopharyngeal samples culture results are indicative of infection in the tracheobronchial tree and that an increase in antibody titre reflects lower, and not upper, airway infection.

Introduction of polymerase chain reaction (PCR) methods in the 1990s ushered in a new wave of studies examining the viral causation of exacerbations of COPD (*Cameron RJ et al, 2006; Falsey AR et al, 2006; Hutchinson AF et al, 2007; Rohde G et al, 2003; Seemungal TA et al, 2000b; Seemungal T et al, 2001*). These studies report the presence of viral nucleic acid in 30% - 60% of exacerbations. At least one virus is detected by PCR in 64% of exacerbations of COPD patients and these patients have a higher exacerbation frequency than patients in whom viruses are not detected (*Seemungal T et al, 2001*). COPD patients with a history of frequent exacerbations may be more susceptible to respiratory viral infections, although the nature of this susceptibility has not yet been defined. It is possible that up-regulation of the intercellular adhesion molecule-1, which acts as a receptor for rhinoviruses, in airway epithelial cells is important (*Patel IS et al, 2003*). Rhinovirus can be recovered from the sputum more easily than from the upper airways, indicating that these viruses directly infect the lower respiratory tract (*Rohde G et al, 2003; Seemungal T et al, 2000b*). Beckham et al (*Beckham JD et al, 2005*) found viruses by culture in 23.4% of 194 upper airway samples obtained from two studies of adults with respiratory illness, including exacerbations of COPD. When these samples were subjected to reverse-transcriptase PCR viral nucleic acid detection, the viral yield increased to 41.8% (*Beckham JD et al, 2005*). In some of the studies with the highest rates of detection, a higher rate of detection in subsequent stable state samples was also seen (*Rohde G et al, 2003;*

Seemungal T et al, 2001). The spectrum of viral pathogens detected by the molecular techniques was similar to that seen by culture in earlier studies, with the exception of newly discovered viruses, such as human metapneumovirus (*Martinello RA et al, 2006*). The relative frequency of viruses also changed. Influenza was detected less often, and respiratory syncitial virus was detected more often (*Falsey AR et al, 2005*). This redistribution could also reflect the change in method of detection or changes in prevalence as a result of influenza vaccination. Of interest, detection of viral nucleic acid was higher using sputum as opposed to nasopharyngeal samples when both sites were simultaneously sampled (*Seemungal TA et al, 2000b; McManus TE et al, 2008*). Sputum samples are considered to be more representative of lower airway infection than are nasopharyngeal samples, provided the samples meets the quality criteria of > 25 white blood cells and < 10 epithelial cells per low-power field.

Molecular detection of virus in sputum is sensitive, specific, and less traumatic than that in nasopharyngeal swab specimens. The problem is the interpretation of the results. Investigators are not sure to conclude that the presence of viral nucleic acids, detected by PCR of sputum samples, implies and proves infection by the virus. The fact is that PCR can detect as few as 10–100 copies of a target respiratory virus. Whether such low viral titres are of pathological significance is unclear (*Borg I et al, 2003*). One limitation of PCR studies is the lack of immunological assays to determine the presence or absence of an antibody. Other markers of the host response might help. Papi et al (*Papi A et al, 2006*) report sputum eosinophilia only when viruses are detected by PCR in sputum during an exacerbation, suggesting therefore that different inflammatory mediators are involved. Viral infection is a very common cause of acute exacerbation and is also associated with severe exacerbations (*Wedzicha JA, 2004*). Accordingly, a viral cause was identified in 43% of 105 patients requiring mechanical ventilation for COPD (*Cameron RJ et al, 2006*). In other studies, increased levels of sputum interleukin 6 were reported using molecular detection of virus (*Hutchinson AF et al, 2007*). Molecular detection of viral pathogens will likely become the diagnostic method of choice in exacerbations of COPD in the future because of its rapidity, convenience, and sensitivity, compared with culture. Development of new antiviral drugs will likely spur the use of molecular diagnosis in the clinical setting.

Role of bacteria

Prior studies that attempted to determine the extent of bacterial causation of exacerbations in COPD were unsuccessful (*Tager I et al, 1975*). Bacteria colonize the tracheobronchial tree in stable COPD. Therefore, simply detecting bacteria in sputum samples from patients with COPD does not differentiate between colonization and infection, as was shown in early studies of the bacteriology of sputum in COPD (*Gump DW et al, 1976; McHardy VU et al, 1980*). Early studies based on culture of respiratory secretions and serological tests revealed that about one-third of exacerbations were related to bacterial infection. However, in the remaining cases, the aetiology appeared to be uncertain; specifically, the significance of bacterial isolation from sputum was unclear (*Gump DW et al, 1976*). A causal relationship between bacteria and exacerbation was largely discredited when longitudinal studies showed similar rates of isolation of *Streptococcus pneumoniae* and *Haemophilus influenzae* from sputum during both acute exacerbations and stable disease (*Fagon JY et al, 1996; Gump DW et al, 1976; McHardy VU et al, 1980; Smith CB et al, 1976; Tager I et al, 1975*). A significant limitation of these studies was their failure to differentiate among strains within a bacterial species (*Sethi S et al, 2002*), as the technology was not available at that time for such differentiation. Consequently, changes in strains within a species in the airways of individual patients over time were undetected.

In recent years, new research techniques, including molecular typing, have led to renewed interest in the area of bacteria and COPD. Recent studies have used more sophisticated diagnostic tools and the application of molecular technologies to further explore a causal relationship between infection and exacerbation. Acquisition of new bacterial strains from the environment has been shown to be the major driver of exacerbations (*Veeramachaneni SB et al, 2006*). In this model, following acquisition of a new bacterial strain, the balance between the virulence of the pathogen and the host lung defence determines the degree of excess airway and systemic inflammation engendered by the bacterial pathogen. The degree of increased inflammation in turn determines the extent of symptoms, which, if they lead to the patient seeking

healthcare, are diagnosed as an acute exacerbation. The host mounts an adaptive immune response to the infecting bacterial strain, which, possibly augmented by the use of antibiotics, controls and eventually eliminates the infecting strain. However, because the immune response is strain-specific, antigenically unrelated strains from the same species and of course other bacterial species cause recurrent exacerbations. In a prospective cohort study it was found that the frequency of exacerbations increased more than two-fold at clinic visits at which a new strain with one of these four major pathogens was isolated from sputum (*Sethi S et al, 2002*). However, less than 15% of all exacerbations recorded by the authors could be attributed to the acquisition of new strains, thus indirectly supporting the view that the vast majority of COPD exacerbations might be caused by viral infections. Statistically significant increased risk of exacerbations was seen with *H. influenzae, S. pneumoniae* and *Moraxella catarrhalis* acquisition.

There is a clear relationship between the acquisition of new strains and exacerbations of COPD (*Sethi S et al, 2002*). Furthermore, exacerbations with new strains are associated with mucosal and systemic immune response to the infecting strain and are strongly associated with a neutrophilic inflammatory profile in sputum (*Hill AT et al, 2000; Murphy TF et al, 2005; Murphy TF et al, 2008; Sethi S et al, 2004a; Sethi S et al, 2008b*). These studies clearly established non-typeable *H. influenzae*, *S. pneumoniae*, *M. catarrhalis,* and *Pseudomonas aeruginosa* as causative for a significant proportion of COPD exacerbations. All observations to date are based on the use of sputum cultures to identify the presence of bacterial infection. In addition, White et al (*White AJ et al, 2003*) have shown that clearance of bacteria following 10 days of treatment with antibiotics for purulent sputum exacerbations was associated with a reduction in neutrophilic inflammation, while bacterial persistence was associated with persistent elevation of airway inflammation.

The contribution of bacterial load to the occurrence of exacerbations of COPD is, however, uncertain. Sethi et al observed that concentrations of *Haemophilus parainfluenzae* were significantly lower during exacerbations than during stable periods. Among new strains of *M. catarrhalis* and *H. influenzae*, however, increased concentrations of during exacerbation, as compared with during stable visits (*Sethi S et*

al, 2007). Although statistically significant, this small difference in bacterial load is unlikely to be biologically significant (*Wilkinson TM, 2007*). Bacterial load is also an important determinant of airway inflammation, with increasing concentrations associated with greater intensity of neutrophilic airway inflammation (*Hill AT et al, 2000; Sethi S et al, 2000*).

Microbial pathogen presence in the airways of patients with COPD has been regarded as 'colonisation', primarily because of the absence of acute symptoms of infection. However, the appropriate definition of colonisation is the presence of a pathogen that does not cause damaging effects to the host or elicit a host response. In contrast, several recent studies show that bacterial pathogens are associated with host inflammatory and immune responses in stable COPD (*Bandi V et al, 2001; Banerjee D et al, 2004; Hogg JC et al, 2004; Laurenzi GA et al, 1961; Murphy TF et al, 2004; Sethi S et al, 2006; Soler N et al, 1999*). These findings suggest that application of the term colonisation to the lower airway bacterial presence in COPD is a misnomer, because it is likely that it is a low-grade chronic infection, with significant pathophysiological consequences. Various microbial pathogens have been implicated in chronic infection in COPD. These include typical bacteria such as non-typeable *H. influenzae* and *P. aeruginosa*, atypical bacterium such as *Chlamydophila pneumoniae*, viruses such as adenovirus and possibly respiratory syncytial virus, and recently a fungus, *Pneumocystis jiroveci* (Table 2).

The vicious circle hypothesis is a useful conceptual model showing how chronic infection can contribute to COPD progression (*Banerjee D et al, 2004; Sethi S et al, 2006; Soler N et al, 1999*). Evidence supporting this hypothesis is accumulating, such as the demonstration of a microbial colonisation-associated lower airway neutrophilic inflammation. Additional support for this hypothesis comes from the demonstration of persistent inflammation in ex-smokers with COPD, pathological evidence of local adaptive immune responses in the small airways in COPD, and radiological evidence of bronchiectasis developing in advanced disease (*Bandi V et al, 2001; Hogg JC et al, 2004; Laurenzi GA et al, 1961; Murphy TF et al, 2004*). Chronic microbial infection can contribute to inflammation in COPD as a direct inflammatory stimulus or indirectly by altering the host response to tobacco smoke. In order to further test the hypothesis

that bacterial colonisation is associated with airway inflammation in stable COPD, Sethi et al obtained bronchoalveolar lavage in three groups of subjects: 26 ex-smokers with stable COPD, 20 ex-smokers without COPD (ex-smokers), and 15 healthy non-smokers (*Sethi S et al, 2006*). Quantitative bacterial cultures, cell counts, chemokine, cytokine, proteinase/antiproteinase, and endotoxin levels in the bronchoalveolar lavage fluid were compared. Potentially pathogenic microorganisms were recovered in 34.6% of COPD, 0% of ex-smokers, and 6.7% of non-smokers. Colonised COPD subjects had significantly greater relative and absolute neutrophil counts, interleukin 8, active matrix metalloproteinase-9 and endotoxin levels in the bronchoalveolar lavage than the non-colonised COPD subjects. Several inflammatory constituents of bronchoalveolar lavage were also significantly elevated in colonised COPD subjects when compared with ex-smokers and non-smokers. These results further demonstrate that bacterial colonisation drives inflammation of the distal airways in patients with COPD (*Sethi S et al, 2006*).

Although the rate of decline in lung function following smoking cessation returns to that of a non-smoker in patients with early COPD, this may not be the case with more advanced disease. Persistent airway inflammation in ex-smokers is observed in relation to microbial colonisation. Whether this microbial colonisation-induced inflammation contributes to COPD disease progression is not clear, though some suggestive evidence exists. In a small study of thirty patients with advanced COPD, Wilkinson et al (*Wilkinson TM et al, 2003*) observed that an increase in airway bacterial load over the 1-year follow-up was related to a decline in FEV_1. Additional larger studies are probably required to confirm and extend these observations. Table 2 shows the updated information about the role of the different bacterial agents both in exacerbations and during the stable COPD.

Mixed bacterial-viral aetiology

There is increasing recognition that many patients with exacerbations have concomitant viral and bacterial infection. Approximately 25% of patients admitted to hospital with an exacerbation of COPD had co-infection with bacteria and viruses, and

these patients had more severe exacerbations, as measured by length of hospitalisation (*Papi A et al, 2006*). In a recent survey, approximately 70% of exacerbations were associated with an increase in *H. influenzae* and those patients who had concomitant rhinovirus infection had a greater fall in FEV_1 and rise in serum interleukin 6 and sputum interleukin 8 (*Wilkinson TM et al, 2006*). This suggests that patients co-infected with a virus and bacteria may have more severe exacerbations.

Non-infectious aetiology

However, many patients (up to 25% of the cases) suffer from exacerbations where no specific causes can be identified. Some episodes appear to be related to environmental or irritant exposures. Epidemiological studies have shown that hospital admissions with COPD exacerbations increase slightly with a rise in atmospheric levels of sulphur dioxide, ozone, nitrogen dioxide and particulates (*Anderson HR et al, 1997*). There is convincing evidence that exposure to particulates with a 50% cut-off aerodynamic diameter of 10 µm is associated with increased hospital admissions in COPD patients (*Wordley J et al, 1997*). Particulates induce oxidative stress and, in vitro, this leads to activation of different inflammatory markers, such as interleukin and histone acetylation (*Gilmour PS et al, 2003*). Gilmour et al suggested that there may be an interaction between virus infection and air pollution in triggering exacerbations (*Gilmour PS et al, 2001*).

Low temperatures may also be associated with exacerbations of COPD. Reduced temperatures in the bedroom and outside air have been associated with falls in the lung function of COPD patients and an increased frequency of exacerbations (*Donaldson GC et al, 1999*). The mechanisms are not yet understood but may relate in part to increased susceptibility to upper respiratory tract virus infections in cold weather. In patients admitted to hospital with severe COPD exacerbations of unknown cause, 25% had pulmonary embolism confirmed by spiral computerised tomography (*Tillie-Leblond I et al, 2006*). Heart failure may also lead to a symptomatic exacerbation of COPD, although it may be difficult to differentiate the symptoms of increased heart failure from those of a COPD exacerbation (*Rutten FH et al, 2006*).

TABLE 2. Microbial pathogens in chronic obstructive pulmonary disease

Microbe	Role in exacerbations	Role in stable disease
Bacteria		
Haemophilus influenzae	20-30% of exacerbations	Major pathogen
Streptococcus pneumoniae	10-15% of exacerbations	Minor role
Moraxella catarrhalis	10-15% of exacerbations	Minor role
Pseudomonas aeruginosa	5-10% of exacerbations, prevalent in advanced disease	Likely important in advanced disease
Enterobacteriaceae	Isolated in advanced disease, pathogenic significance undefined	Undefined
Haemophilus haemolyticus	Isolated frequently, unlikely cause	Unlikely
Haemophilus parainfluenzae	Isolated frequently, unlikely cause	Unlikely
Staphylococcus aureus	Isolated infrequently, unlikely cause	Unlikely
Viruses		
Rhinovirus	20-25% of exacerbations	Unlikely
Parainfluenza	5-10% of exacerbations	Unlikely
Influenza	5-10% of exacerbations	Unlikely
Respiratory syncytial virus	5-10% of exacerbations	Controversial

Coronavirus	5-10% of exacerbations	Unlikely
Adenovirus	3-5% of exacerbations	Latent infection seen, pathogenic significance undefined
Human metapneumovirus	3-5% of exacerbations	Unlikely
Atypical bacteria		
Chlamydophila pneumoniae	3-5% of exacerbations	Commonly detected, pathogenic significance undefined
Mycoplasma pneumoniae	1-2% of exacerbations	Unlikely
Fungi		
Pneumocystis jiroveci	Undefined	Commonly detected, pathogenic significance undefined

Use of biomarkers in exacerbations of COPD

A novel approach to estimate the presence of an infection and its treatment response is the use of biomarkers. A biomarker refers to the measurement of any molecule or material (cells and tissue) that reflects the disease process. In COPD, several types of biomarker have been measured that are related to disease pathophysiology and the inflammatory and destructive process in the lung, but there are few measurements during exacerbations (*Barnes PJ et al, 2006*). Biomarkers have been measured in blood, urine, sputum, bronchoalveolar lavage and exhaled breath. So far there is little information about whether biomarkers can predict exacerbations or distinguish between different causal mechanisms for exacerbations, thus providing a means of guiding the therapy.

A wide variety of surrogate markers of the inflammatory process have been measured in the stable state and during acute exacerbation (*Aaron SD et al, 2001; Bhowmik A et al, 2000; Bozinovski S et al, 2008; Gompertz S et al, 2001b; Rahman I et al, 1996; Roland M et al, 2001; Sahin U et al, 2001*). Various inflammatory biomarkers, including tumour necrosis factor α, interleukin 6 and C-reactive protein (CRP) are increased in the plasma of patients with stable COPD, but not all of them predict exacerbations. There is an increase in plasma concentrations of inflammatory markers during acute exacerbations and this may represent overspill from the lung (*Calikoglu M et al, 2004; Wedzicha JA et al, 2000*). A recent study measured 36 plasma biomarkers during acute exacerbations in 90 patients with COPD and compared concentrations with the baseline state (*Hurst JR et al, 2006a*). The most selective biomarker turned out to be CRP, although it was not specific for an exacerbation. The interrelationships between the various biomarkers suggested that there was an increase in monocyte and lymphocyte activation during an exacerbation. None of the biomarkers proved to be useful in predicting the clinical severity of an exacerbation. Plasma leptin concentrations are increased during an exacerbation and this may indicate negative energy balance during an acute exacerbation (*Calikoglu M et al, 2004; Creutzberg EC et al, 2000).* Systemic oxidative stress is also increased during exacerbations, with increased concentrations of markers of oxidative stress and reduced antioxidants (*Rahman I et al, 1997*).

Several inflammatory markers are increased in induced sputum of COPD patients during acute exacerbations and fall during recovery. Increased sputum concentrations of tumour necrosis factor α, interleukins 6 and 8 and endothelin-1 have been reported (*Aaron SD et al, 2001; Bhowmik A et al, 2000; Gompertz S et al, 2001b; Roland M et al, 2001; Tsoumakidou M et al, 2005*). The increased purulence and colour change of sputum during exacerbations reflects the increased numbers of neutrophils containing the green pigment myeloperoxidase (*Stockley RA et al, 2001*). The colour may be useful in guiding whether antibiotic therapy is likely to be effective (*Hill AT et al, 2000*).

Brain natriuretic peptide levels independently predict the need for intensive care. Brain natriuretic peptide levels; however, failed to adequately predict short-term and long-term mortality rates in patients with acute exacerbations (*Stolz D et al, 2008a*). In

another study, midregional proatrial natriuretic peptide level has been shown to be higher on admission for exacerbation, compared with recovery and stable state. Midregional proatrial natriuretic peptide was also an independent predictor of mortality (*Bernasconi M et al, 2011*). The potent vasodilator peptide proadrenomedullin independently predicted 2-year survival in patients admitted for COPD exacerbation (*Stolz D et al, 2008b*). Serum angiopoietin-2 concentrations have been shown to be significantly higher in patients with acute exacerbations of COPD than in those with stable COPD or control subjects (*Cho YJ et al, 2011*). Copeptin is another marker of inflammation recently studied in patients with exacerbations of COPD. Copeptin is the C-terminal part of the vasopressin precursor and thus it reliably reflects levels of vasopressin. Copeptin is increased in patients with critical care illness and it correlates with the severity of the primary disease (*Seligman R et al, 2008*). Müller et al (*Müller B et al, 2007*) demonstrated that copeptin levels were elevated in patients hospitalized with a lower respiratory tract infection and it was a predictor of outcome. In a subgroup of patients with exacerbations of COPD and acute bronchitis due to lower respiratory tract infection, copeptin levels were elevated compared with controls; however, the severity of exacerbation did not significantly affect the levels. Authors also found that a copeptin threshold of 53 pmol/l had a sensitivity of 58% and specificity of 80% in predicting mortality. A recent study by Stolz et al found that copeptin levels correlated significantly with length of hospital stay and length of intensive care unit stay in patients admitted with exacerbations of COPD. A cut-off level of 40 pmol/l on hospital admission was associated with additional 5 days of hospitalization and has an odds ratio for long-term clinical failure of 3.1. The Kaplan–Meier survival curve shows that in the patient with long-term clinical failure, copeptin level was significantly higher compared with those with long-term clinical success. Copeptin level on the hospital admission was the only factor significantly associated with hospital outcome and length of hospital stay independent of lung function impairment, hypoxemia, and comorbidities. Incorporating the simple information about history of hospitalization due to exacerbations of COPD within the previous year further enhances prognostic value of copeptin as a biomarker (*Stolz D et al, 2007a*). No studies, however, have been carried out with this biomarker in the outpatient setting.

The levels of exhaled nitric oxide measured at the mouth are usually normal in patients with COPD (*Kharitonov SA et al, 2001*) but when exhaled nitric oxide is partitioned by the multiple flow technique, peripheral nitric oxide (including small airways and lung parenchyma) is increased, whereas bronchial nitric oxide is normal (*Brindicci C et al, 2005*). Exhaled nitric oxide is a promising biomarker for acute exacerbations of COPD. In fact, it is increased during exacerbations (*Agustí AG et al, 1999; Maziak W et al, 1998; Bhowmik A et al, 2005*). This may reflect increased nitrative stress during exacerbations and this hypothesis is supported by the demonstration of increased numbers of nitrotyrosine-positive cells, as a result of increased nitrite and peroxynitrite formation, in induced sputum during an exacerbation compared to the stable state (T*soumakidou M et al, 2005*). Several inflammatory mediators and markers of oxidative stress have been measured in exhaled breath condensate. There is a high variability in the measurement and dilution results in very low concentrations of many mediators, making this a difficult measurement (*Horvath I et al, 2005*). However, this is a non-invasive measurement and is suited to serial measurements during an exacerbation of COPD. An increased concentration of hydrogen peroxide in exhaled breath condensate has been reported during exacerbations of COPD, suggesting increased oxidative stress (*Dekhuijzen PNR et al, 1996; Gerritsen WB et al, 2005*). Acute exacerbations of COPD are associated with an increase in several cytokines in exhaled breath condensate, including tumour necrosis factor α and interleukins 1, 6 and 8 (*Gessner C et al, 2005; Seemungal T et al, 2001*). Kersul et al recently have reported that COPD exacerbations are characterised by high levels of nitric oxide in exhaled air, plasma CRP and interleukins 6, 8 and 10 in sputum compared with stable COPD and controls (*Kersul AL et al, 2011*).

Another biomarker, neopterin, has not been proven to be useful in exacerbations of COPD. Lacoma et al (*Lacoma A et al, 2011*) included 318 consecutive COPD patients: 46 in a stable phase, 217 undergoing an exacerbation, and 55 with pneumonia. A serum sample was collected from each patient at the time of being included in the study. A second sample was also collected 1 month later from 23 patients in the exacerbation group. Procalcitonin and CRP showed significant differences among the three patient groups, being higher in patients with pneumonia, followed by patients with

exacerbation. For the 23 patients with paired samples, both procalcitonin and CRP levels decreased 1 month after the exacerbation episode, while neopterin increased (*Lacoma A et al, 2011*).

Hence, some of these biomarkers allow prediction of the onset of an exacerbation and provide laboratory confirmation supporting the diagnosis of the exacerbation. Unfortunately, except for CRP and procalcitonin, their role in patient management is far from certain, as intervention studies are not available (*Hurst JR et al, 2006a; Stolz D et al, 2007a; Stolz D et al, 2007b; Stolz D et al, 2008b*).

Procalcitonin is found in very low levels in healthy individuals. In the presence of infection, the circulating concentrations of procalcitonin increase rapidly. The ubiquitous release of procalcitonin during bacterial infections is induced either directly by microbial toxins or indirectly by humoral factors or the cell-mediated host response (*Linscheid P et al, 2004*). This induction is rather attenuated by cytokines released during viral infections, such as interferon-γ (*Linscheid P et al, 2004*). Therefore, circulating levels of procalcitonin are markedly elevated in bacterial infections as compared to viral infections or other inflammatory conditions (*Becker KL et al, 2004*). Procalcitonin serum levels > 0.25 ng/ml showed a high specificity (97.7%) for bacterial lower respiratory tract infection requiring antibiotic therapy (*Stolz D et al, 2006*). Within this context, the usefulness of procalcitonin for guiding antibiotic therapy in 208 patients admitted for acute exacerbation of COPD has been analysed (*Stolz D et al, 2007b*). At admission, patients were randomized either to a procalcitonin-guided strategy or to the standard approach, in which antibiotics were prescribed according to the decision of the physician in charge. Patients assigned to the procalcitonin-guided group were treated with antibiotics according to serum procalcitonin levels. A procalcitonin level < 0.1 μg/l was considered to be nonbacterial and antimicrobial use was discouraged. In those with a procalcitonin level > 0.25 μg/l, the exacerbation was believed to be bacterial and antimicrobial therapy was encouraged. For patients with procalcitonin levels between 0.1 μg/l and 0.25 μg/l, the use of antimicrobial agents was based on the stability of the clinical condition. Patients were followed up during the hospitalization, at a short-term visit, and through 6 months. Procalcitonin guidance reduced antibiotic prescription from 72 to 40% at acute exacerbations, allowing a

significant sustained reduction in total antibiotic exposure for up to 6 months (RR: 0.76, 95% CI: 0.64 – 0.92). Clinical outcome and improvement in FEV_1 were not compromised. Exacerbation rate and time to next exacerbation did not differ between both randomized groups. Given the fact that similar results have been reported in lower respiratory tract infection, community-acquired pneumonia, and severe bacterial infection (*Christ-Crain M et al, 2004; Christ-Crain M et al, 2006; Nobre V et al, 2008*), these findings suggest that procalcitonin guidance offers a sustained advantage in reducing antibiotic use for acute exacerbation. The absolute risk reduction of 32% in the antibiotic exposure implies that for one in every four patients admitted because of acute exacerbation, one antibiotic course can be prevented (number needed to treat: 3.2, 95% CI: 2.3 – 5.3). Despite the promising results, it still needs to be defined whether these results can be replicated in a multicentre trial (*Martínez FJ et al, 2007*).

CRP is an acute phase reactant, which is increased in most forms of tissue damage, inflammation, and/or infection (*Antonescu-Turcu A et al, 2009*). CRP is a protein produced by the liver in response to stimulation by interleukin 6 (*Pepys MB et al, 2003*). A systematic review by Gan et al (*Gan W et al, 2004*) concluded that patients with COPD have elevated CRP levels that were on average 1.86 mg/l higher than those of control, a difference that is clinically relevant (*Dahl M et al, 2007; Sin D et al, 2003).* Several studies have shown that high CRP levels have been associated with reduced lung function, 6-minute walking distance, pO_2 and impaired energy metabolism (*Broekhuizen R et al, 2006; de Torres JP et al, 2006*).

