

# **Caring for adult patients with acute exacerbations of asthma or COPD in general practice**

*Exploration of current practice and options for improved assessment and care*

## **Relevance**

Exacerbation of asthma and COPD causes great suffering, premature deaths and considerable health care expenditures in our society. Such exacerbations are treated in hospitals as well as in primary care. However, according to national strategy (Najonal strategi for KOLS-området 2006-2011), general practitioners (GPs) will have an increasingly important role in the care of COPD patients. The project encompasses clinical research in primary care settings, questionnaires among hospitalized patients, and qualitative interviews with patients and doctors. The General Practice Research Unit in Tromsø (AFE Tromsø) will through the project cooperate with GPs from seven Norwegian GP offices, the General Practice Research Unit in Oslo, pulmonologists at the University hospital of North Norway and three district hospitals (Helgelandssykehusene), as well as GP researchers from 5 other European countries. Young GP researchers will be recruited to the project, which will give material for at least two ph.d. theses in the field of general practice.

## **Aspects relating to the research project**

### **Background and status of knowledge**

The prevalence of chronic obstructive pulmonary disease (COPD) among those aged 40 years or older can be estimated to be 5-10 %<sup>1</sup>. Smoking is the main cause of the disease. The prevalence of self reported current asthma was 4.5 %, in a population based survey in USA<sup>2</sup>. Asthma may develop into COPD<sup>3</sup>, and COPD patients may exhibit bronchial hyperresponsiveness like in asthma<sup>4</sup>. Accordingly, in many adults it is difficult to distinguish between these diagnoses<sup>5</sup>. Some patients are treated with anti-asthma drugs without fulfilling established criteria for any of the obstructive pulmonary diseases, just by being at risk of getting COPD<sup>6</sup>.

Exacerbations of COPD are 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 that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication”<sup>7</sup>. COPD exacerbations are caused by a respiratory infection (viral, bacterial or combined) in approximately 80% of cases<sup>8</sup>, and viral infections are also common causes in exacerbations of asthma<sup>9</sup>.

Exacerbations of asthma and COPD can present with all degrees of severity, from prolonged cough after an airway infection (RTI) to life-threatening respiratory distress. Exacerbations are associated with reduced quality of life<sup>10</sup>, premature deaths<sup>1</sup>, and great health care costs<sup>11</sup>. Treatment with antibiotics may be crucial in severe cases, and there is evidence that early treatment may be beneficial in bacterial COPD exacerbations, reducing the admission rate to secondary care<sup>12</sup>. There is also a documented effect of treating exacerbations of asthma and COPD with a course of oral corticosteroids<sup>13</sup>. Such treatment is recommended in current guidelines<sup>7;14</sup>. The average exacerbation rate in COPD patients is probably 2-3 per year<sup>11</sup>.

### *Assessment*

The 2007 GOLD guideline recommends pulse oximetry and chest radiography when assessing COPD exacerbations, while routine use of spirometry is not recommended<sup>7</sup>. The

assessment of COPD exacerbations are, however, still mainly symptom based, and laboratory results and radiographic findings are not included among indications for hospital assessment in GOLD guidelines<sup>7</sup>. Anthonisen set up three criteria for classifying COPD exacerbations in his landmark clinical trial published in 1987: Increased dyspnoea, increased amount of sputum, and increased purulence of sputum<sup>15</sup>. If only one of these symptoms was present, antibiotics could not be recommended. Recommendations on antibiotic treatment for COPD exacerbations are still based on the presence of these symptoms<sup>7;16</sup>.

When Anthonisen's criteria were formulated, there was less awareness about bacterial resistance. Somewhat stricter criteria have been recommended by European guidelines from 2005, reserving antibiotics to COPD exacerbation fulfilling all three of Anthonisen's criteria<sup>17</sup>. Dutch guidelines recommend reserving antibiotics to patients with very poor lung function or other risk factors of severe disease course<sup>14</sup>. We do not know to which degree the guidelines are followed in