Numerous prospective studies showed that serum level of CRP is independently associated with mortality in whole spectrum of different diseases such as coronary heart disease (*Lowe GD et al, 2006*), high blood pressure, metabolic syndrome, obstructive sleep apnoea, diabetes, and renal disease (*Linnemann B et al, 2006; Racki S et al, 2006).* Two large epidemiological studies (*Dahl M et al, 2007; Man SF et al, 2006*) showed that increased CRP values are associated with cardiovascular and general mortality in patients with stable mild-to-moderate COPD. Man et al (*Man SF et al, 2006*) found that patients in highest CRP quintile (mean CRP: 70 mg/l) had the highest risk of all-cause mortality, cancer deaths, and cardiovascular events. Dahl et al (*Dahl M et al, 2007*), using the data from Copenhagen City Heart Study, reported that

prospective measurements of CRP levels were predictive of hospitalization and death from COPD. This 8-year follow-up study indicated that the absolute 10-year risk for COPD hospitalization and death in individuals with CRP levels above 30 mg/l were 54 and 57%, respectively, among those with a tobacco consumption above 15 g/day and a FEV_1 less than 50% predicted. These studies concur with previous studies that CRP is a strong predictor of future mortality (*Ridker P, 2003*), but CRP is not associated with an independent risk of COPD death. As patients included had mild-to-moderate COPD and most of their mortality was due to cardiovascular disease, it is possible that elevated CRP is just a marker of increased cardiovascular mortality risk (*Donaldson G, 2007*). Furthermore, de Torres et al (*de Torres JP et al, 2008*) found that baseline serum CRP level was not significantly associated with survival in patients with clinically stable moderate-to-severe COPD. In contrast, the body-mass, airflow obstruction, dyspnoea and exercise capacity index and its components were strong predictors of survival in this group of patients. Of note, the study by de Torres et al was much smaller compared with the two large epidemiological studies mentioned above and included patients with severe COPD.

Multiple studies investigated CRP levels during an episode of acute exacerbation of COPD (*Bircan A et al, 2008; Dev D et al, 1998; Malo O et al, 2002; Spruit MA et al, 2003; Weis N et al, 2006*). In another study, CRP levels were not increased in a large proportion of patients with acute exacerbation (*Hurst JR et al, 2006b*) and initial CRP levels seemed not to be correlated with outcome of acute exacerbation (*Stolz D et al, 2007a*). CRP levels are highest in bacterial infection. In this context, low levels of CRP might just reflect the absence of bacterial infection, thus suggesting that a significant proportion of acute exacerbation is caused by triggers other than bacterial infection, such as viruses or concomitant heart failure. Accordingly, CRP values are markedly increased in COPD patients admitted for acute exacerbation with pneumonia and in those with sputum purulence (*Weis N et al, 2006*). Fluctuation of the CRP levels during an exacerbation of COPD and its relationship with treatment has been addressed in multiple studies. Spruit et al (*Spruit MA et al, 2003*) described a significant decrease in CRP levels with treatment between days 1 and 3 and between days 3 and 8 in patients admitted with acute exacerbations of COPD. More recently, Stolz et al showed that

CRP levels, while significantly elevated during an exacerbation of COPD, decreased substantially thereafter with comparable levels at day 14 and after 6 months (*Stolz D et al, 2006; Stolz D et al, 2007a*).

Given the wide range of variation in elevated CRP level between 61 and 88%, some authors consider that it is a poor biomarker. It is not entirely clear what is the possible explanation for this discrepancy between the studies. There are few possible speculations: up to 50% of variation in CRP levels is determined by inherited characteristics (*Wouter EF, 2006*); relatively small number of patients included in the studies and inclusion bias; inhaled and systemic corticosteroids may blunt CRP response by 50 and 63%, respectively (*Sin D et al, 2004*); and different causes for acute exacerbation have a different impact on CRP levels, in which bacterial infection causes a more dramatic increase compared with nonbacterial cause of COPD exacerbation, such as a viral infection or heart failure. Supporting this latter hypothesis, Dev et al (*Dev D et al, 1998*) showed that patients with proven bacterial infection had markedly elevated CRP levels (mean 103 mg/l). Similarly, Hurst et al (*Hurst JR et al, 2006b*) indicated higher CRP and IL-6 levels in the presence of a bacterial pathogen and levels are proportional to the lower airway inflammation. Other investigators indicated that CRP levels during an exacerbation correlate with different clinical parameters such as sputum characteristics, white blood cell count, presence of an infiltrate on the chest radiograph, and type of exacerbation according to Anthonisen criteria (*Stockley RA et al, 2000, Stolz D et al, 2007a*).

CRP has limitations as well. CRP is increased in response to a number of infectious and inflammatory conditions and therefore is not specific to COPD in general and moreover to episodes of acute exacerbation. The clinical usefulness of a cut-off value of a biomarker depends on the underlying disease and the potential decision for treatment. Important limitation in validation of CRP as biomarker for COPD exacerbation is lack of agreed method in identification of exacerbations of COPD in clinical terms. Based on the available data, CRP is not able to distinguish between infection and non-infectious causes of acute exacerbations of COPD.

Despite this enormous number of studies published in exacerbations of COPD, no studies evaluating the usefulness of CRP on reduction of antibiotic therapy for acute exacerbations of COPD have been performed up to now. However, Cals et al have shown that those general practitioners (GP) who use the CRP rapid test in the consultation as a guidance to prescribe or not antibiotics for lower respiratory tract infections; they prescribe antibiotics more prudently (*Cals JW et al, 2009; Cals JW et al, 2010*). This fact has been also shown in the Happy Study in Spain; those GPs who performed CRP tests prescribed significantly fewer antibiotics for lower respiratory tract infections compared to those who did not use this rapid test (*Llor C, 2010a*).

Antibiotics for exacerbations of non-severe COPD are controversial

The recommendation for prescribing antibiotics in acute exacerbations of COPD is still mainly based on the landmark study by Anthonisen et al (*Anthonisen NR et al, 1987; Celli BR et al, 2004a; El Moussaoui R et al, 2008; National Institute for Clinical Excellence, 2011*). In this double-blinded, cross-over trial, 173 patients were randomly assigned to either antibiotics or placebo. Outcome was defined as success, no resolution, and deterioration and assessed at 21 days. As compared to patients in the placebo group, patients receiving antibiotics had a higher success rate in type I exacerbations, as defined by increased dyspnoea, increased sputum volume, and increased sputum purulence (43 versus 62.9%, $p<0.01$). Patients with type II and type III exacerbations did not statistically benefit from antibiotic therapy. Whereas no differences were seen in the number of patients showing 'no resolution' in all three exacerbation types, patients with type I exacerbation receiving placebo had a higher deterioration rate (30.5 versus 14.3%). Hence, antibiotics prevented deterioration in 9% of all exacerbations treated within the trial. Although this study included moderate-to-severe COPD patients with a mean FEV_1 of 33.1% predicted, 55% of the patients were cured without antimicrobial treatment. Interestingly, time to recovery was similar in both randomized groups for those classified as 'no resolution' or success (11.9 versus 12.8 days). On the basis of these results, it is tempting to speculate that antibiotics might not influence the clinical course of exacerbation including duration of

symptoms but could prevent deterioration in those with underlying bacterial infection. Noteworthy, this trial has a few methodological weaknesses: firstly, patients with type II and III exacerbations could be reclassified as a type I exacerbation if symptoms escalated. Therefore, type I exacerbations were, per definition, more prone to represent non-resolving infections. Secondly, only 42% of patients in both treatment arms received corticosteroids. Currently, corticosteroids represent a standard treatment for acute exacerbations of COPD (*Global Initiative for Chronic Obstructive Lung Disease, 2010*). Finally, the potential benefit of antimicrobial therapy might have been underestimated in this trial given the fact that only narrow-spectrum antibiotics were available at that time. More recent studies failed to demonstrate an association between bacterial infection and Anthonisen type I exacerbations (*Stolz D et al, 2007; van der Valk P et al, 2004*). Nevertheless, a meta-analysis recently included in the Cochrane Library suggests that in acute exacerbations with increased cough and sputum purulence, the use of antibiotics reduces the risk of short-term mortality by 77% and decreases the risk of treatment failure by 53% (*Ram FS et al, 2006*). These results should be interpreted with caution, because they might be driven by a single study including patients with severe exacerbations treated in the intensive care unit and requiring mechanical ventilation (*Nouira S et al, 2001*). Furthermore, there were differences in patient selection, antibiotic choice, small number of included trials, and lack of control for interventions that influence outcome, such as use of systemic corticosteroids and ventilatory support (*Ram FS et al, 2006*). Antibiotics influenced resolution of sputum purulence but did not influence recovery of peak flow or gas exchange (*Ram FS et al, 2006*). Paradoxically, viral exacerbations are associated with more severe exacerbations and prolonged symptom recovery as compared to non-viral exacerbations (13 versus 6 days) (*Ram FS et al, 2006*).

Current guidelines mainly base their decision about antibiotic prescription on the study of Anthonisen (*Anthonisen NR et al, 1987*) and recommend their use in type I and II antibiotics; that is, when two or three of the following criteria are present: increase of dyspnoea, increase of sputum production and/or purulence of sputum COPD (*Global Initiative for Chronic Obstructive Lung Disease, 2010*). However, antibiotics can be withheld in those type III exacerbations; that is, when only one of the former criteria is

present. Purulent sputum has been shown to be the most predictive for bacterial infection (*Stockley RA et al, 2001*).

These recommendations have also been endorsed by many scientific societies in our country, and more particularly, by the Spanish Society of Family and Community Medicine (*Cots JM et al, 2010*). Despite the use of these recommendations, the evidence for antibiotic prescription for exacerbations of non-severe COPD is weak and this fact has been pointed out by three systematic reviews published over the last years.

Systematic reviews of placebo-controlled trials

Three important systematic reviews of placebo-controlled trials about effectiveness of antibiotic therapy in acute exacerbations of non-severe COPD have been published recently (*Puhan MA et al, 2007; Puhan MA et al, 2008; Ram FS et al, 2006*). Those reviews showed that antibiotics have a significant effect on treatment failure in hospitalised patients but not in outpatients.

There are a large number of randomised trials comparing different antibiotics, without placebo control, for the treatment of exacerbations of COPD. Although it may seem plausible that antibiotics are beneficial in about 50% of the COPD patients in whom bacteria are the cause of the exacerbation (*Sethi S, 2004*), there is evidence indicating that antibiotics have a short-term effect only in COPD patients with severe exacerbations but not in mild to moderate exacerbations (*Puhan MA et al, 2007*). Although head-to-head comparisons of different treatment options available in clinical practice can be very useful (*Tunis SR et al, 2003*), an underlying assumption of such trials is that the treatments are effective compared with a placebo (*Djulbegovic B et al, 2001; ICH Steering Committee, 2000; Schwartz D et al, 1967*). While conducting a series of systematic reviews of treatments in COPD, we gained the impression that the evaluation of antibiotics for COPD exacerbations had moved to head-to-head comparisons of different antibiotics with very little research in placebo-controlled trials. Puhan et al (*Puhan MA et al, 2008*) recently set out to test this hypothesis in a more systematic way, counting the number of randomised trials of antibiotic

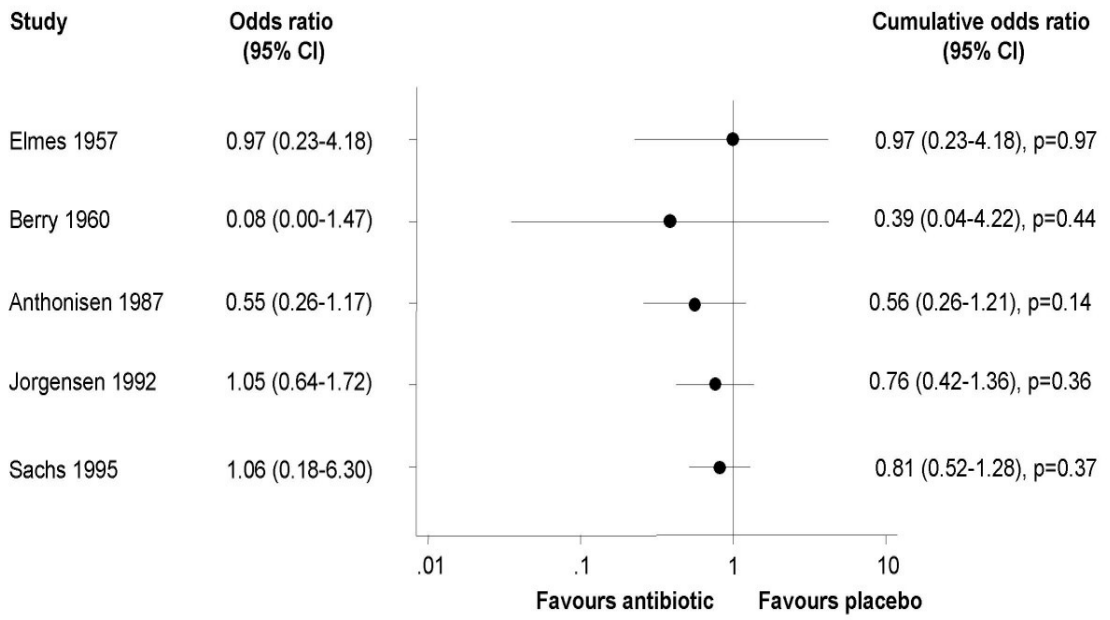
treatment for mild to moderate exacerbations in COPD patients published in the last 50 years, determining whether they used a placebo control or conducted head-to-head comparisons, and contrasting the number of patients studied with the results of a cumulative meta-analysis, using data from a recently published systematic review.

As with any systematic review on this topic, a difficulty is that definitions of COPD have varied over time. In particular, spirometric criteria became widespread only after 1995 and authors generally accept a clinical diagnosis of COPD, chronic bronchitis or emphysema. However, in order to include only trials whose patients were very likely to have COPD, Puhan et al (*Puhan MA et al, 2008*) included studies only if patients with chronic bronchitis were at least 40 years of age and/or if at least 80% were smokers or ex-smokers. The presence of these characteristics (chronic bronchitis, age and smoking history) renders a diagnosis of COPD according to spirometric criteria extremely likely (*Straus SE et al, 2000*). However, Puhan et al defined patients to have mild to moderate exacerbations if they needed any outpatient treatment. Out of 15 placebo-controlled trials, seven enrolled outpatients with non-severe exacerbations. A total of 212 head-to-head trials were identified, of which 101 explicitly enrolled outpatients with mild-to-moderate exacerbations and 63 enrolled inpatients. In 48 trials, patients with any severity of exacerbations were enrolled or severity of the exacerbation could not be determined. From 1957 to 2005, the 101 head-to-head trials enrolled a total of 34,029 patients with mild to moderate exacerbations. The first head-to-head trial in 1963 (*Christiansen I et al, 1963*) included patients with non-severe exacerbations and compared sulphonamide with penicillin, with the aim of finding an antibiotic with fewer adverse events than oxytetracycline, the drug used in the three earlier placebo-controlled trials (*Berry DG et al, 1960; Elmes PCF et al, 1957; Fear EC et al, 1962*). As in many of the following head-to-head trials (*Wegmuller E, 1979*), the role of the antibiotic itself was not questioned. A common reason to justify a head-to-head trial was that antibiotics are effective against organisms most commonly associated with purulent sputum in chronic bronchitis, such as *H. influenzae* and *S. pneumoniae*. Thus rather than citing evidence from placebo-controlled trials, they referred to the *in vitro* activity of antibiotics, for example (*Burrow G et al, 1975; Hamilton BA et al, 1993*). Yet another group of head-to-head trials referred to placebo-controlled trials to justify

their head-to-head trials but selectively cited only those trials with positive results (*Fogarty C et al, 2005; Willey RF et al, 1978*).

The seven trials included a total of 990 outpatients with mild to moderate exacerbations. Figure 1 shows the cumulative meta-analyses for the five trials reporting on treatment failure. In one trial, treatment failure was defined as event-based because of the need for further antibiotics (*Elmes PCF et al, 1957*), and in four trials, a symptom-based definition of treatment failure was used (*Anthonisen NR et al, 1994; Berry DG et al, 1960; Jorgensen AF et al, 1992; Sachs AP et al, 1995*). Cumulative ORs never reached statistical significance and the most recent, published in 1995, cumulative OR was 0.81 (95% CI: 0.52 – 1.28). When the authors also included another trial (*Allegra LG et al, 1991*), the cumulative OR also remained non-significant (0.50, 95% CI: 0.2 – 1.24). In other words, cumulative evidence from placebo-controlled trials did not show any significant effects of antibiotics on treatment failure in COPD patients with mild to moderate exacerbations.

FIGURE 1. Cumulative meta-analyses for the five placebo-controlled trials evaluating effectiveness of antibiotics in non-severe COPD exacerbations



It should be emphasised that the results of Puhan's meta-analysis apply to antibiotic treatment for mild-to-moderate COPD exacerbations. In patients with severe exacerbations, antibiotics show a strong effect not only on treatment failure but also on mortality (*Puhan MA et al, 2008*). This analysis of placebo-controlled trials differs to some extents to that of the Cochrane review (*Ram FS et al, 2006*) because Puhan et al did not include a study (*Elmes PC et al, 1965*) that was not a randomised but a matched controlled study. However, Puhan et al did include the trial by Sachs et al (*Sachs AP et al, 1995*) missed by the Cochrane review and received the original data from the authors. However, the Cochrane review (*Ram FS et al, 2006*) also showed that antibiotics have a significant effect on treatment failure in hospitalised patients but not in outpatients. Similarly, a randomized, placebo-controlled trial in 93 mechanically ventilated patients showed that 10 days of therapy with ofloxacin resulted in decreased hospital mortality (4 versus 22%), shorter length of hospital stay, and shorter duration of mechanical ventilation (*Nouira S et al, 2001*). Interestingly, no concomitant steroid therapy was offered by study design, a factor that might have significantly influenced trial results, given that antibiotic benefits are less prominent if steroids are used concomitantly (*Wilson R et al, 2004*).

The Cochrane review identified only 11 trials investigating a total of 917 patients (*Ram FS et al, 2006*). This is in striking contrast to the enormous number of patients suffering from exacerbations of COPD each year worldwide. This recent analysis showed a reduction of the risk of short-term mortality by 77%, a decrease in the risk of treatment failure by 53% and the risk of sputum purulence by 44%. However, there is a warning that the results have to be interpreted with caution due to the differences in patient selection, antibiotic choice, the small number of trials included and the lack of control for interventions that influence outcome, such as use of systemic corticosteroids and ventilatory support. Most importantly, only three studies (from 1968, 1972 and 2001) with a total of 298 patients were eligible for assessment of mortality. It should be mentioned that, although the combined analysis showed a survival benefit, each individual study was relatively small in size and was underpowered to answer this critical question (*Quon BS et al, 2008*). The same was

true for studies assessing treatment failure (1968, 1972 and 1992; 263 patients) and sputum purulence (1968 and 1972; 205 patients).

In another recent meta-analysis of 13 trials including 1,557 patients assessing the effect of antibiotics on clinically relevant outcomes confirmed that antibiotics do not reduce treatment failure in outpatients (pooled OR: 1.09, 95% CI: 0.75 – 1.59) (*Puhan MA et al, 2007*).

Limitations of the systematic reviews

Definitions used in these trials

A limitation of systematic reviews in COPD is the evolution of definitions and classifications of COPD over the years. This raises uncertainty about the nature of the study populations included in trials published before 1995 or even before 2000. Many placebo-controlled trials included patients with 'chronic bronchitis' who did not present evidence of chronic airflow obstruction or poor reversibility of airflow obstruction.

COPD is a heterogeneous disease

Outcomes of exacerbations worsen and antibiotic benefit in exacerbations increases with worsening underlying airflow obstruction, in frequent exacerbators and with comorbid conditions (*Miravitlles M et al, 2001; Wilson R et al, 2006*). This is likely related to a greater proportion of bacterial aetiology and more severe local immunocompromise in these patients. In grouping together the trials in theses systematic reviews, both Puhan et al and Ram et al (*Puhan MA et al, 2007; Ram FS et al, 2006*) pooled together patients who are very heterogeneous with respect to their COPD disease and, therefore, could not discern a beneficial effect of antibiotics. This is best illustrated by comparing the patient populations of two trials included in their analysis; the trial conducted by Anthonisen et al (*Anthonisen NR et al, 1987*), which showed a significant benefit of antibiotics, and the trial conducted by Sachs et al (*Sachs APE et al, 1995*), which failed to show benefit (*Sethi S, 2008*). In the Anthonisen study (*Anthonisen NR et al, 1987*), there was significant benefit with antibiotics when all 362

exacerbations were considered, but Puhan et al (*Puhan MA et al, 2007*) consider only for their analysis the first exacerbation from the 116 patients in the study, which could alter the results. On the other hand, Sachs et al (*Sachs APE et al, 1995*) included patients of younger age, mild underlying disease and asthma. Not surprisingly, only 11% of their exacerbations were associated with a positive bacterial culture, rather than the usual 40% to 50%. Not surprisingly, antibiotics were of no benefit in this study and, in their placebo arm, there was a 93% resolution rate compared with 55% in the Anthonisen study (*Anthonisen NR et al, 1987*).

Severity of exacerbations

These systematic reviews considered non-severe exacerbations based on the site of treatment, that is, outpatient treatment. This classification is clearly very broad as the site of care will vary among countries and healthcare systems as well as with patient and physician preferences. Furthermore, over time, changes in healthcare delivery and results of outcome studies can change the site of care for the same severity of exacerbation. As Sethi states (*Sethi S, 2008*) a 40-year-old smoker without underlying airway obstruction, infrequent exacerbations and free of comorbid conditions would have been included as a mild-to-moderate exacerbation. On the other hand, a patient with severe COPD, frequent exacerbations and comorbid conditions who does not require hospitalization would also be classified as a mild-to-moderate exacerbation. In the former patient, it is possible that host immunity can adequately deal with the infection and the exacerbation will spontaneously resolve. In the latter patient, such resolution is less likely and complications are more frequent. Grouping these patients together can lead to confusing and contradictory results.

The severity of an exacerbation is a complicated concept, constituted by at least two factors, the severity of the underlying COPD and the acute change induced by the exacerbation itself. Therefore, a patient with severe underlying COPD will have significant clinical consequences from a relatively small change from the baseline state, while a patient with mild COPD will tolerate a much larger change in symptoms and lung function. It is evident that we need more objective measures of severity of exacerbations.

All antibiotics are not the same

An additional consideration is the spectrum of the different antibiotics used to treat COPD. In these meta-analyses, the authors tended to treat all antibiotics as equivalent when used to treat exacerbations of COPD. Antibiotics do differ in their antimicrobial spectrum, pharmacokinetic/pharmacodynamic profiles and ability to penetrate respiratory tissues. Recent studies indeed show differences in clinical outcomes among antibiotics used in exacerbations. A recent meta-analysis of antibiotic comparison trials, which were quite homogenous, demonstrated that amoxicillin results in suboptimal outcomes with increased risk of clinical failures in COPD (*Dimopoulos G et al, 2007*) This has been seen particularly since the early 1990s, when resistance emerged to this agent. Interestingly, two trials, published by Sachs et al (*Sachs APE et al, 1995*) and Jorgensen et al (*Jorgensen AF et al, 1992*) included in these meta-analyses, both not showing a significant benefit of antibiotics, used amoxicillin and were conducted in the 1990s. Two trials comparing fluoroquinolones with non-fluoroquinolone antibiotics, the GLOBE and MOSAIC trials, showed more complete clinical resolution of exacerbations and a prolonged time to the next exacerbation (*Wilson R et al, 2002; Wilson R et al, 2004*).

End-points in exacerbation trials

Analysis of any study should critically examine if its end-points were adequate to demonstrate the potential benefits of the intervention being tested and were clinically relevant. Unfortunately, in the studies evaluated in these systematic reviews, as well as in the vast majority of antibiotic comparison trials in exacerbations of COPD, end-points used favour the demonstration of equivalence rather than differences among the arms (*Sethi S et al, 2004b*). Partly, this is the result of mandates by regulatory agencies. These end-points assessed at 2 to 3 weeks after the onset of symptoms and the initiation of therapy miss differences in therapeutic effect earlier during the course of treatment. In addition, these end-points have minimal relevance to clinical practice. In clinical practice, most physicians and patients expect clinical improvement in their exacerbation at the first week to ten days after initiation of treatment. In fact, with insufficient improvement in that timeframe, therapy is often altered or expanded.

Allegra et al (*Allegra L et al, 2001*) did conduct a placebo-controlled trial where they used a 5-day time-point, showing a substantial benefit of antibiotics.

The adequacy of the traditional goals of treatment of an exacerbation, recovery to baseline clinical status and the prevention of complications, are being questioned because of several new observations. These include realization of the importance of exacerbations in the course of COPD, the role of infection in exacerbations, the high rates of relapse with an adequate initial clinical response, and the role played by chronic infection in the pathogenesis of COPD. Today, confining our goal in the treatment of COPD exacerbations to short-term resolution of symptoms would be analogous to treating acute myocardial infarction with the only aim being resolution of chest pain.

Last studies published

Recently, a placebo-controlled trial investigated the effects of antibiotic treatment with doxycycline in addition to corticosteroids in acute exacerbations of COPD (*Daniels JM et al, 2010*). The primary end-point was clinical success on day 30: this was not significantly different between groups. However, secondary end-points, such as clinical success and clinical cure on day 10, were in favour of antibiotic treatment. This study suggests that it is safe to omit antibiotic treatment in a clinical trial of exacerbations of COPD but it cannot answer the crucial question of whether antibiotics are efficacious, as the results are, again, heterogeneous and the study was underpowered. In addition, the antibiotic used, doxycycline, may not be first choice in most European countries. The latest publication in the field is a retrospective cohort study of hospitalised exacerbations of COPD patients performed at 413 acute care facilities throughout the USA (*Rothberg MB et al, 2010*). The analysis was based on a database developed for measuring healthcare quality and utilisation. The primary end-point was a composite measure of treatment failure, defined as the initiation of mechanical ventilation after hospital day 2, in-hospital mortality and readmission for COPD within 30 days of discharge. It was found that the risk for treatment failure was lower in the antibiotic-treated patients (OR: 0.87; 95% CI: 0.82 – 0.92). However, this analysis has many problems. The groups investigated were hardly comparable, as treated patients

received more short- and long-acting bronchodilators, steroids, morphine and loop diuretics than those not receiving antibiotics. Only administrative data could be used for the analysis, such that physiological differences between groups could not be directly adjusted for. Identification of patients was performed by administrative data review, which implies that classification of patients might have been severely biased. To date, there is no single study sufficiently powered to demonstrate the efficacy of antibiotic treatment in exacerbations of COPD.

Utilization of antibiotics for COPD exacerbations

Antibiotics are widely used for acute exacerbations of COPD. It is estimated that more than 80% of COPD exacerbations are treated on an outpatient basis, which can be regarded as mild-to-moderate exacerbations. Accordingly, antibiotics were prescribed in 85% of 69,820 patients admitted for acute exacerbations of COPD to 360 hospitals throughout the United States (*Lindenauer PK et al, 2006*). In a Spanish study carried out in the primary care setting, antibiotics were prescribed in 89% of the exacerbations (*Miravitlles M et al, 1999a*). More recently, in the Happy Audit study carried out in Spain, antibiotics were prescribed in 81.1% of the cases (*Llor C et al, 2010b*). Antimicrobials are often given either to speed up recovery from a bacterial infection or in a defensive manner to avoid the risk of airway infection progressing to pneumonia (*Wilson R, 2008*).

Antibiotic-resistant strains of pathogenic bacteria are increasingly prevalent in hospitals and the community. The excessive use of antibiotics without clear indication contribute significantly to the increase in antibiotic resistance is believed to be the main cause of the spread of antibiotic-resistant bacteria (*Chen DK et al, 1999; Wenzel RP et al, 1999*). Antibiotic resistance itself is a major threat to our patients, as it results in increased morbidity and mortality. The European Centre for Disease Prevention and Control has been campaigning for several years for a more prudent use of antibiotics (*Earnshow S et al, 2009*). The majority of antibiotics are prescribed for respiratory tract infections (*Bjerrum L et al, 2011*). Given COPD's prevalence and the duration of illness, reduction of antibiotic prescription for acute exacerbation could have a tremendous

impact on the selective pressure for the emergence of bacterial resistance (*Gonzales R et al, 1999; Guillemot D et al, 2001*). In addition, the incidence of antibiotic-related adverse effects ranges from 18 to 24% in acute exacerbations (*Gotfried M et al, 2007*). In this context, discriminate use of antibiotics at exacerbation may be pivotal to improve outcome in patients with COPD. Despite the debatable efficacy of antibiotics in exacerbations of COPD, most GPs will feel compelled to prescribe antibiotics, particularly in deteriorating patients and in those admitted to the hospital but also in the outpatient setting.

Rationale of this thesis

Many head-to-head trials of antibiotics for mild to moderate COPD exacerbations have been conducted although evidence from randomised placebo-controlled trials never showed that antibiotics were effective at all. So, in this case, the evaluation of antibiotics did not follow the general principle that placebo-controlled trials must have shown that the treatment is better than the placebo, before head-to-head trials are to be conducted (*ICH Steering Committee, 2000*). Probably, this is due to the pharmaceutical industry pressure. In general, big pharma tends to favour placebo-controlled trials in order to show large effects and to avoid direct comparison with competitors. Once a treatment, such as antibiotics for COPD exacerbations, is established in clinical practice an attractive market is available. If a company wants to enter this market it needs to provide a trial showing clinical non-inferiority of a new antibiotic and some advantages in terms of adverse effects or costs. This will make it relatively easy to get approval from regulatory agencies, as long as the drug is safe. The Helsinki Declaration emphasises the great importance of conducting experimental studies for medical progress. However, it also states that one should be very careful before embarking on randomised trials with placebo controls because research participants have a right to the best available treatment (*World Medical Association, 2000*). Worries about the 'unethical use of placebo' continue (*Fergusson D et al, 2005; Michels KB et al, 2003*). However, the present thesis tackles the reverse scenario. Might there be cases where experimental treatment did not show superiority over

placebo but where the placebo controls were abandoned nevertheless, thus exposing patients to adverse effects and society to healthcare expenditures not offset by any beneficial effects.

The rationale for the first placebo-controlled trials was reported to be the uncertainty about the benefits of a short course of intermittent antibiotic therapy for exacerbations (*Berry DG et al, 1960; Elmes PCF et al, 1957; Fear EC et al, 1962*). The authors explicitly stated the short duration of antibiotic treatment because prophylactic long-term use of antibiotics to prevent exacerbations was quite common at that time. However, prophylactic long-term use of antibiotics is not recommended nowadays even though some papers have been published very recently (*Albert RK et al, 2011*). Over the following 40 years, authors of placebo-controlled trials argued that these trials were required because the role of the antibiotic therapy was not clear (*Anthonisen NR et al, 1987*) or because it was still not sufficiently clarified whether acute exacerbations of chronic bronchitis should be treated with antibiotics (*Jorgensen AF et al, 1992*). These statements reflect the ongoing debate about the usefulness of antibiotics for COPD exacerbations. The three systematic reviews of placebo-controlled trials about effectiveness of antibiotic therapy in non-severe exacerbations of COPD failed to conclude that they are effective in mild-to-moderate exacerbations. In spite of the high prevalence of COPD and the resulting high number of exacerbations worldwide, there are only a very limited number of studies on the efficacy of antibiotic treatment in exacerbations of COPD. There is significant heterogeneity in findings across these studies, indicating a lack of consistency and robustness in the results (*Rohde GG, 2010*). It is obvious that there is a paucity of reliable data on the use of antibiotics for acute exacerbations of non-severe COPD. Most of the studies lack an objective definition of COPD and cannot be compared to the standards of current guidelines, such as those of the GOLD. Differences in disease definition may have severely biased the results obtained. The different study populations showed clinically important differences in severity of COPD exacerbations. The small number of studies so far does not allow for stratified analysis according to severity of COPD exacerbations. There may also be substantial publication bias, as during the time most of the studies were performed, mainly the 1970s, negative results might not have been

published, and such studies were not centrally captured and published. A very important limitation of nearly all studies on the topic is the lack of a standardised treatment for exacerbation. So far, only one clinical trial included standardised treatment, but the results were not unequivocal (*Daniels JM et al, 2010*).

The other reason for conducting this thesis is the overprescription of antibiotics not only for acute exacerbations of COPD but also for other lower respiratory tract infections. Even though antibiotics are currently recommended for patients with severe exacerbations or severe underlying COPD and in those with type I and II exacerbations, they are widely prescribed worldwide.

Most episodes of acute exacerbations of COPD are, however, mild-to-moderate and not severe. This fact is even clearer in the primary care setting, with patients with mild and moderate airway obstruction as the most frequently attended by GPs. At the moment, there is no clear recommendation for antibiotic treatment for these patients. These facts underline the need for this thesis, sufficiently powered, randomised, placebo-controlled trial of antibiotics for mild-to-moderate acute exacerbations of COPD.

The present thesis is therefore clearly justified. Despite the fact that evidence for antibiotic prescription for exacerbations of non-severe COPD is not compelling, antibiotics are widely prescribed in this condition. GPs are confirmed in their habit of antibiotic prescription because most outpatients with mild-to-moderate exacerbations recover within 2 weeks. Yet they do not seem to be aware of the natural recovery rate that is, without antibiotics, in these patients, which is 80% or more and equal to that in patients receiving placebo (*Puhan MA et al, 2007*). Furthermore, recent American College of Physicians/American College of Chest Physicians guidelines for COPD exacerbations alerts about the generalised use of broad-spectrum antibiotics (*Bach PB, 2001*). Undoubtedly, as stated in the systematic reviews published so far, we need to enlarge our evidence base for the treatment of exacerbations with placebo-controlled trials. However, as highlighted in this commentary, these trials should use contemporary end-points so that we do not miss important, clinically relevant benefits of antibiotics, not assessed by traditional end-points. This thesis tries to answers these

questions and clearly overcome the limitations of the placebo-controlled trials published so far (Table 3).

TABLE 3. Limitations of published placebo-controlled antibiotic trials in acute exacerbations of chronic obstructive pulmonary disease

Limitation of study design	Potential consequences	Proposed goal
Subjects with no underlying COPD included (non-smokers, chronic bronchitis, no spirometric validation)	Diminished overall perceived efficacy of antibiotics	To carry out studies that include only patients aged 40 or more, who are smoking or have smoked at least 10 packs-year, and need of spirometric-based diagnosis of COPD
Non-bacterial exacerbations included (bronchitis, non-smokers)	Diminished overall perceived efficacy of antibiotics	Include only COPD patients
Small number of subjects	Type 2 error	To carry out studies with good power
Inpatients only included	External validity compromised	To carry out studies that include all stages of COPD
Antibiotics are more controversial in mild-to-moderate COPD patients	Increased overall perceived efficacy of antibiotics	Include mainly non-severe COPD patients, since most of the patients are non-severe
Different definitions of exacerbation	External validity compromised	Consider the presence of at least one of the Anthonisen criteria
End-points compared at 3	Spontaneous resolution mitigates	Consider clinical outcome at the

weeks after onset	differences between arms	first week and at 10 days
Speed of resolution not measured	Clinically relevant end-point not assessed	Symptom diaries to be delivered to patients
Lack of long-term follow-up	Time to next exacerbation not assessed	Needs long-term follow-up after treatment, at least one year
Antibiotic resistance to agents with limited *in vitro* antimicrobial efficacy	Diminished overall perceived efficacy of antibiotics.	Consider only first-choice antibiotics
Systemic inflammation not consider	Persistence of systemic inflammation predicts early relapse	Consider the most important biomarkers
Concurrent therapy not controlled	Undetected bias in use of concurrent therapy	Double-blind clinical trials needed

OBJECTIVES

Principal objectives

- To evaluate the effectiveness of antibiotic therapy compared with placebo at days 9-11 in acute exacerbations of mild-to-moderate COPD
- To assess which symptoms, signs, and other variables allow identification of patients with acute exacerbations of mild-to-moderate COPD who will recover without antibiotic therapy

Secondary objectives

- To evaluate the rate of clinical success of antibiotic therapy compared with placebo at day 20
- To assess the clinical variables most associated with clinical success in both groups
- To assess the relationship between CRP concentrations and the resolution of symptoms in both groups
- To assess the relationship between sputum colour and the resolution of symptoms in both groups
- To evaluate if the presence of comorbid conditions is associated with a worse resolution of the symptoms in both groups
- To evaluate the secondary effects and adverse events in both groups
- To evaluate the speed of resolution of symptoms of antibiotic therapy compared with placebo
- To assess the utility of peak-flow determination and the variation between the basal and another determination at day 9-11 for predicting the clinical outcome in both groups
- To assess the symptom-free interval, i.e. number of days till next exacerbation in both groups

MATERIAL AND METHODS

Design

Multicentre, parallel, double-blinded placebo-controlled randomized clinical trial carried out from January 2006 to June 2011.

Study setting

Twenty-three primary care centres in Catalonia, Spain.

- Main centre: Primary Healthcare Centre Jaume I, Tarragona
- Secondary centres: Primary Healthcare Centre Les Muralles, Tarragona; Primary Healthcare Centre La Marina, Barcelona; Primary Healthcare Centre Breda-Hostalric, Beda; Primary Healthcare Centre Montilivi, Girona; Primary Healthcare Centre Reus-3, Reus; Primary Healthcare Centre Girona-3; Primary Healthcare Centre Olot, Primary Healthcare Centre Girona-4; Primary Healthcare Centre Valls Urbà, Valls; Primary Healthcare Centre Ponts; Primary Healthcare Centre Jaume Soler, Cornellà; Primary Healthcare Centre Martí Julià, Cornellà; Primary Healthcare Centre SantIldefons, Cornellà; Primary Healthcare Centre Lluís Millet, Esplugues de Llobregat; Primary Healthcare Centre Can Vidalet, Esplugues de Llobregat; Primary Healthcare Centre 17 de setembre, Prat de Llobregat; Primary Healthcare Centre Rambla, Sant Feliu de Llobregat; Primary Healthcare Centre Vallirana; Primary Healthcare Centre Sant Just Desvern; Primary Healthcare Centre Les Planes, Sant Joan; Primary Healthcare Centre Molins de Rei; and Primary Healthcare Centre Bagà

Inclusion criteria

All the following criteria had to be fulfilled:

- Patients aged 40 or older
- Smokers or ex-smokers of ten packs-year or more
- Spirometrically-based diagnosis of mild-to-moderate COPD:

- FEV_1 > 50% expected, and
- FEV_1/FVC ratio < 0.7% expected

From a post-bronchodilator lung function test performed within 24 months prior to inclusion, and

- Presence of an acute exacerbation defined as the presence of at least one of the following signs and symptoms: increase of dyspnoea, increase in sputum volume and/or increase of sputum purulence

Exclusion criteria

Any of the following criteria:

- Patients less than 40 years of age
- Severe COPD
- Bronchial asthma
- Cystic fibrosis
- Bronchiectasis of origin other than COPD
- Active neoplasm
- Tracheotomy
- Presence of radiological signs of pneumonia
- Hospital admission criteria, such as presence of confusion, respiratory rate greater than 35 breaths/minute, or respiratory failure
- Antibiotic use in the previous two weeks
- Immunosuppression or use of immunosuppressive drugs
- Hypersensitivity to beta-lactams
- Intolerance to clavulanic acid or lactose
- History of digestive intolerance to clavulanic acid
- Institutionalization in a residence
- Subjects unable to personally provide informed consent
- Difficulty to attend the programmed visits
- Non-availability of a spirometry performed over the last two years

- Those who refused to participate in the study

Measurements and interventions

The patients were randomised into two treatment groups:

- Amoxicillin and clavulanic acid, 500/125 mg three times daily for 8 days; or
- Placebo, three times daily for 8 days

Both drugs were requested to be taken after meals. The two medications were kept at room temperature and were replaced when the expiry date was reached. Subject numbers were assigned sequentially as each subject entered the study. The subjects were assigned study drug through a randomization schedule based on the randomization plan. Since this was a multicentric study a block procedure was undertaken for the assignment of each primary care centre participating in the study. The study drug was labelled with the study number and unique identification number. Since it was a double-blinded clinical trial, neither the physician nor the patient did not know the treatment administered.

The use of antithermics or analgesics, such as acetaminophen, acetylsalicylic acid or ibuprofen was allowed in cases of fever or pain, as were short-acting and long-acting β-adrenergics, anticholinergics, theophyllines, inhaled or a short course of oral corticosteroids in cases of bronchospasm and mucolytics, anti-cough and any medication that the patient may been have taken for chronic disease and which had been initiated three months prior to inclusion in the study, except for antibiotics.

Each participant had the right to withdraw study at any time. In addition, the investigator might have discontinued a participant from the study at any time if the investigator considered it necessary for any reason including ineligibility (either arising during the study or retrospective having been overlooked at screening), significant protocol deviation, significant non-compliance with treatment regimen or study requirements, the presence of an adverse effect which required discontinuation of the study medication or resulted in inability to continue to comply with study procedures, consent withdrawn, or lost to follow-up. The patient was required to return all the

medication samples not taken to the investigator. If the remaining medication was not returned, compliance was evaluated as insufficient. Compliance with the prescription was assessed on visits 2 and 3. The reason of withdrawal was recorded in the case report form [Appendix 1]. If the participant withdrawn was due to an adverse effect, the investigator general practitioner was asked to arrange the follow-up visits or phone calls until the adverse effect has resolved.

Outcome variables

Primary endpoints

Efficacy of treatment at day 9-11. Clinical response was defined as follows:

- Cure: disappearance of the acute signs and symptoms related to the infection, with complete return to the previous situation of stability
- Improvement: non-complete resolution of the symptoms
- Failure: insufficient reduction in the signs and symptoms of infection

Clinical success was considered when either cure or improvement was observed. In cases of clinical deterioration the medical investigator was asked to open the randomization code and evaluate the need for hospitalization or prescribe another antibiotic according to his/her clinical judgement.

The situations in which treatment with antibiotics of exacerbations of mild to moderate COPD is not necessary was analysed by means of multivariate logistic regression with all the cases not treated with antibiotics.

Secondary endpoints

The secondary outcome variables considered in this thesis were the following:

- Efficacy of the treatment at day 20 (visit 4). The same outcomes were considered: cure, defined as the disappearance of the acute signs and symptoms related to the infection (complete return to the previous situation of stability), improvement,

defined as the non-complete resolution of the symptoms and failure, with an insufficient reduction in the signs and symptoms of infection. Clinical success was considered when either cure or improvement was observed

- CRP concentration on capillary blood assessed in the first visit, with Orion Diagnostica apparatus QuikRead CRP®. All the primary healthcare centres were provided with this device. All the participants undertook a workshop about how the procedure is performed and they were all given a summary chart [Appendix 2]. This apparatus is able to give the CRP result in approximately three minutes after the blood has been taken. The patients were invited to undertake this test once they were fully informed about the procedure and the interpretation of the results. The procedure was carried out following the recommendations of the manufacturer
- Adverse events observed in both groups, assessed in visits 2, 3 and 4 and were ranked by intensity (mild, moderate, severe and serious) and relationship to the study medication
- Time of symptom resolution by means of the symptom diaries and reduction in the total daily score of the symptom diary (visit 3). This diary was given to the patient by the participating physician in visit 1. This diary was developed by the investigators of this study based on the description of Woolhouse et al (*Woolhouse IS et al, 2001*) and was aimed at collecting the symptoms by the patient every day before bedtime during the following eight days [Appendix 3]. The diary card consisted of nine items: general well-being graded from 0 (excellent) to 4 (bad), breathing from 0 (excellent) to 4 (bad), cough from 0 (occasionally) to 3 (persistently), sputum consistence from 0 (watery) to 3 (solid), sputum colour from 0 (colourless) to 2 (green colour), volume of sputum from 0 (none) to 4 (cupful or more), if the patient had taken the pill given or not (0-1), daytime symptoms – impact of respiratory symptoms on ability to perform normal daily activities– from 0 (none) to 5 (unable to perform normal daily activities), and return to the basal status or not (0-1). The sum of the different items was only taken into account in cases in which all had been scored. The score given by the patient to each item for the diary card was used in the analysis. In addition, a total diary card score was obtained by adding all of the individual scores together and ranged from 0 (best) to

27 (worse). In cases of failure the diaries were considered to be completed if the patient filled out at least two days, considering the score of day 8 the last one that the patient was able to filled in. In case of improvement or cure, the diaries were considered to be completed if the patient filled in the eight days. In case of partially incomplete diaries the physicians were instructed to help the patients to filled them out when they returned them

- Peak-flow measurements on days 1 and 9-11 and variation between both observations. The best measurement out of three determinations was only taken into account. All the investigators were requested to proceed to performed these determinations uniformly [Appendix 4]
- Time until next exacerbation in days. Patients were monitored over a period of 365 days on a three-monthly base. When patients could not attend this scheduled visit, they were contacted by telephone. Patients were instructed to contact the physician immediately if there was any change in their health status. Diagnosis of a new exacerbation was based on the same clinical criteria as the previous. In agreement with the studies of Chodosh et al and Lode et al (*Chodosh S et al, 1998; Lode H et al, 2004*) all clinical failures during the study therapy were counted as zero exacerbation-free interval days. For patients with no new exacerbation during the 1-year observation period, the time till next exacerbation was considered to be the number of days that had elapsed between the index exacerbation and the time point of the last information available (censored data). In all other cases, the number of days that had elapsed between the onset of exacerbation was taken into account. For calculation, the onset of an exacerbation was considered the day of medical attendance reported by the patient.

Schedule of visits

The schedule of visits was the following:

- Visit 1, randomization. On fulfilling the inclusion criteria the nature of the study was explained to the patient and informed consent was requested. The study scheme and the visit program were also explained to the patient. The patients

were randomized to either of the two treatment groups and the medication given. On this visit a peak flow measurement and a CRP rapid test were performed. Physicians were instructed to request a chest X-ray in case of suspected pneumonia; more specifically, they all were instructed to order this procedure in case of suspected abnormalities on chest auscultation, temperature > 38ºC, and/or CRP > 20 mg/l. In case of a radiological image compatible with pneumonia the patient was excluded of the study. In addition, a symptom diary was given as was an explanation as to how to fill it in

- Visit 2, follow up visit at 2-4 days. On this visit worsening of the clinical evolution of the symptoms and signs situation of the patient was evaluated and, in the case of worsening of the symptoms, hospital referral or the administration of antibiotic treatment was considered. Likewise, compliance and possible secondary effects of the treatment were evaluated
- Visit 3, follow up visit at 9-11 days. On this visit the clinical efficacy was assessed and in the case of failure, hospital referral or the administration of antibiotic treatment was considered. A review of adherence to the study drug and an evaluation of the presence of side effects and adverse effects were also evaluated. On this visit a peak flow measurement was carried out. The symptom diary was collected. In case of a partially incomplete diary the physician was instructed to help the patients to filled it out in this visit
- Visit 4, follow-up visit at day 20.On this visit, efficacy of the treatment was reassessed and in case of failure, hospital referral or the administration of antibiotic treatment was considered. The patients were instructed to contact again in case of a new exacerbation
- Visit 5, follow-up visit at month 3. The patient was asked to attend a visit at month 3 after being included. When the patient could not attend a scheduled visit a contact by phone was done. Diagnosis of a new exacerbation was based on the same clinical criteria as the previous
- Visit 6, follow-up visit at month 6. The patient was asked to attend a visit at month 6 after being included. When the patient could not attend a scheduled visit a contact by phone was done. Diagnosis of a new exacerbation was based on the same clinical criteria as the previous

TABLE 4. Schedule of events

	Visit 1 Day 0	Visit 2 Day 2-4	Visit 3 Day 9-11	Visit 4 Day 20	Visit 5 Day 90	Visit 6 Day 180	Visit 7 Day 270	Visit 8 Day 365
Informed consent form	x							
Medical history	x	x	x					
Randomization	x							
C-reactive protein	x							
Chest X-ray	x (1)							
Peak flow	x		x					
Hand-out of the symptom diary	x							
Adverse reactions assessment		x	x	x				
Evaluation of clinical evolution		x	x	x				
Review of adherence		x	x					
Collection of symptom diary			x					
Time till next exacerbation (2)					x	x	x	x

(1) In case of suspected pneumonia on clinical grounds

(2) These visits could be carried out by phone

- Visit 7, follow-up visit at month 9. The patient was asked to attend a visit at month 9 after being included. When the patient could not attend a scheduled visit a contact by phone was done. Diagnosis of a new exacerbation was based on the same clinical criteria as the previous
- Visit 8, follow-up visit ay day 365. The patient was asked to attend a visit at the first year after being included. When the patient could not attend a scheduled visit a contact by phone was done. Diagnosis of a new exacerbation was based on the same clinical criteria as the previous

A summary of the events performed in this thesis is more clearly described in table 4.

Variables

- Sociodemographic and toxic habits: date of birth, gender, smoking status, and packs-year
- Comorbidities: diabetes, heart failure, high blood pressure, ischemic heart disease, others
- Chronic treatment: short-acting β-adrenergics, long-acting β-adrenergics, inhaled corticosteroids, theophyllines, oral corticosteroids, anticholinergics
- Colour of the sputum: uncoloured, yellowish or yellowish-green
- Clinical manifestations of the patient: increase of dyspnoea, increase in sputum volume and/or increase of sputum purulence, fever (temperature > 38ºC)
- Type of exacerbation: I, II or III, depending on the presence or not of the Anthonisen criteria (*Anthonisen NR et al, 1987)*
- Concentration of CRP in capillary blood
- Lung function parameters: FEV_1 in ml and %, CVF in ml and %, FEV_1/FVC ratio in %
- Chest X-ray: was considered positive if there is any complication such as pulmonary consolidation (in which case, the patient is excluded from the study) or negative
- Symptom diary: nine items were evaluated: general well-being, breathing, cough, sputum consistence, sputum colour, volume of sputum, if the patient had taken the pill given or not, daytime symptoms, and return to the basal status or not

- Treatment administered by the physician: mucolytics or expectorants, bronchodilatadors, oral corticosteroids, antitussives, analgesics, antithermics
- Efficacy outcomes: cure, improvement or failure
- Adverse events which might have been appeared in both treatment arms
- Number of days till next exacerbation

Statistical analysis

The intention-to-treat (ITT) population included all randomized patients receiving at least one dose of study drug and the per-protocol (PP) population included patients with received no systemic antimicrobial agents other than study drug for at least three days in the case of clinical failure or ≥ 80% of study medication in case of cure, with adequate documentation of compliance and absence of major protocol violations.

For the sample size calculation, we accepted a null hypothesis if the cure rate in the intervention group was the same or ± 7% as that observed in the placebo arm. Based on the literature, the expected rate of cure among patients assigned to antibiotic therapy is 90%. For an alpha of 0.05 and a beta of 0.2 and accepting possible losses of 15%, we calculated that the sample size is 667 patients in total.

Bivariate analysis was performed with comparison of proportions of the different outcomes between both groups of treatment using the chi-square test and the Student t was used to assess the relationship between quantitative variables for both independent and paired data. Only p values less than 0.05 were considered as statistically significant. To further evaluate the prognostic usefulness of the Anthonisen criteria based on dichotomous classification for both physicians with CRP and without CRP accessibility, we considered receiver operating characteristic (ROC) curve analysis. For each ROC curve, we calculated the area under the curve (AUC), which ranges from 0.5 (for a non-informative marker) to 1 (for a perfect marker). Bootstrap method was used to calculate the confidence intervals for AUC. Another ROC curve aimed at analysing the trade-off between the false negative and false positive rates across a series of cut-off points of CRP concentration was carried out, calculating the Youden index.

A logistic regression model was constructed to identify the variables independently associated with clinical outcome by means the use of ORs.The variables were included in the model if they were associated with a high score with a p of less than 0.10 and were subsequently eliminated from the model using the stepwise automatic variable screening method, the alpha thresholds for inclusion and exclusion being set at 0.20. In addition, to analyse the time until the next exacerbation a survival analysis was carried out using the Kaplan-Meier method. The Wilcoxon test and log-rank test were applied to compare the survival curves for each study drug group.

Ethical considerations

Approval was previously obtained from the Ethical Committee of Investigation in Primary Care (*Fundació d'Investigació en Atenció Primària*) [Appendix 5]. This study has been conducted in accordance with the principles of the Declaration of Helsinki and in full conformity with relevant regulations. The study has obtained a grant from the *Fondo de Investigación Sanitaria* of the Ministry of Health [Appendix 6] and has been registered in the ClinicalTrials.govdatabase (ID number NCT00495586).

All the participants were recruited by the physicians in the different health care centres and personally signed and dated the latest approved version of the informed consent form before any study specific procedures were performed [Appendix 7]. Informed consent was requested from all the participants in the study, respecting subject autonomy in their decision. To achieve this, the medical investigators read the informed consent sheet to the patients and clarified any doubt which might have been arising during the reading. Thereafter, patient comprehension of the information was always determined and, in the case of acceptation to participate, the patient was asked to sign the form. The participants were free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The participants were allowed as much time as wished to consider the information, and the opportunity to question their general practitioners or other independent parties to decide whether they would have participated in the study. The different physicians who obtained the consent were suitably qualified and

experienced, and were authorized to do so by principal Investigator. A copy of the signed informed consent was given to the participants. The original signed form was retained at the study site.

This study did not require the use of unusual, additional tests: only a chest X-ray was undertaken to rule out a pneumonic process and both a peak flow measurement and a CRP determination during the visit to know the severity of the infection, being tests that were total justified in this project. From an ethical point of view, this is to certify that the objective of this study has been important and relevant for primary care, the power of the study has been considered as reasonable, this is an original study, the risks which the participants might have been incurred justify the investigation being carried out with a totally favourable benefit/risk quotient, and the external validity of the study to the primary care reality can be ensured, with the inclusion and exclusion criteria described. Vulnerable populations were not participating in this study and neither was economic compensation being given to patients for their participation. The investigators are free to publish the results of this study, regardless of the results obtained. The anonymity and confidentiality of the data can be guaranteed and the protocol of the study safeguarded that in results of the study all the participants and their individual results have been taken into account. Participants were identified only by a participant ID number on the case report form. The privacy of the participants has been therefore protected and with the randomized design of the study the subjects were equally invited to participate and that the possible benefits or adverse effects of the investigation were equally shared among all the participants. All documents have been stored securely and only accessible by trial staff and authorized personnel.

RESULTS

Descriptive results

During the course of 5.5 years, 353 subjects were included in the study. Forty-three patients were excluded as they did not fulfil the inclusion criteria. The main reasons for exclusion were not having a spirometric diagnosis of mild-to-moderate COPD (32 cases) and refusing to take part in the study or their follow-up data were incomplete (8 cases). A chest x-ray was ordered in 64 cases; of which, three were positive for consolidation and were therefore excluded from the study (Figure 2).

Three hundred ten (158 patients in the amoxicillin and clavulanic acid arm and 152 patients in the placebo arm) fulfilled all the criteria for efficacy analysis and constituted the ITT population. Only two patients in the amoxicillin and clavulanic acid arm failed to comply with the medication and ere excluded from the PP population (Figure 2). A total of 161 patients were included in the main primary healthcare centre (51.9%), where seven general practitioners finally recruited at least one patient. Other thirty physicians from other twenty-two primary healthcare centres recruited at least one patient.

As is shown in table 5, the mean age was 68.1 ± 10.4 years and 251 were male (81%). Despite the fact of observing more male patients among those assigned to the intervention group no statistically differences were observed. The mean packs-year observed was 38.1 ± 18 and a total of 175 patients were current smokers when they were included in the study (56.5%), being former smokers the rest of the sample. The comorbid condition more often associated was the high blood pressure since 137 patients were recorded to have hypertension at the time of recruitment (44.2%), followed by diabetes mellitus, with 57 patients (18.4%), No differences were found between the two groups regarding these variables.

Concerning previous therapy for COPD the pharmacological groups more commonly taken were the anticholinergics (107 cases, 34.5%) followed by the inhaled corticosteroids (88 cases, 28.4%), the short-acting β-adrenergics (71, 22.9%) and the long-acting β-adrenergics (69, 22.3%). As is set out in the table 6, few patients were previously taken either oral corticosteroids or theophyllines. No differences were found between the two groups regarding these variables.

FIGURE 2. Flow of patients throughout the study

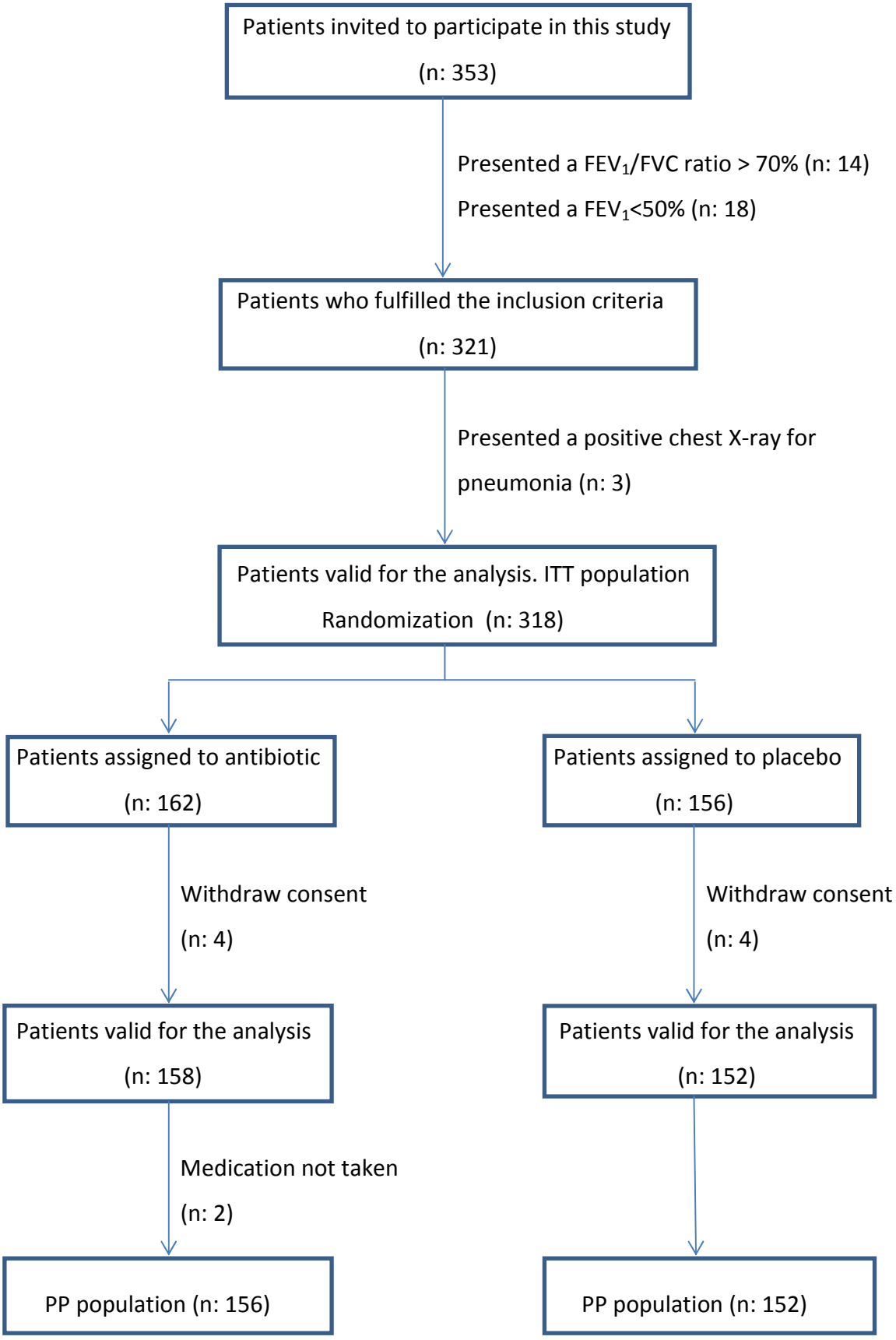


TABLE 5. Sociodemographic and comorbid conditions of the whole sample and depending on the group treatment

	Antibiotic (n: 158)	Placebo (n: 152)	Total (n: 310)	p
Age (years), mean (SD)	68.4 (9.9)	67.8 (11.0)	68.1 (10.4)	NS
Male sex, n (%)	132 (83.5)	119 (78.3)	251 (81.0)	NS
Smoking status:				
- **Current, n (%)**	86 (54.4)	89 (58.6)	175 (56.5)	
- **Former, n (%)**	72 (45.6)	63 (41.4)	135 (43.5)	NS
Packs-year, mean (SD)	38.3 (16.9)	37.9 (19.2)	38.1 (18.0)	NS
High blood pressure, n (%)	64 (40.5)	73 (48.0)	137 (44.2)	NS
Diabetes mellitus, n (%)	29 (18.4)	28 (18.4)	57 (18.4)	NS
Heart failure, n (%)	2 (1.3)	3 (2.0)	5 (1.6)	NS
Coronary heart disease, n (%)	15 (9.5)	19 (12.5)	34 (11.0)	NS

SD: standard deviation; NS: non-significant

TABLE 6. Previous treatment taken by the patients recruited in the study and depending on the treatment group

	Antibiotic (n: 158)	Placebo (n: 152)	Total (n: 310)	p
Short-acting β-adrenergics, n (%)	35 (22.2)	36 (23.7)	71 (22.9)	NS
Long-acting β-adrenergics, n (%)	37 (23.4)	32 (21.1)	69 (22.3)	NS
Anticholinergics, n (%)	55 (34.8)	52 (34.2)	107 (34.5)	NS
Theophyllines, n (%)	2 (1.3)	2 (1.3)	4 (1.3)	NS
Oral corticosteroids, n (%)	1 (0.6)	2 (1.3)	3 (1.0)	NS
Inhaled corticosteroids, n (%)	46 (29.1)	42 (27.6)	88 (28.4)	NS

SD: standard deviation; NS: non-significant

TABLE 7. Lung function variables, peak flow measurement and classification of COPD of the patients included in the study and depending on the treatment group

	Antibiotic (n: 158)	Placebo (n: 152)	Total (n: 310)	p
FVC (ml), mean (SD)	2,753.4 (851.5)	2,763.4 (955.5)	2,758.3 (902.5)	NS
FVC (%), mean (SD)	70.2 (15.8)	71.5 (18.3)	70.8 (17.1)	NS
FEV_1 (ml), mean (SD)	1,709.6 (548.6)	1,722.3 (641.5)	1.715.8 (595.0)	NS
FEV_1 (%), mean (SD)	64.2 (11.8)	65.9 (12.1)	65.0 (11.9)	NS
FEV_1/FVC ratio, mean (SD)	62.3 (6.0)	62.2 (5.8)	62.2 (5.9)	NS
COPD classification:				
- **Mild, n (%)**	15 (9.5)	20 (13.2)	35 (11.3)	
- **Moderate, n (%)**	143 (90.5)	132 (86.8)	275 (88.7)	NS
Basal peak-flow (l/min), mean (SD)	225.3 (83.6)	227.6 (81.9)	226.4 (82.4)	NS

SD: standard deviation; NS: non-significant; FVC: forced vital capacity; ml: millilitres; FEV_1: forced expiratory volume in one second; l/min: litres/minute

Table 7 describes the lung function variables observed in the spirometric study performed within the previous twenty-four months in all the patients included and depending on the treatment group. Both FVC and FEV_1, both measured in ml, were slightly worse among patients assigned to amoxicillin and clavulanic acid but these differences were not clinically relevant. No statistically significant differences were observed between both groups in terms of % predicted. The mean FEV_1 of the whole sample was 65 ± 11.9%. Only 35 patients were classified as mild COPD (11.3%) since they had a FEV1 of 80% or more. Conversely, most of the patients had a moderate COPD (275 cases; 88.7%). The basal peak-flow was also similar in both groups; with an overall mean of 226.4 l/min.

TABLE 8. Characteristics of the exacerbations of the patients included in the study and depending on the treatment group

	Antibiotic (n: 158)	Placebo (n: 152)	Total (n: 310)	p
Increase of the sputum volume, n (%)	125 (79.1)	117 (77.0)	242 (78.1)	NS
Increase of dyspnoea, n (%)	109 (69.0)	98 (64.5)	207 (66.8)	NS
Sputum colour:				
- **Uncoloured, n (%)**	73 (46.2)	53 (34.9)	126 (40.6)	
- **Yellowish, n (%)**	36 (22.8)	46 (30.3)	82 (26.5)	
- **Yellow-greenish, n (%)**	49 (31.0)	53 (34.9)	102 (32.9)	NS
Sputum purulence, n (%)	85 (53.8)	99 (65.1)	184 (59.4)	<0.05
Fever, n (%)	11 (7.0)	14 (9.2)	25 (8.1)	NS
Type of exacerbation*:				
- **Type I, n (%)**	40 (25.3)	45 (29.6)	85 (27.4)	
- **Type II, n (%)**	81 (51.3)	72 (47.4)	153 (49.4)	
- **Type III, n (%)**	37 (23.4)	35 (23.0)	72 (23.2)	NS
Drugs administered or adjusted for the exacerbation:				
- **Short-acting β-adrenergics, n (%)**	54 (34.2)	53 (34.9)	107 (34.5)	NS
- **Oral corticosteroids, n (%)**	26 (16.5)	27 (17.8)	53 (17.1)	NS
CRP, median (IQR)	18 (35)	17 (23)	18 (31)	NS

SD: standard deviation; NS: non-significant; CRP: C-reactive protein; IQD: interquartiile range

*Type I: all the Anthonisen criteria present (increased dyspnoea, increased sputum volume and purulent sputum); type II: only two criteria present; type III: only one criterion present

Table 8 describes the symptoms and signs of the exacerbations, their type and the characteristics of the sputum. More patients assigned to placebo had their sputum purulent, with differences that were statistically significant (65.1% of the patients

assigned to placebo group vs. 53.8% of the patients allocated to the intervention group; p<0.05). However, concerning the other Anthonisen criteria, their presence was slightly greater among patients assigned to the intervention therapy (79.1% vs. 77% had an increase of the sputum volume and 69% vs. 64.5% presented an increase of the dyspnoea). When the variable of sputum colour was classified in three categories, this difference disappeared. Concerning treatment adjusted or given for the exacerbation, β-adrenergics were given or adjusted in 107 patients (34.5%) and oral corticosteroids were taken by 53 patients (17.1%), without differences between the two treatment groups. In fact, only 26 patients assigned to antibiotic (16.5%) and 27 assigned to placebo group (17.8%) were given oral corticosteroid therapy for the acute exacerbation.

A total of 85 patients had type I exacerbations (27.4%) and 153 were type II (49.4%). The table also shows the drugs administered or adjusted for the exacerbation and the CRP concentrations during the basal visit to the physician. Since CRP was not a normally-distributed variable, the median and the interquartile range are presented instead. No differences were found between the two groups regarding the variables analysed.

Main outcome results

Primary outcome: clinical outcome at day 9-11

In the ITT population, a total of 117 patients assigned to the intervention group (74.1%) and 91 to control group (59.9%) were considered cured by their general practitioners at the end of therapy (p<0.05) (Table 9). Twenty-six patients assigned to amoxicillin and clavulanic acid and thirty-two patients assigned to placebo group presented an improvement. On the other hand, clinical failure was observed in 15 patients who received antibiotic therapy (9.5%) and in 29 patients assigned to placebo (19.1%). In the PP population we found similar results (75 vs. 59.9%, respectively, p<0.01). Clinical success, i.e, those with cure or improvement, was also greater in the intervention group compared with placebo (90.5% vs. 80.9%; p<0.05).

TABLE 9. Summary of clinical efficacy results at day 9-11 in both study groups

	ITT population			PP population		
	Antibiotic n/total (%)	Placebo, n/total (%)	p	Antibiotic, n/total (%)	Placebo, n/total (%)	p
Clinical cure at day 9-11	117/158 (74.1)	91/152 (59.9)	0.016	117/156 (75.0)	91/152 (59.9)	0.007
Clinical success at day 9-11	143/158 (90.5)	123/152 (80.9)	0.022	143/156 (91.7)	123/152 (80.9)	0.008

ITT: intention to treat, PP: per protocol

Comparison of the results depending of clinical success on day 9-11

The next tables (10 - 13) show the different results obtained depending on the clinical outcome.

More patients with both high blood pressure and coronary heart disease were observed among patients who had a worse outcome. However, the number of diabetic patients was similar among patients with good and bad clinical outcome (Table 10). Age and gender were not associated with a worse clinical outcome. Neither the smoking status nor the number of pack-years was associated as is shown in this table.

Concerning the basal treatment of the patients included in this study no differences were observed between those who had a clinical success and those who failed (Table 11). Only the use of anticholinergics was greater among those who failed compared with the patients who had a positive outcome ($p<0.05$). Even though all the patients who received teophyllines and oral corticosteroids were observed among those with clinical success at the end of the treatment, no statistically differences were observed between those who had a favourable and those with an unfavourable evolution of the exacerbations, since the figures were very low.

TABLE 10. Sociodemographic and comorbid conditions depending of the clinical success on day 9-11

	Success (n: 266)	Failure (n: 44)	Total (n: 310)	p
Age (years), mean (SD)	68.2 (10.4)	67.2 (10.5)	68.1 (10.4)	NS
Male sex, n (%)	214 (80.5)	37 (84.1)	251 (81.0)	NS
Smoking status:				
- **Current, n (%)**	148 (55.6)	27 (61.4)	175 (56.5)	
- **Former, n (%)**	118 (44.4)	17 (38.6)	135 (43.5)	NS
Packs-year, mean (SD)	37.5 (18.2)	41.3 (16.5)	38.1 (18.0)	NS
High blood pressure, n (%)	112 (42.1)	25 (56.8)	137 (44.2)	<0.05
Diabetes mellitus, n (%)	48 (18.0)	9 (20.5)	57 (18.4)	NS
Heart failure, n (%)	5 (1.9)	0 (-)	5 (1.6)	NS
Coronary heart disease, n (%)	25 (9.4)	9 (20.5)	34 (11.0)	<0.05

SD: standard deviation; NS: non-significant

TABLE 11. Previous treatment taken by the patients recruited in the study depending of the clinical success on day 9-11

	Success (n: 266)	Failure (n: 44)	Total (n: 310)	p
Short-acting β-adrenergics, n (%)	61 (22.9)	10 (22.7)	71 (22.9)	NS
Long-acting β-adrenergics, n (%)	56 (21.1)	13 (29.5)	69 (22.3)	NS
Anticholinergics, n (%)	86 (32.3)	21 (47.7)	107 (34.5)	<0.05
Theophyllines, n (%)	4 (1.5)	0 (-)	4 (1.3)	NS
Oral corticosteroids, n (%)	3 (1.1)	0 (-)	3 (1.0)	NS
Inhaled corticosteroids, n (%)	72 (27.1)	16 (36.4)	88 (28.4)	NS

SD: standard deviation; NS: non-significant

Table 12 shows the results of the lung function between these two groups. The FEV_1 was lower among patients who failed (65.3% predicted vs. 63.3% among patients who had a clinical success) but the differences were not statistically significant. Curiously, the mean basal peak-flow measurement was slightly better among those assigned to the control group, since they had a mean of 236.7 l/min (vs. 224.7 l/min observed in the intervention group). Similarly, the percentage of patients with mild COPD was slightly greater among those with favourable evolution while the percentage of moderate COPD was slightly greater among those who had a clinical failure (Table 12).

TABLE 12. Lung function variables, peak flow measurement and classification of COPD of the patients included in the study depending of the clinical success on day 9-11

	Success (n: 266)	Failure (n: 44)	Total (n: 310)	p
FVC (ml), mean (SD)	2,763.5 (893.1)	2,727.0 (967.8)	2,758.3 (902.5)	NS
FVC (%), mean (SD)	70.7 (16.7)	71.6 (19.3)	70.8 (17.1)	NS
FEV_1 (ml), mean (SD)	1,721.8 (590.2)	1,680.0 (629.6)	1.715.8 (595.0)	NS
FEV_1 (%), mean (SD)	65.3 (11.7)	63.3 (12.4)	65.0 (11.9)	NS
FEV_1/FVC ratio, mean (SD)	62.3 (6.0)	61.5 (5.5)	62.2 (5.9)	NS
COPD classification:				
- **Mild, n (%)**	31 (11.7)	4 (9.1)	35 (11.3)	
- **Moderate, n (%)**	235 (88.3)	40 (90.9)	275 (88.7)	NS
Basal peak-flow (l/min), mean (SD)	224.7 (80.9)	236.7 (92.9)	226.4 (82.4)	NS

SD: standard deviation; NS: non-significant; FVC: forced vital capacity; ml: millilitres; FEV_1: forced expiratory volume in one second; l/min: litres/minute

The percentage of patients with increase of dyspnoea was significantly greater among those who failed ($p<0.05$). Similarly, more patients with purulent sputum were found

among those who presented a clinical failure at day 9-11 (p<0.05). In fact, among patients with clinical failure more than half had green sputum while 43.2% of those with good clinical outcome the sputum were uncoloured (p<0.05) (Table 13). More patients taking oral corticosteroids were observed among patients with therapeutic failure even though the differences were not found to be statistically significant.

TABLE 13. Characteristics of the exacerbations of the patients included in the study depending of the clinical success on day 9-11

	Success (n: 266)	Failure (n: 44)	Total (n: 310)	p
Increase of the sputum volume, n (%)	204 (76.7)	38 (86.4)	242 (78.1)	NS
Increase of dyspnoea, n (%)	172 (64.7)	35 (79.5)	207 (66.8)	<0.05
Sputum colour:				
- **Uncoloured, n (%)**	115 (43.2)	11 (25.0)	126 (40.6)	
- **Yellowish, n (%)**	72 (27.1)	10 (22.7)	82 (26.5)	
- **Yellow-greenish, n (%)**	79 (29.7)	23 (52.3)	102 (32.9)	<0.05
Sputum purulence, n (%)	151 (56.8)	33 (75.9)	184 (59.4)	<0.05
Fever, n (%)	23 (8.6)	2 (4.5)	25 (8.1)	NS
Type of exacerbation:				
- **Type I, n (%)**	65 (24.4)	20 (45.5)	85 (27.4)	
- **Type II, n (%)**	131 (49.2)	22 (50.0)	153 (49.4)	
- **Type III, n (%)**	70 (26.3)	2 (4.5)	72 (23.2)	<0.001
Drugs administered or adjusted for the exacerbation:				
- **Short-acting β-adrenergics, n (%)**	93 (35.9)	14 (31.8)	107 (34.5)	NS
- **Oral corticosteroids, n (%)**	43 (16.2)	10 (22.7)	53 (17.1)	NS
CRP, median (IQR)	16 (23)	50 (49)	18 (31)	<0.001

SD: standard deviation; NS: non-significant; CRP: C-reactive protein; IQR: interquartiile range

In the following tables a differentiation between those assigned to the different treatment groups is presented. In these tables the clinical success is presented (cure + improvement). Table 14 shows the demographic and comorbidities presented depending on the clinical success on day 9-11 and the treatment group. Curiously, patients of intervention group who failed were younger than those who had a clinical success and on the contrary, among patients not treated with antibiotics those who failed were slightly older. Among those who failed there were more women in the intervention group and more men in the control group. The most striking figures corresponded to the percentage of patients with comorbidities who failed. In fact, the percentage of high blood pressure and coronary heart disease were much greater than the observed percentages among both intervention and control groups who had favourable evolution.

TABLE 14. Sociodemographic and comorbid conditions depending of the clinical success on day 9-11 and the treatment group

	Antibiotic (n: 158)		Placebo (n: 152)	
	Success (n: 143)	Failure (n: 15)	Success (n: 123)	Failure (n: 29)
Age (years), mean (SD)	69.0 (9.8)	62.3 (9.7)	67.4 (11.2)	69.7 (10.2)
Male sex, n (%)	120 (83.9)	12 (80.0)	94 (76.4)	25 (86.2)
Smoking status:				
- **Current, n (%)**	76 (53.1)	10 (66.7)	72 (58.5)	17 (58.6)
- **Former, n (%)**	67 (46.9)	5 (33.3)	51 (41.5)	12 (41.4)
Packs-year, mean (SD)	38.3 (17.0)	37.4 (15.9)	36.6 (19.6)	43.3 (16.7)
High blood pressure, n (%)	57 (39.9)	7 (46.7)	55 (44.7)	18 (62.1)
Diabetes mellitus, n (%)	24 (16.8)	5 (33.3)	24 (19.5)	4 (13.8)
Heart failure, n (%)	2 (1.4)	0 (-)	3 (2.4)	0 (-)
Coronary heart disease, n (%)	13 (9.1)	2 (13.3)	12 (9.8)	7 (24.1)

SD: standard deviation

TABLE 15. Previous treatment taken by the patients depending of the clinical success on day 9-11 and the treatment group

	Antibiotic (n: 158)		Placebo (n: 152)	
	Success (n: 143)	Failure (n: 15)	Success (n: 123)	Failure (n: 29)
Short-acting β-adrenergics, n (%)	35 (24.5)	0 (-)	26 (21.1)	10 (34.5)
Long-acting β-adrenergics, n (%)	32 (22.4)	5 (33.3)	24 (19.5)	8 (27.6)
Anticholinergics, n (%)	47 (32.9)	8 (53.3)	39 (31.7)	13 (44.8)
Theophyllines, n (%)	2 (1.4)	0 (-)	2 (1.3)	0 (-)
Oral corticosteroids, n (%)	1 (0.7)	0 (-)	2 (1.6)	0 (-)
Inhaled corticosteroids, n (%)	41 (28.7)	5 (33.3)	31 (25.2)	11 (37.9)

TABLE 16. Lung function variables, peak flow measurement and classification of COPD depending of the clinical success on day 9-11 and the treatment group

	Antibiotic (n: 158)		Placebo (n: 152)	
	Success (n: 143)	Failure (n: 15)	Success (n: 123)	Failure (n: 29)
FVC (ml), mean (SD)	2,725.9 (859.5)	3,016.0 (745.6)	2,807.2 (932.2)	2,577.6 (1,045.3)
FVC (%), mean (SD)	70.0 (15.9)	71.5 (15.1)	71.4 (17.6)	71.6 (21.4)
FEV_1 (ml), mean (SD)	1,687.8 (549.7)	1,918.0 (508.5)	1,761.3 (633.9)	1,556.9 (658.4)
FEV_1 (%), mean (SD)	64.3 (12.0)	63.7 (9.6)	66.5 (11.6)	63.1 (13.8)
FEV_1/FVC ratio, mean (SD)	62.1 (6.2)	63.6 (4.6)	62.6 (5.8)	60.4 (5.7)
COPD classification:				
- **Mild, n (%)**	14 (9.8)	1 (6.7)	17 (13.8)	3 (10.3)
- **Moderate, n (%)**	129 (90.2)	14 (93.3)	106 (86.2)	26 (89.7)
Basal peak-flow (l/min), mean (SD)	223.5 (83.3)	242.0 (87.0)	226.1 (78.3)	234.0 (97.2)

SD: standard deviation; l/min: litres/minute

As is described in table 15, more patients taking long-acting β-adrenergics, anticholinergics and inhaled corticosteroids were observed among both therapeutic groups who had an unfavorable evaluation on day 9-11. Among patients receiving antibiotic all the patients taking short-acting β-adrenergics cured or improved.

TABLE 17. Characteristics of the exacerbations of the patients included in the study depending of the clinical success on day 9-11 and the treatment group

	Antibiotic (n: 158)		Placebo (n: 152)	
	Success (n: 143)	Failure (n: 15)	Success (n: 123)	Failure (n: 29)
Increase of sputum volume, n (%)	112 (78.3)	13 (86.7)	92 (74.8)	25 (86.2)
Increase of dyspnoea, n (%)	95 (66.4)	14 (93.3)	77 (62.6)	21 (72.4)
Sputum colour:				
- **Uncoloured, n (%)**	65 (45.5)	8 (53.3)	50 (40.7)	3 (10.3)
- **Yellowish, n (%)**	34 (23.8)	2 (13.3)	38 (30.9)	8 (27.6)
- **Yellow-greenish, n (%)**	44 (30.8)	5 (33.3)	35 (28.5)	18 (62.1)
Sputum purulence, n (%)	78 (54.5)	7 (46.7)	73 (59.3)	26 (89.7)
Fever, n (%)	11 (7.7)	0 (-)	12 (9.8)	2 (6.9)
Type of exacerbation:				
- **Type I, n (%)**	35 (24.5)	5 (33.3)	30 (24.4)	15 (51.7)
- **Type II, n (%)**	72 (50.3)	9 (60.0)	59 (48.0)	13 (44.8)
- **Type III, n (%)**	36 (25.2)	1 (6.7)	34 (27.6)	1 (3.4)
Drugs administered or adjusted for the exacerbation:				
- **Short-acting β-adrenergics, n (%)**	50 (35.0)	4 (26.7)	43 (35.0)	10 (34.5)
- **Oral corticosteroids, n (%)**	25 (17.5)	1 (6.7)	18 (14.6)	9 (31.0)
CRP, median (IQR)	16 (32)	44 (48)	15 (17)	51 (56)

SD: standard deviation; CRP: C-reactive protein; IQD: interquartiile range

Table 16 shows the different spirometric variables for both therapeutic groups depending on the clinical outcome. The FEV_1% figures were lower among both groups who failed. Only seven patients with purulent sputum in the intervention group failed and among these patients only one was given an oral corticosteroid (Table 17). On the contrary, 26 out of 29 of patients with purulent sputum assigned to placebo failed. Those who failed in the intervention group might not have a bacterial infection.

Best CRP cut-off point for predicting clinical success with placebo

The best CRP serum cut-off point for predicting clinical success with placebo was calculated. The ROC curve obtained by plot at different cut-offs is shown in figure 3.

FIGURE 3. ROC curve of CRP for predicting clinical success among patients not treated with antibiotics

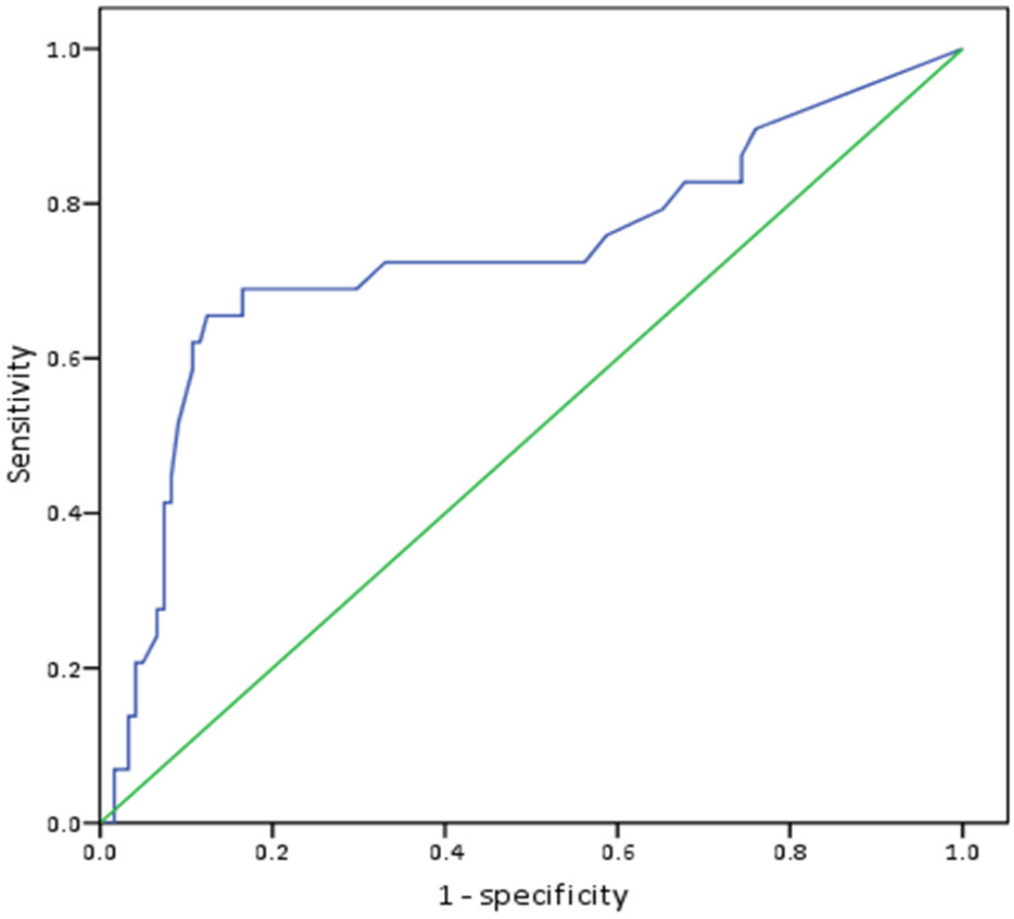


TABLE 18. Sensitivity and (1 – specificity) for CRP at different cut-off points for predicting clinical success among patients assigned to control group

CRP concentration	Sensitivity	1- specificity	Youden's index
3.0	1.000	1.000	**0.000**
10.5	0.828	0.678	**0.150**
15.5	0.724	0.479	**0.245**
20.5	0.724	0.380	**0.344**
25.5	0.690	0.231	**0.458**
30.5	0.690	0.165	**0.524**
35.0	0.655	0.140	**0.515**
37.5	0.655	0.132	**0.523**
40.0	**0.655**	**0.124**	**0.531**
42.5	0.621	0.116	**0.505**
43.5	0.621	0.107	**0.513**
45.0	0.586	0.107	**0.479**
50.0	0.517	0.091	**0.426**
60.5	0.414	0.074	**0.339**
70.0	0.241	0.066	**0.175**
80.0	0.172	0.041	**0.131**
90.0	0.069	0.033	**0.036**
107.5	0.069	0.017	**0.052**
116.5	0.034	0.017	**0.018**
141.0	0.000	0.017	**0.017**
160.0	**0.000**	**0.000**	**0.000**

CRP: C-reactive protein

The best cut-off was 40 mg/l; at this concentration, the sensitivity and specificity were 0.655 and 0.876 respectively. The area under the curve was 0.732 (95% CI: 0.614 –

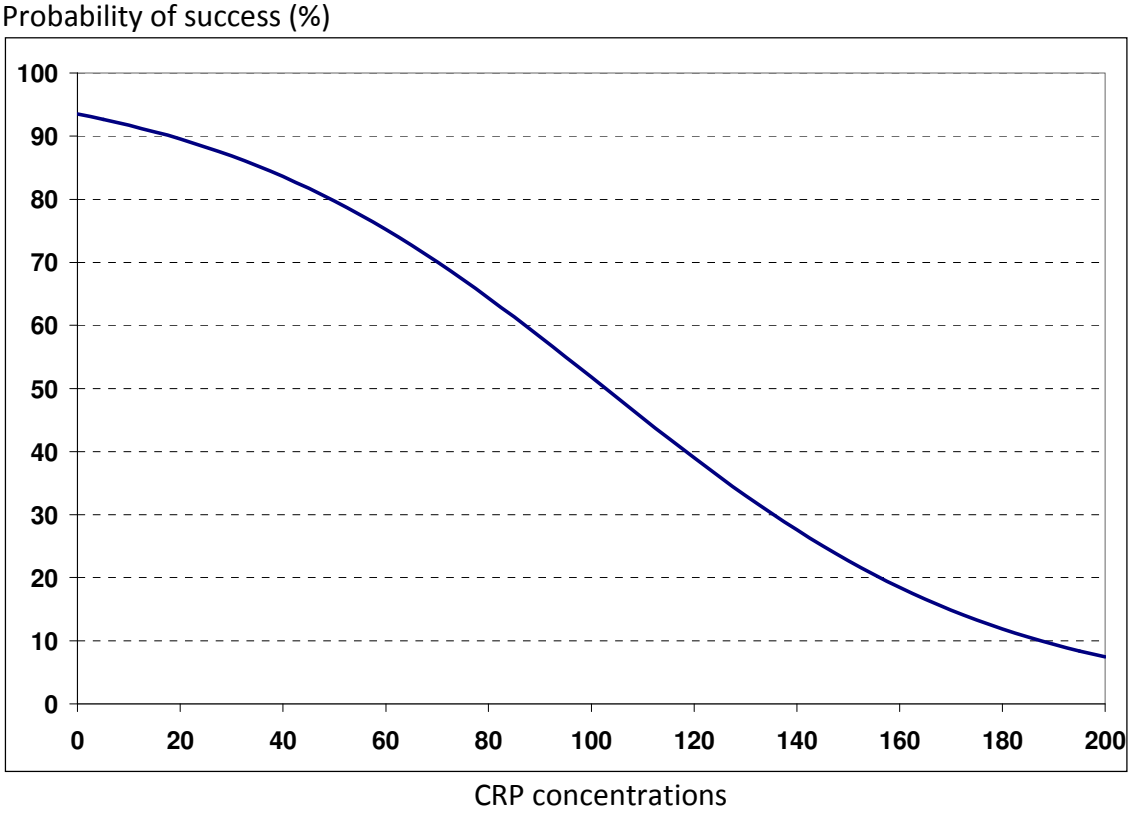
0.851), indicating that the CRP concentration is a good indicator to anticipate the clinical success of acute exacerbations of mild-to-moderate COPD not treated with antibiotics. As shown in table 19, more patients with high levels of CRP failed compared with those with concentrations lower than 40 mg/l (p<0.001). As is also shown, 77.3% of all determinations presented concentrations lower than forty.

TABLE 19. CRP concentrations depending on clinical success on day 9-11

CRP concentrations	Success	Failure	Total
< 40 mg/l	106 (87.6)	10 (34.5)	116 (77.3)
≥ 40 mg/l	15 (12.4)	19 (65.5)	34 (22.7)
Total	121 (100.0)	29 (100.0)	150 (100.0)

CRP: C-reactive protein

FIGURE 4. Probability of clinical success depending of CRP concentrations among patients not treated with antibiotics

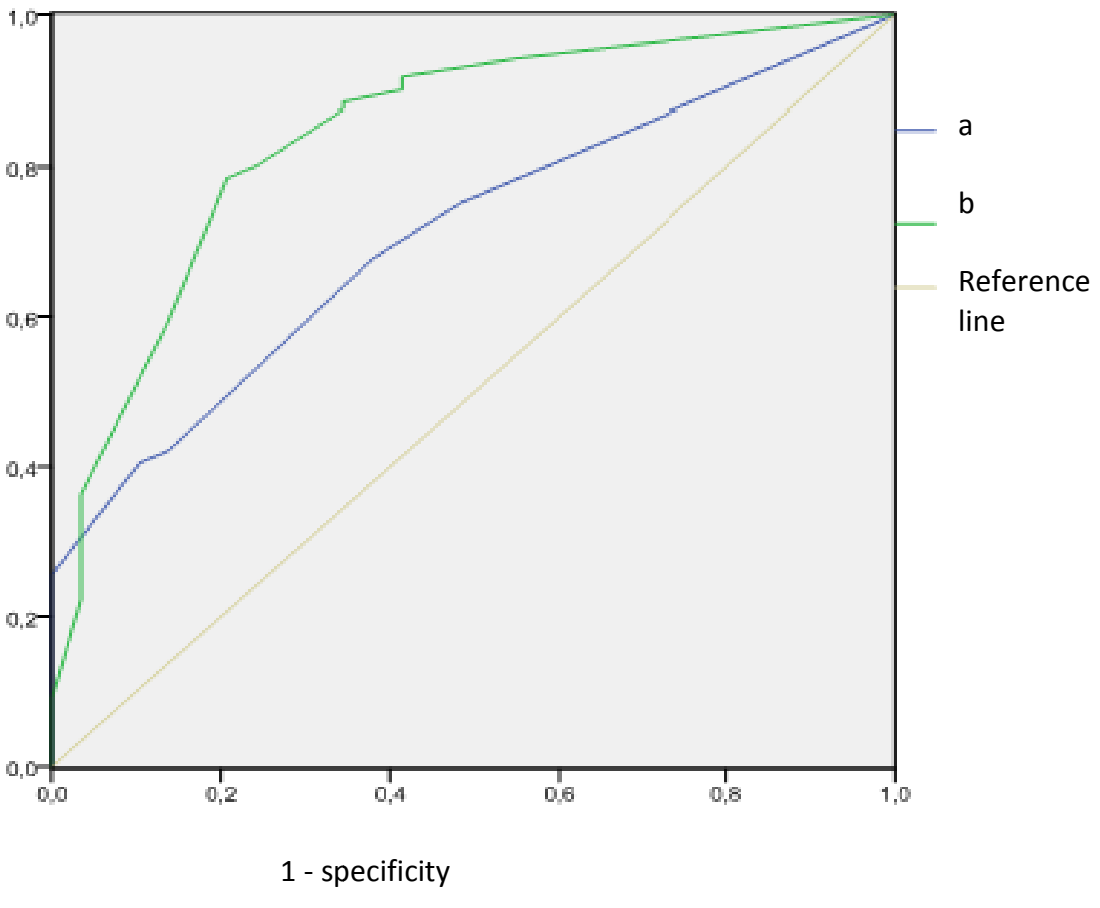


The curve represented in figure 4 clearly indicates that the highest concentrations of CRP are associated with the poorer outcomes. Conversely, when the concentrations of CRP are lower than 20 mg/l, the likelihood of clinical success exceeds 90% of the cases.

Predictive value of Anthonisen criteria for predicting clinical outcome in patients receiving placebo

The ROC curve depicted in figure 5 shows the predictive value of the Anthonisen criteria (without and with CRP) for clinical outcome at the end of therapy.

FIGURE 5. ROC curves showing the predictive value of a) the classical Anthonisen criteria and b) with the addition of another criterion (CRP ≥ 40 mg/l) for predicting clinical outcome among mild-to-moderate COPD patients with exacerbations not treated with antibiotics



When taking the classical criteria reported by Anthonisen (increase of dyspnoea, increase of sputum production and increase of purulence of sputum) into account, the AUC for predicting clinical outcome at day 9-11 was 0.708 (95% CI: 0.616 - 0.801; p: 0.001).

By adding the variable CRP ≥ 40 mg/l, the AUC rose to 0.842 (95% CI: 0.76 – 0.924; p<0.001). As is shown in figure 5, it seems from the ROC curves that considering four criteria instead of the classical Anthonisen criteria results in a significant improvement for anticipating the clinical outcome of acute exacerbations of mild-to-moderate COPD not treated with antibiotics.

Predictors for clinical failure among patients not treated with antibiotics

A multivariate logistic regression analysis was carried out in order to analyse the criteria that mostly predicted the clinical success on day 9-11 among patients not treated with antibiotics.

TABLE 20. Multivariate logistic regression analysis for predicting clinical success at day 9-11 among patients not treated with antibiotics with and without availability of CRP rapid test

Variable	Without CRP		With CRP	
	OR (95% CI)	p	OR (95% CI)	p
Increase of dyspnoea	0.4 (0.2 – 1.1)	NS	0.8 (0.3 – 2.3)	NS
Increase of sputum production	0.5 (0.2 – 1.8)	NS	1.6 (0.4 – 6.5)	NS
Increase of purulence	0.2 (0.0 – 0.6)	0.005	0.2 (0.0 – 0.7)	0.012
CRP ≥ 40 mg/l	NA	NA	0.1 (0.0 – 0.2)	<0.001

CRP: C-reactive protein; OR: odds ratio; CI: confidence interval; NS: not-significant; NA: not available

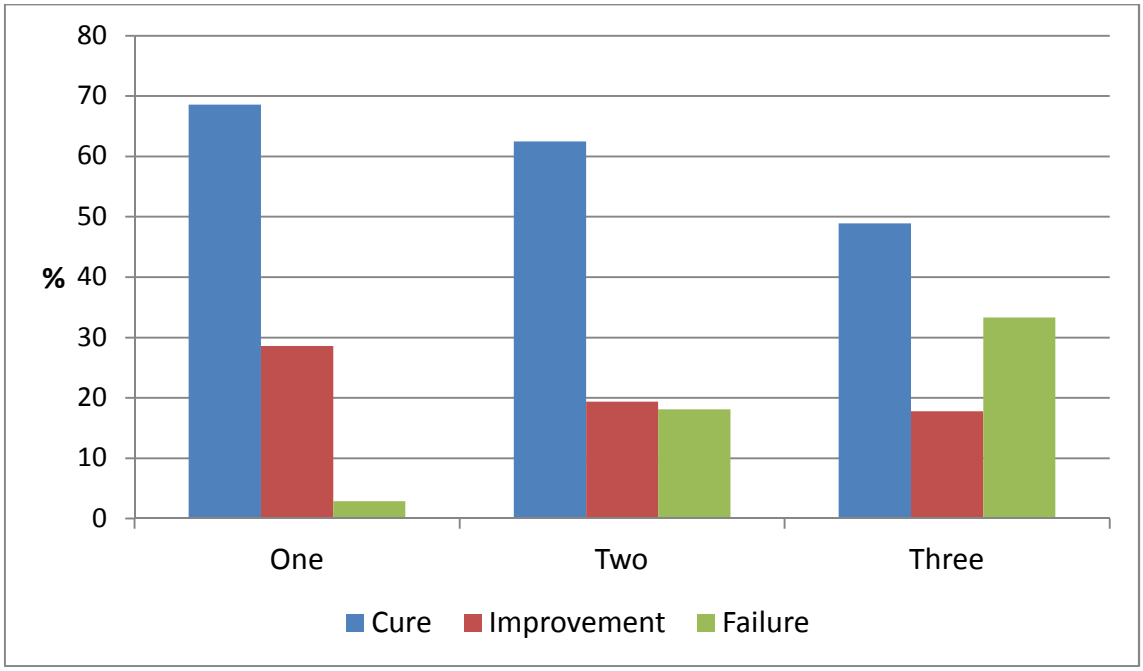
We carried out all the analyses for both those physicians who have not accessibility to CRP rapid test determination and for those with CRP availability. For the former, only the increase of purulence of expectoration was statistically associated with clinical failure (OR of cure: 0.2; 95% CI: 0 – 0.6). Neither increase of dyspnoea (OR: 0.4; 95% CI: 0.2 – 1.1) nor increase of sputum production were associated with failure.

In case of CRP availability, among mild-to-moderate COPD patients with exacerbations not treated with antibiotics clinical predictors for failure were CRP ≥ 40 mg/l (OR of cure 0.1; 95% CI: 0 – 0.2) and sputum purulence (OR of cure: 0.2; 95% CI: 0 – 0.7). Both increase of dyspnoea and increase of sputum production did not achieve statistically significant differences (Table 20).

The next graphs (figures 6 and 7) show the relationship between the number of Anthonisen criteria present in the patient and the outcome. Figure 6 describes the relationship between the criteria described by Anthonisen (*Anthonisen NR et al, 1987*) and the outcome at day 9-11. This is equivalent to the situation of that physician who has no accessibility to a CRP rapid test. However, figure 7 adds the variable 'CRP concentration ≥ 40 mg/l'. This is the situation of the general practitioner that has accessibility to the CRP test.

As is shown in the figure 6, the most frequent outcome in the three cases was the cure even though the greater was the number of criteria the lower this percentage was observed. Similarly, the percentage of failure was greater with the presence of the three criteria compared with patients with two or one criteria ($p<0.01$). As shown in figure 7, among patients with acute exacerbations of mild to moderate COPD not treated with antibiotics, most of the patients with only one modified Anthonisen criteria were considered cured by the physician at day 9-11, and only 3.2% failed. Among patients with two modified Anthonisen criteria, 11.3% of the patients presented a failure. This percentage rose to 21.6% among those with three modified criteria. As is clearly shown in this graph, most of patients with four criteria actually failed and only a bit more of 45% of the patients had a favourable assessment ($p<0.001$).

FIGURE 6. Association between the number of Anthonisen criteria (increase of dyspnea, increase of sputum volume, and/or increase of sputum purulence) presented in patients with acute exacerbations of mild-to-moderate COPD not treated with antibiotics and clinical outcome at day 9-11



The tables 21 and 22 summarize the most important results of this thesis. Both tables describe different clinical scenarios and the associated clinical success rates observed when antibiotic therapy is withheld. The first of this table is valid for GPs without CRP test and the following table incorporates the possibility of performing a CRP test in the consultation.

Since clinical failure among patients treated with antibiotics was nearly 10%, we assume in this study that this percentage should be the maximum risk to be considered when antibiotic therapy is not given. Clinical success among patients not treated with antibiotics was observed in 65.1% of those with the type I exacerbations, ranged from 77.4 to 92.1% in type II exacerbations and ranged from 88.8 to 96.5% for those with type III exacerbations. Both in patients with type II and III exacerbations, the presence of purulent sputum was associated with a probability of success less than 90% (Table 21).

FIGURE 7. Association between the number of modified Anthonisen criteria (increase of dyspnea, increase of sputum volume, increase of sputum purulence, and/or CRP ≥ 40 mg/l) presented in patients with acute exacerbations of mild-to-moderate COPD not treated with antibiotics and clinical outcome at day 9-11

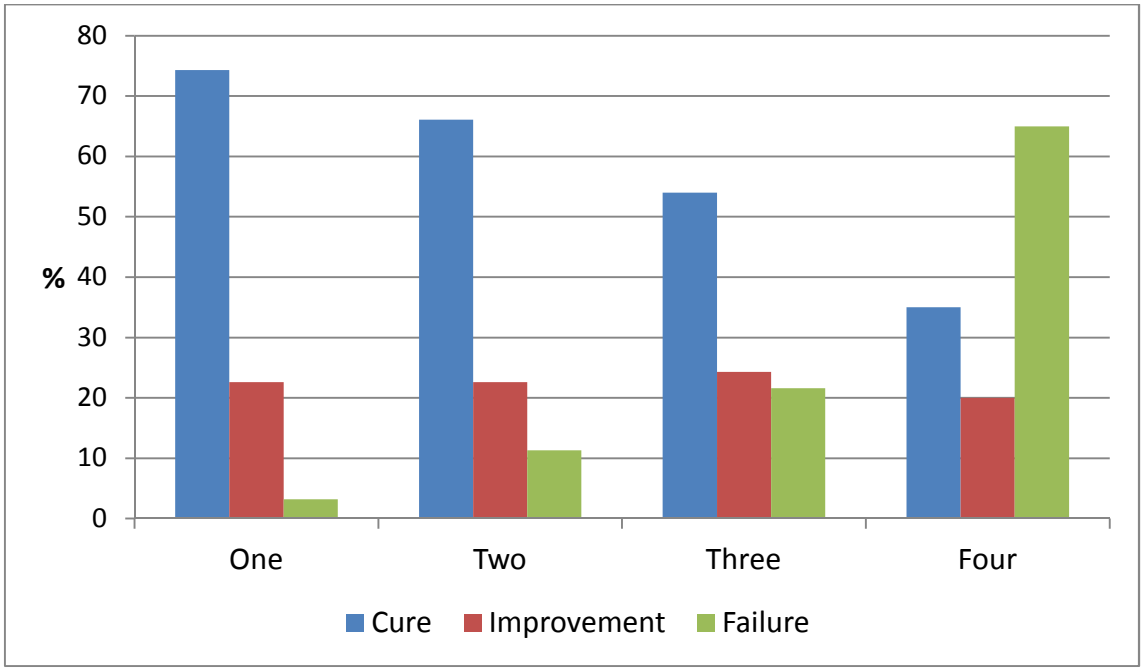


Table 22 shows the probability of clinical success among patients with exacerbations of mild to moderate COPD not treated with antibiotics with availability of CRP.

In this case we considered four criteria (increase of dyspnoea, increase of sputum production, increase of purulence of expectoration and CRP concentrations ≥ 40 mg/l). As is shown in this table, the presence of the four criteria was associated with a probability of clinical success of 34.7%. Clinical success rates ranged from 24.4 to 87.7% with the presence of three criteria, from 29.5 to 90.2% with the presence of two criteria and from 71.9 to 98.3% with only one criterion. More specifically, the presence of either sputum purulence or CRP ≥ 40 mg/l was associated with a probability of failure of 10% or greater. Only the association of increase of sputum production and the increase in sputum volume was associated with a clinical success rate of more than 90%.

When none of the Anthonisen criteria are present, the percentage of clinical success was then greater than 97%.

TABLE 21. Probability of clinical success among patients with exacerbations of mild to moderate COPD not treated with antibiotics without availability of CRP

Criteria	% success
NONE	**98.0**
No criteria	98.0
ONE CRITERION	**88.8 – 96.5**
Increase of dyspnoea	95.6
Increase in sputum volume	96.5
Increase of sputum purulence	88.8
TWO CRITERIA	**81.2 – 92.1**
Increase of dyspnoea + increase in sputum volume	92.1
Increase of dyspnoea + increase of sputum purulence	77.4
Increase in sputum volume + increase of sputum purulence	81.2
THREE CRITERIA	**65.1**
Increase of dyspnoea + increase in sputum volume + increase of sputum purulence	65.1

Probability of clinical success among patients with acute exacerbations of mild to moderate COPD not treated with antibiotics without availability of CRP= $\text{Exp}(\beta) / (1+\text{Exp}(\beta))$ in which $\beta = 3.913 – 0.843$ (in case of increase of dyspnoea) $– 0.609$ (in case of increase of sputum volume) $– 1.838$ (in case of increase of sputum purulence)

TABLE 22. Probability of clinical success among patients with exacerbations of mild to moderate COPD not treated with antibiotics with availability of CRP

Criteria	% success
NONE	**97.2**
No criteria	97.2
ONE CRITERION	**71.8 – 98.3**
Increase of dyspnoea	96.4
Increase in sputum volume	98.3
Increase of sputum purulence	84.9
CRP ≥ 40 mg/l	71.9
TWO CRITERIA	**29.5 – 90.2**
Increase of dyspnoea + increase in sputum volume	97.8
Increase of dyspnoea + increase of sputum purulence	81.2
Increase of dyspnoea + CRP ≥ 40 mg/l	66.3
Increase in sputum volume + increase of sputum purulence	90.2
Increase in sputum volume + CRP ≥ 40 mg/l	80.8
Increase of sputum purulence + CRP ≥ 40 mg/l	29.5
THREE CRITERIA	**24.4 – 87.7**
Increase of dyspnoea + increase in sputum volume + increase of sputum purulence	87.7
Increase of dyspnoea + increase in sputum volume + CRP ≥ 40 mg/l	76.5
Increase of dyspnoea + increase of sputum purulence + CRP ≥ 40 mg/l	24.4
Increase in sputum volume + increase of sputum purulence + CRP ≥ 40 mg/l	40.9
FOUR CRITERIA	**34.7**
Increase of dyspnoea + increase in sputum volume + increase of	34.7

sputum purulence + CRP ≥ 40 mg/l

Probability of clinical success among patients with acute exacerbations of mild to moderate COPD not treated with antibiotics with availability of CRP= Exp(β) / (1+Exp(β)) in which β = 3.535 – 0.261 (in case of increase of dyspnoea) + 0.499 (in case of increase of sputum volume) – 1.809 (in case of increase of sputum purulence) – 2.595 (in case of CRP ≥ 40 mg/l)

CRP: C-reactive protein

Multivariate analysis of the whole population for evaluating risk factors for failure

TABLE 23. Bivariate and multivariate logistic regression analysis for predicting clinical failure at day 9-11 among patients with exacerbations of mild to moderate COPD

	Bivariate analysis			Multivariate analysis (without CRP)			Multivariate analysis (with CRP)		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Treatment with placebo	2.2	1.2–4.4	0.02	2.2	1.1–4.4	0.02	2.9	1.4–6.0	0.01
High blood pressure	1.8	0.9–3.5	0.07						
Coronary heart disease	2.5	1.1–5.7	0.03				2.6	1.0–6.7	0.05
Increase of dyspnoea	2.1	1.0–4.6	0.06	2.6	1.2–5.7	0.02			
Sputum purulence	2.3	1.1–4.7	0.03	2.4	1.1–5.0	0.02			
CRP levels ≥ 40 mg/l	6.6	3.3–13	0.00				7.9	3.9–16.3	0.00

OR: odds ratio; CRP: C-reactive protein

Bivariate analyses of logistic regression were carried out for the following variables: treatment, age (years), sex, pack-years, high blood pressure, heart failure, coronary heart disease, diabetes mellitus, FVC%, FEV_1%, CRP ≥ 40 mg/L, sputum colour, increase of dyspnea, increase of sputum production, fever, number of Anthonisen criteria, and basal peak-flow.

TABLE 24. Probability of clinical failure at day 9-11 among patients with acute exacerbations of mild to moderate COPD in case of CRP non-availability

Criteria	% failure
NONE	**2.9**
No criteria	2.9
ONE CRITERION	**6.2 – 7.1**
Treatment with placebo	6.2%
Increase of dyspnoea	7.1%
Sputum purulence	6.7%
TWO CRITERIA	**14.5 – 15.5**
Treatment with placebo + increase of dyspnoea	14.5%
Treatment with placebo + sputum purulence	13.7%
Increase of dyspnoea + sputum purulence	15.5%
THREE CRITERIA	**29.0**
Treatment with placebo + increase of dyspnoea + increase of sputum purulence	29.0%

Probability of failure among patients with acute exacerbations of mild to moderate COPD without availability of CRP = Exp(β) / (1+Exp(β)) in which β = 3.513 + 0.800 (in case of treatment with placebo) + 0.940 (in case of increase of dyspnoea) + 0.876 (in case of sputum purulence)

The table 23 shows the bivariate analysis and the multivariate analysis. In the multivariate analysis we distinguished those physicians with access to CRP and those without this point-of-care test. Without access to CRP clinical failure was associated with increase of dyspnea (OR: 2.6; 95% CI: 1.2 – 5.7), sputum purulence and treatment with placebo. Among physicians with access to CRP test, failure was associated with CRP ≥ 40 mg/l (OR: 7.9; 95% CI: 3.9 – 16.3), placebo treatment (OR: 2.9; 95% CI: 1.4 – 6), and presence of coronary heart disease (OR: 2.6; 95% CI: 1 – 6.7).

TABLE 25. Probability of clinical failure at day 9-11 among patients with acute exacerbations of mild to moderate COPD in case of CRP availability

Criteria	% failure
NONE	**3,5**
No criteria	3.5
ONE CRITERION	**9.4 – 22.1**
Treatment with placebo	9.4%
Coronary heart disease	8.5%
CRP ≥ 40 mg/l	22.1%
TWO CRITERIA	**21.2 – 42.4**
Treatment with placebo + coronary heart disease	21.2%
Treatment with placebo + CRP ≥ 40 mg/l	45.0%
Coronary heart disease + CRP ≥ 40 mg/l	42.4%
THREE CRITERIA	**68.0**
Treatment with placebo + coronary heart disease + CRP ≥ 40 mg/l	68.0%

Probability of failure among patients with acute exacerbations of mild to moderate COPD with CRP availability = Exp(β) / (1+Exp(β)) in which β = 3.329 + 1.061 (in case of treatment with placebo) + 0.954 (in case of coronary heart disease) + 2.069 (in case of CRP ≥ 40 mg/l)

Tables 24 and 25 present combinations of these criteria among those without and with access to CRP and the associated clinical failure observed in each case. In the former, the presence of three criteria (treatment with placebo + increase of dyspnoea + increase of sputum purulence) was associated with a 29% of probability of failure. Conversely, when the patient presented neither of these criteria, the risk for failure was only 2.9%. In case of CRP availability, the presence of the three criteria (treatment with placebo + coronary heart disease + CRP ≥ 40 mg/l) was associated with a risk of 68% for failure. Conversely, when the patient presented neither of these criteria, the risk for failure was only 3.5%.

FIGURE 8. Failure observed in both treatment groups depending on the number of modified Anthonisen criteria (increase of dyspnoea, increase in the expectoration volume, sputum purulence and capillary CRP concentration ≥ 40 mg/l)

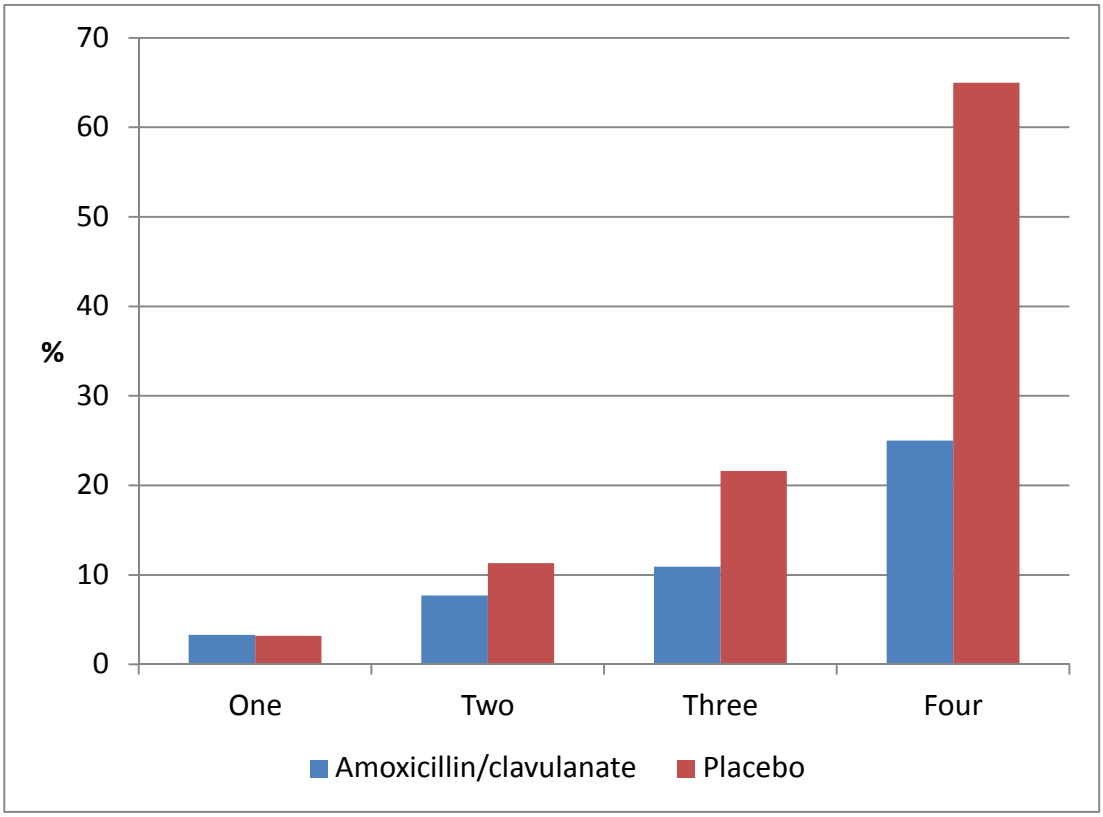


Figure 8 clearly shows the importance of considering the four criteria, not only those described by Anthonisen et al (Anthonisen NR et al, 1987). The greater the number of modified Anthonisen criteria the greater the risk for failure, even though this percentage is much higher among patients not treated with antibiotics.

Secondary outcome results

Clinical cure and success at day 20

A total of 232 patients were considered cured on day 20, accounting for 74.8 of the whole sample. Cure at day 20 was greater among patients assigned to antibiotic (129 cases, 81.6%) vs. 103 patients observed among the control group (67.8%; $p<0.05$). On the one hand, clinical success at day 20 was found in 143 patients who received antibiotic (90.5%), significantly greater than those who did not (122 cases, 80.3%; $p<0.01$). On the other hand, failure was observed in fifteen patients assigned to intervention (9.5%) and in thirty patients allocated to placebo (19.7%; $p<0.01$). One of the patients assigned to the placebo group and was considered as improved on day 9-11 presented a failure on day 20 (Table 26).

TABLE 26. Clinical response of the exacerbations of mild-to-moderate COPD evaluated at day 20

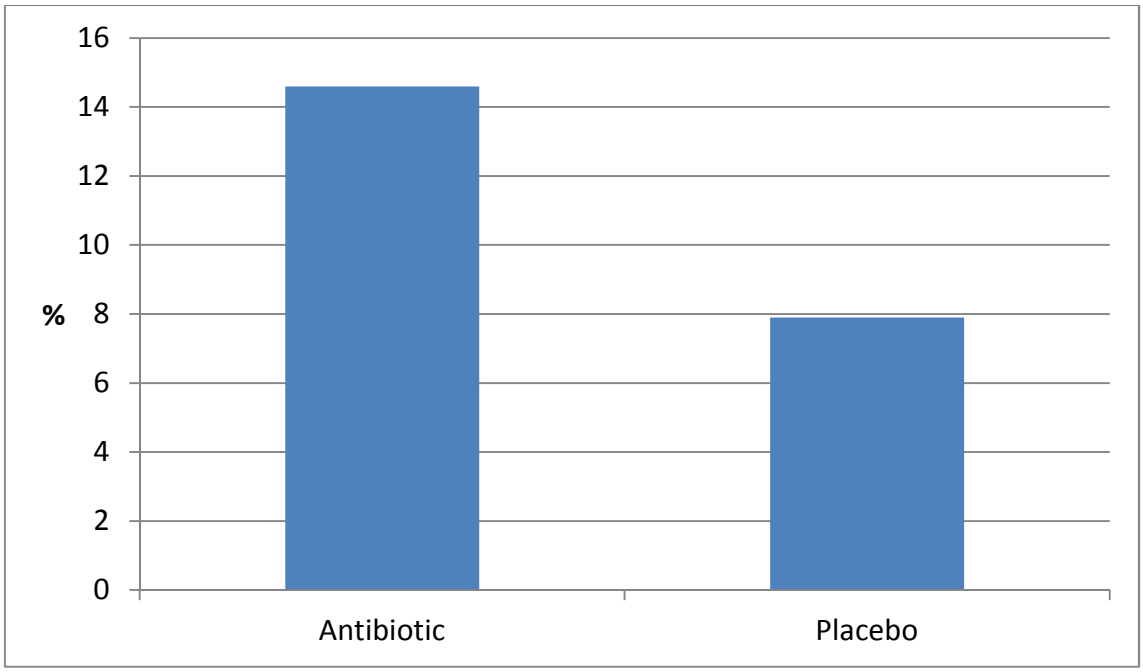
	Antibiotic (n: 158)	Placebo (n: 152)	Total (n: 310)
Cure	129 (81.6)	103 (67.8)	232 (74.8)
Improvement	14 (8.9)	19 (12.6)	33 (10.6)
Failure	15 (9.5)	30 (19.7)	45 (14.5)
Total	158 (100)	152 (100)	310 (100)

Adverse events

A total of 35 adverse events were observed in the whole sample. Thirty-two corresponded to gastrointestinal adverse events and two were allergic reactions. There is no information of the type of the adverse reaction observed in another patient. Among patients assigned to antibiotic therapy, twenty-three presented an adverse event (14.5%), being this percentage greater than the percentage of adverse reactions found among patients allocated to the control group (12 cases, 7.9%; $p<0.05$) (Figure 9). Curiously, the two skin adverse events were seen among patients assigned to placebo.

Most of the adverse reactions observed in this study were mild, since only two of these reactions led to discontinuation of the treatment, both cases among patients who were treated with antibiotics. No patients assigned to the placebo group discontinued the treatment because of the presence of adverse reactions. No serious adverse reactions were reported in this study.

FIGURE 9. Adverse events observed in both treatment groups



Speed of recovery

Speed of recovery was evaluated through the information contained in the diaries that were filled in by the patients who participated in this study. All the patients were instructed to deliver the diaries in the third visit (day 9-11), even those who presented clinical failure. Information about 298 symptom diaries was available (96.1%). Twelve patients did not return the diaries. When the diary was partially incomplete the investigator completed it with the aid of the patient. However, diaries were clearly incomplete in eight cases. Therefore, complete diaries were obtained in 290 cases (93.5%). The mean global symptom score at the first day was 15.14 ± 4, being of 7.24 ± 4.9 at day 8, with a variation of 7.88 ± 4.7 during this 8-day period. The mean score at the beginning was similar in both treatment groups (14.9 ± 3.6 in the intervention group and 15.4 ± 4.3 among patients assigned to placebo). However, global score at day eight was lower in the intervention group (6.6 ± 4 vs. 7.9 ± 5.7; $p<0.05$) (Figure 10). However, the variation between days 1 and 8 was not significantly different between both groups (8.3 ± 4.4 vs. 7.4 ± 5, respectively).

FIGURE 10. Variation of the mean global symptom score between days one and eight in both treatment groups

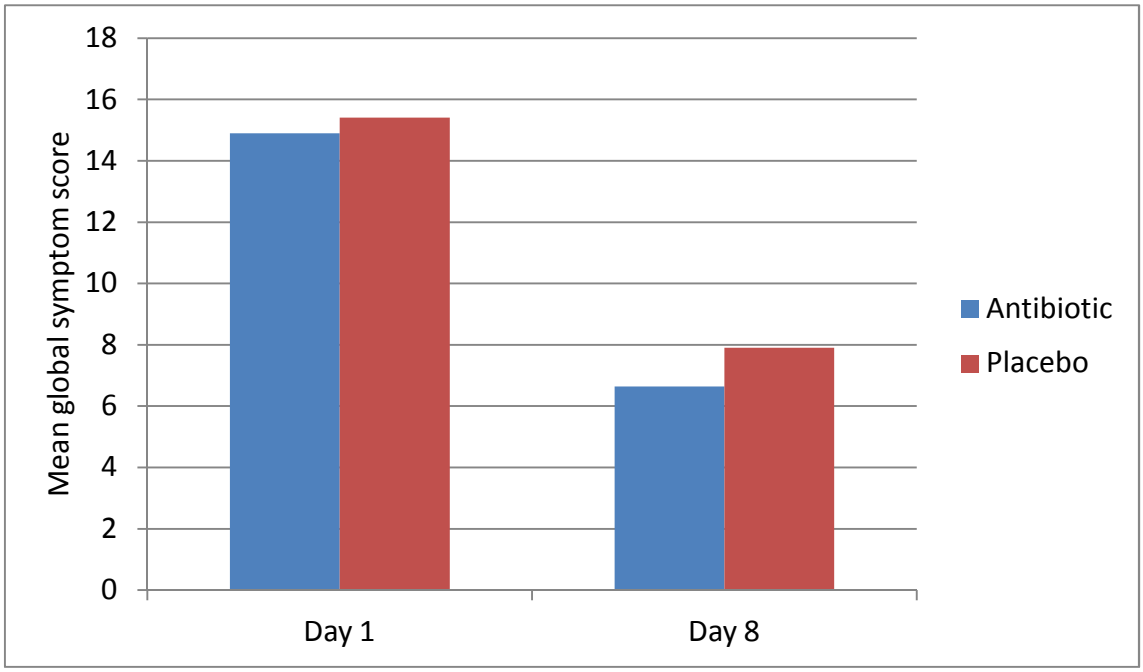
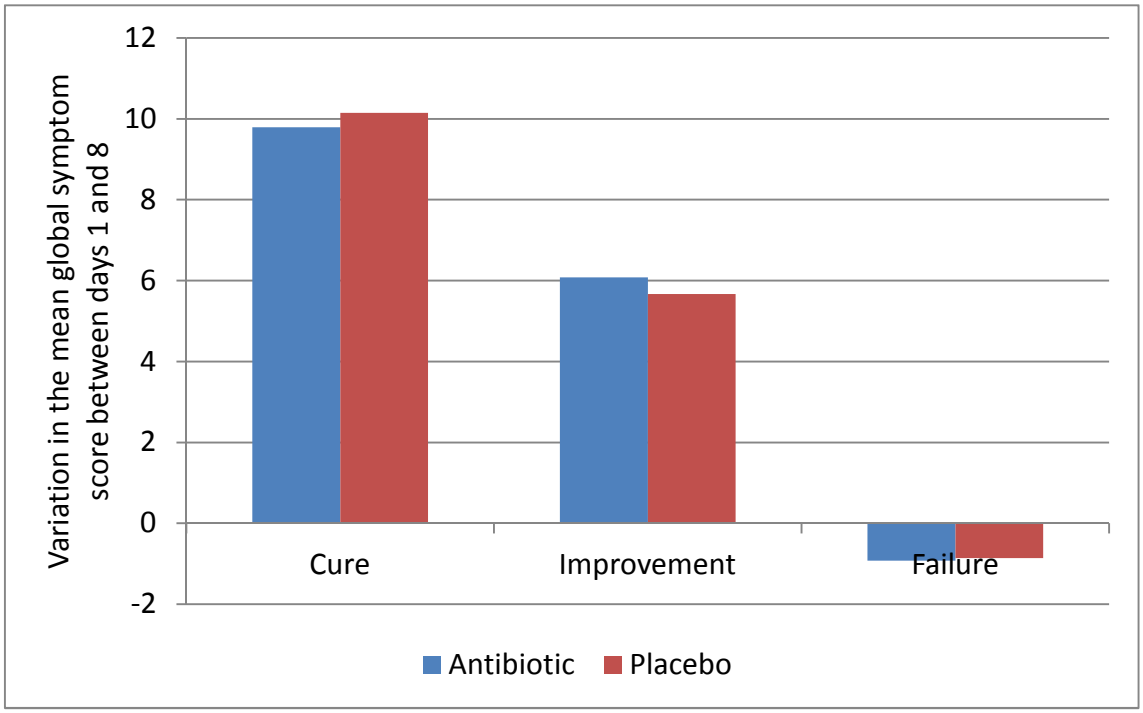


FIGURE 11. Variation of the mean global symptom diary score between days one and eight depending on the clinical outcome on day 9-11 and the treatment group



Out of the 290 cases with completed symptom diaries, 201 corresponded to cases that were cured at day 9-11, fifty-four to cases with improvement and thirty-five to failures. As commented in the methods section, in cases of failure the diaries were considered to be completed if the patient filled out at least two days, considering the score of day 8 the last one that the patient was able to filled in.

As is shown in figure 11, the variation of the mean global symptom score was greater among patients who were considered as cured by the investigator (10 ± 3.3), followed by those who improved (5.9 ± 2.5) while among patients with failure a slight increase of the symptom score was even found (- 0.9 ± 2.2; $p<0.001$). No differences were observed between both treatment groups. Table 27 describes the different mean scores observed depending on the clinical success on day 9-11. The scores in both treatment groups were very similar.

TABLE 27. Mean global symptom scores obtained in both treatments groups on days 1 and 8 and variation between the last and the first days depending on the clinical success

	Antibiotic	Placebo	Total
	Day 1		
Clinical success (n: 257)	14.89 (3.6)	15.06 (3.9)	14.96 (3.8)
Failure (n: 41)	15.00 (3.7)	16.93 (5.5)	16.27 (5.0)
Total (n: 298)	14.90 (3.6)	15.41 (4.3)	15.14 (4.0)
	Day 8		
Clinical success (n: 255)	5.75 (2.6)	6.04 (3.6)	5.88 (3.1)
Failure (n: 35)	16.15 (3.7)	17.68 (4.9)	17.11 (4.5)
Total (n: 290)	6.64 (4.0)	7.90 (5.7)	7.24 (4.9)
	Variation between days 1 and 8		
Clinical success (n: 255)	9.15 (3.5)	8.99 (3.6)	9.08 (3.6)
Failure (n: 35)	- 0.92 (1.8)	- 0.86 (2.4)	- 0.89 (2.2)
Total (n: 290)	8.29 (4.4)	7.42 (5.0)	7.98 (4.7)

Change of peak-flow measurements between days 1 and 9-11

The peak-flow measurement was obtained from 298 patients on day 9-11 (96.1%). The mean peak-flow measurement on day 1 was 226.40 l/min (SD: 82.6 l/min). The mean peak-flow measurement on day 9-11 was 273.94 l/min (SD: 88.7 l/min). As commented in the methods section the best of three repeated measurements were taken into account. No differences were observed between treatments groups.

Patients receiving amoxicillin and clavulanic acid had a peak expiratory flow on day 9-11 that was 8.55 litres per minute higher than that of patients receiving placebo (95% CI: -11.7 to 28.8), with a change from basal data and end of the therapy visit that was greater among patients assigned to antibiotic treatment (53 vs. 38.5 l/min; $p<0.05$) (Table 2). The results were exactly the same both for ITT and PP population.

TABLE 28. Mean peak-flow measurements obtained in both treatments groups on days 1 and 8 and variation between the last and the first days depending on the clinical success

	Antibiotic	Placebo	Total
Day 1			
Clinical success (n: 266)	223.50 (83.3)	226.08 (78.3)	224.69 (80.9)
Failure (n: 44)	242.00 (87.0)	233.97 (97.2)	236.70 (92.9)
Total (n: 310)	225.25 (83.6)	227.59 (81.9)	226.40 (82.6)
Day 9-11			
Clinical success (n: 262)	283.61 (88.8)	275.53 (83.9)	279.85 (86.5)
Failure (n: 36)	218.85 (82.8)	237.83 (101.3)	230.97 (94.3)
Total (n: 298)	278.10 (89.9)	269.55 (87.6)	273.94 (88.7)
Variation between days 1 and 9-11			
Clinical success (n: 262)	58.86 (59.9)	49.65 (46.0)	54.47 (54.0)
Failure (n: 36)	- 11.15 (45.9)	- 20.43 (67.6)	- 17.08 (60.1)
Total (n: 298)	52.75 (61.8)	38.53 (56.0)	45.83 (59.4)

Table 28 describes the mean results of peak-flow meter measurements observed on days 1, 9-11 and variation between both days. On day 9-11, the mean measurement for those with clinical success was significantly greater (279.85 ± 86.5 l/min) compared with those who presented an unfavourable evolution (230.97 ± 94.3 l/min; $p<0.01$). Variations between days 1 and 8 were positive for patients with clinical success while they were negative for those who failed ($p<0.001$).

Time till next exacerbation

The patients were instructed to communicate when a new exacerbation was present. A total of 217 new exacerbations were reported within the following year after the inclusion of the patients. This variable was found not to be normally distributed.

Because of this, the mean was not taken into account and the non-parametric measures were considered instead.

The days until the next exacerbation are presented in table 29. A total of 173 new exacerbations were reported within the following year after the inclusion among those patients who had clinical success (83 in the intervention group, 67.5%, vs. 90 in the control group, 62.9%).

TABLE 29. Time till next exacerbation in days among patients with clinical success at day 9-11

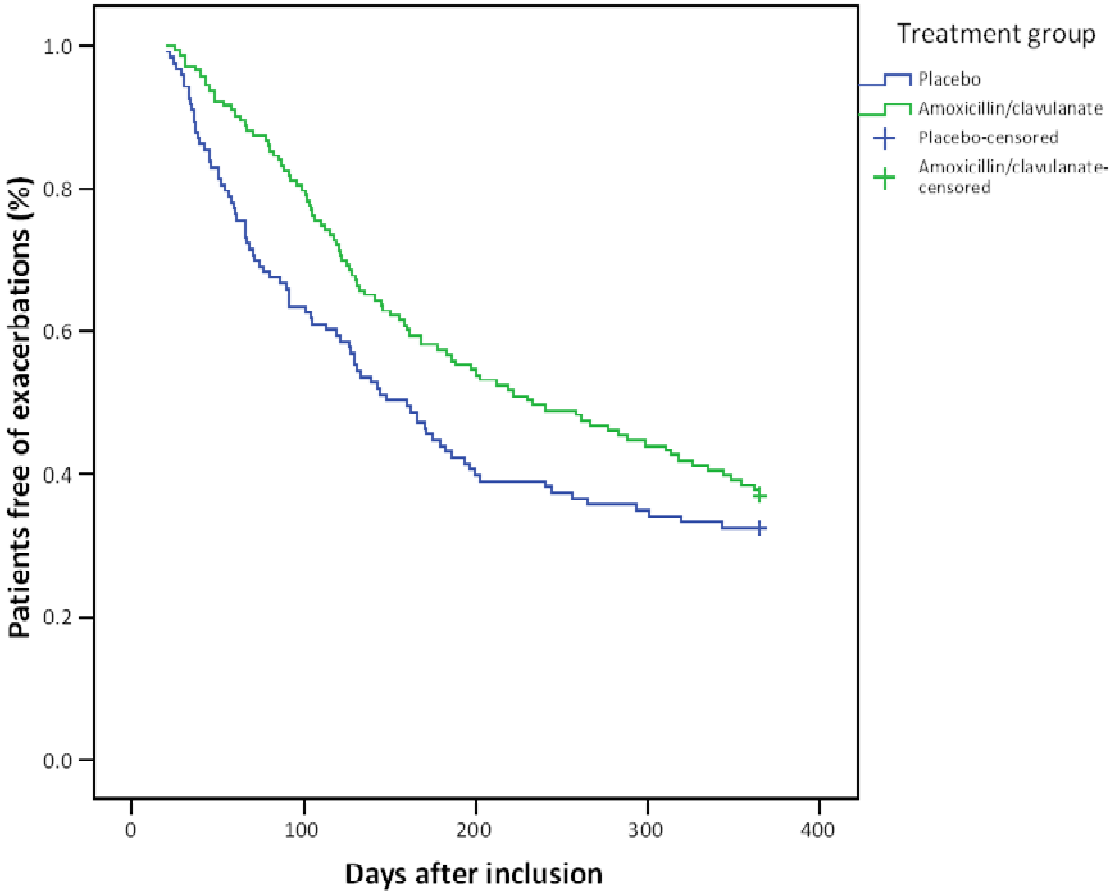
Population	n	Antibiotic	Placebo	p
ITT	266	160 (66 – 110)	233 (110 – 365)	0.089
PP	266	160 (66 – 365)	233 (110 – 365)	0.089
Age				
< 65 years	80	365 (132 – 365)	170 (66 – 365)	0.060
≥ 65 years	186	198.5 (196 – 365)	152 (63 – 365)	0.320
Severity of airway obstruction				
FEV_1 < 65%	134	156.5 (91 – 326)	96 (38.5 – 194)	0.081
FEV_1 ≥ 65%	132	365 (197 – 365)	240 (91 – 365)	0.022
CRP concentration				
CRP < 40 mg/l	212	280 (121 – 365)	173 (76 – 365)	0.167
CRP ≥ 40 mg/l	51	143.5 (92 – 360)	46 (33 – 70)	0.002

ITT: intention to treat, PP: per protocol; FEV_1: forced expiratory volume in one second
CRP: C-reactive protein

Among patients with clinical success – 143 patients in the intervention analysis and 123 in the control group – the median time to the next exacerbation was slightly lower among patients assigned to antibiotic therapy, being of 160 days (IQR: 121.5 – 198.5 days) compared with 233 days (IQR: 154.9 – 311.1 days) observed among patients assigned to placebo (p: 0.089). The number of days till next exacerbation was

statistically greater among patients not treated with antibiotics compared with those who did receive them when CRP concentrations were greater than 40 mg/l and in those cases with $FEV_1 \geq 65\%$ (Table 29). Figure 12 shows the Kaplan-Meier survival analysis revealing the time in days until the next exacerbation for both treatment groups.

FIGURE 12. Kaplan-Meier survival analysis of exacerbation-free interval in patients who had clinical success at day 9-11



DISCUSSION

Summary of main findings

Treatment of acute exacerbations of mild-to-moderate COPD with amoxicillin and clavulanic acid is more effective than placebo, since 74.1% of the former group and 59.9% of the latter were considered cured at days 9-11 ($p<0.05$). Among patients not treated with antibiotics clinical predictors for failure were CRP ≥ 40 mg/l (OR of cure: 0.1; 95% CI: 0 – 0.2) and sputum purulence (OR of cure: 0.2; 95% CI: 0 – 0.7). Regardless of the number the Anthonisen criteria, the presence of both low levels of CRP and uncoloured sputum was associated with a clinical success greater than 90% among patients not treated with antibiotics.

Strengths and weaknesses of the study

The required sample size could not be achieved. The main reason for the recruitment problems was that this trial was only partially funded by an independent institution (Ministry of Health) and the others fund bodies listed at the end of this thesis gave only little money. This trial was carried out only in primary care centres with availability of spirometric study and postbronchodilation administration. Some patients did not fulfil the criteria for non-severe COPD and others received antibiotic treatment before being attended, which were exclusion criteria. The prevalence of exacerbations was extremely low in two years. Since this study was scheduled to be terminated in three years and no improvement in the inclusion rate was expected, recruitment was stopped. The difference of the percentage of clinical success at day 9-11 between the intervention and control groups was 10.7% in the present clinical trial, slightly greater than the predicted minimal difference used for the sample calculation. Even though this study was stopped before reaching the sample size initially calculated, in the per-protocol population a statistically significant result was observed (91.7% with antibiotic and 80.9% with placebo, $p<0.01$), achieving a power of 80%.

No microbiological study was performed in this study. This actually constitutes the main limitation of this thesis, even though in my opinion, this weakness can be considered as minor. This trial was exclusively carried out in the primary health care setting in which COPD is usually treated in both the stable phase and for

exacerbations. Although it is true that some exacerbations of severe COPD are managed in emergency departments or hospitals, most mild-moderate episodes of the disease are attended in health care centres. Even though recent data suggest that approximately 70% of exacerbations are infectious in origin, only 20 – 30% can be related to bacteria detected by sputum culture (*Celli BR et al, 2007*). It is difficult to prove that pathogens detected in sputum are the relevant triggers of exacerbation, as detection is not proof of infection. Recent findings have shown that growth of bacteria in sputum cultures of COPD patients can also result from colonisation of the airways (*Sethi S et al, 2002*). Moreover, respiratory viruses are detected in > 50% of exacerbations and also have to be considered as major infectious triggers (*Rohde G et al, 2003*). On the basis of different studies, mainly carried out with severe patients, bacteria can be cultured from the tracheal-bronchial tree in a percentage that ranges from 19% to 72% of all episodes of acute exacerbations (*Eller J et al, 1998; Ewig S et al, 2000; Miravitlles M et al, 2002b; van der Valk P et al, 2004*). However, bacteria can also be isolated from the sputum of stable COPD patients and several studies did not find a significant difference in bacterial infection in patients at stable state and exacerbation (*Papi A et al, 2006*). Reported factors associated with positive sputum culture include bronchiectasis, long-term oxygen therapy, and low FEV_1 (*Roche N et al, 2007*). We also know that the type of sputum bacterial growth at exacerbations changes according to the severity of underlying airway obstruction; for example, gramnegative bacteria, such as *Enterobacteriaceae* and *Pseudomonas aeruginosa*, are particularly common among patients with FEV_1 < 35% predicted (*Eller J et al, 1998; Miravitlles M et al, 1999b*). However, up to one quarter of patients with moderate COPD are colonized by potentially pathogenic microorganisms (*Rosell A et al, 2005*). A combination of a negative result of sputum Gram stain, a relevant nonclinical decrease in lung function (compared to baseline measurements), and the occurrence of less than two exacerbations in the previous year have been proposed to be 100% predictive for a non-bacterial origin of the exacerbation (*van der Valk P et al, 2004*). Therefore, microbiological studies with the isolation of potentially pathogenic microorganisms with sputum cultures and serologic studies are of little utility in this disease, particularly in non-severe COPD. Indeed, the proportion of positive sputum cultures is small in the mild form of the disease and serologic studies should be correlated with

the isolation of germs. In addition, this study was undertaken in primary care where all the exacerbations are generally managed based on clinical criteria without any complementary test. Only chest X-ray may be requested on suspicion of pneumonia and CRP rapid tests were available. Thus, microbiological studies were not performed. Moreover, in the best study to date published by Anthonisen et al (*Anthonisen NR et al, 1987*), microbiological studies were not carried out either.

Another limitation of this clinical trial is the possibility of heterogeneity. This study was performed in twenty-three different health care centres with an investigator-monitor figure in each. The methodology used was very simple (as it should be in primary care) and the holding of previous meetings with these figures and all the participating physicians of the different health care centres allowed the necessary homogeneity to undertake the study. However, more than half of the patients recruited came from only one centre. Similarly, the marked variability and inconsistency in the use of spirometry to diagnose COPD has been published (*Bolton CE et al, 2005; Lee TA et al, 2006*), with a lack of device calibration and quality control (*de Miguel Díez J et al, 2003*) as well as formal and accurate technical training (*Hueto J et al, 2006*) in primary care. All the nurses responsible for performing the spirometry in each of these centres were instructed to follow the recommendations and perform the spirometric study after a post-bronchodilator administration. We think, as Tumoisto states, that it is possible to achieve good quality spirometry in primary care (*Tuomisto L et al, 2008*) and at levels similar to those achieved in the majority of pulmonary function laboratories (*Soriano JB et al, 2009*).

This study has other limitations, albeit of little importance. Firstly, adjuvant treatment other than the treatment of the study was allowed to be prescribed according to the criteria of the investigator. We think that this possible bias is eliminated by the sample size considered as well as the nature of the methodology used in this study as a randomised, double-blind clinical trial. Secondly, no haematologic tests were performed. Although these tests may be performed within the primary care setting, they are not justified in this study since it was not one of safety but rather was one of efficacy. In addition, the antibiotic used has been in the Spanish pharmaceutical market for more than 25 years and is currently the most frequently prescribed by

Spanish family physicians (*Agencia Española de Medicamentos y Productos Sanitarios y Dirección General de Farmacia y Productos Sanitarios, 2010*). Another limitation of this study is the definition of the exacerbation itself. In practice, the diagnosis is clinical since there are no complementary tests for its diagnosis. This study took the criteria considered in other studies into account and is based on the presence of at least one of the classical criteria of Anthonisen (increase in dyspnoea, increase in sputum volume and/or an increase in sputum purulence), although the clinical manifestations may often be accompanied by an increase in cough and fever or rise in temperature (*Anthonisen NR et al, 1987*). Of interest, patients seek health care for only half the episodes that meet the definition of exacerbations of COPD (reported exacerbations) (*Langsetmo L et al, 2008*). The unreported episodes are milder than the reported exacerbations but still have significant long term-impact on the course of COPD (*Langsetmo L et al, 2008*). Lastly, some secondary effects of the antibiotic treatment used in this clinical study (gastrointestinal effects of the association of amoxicillin and clavulanic acid) may break the double-blindness. Nonetheless, the literature reports a maximum of 12% of gastrointestinal intolerance with this antibiotic and thus we do not consider this a bias (*Lode H, 2010*).

In contrast with the study by Anthonisen et al (*Anthonisen NR et al, 1987*), we believe that the approach described presents a series of fundamental strengths. It is of note that we have used different criteria of cure such as the time of cure and the time till next exacerbation. We used CRP which has not been used in other studies in the community setting and performed chest X-rays in all the patients with suspected pneumonia thereby ruling out its presence. In fact, a major cause of hospitalisation and a common cause of death, community-acquired pneumonia, is most commonly seen in individuals who smoke cigarettes and/or have COPD (*Ginesu F et al, 1995*). The impact of underlying COPD on the outcome of pneumonia is at present unclear. Some retrospective studies of patients with COPD have reported increased mortality risks (*Rello J et al, 2006; Restrepo MI et al, 2006*) but others have not (*García-Vidal C et al, 2007; Ruiz de Ona JM et al, 2003*). Inclusion of patients with pneumonia in a clinical trial evaluating the effectiveness of antibiotic therapy versus placebo is also unethical, since this infectious disease should be treated always with antibiotics as quickly as

possible. In this study, not all the patients undertook a radiographic study but those with suspected pneumonia, i.e. high temperature, auscultation abnormalities or CRP greater than 20 mg/l were all studied. We believe that the likelihood of having recruited a case with pneumonia in our study is negligible.

Contrary to other studies, we considered the antibiotic of choice in Spain and in many other countries, that of amoxicillin and clavulanic acid which is recommended by most of the current clinical guidelines since it covers pneumococci and *Haemophilus* well (*Cots JM et al, 2010; Llor C et al, 2011*). Although the latter is the most frequently isolated, in some series carried out strictly in the community pneumococci are also frequently presented (*Llor C et al, 2006*). Neither did we use macrolides – not only because these are not considered as first line treatment for exacerbations of COPD but rather to avoid the so-called antiinflammatory effect that some studies have associated with these antibiotics (*Sevilla-Sánchez D et al, 2010*). Fluoroquinolones were not considered either, because the clinical studies undertaken to date have not shown the use of these antibiotics to be superior to the association of amoxicillin and clavulanic acid in non-severe COPD, and in this study we did not take the more severe patients into account. This is important since patients with COPD with $FEV_1 > 50\%$ rarely have infection by gramnegative microorganisms in contrast with more severe patients (*Miravitlles M, 2002b*).

Other strengths of note in our study are the use of a larger sample size than used in previously published studies since we accepted a difference of 10% among treatments as significant, the fact of it having been carried out in a country with one of the highest rates of resistance and that only patients with mild-to-moderate COPD diagnosed by spirometry were included. The methodology used as a double-blind clinical study allowed neither the patient nor the physician to know the treatment administered, representing another strength of the study. This is the only way to determine the efficacy of antimicrobial treatment in exacerbations of mild-moderate COPD and to evaluate what situations are associated with better clinical response to antimicrobial treatment and to know the clinical situations which allow identification of the patients who recover from an exacerbation without the need for antibiotics.

Comparison with other studies

Fourteen patients diagnosed of COPD in the different primary healthcare centres did not fulfil the diagnostic criteria based on an FEV_1/FVC ratio < 0.7 after inhaled bronchodilatador administration. In addition, eighteen patients had a severe airways obstruction. This issue is also observed in other studies mainly carried out in primary care. While spirometry is an essential part of the clinical diagnosis of COPD, with diagnostic criteria based on an this ratio (*Global Initiative for Chronic Obstructive Lung Disease, 2010*), 21% – 63% of patients registered as having COPD in both primary and secondary care do not fulfil the disease criteria largely due to a lack of spirometric data (*de Miguel Díez J et al, 2003; Naberan K et al, 2006; Pellicer Ciscar C et al, 2010; Sichletidis L et al, 2007*).

Another reason of having included so many patients without spirometric criteria for non-severe COPD is the fact that in this study some physicians included patients not previously diagnosed of COPD but with high suspicion of having a positive spirometry. In those cases physicians were instructed to perform the spirometric study one month after the inclusion of the patient. In some cases, the patients were correctly diagnosed of non-severe COPD but in other cases, the patients were finally excluded due to either not fulfil the diagnostic criteria of COPD or have a severe obstruction. Most patients with non-severe COPD remain undiagnosed in the community. A Spanish study in 1999 of adults aged 40–70 years revealed that, from a prevalence of 9.1%, only 22% of COPD patients had a previous diagnosis of the disease (*Pena VS et al, 2000*), which rose to just 27% ten years later (*Miravitlles M et al, 2009*). Overall, 45% – 85% of COPD patients are not formally diagnosed, as many accept breathlessness and limited exercise tolerance as features of ageing and regard their smoker's cough as normal (*Halpin DM et al, 2006*). Both patients and physicians play a role in the high rates of COPD underdiagnosis. One survey showed that, of 7,000 respondents, 33% said that they suffered from chronic respiratory symptoms, but only 56% of those consulted a physician (*Miravitlles M et al, 2006*). Of those individuals who consulted a physician with respiratory symptoms, only 42.6% underwent spirometry (*Miravitlles M et al,*

2006). In addition, just 56% of primary care practices were found to have a spirometer in a recent nationwide survey of Spain (*Miravitlles M et al, 2007*). Even though the undiagnosed airflow is typically very mild, approximately 5% of the general population has an FEV_1 < 75% predicted (*Coultas DB et al, 2001*). The International Primary Care Respiratory Group suggests that all smokers aged 35 years and older, individuals who have symptoms suggestive of COPD and those who have positive findings on a COPD risk evaluation questionnaire should either have initial case-identification spirometry or proceed directly to full diagnostic spirometry (*Price D et al, 2009*). This 'case-finding' approach of first harnessing symptoms, patient characteristics and lung function indicators should improve the recognition of COPD (*Soriano JB et al, 2009*). The NICE guideline recommends the identification of early COPD and that spirometry be performed in subjects aged over 35 years, current or ex-smokers and those with a chronic cough (*National Institute for Clinical Excellence, 2011*). It also suggests that spirometry be considered in patients with chronic bronchitis; as a significant proportion of these will go on to develop airflow limitation (*National Institute for Clinical Excellence, 2011*). In our study, in an attempt of recruiting correct cases we narrowed these critera and only patients aged 40 or more with a smoking history of greater than ten pack-years were taken into account.

In this study, use of concomitant therapy showed no influence on the different outcomes considered. Other studies performed with mild and moderate COPD patients showed similar results. The EUROSCOP study (*Pauwels RA et al, 1999*) investigated the benefits of active treatment in patients with mild-to-moderate COPD. For this study, 1,277 individuals with post-bronchodilator FEV_1 50% – 100% predicted and FEV_1/FVC < 70% who continued smoking were randomised to budesonide 400 µg or placebo twice daily. After 3 years, there was no difference in the rate of decline in FEV_1 in patients treated with budesonide compared with those receiving placebo. A randomised, double-blind, parallel-group clinical trial nested in the Copenhagen City Heart Study indicated that, in 290 patients with an FEV_1 86% predicted, budesonide 400 µg bid, compared with placebo, did not have a significant impact on the rate of decline of FEV_1 or the number of exacerbations (*Vestbo J et al, 1999*). In the Lung Health Study II, which compared triamcinolone acetonide 600 µg or placebo bid in

1,116 patients with mild-to-moderate COPD, active treatment had, again, a non-significant effect on the rate of decline in FEV_1. Nevertheless, there was a significant reduction in respiratory symptoms with triamcinolone acetonide and in visits to a physician due to respiratory illness (*Group LHSR, 2000*). A post-hoc analysis of the ISOLDE trial of 751 patients treated with fluticasone proprionate 500 µg or placebo bid showed that, in 391 patients with an $FEV_1 \geq 50\%$ predicted, fluticasone propionate had no impact on the number of exacerbations per patient per year, at 1.5 versus 1.8. However, the proportion of patients with more than one exacerbations/year treated with oral corticosteroids was reduced significantly with active treatment, at 8% versus 16% for placebo (*Jones PW et al, 2003*). In the ISOLDE trial as a whole, the annual rate of decline in FEV_1 was similar in both groups (*Burge PS et al, 2000*).

The MISTRAL study, published in 2006, randomised 1,010 COPD patients to tiotropium 18 µg or placebo once daily for 1 year. Among 426 patients with an $FEV_1 > 50\%$ predicted, tiotropium was associated with a significant reduction in the number of exacerbations per patient per year, at 1.2 versus 2, alongside which there was a non-significant reduction in the number of patients experiencing one or more exacerbations in patients with mild COPD (*Dusser D et al, 2006*). For the BRONCUS study, 523 COPD patients were randomly assigned to N-acetylcysteine 600 mg daily or placebo and followed-up for 3 years. N-acetylcysteine was found to have, compared with placebo, no significant effects on either the decline in FEV_1 or the decline in vital capacity in 389 participants with GOLD stage II COPD (*Decramer M et al, 2005*).

In this thesis, the effect of antibiotic therapy on the main clinical outcome at the end of therapy visit was greater than the effect observed among those patients assigned to placebo. A similar result has been published in other studies. Taking all the studies comparing antibiotic therapy and placebo for acute exacerbations of COPD into account, the median treatment failure rate was 0.12 for the antibiotic groups, ranging from 0 to 0.47, and 0.34 for the placebo groups, ranging from 0.1 to 0.8 (*Puhan et al, 2007*). Thus across all trials, one out of eight patients with antibiotics had a treatment failure whereas one out of three patients had a treatment failure with placebo. Anyway, the effects of antibiotics were very heterogeneous across all the trials published. Antibiotics had a large effect in severe exacerbations in Puhan's meta-

analysis (OR 0.25, 95% CI: 0.16–0.39) with a number-needed to treat of 4 (95% CI: 3–5) (*Puhan MA et al, 2007).*

In this thesis, a bit more of 80% of patients with acute exacerbations of mild-to-moderate COPD had a favourable course despite not being treated with antibiotics. This is an important message since many GPs are reluctant to withhold antibiotic therapy among patients diagnosed of COPD. In Anthonisen's study, roughly 55% of the patients not treated with antibiotics presented clinical success (*Anthonisen R et al, 1987*). In this study, treatment success with antibiotics compared to placebo was especially apparent in patients with severe functional impairment – the mean FEV_1 of the patients recruited in this landmark paper was 33% predicted –, suggesting that the severity of the underlying disease might be an important indicator for antibiotic treatment. This sentence is backed up by the observation of the five clinical trials included in Puhan's meta-analysis (*Puhan et al, 2008*). Clinical success was also observed in approximately 80% of the cases not treated with antibiotics, a figure that is not different from the one observed in this thesis (*Anthonisen NR et al, 1994; Berry DG et al, 1960; Elmes PCF et al, 1957; Jorgensen AF et al, 1992; Sachs AP et al, 1995*).

The final decision whether to prescribe antibiotics or not in the setting of exacerbation can be based on markers of either disease severity or exacerbation severity. Markers of disease severity include the degree of airway obstruction, exacerbation rate, and presence of comorbidities. Patients with frequent exacerbations also present a higher incidence of viral exacerbations as compared to patients with infrequent exacerbations (*Seemungal T et al, 2001; Rohde G et al, 2003*). Exacerbation severity factors commonly considered the presence of clinical symptoms (dyspnea, increase in sputum production, and sputum purulence, treatment setting, sputum colour, and sputum examination, but also serum biomarkers (*Anthonisen NR et al, 1987; Balter MS et al, 2003; Grossman RF, 1997; Nouria S et al, 2001*). According to the updated guideline of GOLD, antibiotics should be given to patients with the following three cardinal symptoms: increased dyspnoea, increased sputum volume and increased sputum purulence or in patients with increased sputum purulence and one other cardinal symptom. On the basis of the results of this thesis, this recommendation should be changed. Three criteria were associated with clinical failure: placebo assignment,

coronary heart disease and high CRP levels. Coronary heart disease has been shown to increase the rate of treatment failure in other papers (*Adams SG et al, 2000; Dewan NA et al, 2000*). Purulent sputum has been shown to be associated with failure in the present study with the bivariate analysis but not in the multivariate logistic regression. However, its presence is associated with a clinical success of less than 90% of the cases not treated with antibiotics, regardless the number of Anthonisen criteria. Allegra et al showed that expectoration of greenish sputum was 94% sensitive and 77% specific for the yield of a high bacterial load in exacerbations of COPD. Accordingly, a positive bacterial culture was obtained from 84% of patients' sputum if it was purulent as compared with 38% if it was mucoid (*Allegra L et al, 2005*). Another study revealed similar figures (sensitivity 89.5%, specificity 76.2%) and suggested that the self-reporting presence of purulence in the sputum predicted the presence of bacterial infection in the distal airways (OR: 27.2, 95% CI: 4.6–60.9) (*Soler N et al, 2007*). However, this finding has not been invariably replicated (*van der Valk P et al, 2004*). In this thesis, CRP levels were much higher among patients with green sputum than those with yellow and these more than patients with discoloured sputum. This phenomenon has also been reported in other papers (*Allegra L et al, 2005*).

The most striking result of this thesis is the usefulness of CRP as a predictor for clinical failure. Furthermore, CRP has been shown to be the variable that is more associated with failure among patients not treated with antibiotics. This result, however, has also been observed in other papers and, in fact, CRP has been extensively evaluated as potential confirmatory and predictive parameter in patients with exacerbation of COPD. Stolz et al observed among inpatients that those patients admitted with low serum CRP levels did not seem to benefit from antimicrobials (*Stolz D, 2009*). Hurst et al (*Hurst J et al, 2006a*) assessed the value of 36 biomarkers in 90 patients from the London COPD study before and during an exacerbation of COPD. CRP was found to be the most selective biomarker that differentiates an exacerbation from day-to-day symptom variation. Sensitivity and specificity of CRP at 50 mg/l for the confirmation of exacerbation was only 74.4 and 57.5%, respectively, resulting in AUC of 0.73. Those values do not portray significant clinical relevance, as the assay of any biomarker in isolation was no better than the presence of an increase in any one of the major

exacerbation symptoms alone on that day (AUC: 0.83). When CRP concentration was combined with a major exacerbation symptom, AUC significantly increased to 0.88; although value is more attractive, this association has questionable statistical validity because of inclusion of a major criterion of exacerbation of COPD. Authors concluded that the combination of CRP with any one increased major exacerbation symptom is useful in the confirmation of COPD exacerbation (*Hurst J et al, 2006a*). In our thesis we found similar results, with the AUC being of 0.708 (95% CI: 0.616 - 0.801) for the Anthonisen criteria and rose to 0.842 (95% CI: 0.76 – 0.924; p<0.001) when high levels of CRP were added. This high value of the AUC suggests that we have identified important explanatory variables, which could be easily obtained from a mild-to-moderate COPD exacerbation at the GP's consultation.

Different CRP cut-off values can be chosen to optimize sensitivity and specificity, as demonstrated by Hurst et al (*Hurst J et al, 2006a*). In this study, an increase in CRP cut-off up to 27.6 mg/l resulted in an increase in specificity up to 90%, but was only 40% sensitive. More recently, Bircan et al (*Bircan A et al, 2008*) used a CRP cut-off of 10 mg/l to predict an exacerbation of COPD; in their study, CRP level had a sensitivity and specificity of 72.5 and 100%, respectively. Interestingly, Stolz et al (*Stolz D et al, 2006*) showed that a CRP value of 50 mg/dl had a sensitivity of 93.8% to detect bacterial infection, requiring antibiotics in 243 patients who presented with lower respiratory tract infection. In this thesis, the best cut-off level among patients treated with placebo is 40 mg/l, with an AUC of 0.732. Among these patients, 77.3% of the patients presented results lower than 40 mg/l and only 23.7% had concentrations greater than this figure. Elevation in the CRP levels is not an uncommon phenomenon in stable patients with COPD; using the database from the Third National Health and Nutrition Examination Survey, Mannino et al (*Mannino DM et al, 2003*) revealed that up to 52% of patients with moderate-to-severe COPD have CRP levels higher than 30 mg/l and levels above 100 mg/l occur in up to 23% of the patients. In a recent study, Dahl et al observed that elevated plasma CRP > 30 mg/l compared with < 10 mg/l was associated with risk estimates of 1.8 and 2.8 for spirometry-based COPD and of 1.6 and 1.8 for hospitalisation due to COPD in the Copenhagen City Heart Study and the Copenhagen General Population Study (*Dahl M et al, 2011*).

Clinical parameters are non-specific and unreliable predictors of outcomes in patients with exacerbation of COPD. Few investigators assessed the role of CRP as potential predictor of outcome in this group of the patients. Perera et al (*Perera WR et al, 2007*) conducted a prospective study in a well characterized cohort of 73 patients with COPD, in whom airway (sputum interleukin 6 and interleukin 8) and systemic inflammation (CRP and interleukin 6) were assessed in the stable state, at exacerbation onset prior to treatment, and throughout recovery period at days 7, 14, and 35. The authors concluded that assessment of CRP concentration 14 days after an exacerbation was predictive of a failure to completely resolve symptoms and can prognosticate recurrence of exacerbation within 50 days. In our study, however, the CRP concentrations were not predictive for the presence of a new exacerbation or for a shorter exacerbation-free interval. However, we found than among patients with high CRP levels, antibiotics were associated with a shorter exacerbation-free interval than those not treated with antbiotics. In another study, in patients with end-stage respiratory failure due to COPD, Cano et al (*Cano NJ et al, 2004*) demonstrated that survival was independently correlated with systemic inflammation measured by CRP levels (cut-off CRP level > 100 mg/l). On the other hand, Stolz et al (*Stolz D et al, 2007a*) studied the prognostic value of three plasma biomarkers (CRP, copeptin, and procalcitonin) in 167 patients admitted with COPD exacerbations. Contrary to the results of the previous studies, the authors did not find any correlation between CRP level and short-term or long-term outcome of exacerbation such as length of hospital stay, intensive care unit length of stay, in-hospital, and 6-month mortality.

The impact of corticosteroids on the attenuation of CRP levels remains unclear. Some papers have observed an interaction of CRP levels with the use of systemic corticosteroids. We did not observe this interaction, since only two patients assigned to control group were previously taking. Malo et al (*Malo O et al, 2002*) did not find a significant change in CRP levels during recovery in patients with exacerbations of COPD treated with intravenous corticosteroids, whereas Sin et al (*Sin D et al, 2004*) found a 63% reduction in CRP levels in patients treated with oral corticosteroids. Similar controversy exists in patients treated with inhaled corticosteroids. Some investigators reported lower CRP levels in COPD patients treated with inhaled corticosteroids (*Pinto-*

Plata VM et al, 2006; Sin D et al, 2004) whereas de Torres et al (*de Torres JP et al, 2006*) reported no difference in CRP levels in those patients. Most of those studies are observational, therefore this controversy demands well designed randomized controlled trials, which could clarify whether this biomarker is a useful guide to assess efficacy of therapy. Neither did we observe an effect of inhaled corticosteroids on CRP levels, probably because of the fact than only one quarter of these patients were taking these drugs on a chronic basis.

The results of this thesis prove the role of CRP as a predictor of the clinical outcome in exacerbations of COPD. This suggests that CRP may be used as a marker of significant bacterial infection and that it may be used when deciding whether or not to start antibiotic treatment. This clinical trial suggests that high CRP values may indicate a bacterial exacerbation in COPD patients.

Another aspect in this thesis is the use of other clinical outcomes such as the time till next exacerbation. Among patients with clinical success at day 9-11 those assigned to antibiotic therapy had a slightly shorter interval between exacerbations than those assigned to placebo. Statistically significant dfferences were only observed in subgroup of patients, such as those with CRP levels ≥ 40 mg/l and those with FEV_1 ≥ 65%. A post-hoc analysis of a randomized trial showed that time to next exacerbation might be prolonged if patients received moxifloxacin for treatment of the index exacerbation (*Wilson R et al, 2004*). Lode et al studied the exacerbation-free interval comparing levofloxacin and clarithromycin. Patients assigned to the quinolone presented a longer symptom-free interval than those patients who took the macrolide (*Lode H et al, 2004*). However, in a prospective, randomized study, time to next exacerbation was similar in the group of patients with low procalcitonin serum levels who did not receive antibiotics and in the group of patients receiving antibiotics according to guidelines (*Stolz D et al, 2007b*).

In the face of the fact that respiratory viruses are detected in 50% of exacerbations, a major task is the reduction of unnecessary antibiotic treatment in patients with mild-to-moderate exacerbation of COPD to stop the threatening increase in antibiotic resistance. It has been convincingly shown that prudent reduction of antibiotic use

confers low bacterial resistance without increase in complications (*Mölstad S et al, 2008*). Daniels et al showed recently that it is safe to treat acute exacerbations of COPD patients of all grades of severity (GOLD stages I–IV) with placebo if standardised treatment is provided (*Daniels JM et al, 2010*). In this thesis we have observed that antibiotics should be discouraged in most of the acute exacerbations of non-severe COPD. Among patients treated with antibiotics nearly 10% of the patients failed. Therefore, we can safely consider that antibiotics could and should be withheld when the risk of failure exceeds 10% of the cases. It means that we should definitely discourage the prescription of antibiotics in exacerbations with CRP levels lower than 40 mg/l. In this thesis, 77.3% of all CRP determinations presented concentrations lower than this cut-off level.

The presence of adverse events is indeed an important issue. In this thesis, significantly more patients assigned to antibiotic therapy compared to those assigned to placebo presented adverse effects. It has been shown in several trials that adverse events are higher in patients treated with antibiotics than in patients administered a placebo (*Ram FS et al, 2006*). The rate of adverse effects observed in this thesis is very similar to the one observed by Puhan's meta-analysis (*Puhan MA et al, 2007*). The percentage of adverse reactions in this meta-analysis, mostly mild gastrointestinal complaints, was 0.15 (range 0.05–0.60) for the antibiotic and 0.08 (range 0.04–0.13) for the placebo groups (*Puhan MA et al, 2007*). Hence, the individual patient might benefit from reduced adverse events associated with antibiotic treatment if antibiotics are no longer prescribed for this indication. In addition, the individual patient might also benefit from decreased selection of antibiotic-resistant strains by reduction of antibiotic consumption. Society will clearly benefit if unnecessary antibiotic prescriptions are reduced. This has been convincingly shown in other settings (*Mölstad S et al, 2008*). In addition, there is the potential economic impact. Antibiotic therapy can be costly and it has been shown that reduction in antibiotic use significantly reduces costs (*Bantar C et al, 2003*).

In conclusion, this thesis has two core take-home messages. On the one hand, the present thesis, powered enough to definitively show a benefit of antibiotics, clearly show their benefit in acute exacerbations of mild-to-moderate COPD exacerbations.

On the other hand, we show that antibiotics can be withheld in patients without sputum purulence (if there is no availiabillity of CRP) and in patients with sputum purulence or low CRP levels (with CRP availability). We have to assume that antibiotic treatment of acute exacerbations of COPD contributes significantly to the misuse of antibiotics worldwide and the misuse of antibiotics has been shown to be a major cause of the development of antibiotic-resistant bacteria, a fact that has not been addressed at all in antibiotic studies in acute exacerbations so far. The present thesis definitely indicates situations in which antibiotics can be safely withheld.

CONCLUSIONS

1. Treatment of acute exacerbations of mild-to-moderate COPD with amoxicillin and clavulanic acid is more effective than placebo (cure of 74.1% vs. 59.9% on day 9-11; $p<0.05$)
2. Clinical success on day 9-11 is observed in 90.5% of exacerbations treated with antibiotic and in 80.1% of the cases in which antibiotic treatment is not given ($p<0.05$)
3. The best CRP cut-off point for predicting clinical success with placebo is 40 mg/l. The area under the curve is 0.732 (95% CI: 0.614 – 0.851). Concentrations lower than 40 mg/l are observed in 77.3% of the exacerbations of mild-to-moderate COPD
4. The predictive value of the Anthonisen criteria for predicting clinical outcome, represented by the area under the ROC curve, is 0.708 (95% CI: 0.616 - 0.801) and rises to 0.842 (95% CI: 0.76 – 0.924; $p<0.001$) when CRP ≥ 40 mg/l is added
5. Only the increase of sputum purulence is statistically associated with clinical failure in case of CRP non-availability (OR of cure: 0.2; 95% CI: 0 – 0.6). In case of CRP availability, clinical predictors for failure are CRP ≥ 40 mg/l (OR of cure: 0.1; 95% CI: 0 – 0.2) and sputum purulence (OR of cure: 0.2; 95% CI: 0 – 0.7)
6. Without CRP utilization, clinical success among patients not treated with antibiotics is observed in 65.1% of those with the type I exacerbations, in 77.4 – 92.1% of type II exacerbations and in 88.8 – 96.5% of type III exacerbations. In all cases, the presence of purulent sputum is associated with a probability of failure of 10% or greater
7. Regardless of the number of Anthonisen criteria, the presence of either sputum purulence or CRP ≥ 40 mg/l is associated with a probability of failure of 10% or greater among patients not treated with antibiotics
8. Clinical cure at day 20 is greater among patients assigned to antibiotic (81.6% vs. 67.8%; $p<0.05$)
9. Adverse events are greater among patients treated with amoxicillin and clavulanic acid (14.5% vs. 7.9% observed with placebo; $p<0.05$)
10. In the multivariate regression analysis, failure in the whole population is associated with CRP concentrations ≥ 40 mg/l (OR: 7.9; 95% CI: 3.9 –16.3), placebo treatment

(OR: 2.9; 95% CI: 1.4 – 6), and presence of coronary heart disease (OR: 2.6; 95% CI: 1 – 6.7)

11. Speed of recovery is not significantly different between intervention and control groups, with variation of global symptom scores between days 1 and 8 of 8.3 and 7.4, respectively. However, the variation of global symptom scores are significantly greater among those patients with clinical success compared to those who failed
12. Patients receiving antibiotic therapy have a peak expiratory flow on day 9-11 that is 8.6 litres per minute higher than that of patients receiving placebo (95% CI: -11.7 – 28.8), with a change from basal data and day 9-11 that was greater among patients assigned to antibiotic (53 vs. 38.5 l/min; $p<0.05$)
13. Among patients with clinical success the median time to the next exacerbation is slightly lower among patients assigned to antibiotic therapy, being of 160 days (interquartile range [IQR] 121.5 – 198.5 days) compared to 233 days (IQR 154.9 – 311.1 days) observed among patients assigned to placebo

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APPENDIXES

APPENDIX 1. Case report form

Codi Pacient ☐☐☐☐

Criteris d'inclusió		
Pacients de 40 anys o més	☐ Sí	☐ No
Fumadors de 10 paquets-any o més	☐ Sí	☐ No
Amb diagnòstic espiromètric d'MPOC lleu-moderada (FEV_1 > 50% i FEV_1/FVC < 0.7%) (espirometria feta en els darrers 2 anys)	☐ Sí	☐ No
Amb una exacerbació, amb almenys un dels següents criteris: augment de dispnea, augment del volum d'expectoració i/o augment de purulència d'esput	☐ Sí	☐ No

Criteris d'exclusió		
Menors de 40 anys	☐ Sí	☐ No
MPOC greu o molt greu	☐ Sí	☐ No
Asma bronquial	☐ Sí	☐ No
Al·lèrgia a la penicil·lina o intolerància a l'àcid clavulànic o lactosa	☐ Sí	☐ No
Pneumònia	☐ Sí	☐ No
Traquoetomia	☐ Sí	☐ No
Neoplàsia	☐ Sí	☐ No
Bronquièctasis d'origen diferent de l'MPOC	☐ Sí	☐ No
Presa d'antibiòtics en les darreres dues setmanes	☐ Sí	☐ No
Criteris de derivació a l'hospital: obnubilació, taquipnea > 35 resp/mn, i/o insuficiència respiratòria	☐ Sí	☐ No
Immunodepressió o amb medicació immunosupressora	☐ Sí	☐ No
Fibrosi quística	☐ Sí	☐ No
Institucionalització en residència	☐ Sí	☐ No
Subjectes que no poden donar consentiment informat	☐ Sí	☐ No
Dificultat per atendre a les visites programades	☐ Sí	☐ No
Negar-se a participar a l'estudi	☐ Sí	☐ No
Espirometria no feta en els darrers dos anys (si no s'ha fet o és anterior, programar per fer espirometria en un mes)	☐ Sí	☐ No

VISITA INICIAL (Visita 1) Data visita inicial ☐☐/☐☐/☐☐☐☐

Dades personals

Edat:.....

Sexe: ☐ Home ☐ Dona

Telèfon:.....

Fuma actualment?	☐ Sí	☐ No
Anys que porta o ha portat fumant:.....		
Número de cigarretes diàries:.....		
Medicació de base:		
- β_2-adrenèrgics acció curta	☐ Sí	☐ No
- β_2-adrenèrgics acció llarga	☐ Sí	☐ No
- Anticolinèrgics	☐ Sí	☐ No
- Teofil·lines	☐ Sí	☐ No
- Corticoides orals	☐ Sí	☐ No
- Corticoides inhalats	☐ Sí	☐ No
Medicació posada avui:		
- β_2-adrenèrgics	☐ Sí	☐ No
- Corticoides orals	☐ Sí	☐ No
Comorbiditat		
- Insuficiència cardíaca	☐ Sí	☐ No
- Cardiopatia isquèmica	☐ Sí	☐ No
- Diabetis mellitus	☐ Sí	☐ No
- Hipertensió arterial	☐ Sí	☐ No

Peak flow ☐☐☐ l/min

Medicació lliurada. Número pot: ☐☐☐☐

Espirometria Data: ☐☐/☐☐/☐☐☐☐

FVC ☐☐☐☐ ml ☐☐,☐ %

FEV_1 ☐☐☐☐ ml ☐☐,☐ % (> 50%)

Ratio FEV_1/ FVC ☐☐,☐ %

Color d'esput declarat pel pacient

Blanc ☐ Groc ☐ Groc – verdós ☐

Clínica

Augment de la dispnea	☐ Sí	☐ No
Augment de la quantitat d'esput	☐ Sí	☐ No
Augment de purulència d'esput	☐ Sí	☐ No
Febre (> 38ºC)	☐ Sí	☐ No

S'ha donat diari de símptomes? ☐ No ☐ Sí

PCR < 8 mg/l ☐ ≥ 8 mg/l: ☐☐☐ mg/l

Radiografia de tòrax

No ☐ Sí, negativa ☐ Sí, positiva ☐

VISITA 2. Dia 3-4 Data visita ☐☐/☐☐/☐☐☐☐

Evolució:
No fracàs ☐
Fracàs (canviar l'antibiòtic o derivació a hospital) ☐

En cas de fracàs, quins són els motius? No presentat ☐ Empitjorament ☐ Efectes adversos ☐

Medicació d'estudi lliurada (en cas de finalització)

Ha retornat els comprimits sobrants? ☐ No ☐ Sí : Nombre de comprimits sobrants ☐☐

VISITA 3. Dia 9-11 Data visita ☐☐/☐☐/☐☐☐☐

Evolució:
Curat (resolució dels criteris d'inclusió) ☐
Millora (resolució parcial, però no necessita canvi de tractament) ☐
Fracàs (canviar l'antibiòtic o derivació a hospital) ☐

En cas de fracàs, quins són els motius? No presentat ☐ Empitjorament ☐ Efectes adversos ☐

Peak flow ☐☐☐ l/min

Medicació d'estudi lliurada (en cas de finalització)

Ha retornat els comprimits sobrants? ☐ No ☐ Sí : Nombre de comprimits sobrants ☐☐

Ha retornat el diari? ☐ No ☐ Sí

VISITA 4. Dia 20 Data visita ☐☐/☐☐/☐☐☐☐

Evolució:
Curat (resolució dels criteris d'inclusió) ☐
Millora (resolució parcial, però no necessita canvi de tractament) ☐
Fracàs (canviar l'antibiòtic o derivació a hospital) ☐

En cas de fracàs, quins són els motius? No presentat ☐ Empitjorament ☐ Efectes adversos ☐

VISITA 5. 3 mesos Data visita ☐☐/☐☐/☐☐☐☐

Ha presentat alguna nova exacerbació? ☐ No ☐ Sí : Data ☐☐/☐☐/☐☐☐☐

VISITA 6. 6 mesos Data visita ☐☐/☐☐/☐☐☐☐

Ha presentat alguna nova exacerbació? ☐ No ☐ Sí : Data ☐☐/☐☐/☐☐☐☐

VISITA 7. 9 mesos Data visita ☐☐/☐☐/☐☐☐☐

Ha presentat alguna nova exacerbació? ☐ No ☐ Sí : Data ☐☐/☐☐/☐☐☐☐

VISITA 8. 1 any Data visita ☐☐/☐☐/☐☐☐☐

Ha presentat alguna nova exacerbació? ☐ No ☐ Sí : Data ☐☐/☐☐/☐☐☐☐

Efectes adversos ☐ No ☐ Sí : Emplenar full d'efectes adversos

Full d'efectes adversos (si se n'observen)

Efecte advers 1

Data inici ☐☐/☐☐/☐☐☐☐ Data finalització ☐☐/☐☐/☐☐☐☐

Quin ha estat l'efecte advers?

Nàusees	☐	Mareig	☐
Vòmits	☐	Cefalea	☐
Diarrees	☐	Astènia	☐
Dispèpsia	☐	Pruïja	☐
Úlcera	☐	Candidiasi	☐
Abdominàlgia	☐	Altres. Especificar:	
Rash cutani	☐	.....	

Quin és el grau de relació de l'efecte advers amb la medicació?
No relacionat ☐ Improbable ☐ Probable ☐ Definitiva ☐

Quina és la intensitat de l'efecte advers?
Lleu ☐ Moderat ☐ Sever ☐

S'ha fet algun tractament?
☐ No ☐ Sí : Quin? .....

Efecte advers 2

Data inici ☐☐/☐☐/☐☐☐☐ Data finalització ☐☐/☐☐/☐☐☐☐

Quin ha estat l'efecte advers?

Nàusees	☐	Mareig	☐
Vòmits	☐	Cefalea	☐
Diarrees	☐	Astènia	☐
Dispèpsia	☐	Pruïja	☐
Úlcera	☐	Candidiasi	☐
Abdominàlgia	☐	Altres. Especificar:	
Rash cutani	☐	.....	

Quin és el grau de relació de l'efecte advers amb la medicació?
No relacionat ☐ Improbable ☐ Probable ☐ Definitiva ☐

Quina és la intensitat de l'efecte advers?
Lleu ☐ Moderat ☐ Sever ☐

S'ha fet algun tractament?
☐ No ☐ Sí : Quin? .....

Efecte advers 3

Data inici ☐☐/☐☐/☐☐☐☐ Data finalització ☐☐/☐☐/☐☐☐☐

Quin ha estat l'efecte advers?

Nàusees	☐	Mareig	☐
Vòmits	☐	Cefalea	☐
Diarrees	☐	Astènia	☐
Dispèpsia	☐	Pruïja	☐
Úlcera	☐	Candidiasi	☐
Abdominàlgia	☐	Altres. Especificar:	
Rash cutani	☐	.....	

Quin és el grau de relació de l'efecte advers amb la medicació?
No relacionat ☐ Improbable ☐ Probable ☐ Definitiva ☐

Quina és la intensitat de l'efecte advers?
Lleu ☐ Moderat ☐ Sever ☐

S'ha fet algun tractament?
☐ No ☐ Sí : Quin? .....

Efecte advers 4

Data inici ☐☐/☐☐/☐☐☐☐ Data finalització ☐☐/☐☐/☐☐☐☐

Quin ha estat l'efecte advers?

Nàusees	☐	Mareig	☐
Vòmits	☐	Cefalea	☐
Diarrees	☐	Astènia	☐
Dispèpsia	☐	Pruïja	☐
Úlcera	☐	Candidiasi	☐
Abdominàlgia	☐	Altres. Especificar:	
Rash cutani	☐	.....	

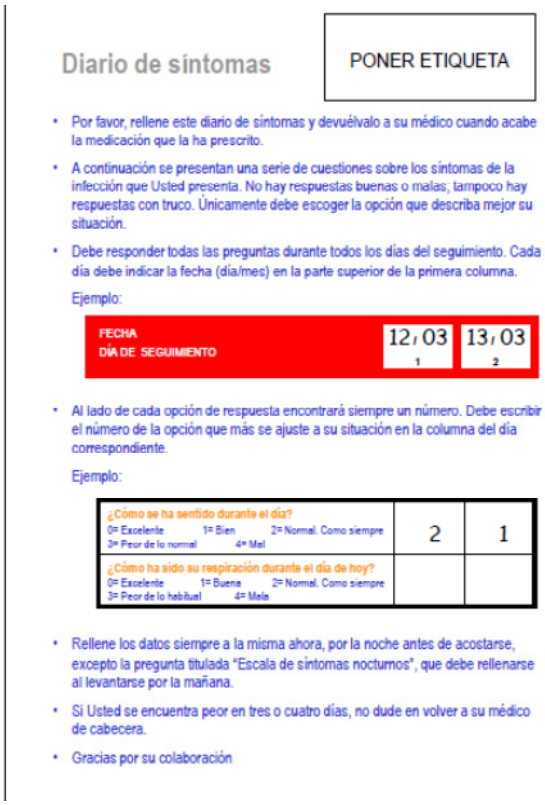
Quin és el grau de relació de l'efecte advers amb la medicació?
No relacionat ☐ Improbable ☐ Probable ☐ Definitiva ☐

Quina és la intensitat de l'efecte advers?
Lleu ☐ Moderat ☐ Sever ☐

S'ha fet algun tractament?
☐ No ☐ Sí : Quin? .....

APPENDIX 2. Instructions given regarding the use of QuikRead CRP®

APPENDIX 3. Symptom diary filled out by patients



Diario de síntomas

PONER ETIQUETA

- Por favor, rellene este diario de síntomas y devuélvalo a su médico cuando acabe la medicación que la ha prescrito.
- A continuación se presentan una serie de cuestiones sobre los síntomas de la infección que Usted presenta. No hay respuestas buenas o malas; tampoco hay respuestas con truco. Únicamente debe escoger la opción que describa mejor su situación.
- Debe responder todas las preguntas durante todos los días del seguimiento. Cada día debe indicar la fecha (día/mes) en la parte superior de la primera columna.

Ejemplo:

FECHA DÍA DE SEGUIMIENTO	12/03 1	13/03 2

- Al lado de cada opción de respuesta encontrará siempre un número. Debe escribir el número de la opción que más se ajuste a su situación en la columna del día correspondiente.

Ejemplo:

¿Cómo se ha sentido durante el día? 0= Excelente 1= Bien 2= Normal. Como siempre 3= Peor de lo normal 4= Mal	2	1
¿Cómo ha sido su respiración durante el día de hoy? 0= Excelente 1= Buena 2= Normal. Como siempre 3= Peor de lo habitual 4= Mala		

- Rellene los datos siempre a la misma ahora, por la noche antes de acostarse, excepto la pregunta titulada "Escala de síntomas nocturnos", que debe rellenarse al levantarse por la mañana.
- Si Usted se encuentra peor en tres o cuatro días, no dude en volver a su médico de cabecera.
- Gracias por su colaboración

FECHA DÍA DE SEGUIMIENTO	/ 1	/ 2	/ 3	/ 4	/ 5	/ 6	/ 7	/ 8
¿Cómo se ha sentido durante el día? 0= Excelente 1= Bien 2= Normal. Como siempre 3= Peor de lo normal 4= Mal								
¿Cómo ha sido su respiración durante el día de hoy? 0= Excelente 1= Buena 2= Normal. Como siempre 3= Peor de lo habitual 4= Mala								
¿Ha tenido tos? 0= Nada o casi nada 1= Ocasional. Muy poca 2= Frecuente. Bastante 3= Persistente. Mucha								
¿Qué consistencia ha tenido hoy su esputo? 0= Líquido 1= Pegajoso 2= Un poco pastoso 3= Pastoso								
¿Cómo es el color de su esputo? 0= Esputo blanco 1= Esputo amarillo 2= Esputo amarillo-verdoso								
¿Qué cantidad aproximada de esputo ha producido durante el día de hoy? 0= Nada 1= Muy poco (menos de una cucharadita de café) 2= Un poco (como una cuchara de sopa) 3= Moderadamente (menos de un vasito de vino) 4= Mucha (más de un vasito de vino)								
¿Ha tomado la pastilla que le dio su médico para tratar la infección respiratoria? 0= Sí 1= No								
Escala de síntomas diurnos Por favor, escriba el número que mejor describa los síntomas que haya podido tener durante el día (sensación de falta de aire, pitidos o "cargazón" del pecho) 0= No síntomas durante el día 1= Síntomas durante un periodo corto de tiempo 2= Síntomas diurnos durante al menos dos periodos cortos de tiempo 3= Síntomas durante casi todo el día, pero que casi no afectan a sus actividades diarias 4= Síntomas durante casi todo el día las cuales afectan a sus actividades diarias 5= Síntomas tan graves que le impiden trabajar o hacer sus actividades diarias								
¿Podría decir que hoy se encuentra como antes de que empeoraran los síntomas? 0= Sí 1= No								

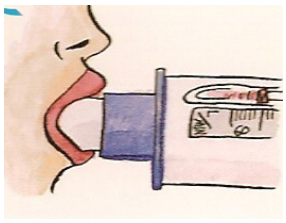
APPENDIX 4. Peak flow measurement instructions

MESURA DEL PEAK FLOW

El *peak-flow meter* o mesurador de pic flux és un aparell usat per a la mesura ambulatòria del flux espiratori màxim o FEM en L/minut. El FEM és la velocitat màxima de l'aire en una espiració forçada realitzada després d'una insuflació màxima pulmonar. Reprodueix el grau d'obstrucció de les vies aèries de gran calibre i s'ha vist que existeix una bona correlació entre FEM i FEV_1.

Com es fa?

- Assegura't de posar la boquilla correctament (figura)
- El pacient ha d'estar dret, amb el cos relaxat (figura)
- S'agafa el mesurador amb una mà, sense obstaculitzar el trànsit de la molla i s'ha de posar l'indicador a 0
- Es treu tot de la boca (p.ex. el xiclet)
- Se li diu al pacient que faci una inspiració profunda
- Es comprova que ajusti bé els llavis a la boquilla (figura), vigilant que no hi hagi fuites
- Se li diu al pacient que bufi de forma ràpida i explosiva (espiració forçada) d'1-2 segons de durada (se li diu que bufi com si volgués apagar una espelma). És important que bufi el més fort possible



Important

- Si el pacient no ho ha fet mai, se li pot dir que faci proves abans
- S'ha de fer les mesures sempre amb el mateix aparell. Cal fer-li al pacient dos dies (dia 0 i dia 9-11). El que es canvia és la boquilla
- **Cal fer 3 mesures i s'anotarà la més alta de les tres en el full**

APPENDIX 5. Ethical Research Committee approval

FUNDACIÓ JORDI GOL i GURINA
Per a la Recerca a l'Atenció Primària de Salut

INFORME DEL COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

Ester Amado Guirado, secretaria del Comité Ético de Investigación Clínica de la Fundación Jordi Gol i Gurina.

CERTIFICA:

Que este Comité en su reunión del día 28 de Junio de 2006, ha evaluado el proyecto de investigación **(P06/31)** titulado: "Situaciones en las que no es necesario tratar con antibióticos las agudizaciones de la EPOC leve – moderada", presentado por el Dr. Carles Llor Vilà.

Considerando que respeta los principios éticos y metodológicos para que pueda ser llevado a cabo, por lo que ha acordado dar su aprobación definitiva al proyecto anteriormente mencionado.

Lo que firmo en Barcelona a 4 de Julio de 2006.

APPENDIX 6. Grant from the Fondo de Investigación Sanitaria of the Spanish Ministry of Health

Instituto de Salud Carlos III

Investigador Ppal.: LLOR VILA, CARLES **Expte:** PI060409

Centro realización: SERVICIO DE ATENCION PRIMARIA TARRAGONA-VALLS

Centro solicitante: IDIAP JORDI GOL

Titulo del proyecto:

SITUACIONES EN LAS QUE NO ES NECESARIO TRATAR CON ANTIBIÓTICOS LAS AGUDIZACIONES DE LA EPOC LEVE-MODERADA

Duracion (años): 3

ANUALIDAD	AÑO 1	AÑO 2	AÑO 3	Total
Personal	0	0	0	0
Bienes y Servicios	20.000	19.000	5.000	44.000
Viajes y Dietas	0	1.500	2.000	3.500
Subtotal	20.000	20.500	7.000	47.500
21 % gastos generales	4.200	4.305	1.470	9.975
TOTAL	24.200	24.805	8.470	57.475

Contratados concedidos: Licenciado: 0
Diplomado: 0
Tecnico F.P.: 0

EQUIPO INVESTIGADOR	CATEGORIA	DEDICACION
BAYONA FARO, CAROLINA	CO	C
HERNANDEZ ANADON, SILVIA	CO	C
COTS YAGO, JOSEP MARIA	CO	C
ROZA FERNANDEZ, CRISTIAN DE LA	BE	C
LLOR VILA, CARLES	IP	C
RODRIGUEZ FERRE, ANA MARIA	CO	C
MIRAVITLLES FERNANDEZ, MARC	CO	C
CEREZO GOYENECHE, CARLOS	CO	C
MORAGAS MORENO, ANA	CO	C
BLADE CREIXENTI, JORDI	CO	C

APPENDIX 7. Written informed consent

Título: Situaciones en las que no es necesario tratar con antibióticos las agudizaciones de la EPOC leve-moderada (Estudio TRANCE)

Se está llevando a cabo un estudio que pretende identificar los factores que podrían ser más beneficiosos en el tratamiento de los pacientes con enfermedad pulmonar obstructiva crónica, que es la enfermedad que usted padece. En ocasiones, esta enfermedad mejora sin necesidad de utilizar antibióticos, pero otras veces es imprescindible utilizarlos. Los resultados del estudio ayudarán a mejorar el uso de los antibióticos y a disminuir el aumento de resistencias que presentan muchos gérmenes.

Para ello le pedimos su colaboración. Ud.puede hacer todas las preguntas que desee sobre el mismo. La participación en el estudio no supone la realización de ninguna intervención fuera de lo habitual; únicamente contactaremos más veces con Usted para comprobar la evolución de la exacerbación que presenta. La participación en el estudio tiene carácter voluntario y si Ud. decide participar tiene la posibilidad de retirarse del estudio en cualquier momento sin perjuicio alguno, sin tener que dar explicaciones y sin que ello afecte a su relación con los médicos o a futuras terapias.

Los datos del estudio son confidenciales, y sólo tendrán acceso a ellos los investigadores y el personal implicado en la monitorización y análisis de los mismos. Las autoridades sanitarias pueden, eventualmente, acceder a los mismos durante una inspección. Los nombres de los participantes no aparecerán en ninguna información o publicación de los datos del estudio. Este estudio ha sido aprobado por el Comité Ético de Investigación Clínica del Instituto de Investigación de Atención Primaria y por las autoridades sanitarias españolas.

Yo,.....(nombre y apellidos)
.....(declaro bajo mi responsabilidad que
.....nombre del participante en el ensayo)

- Ha podido hacer preguntas sobre el estudio.

- Ha recibido suficiente información sobre el estudio.

- Ha sido informado por: ..... (nombre del investigador)

Comprende que su participación es voluntaria.

Comprende que puede retirarse del estudio:
1- Cuando quiera.
2- Sin tener que dar explicaciones.
3- Sin que esto repercuta en sus cuidados médicos.
Y ha expresado libremente su conformidad para participar en el estudio.

Fecha Firma del paciente

Funding sources

Instituto de Salud Carlos III

IDIAP Jordi Gol

Institut Català de la Salut

semFYC
Sociedad Española de Medicina de Familia y Comunitaria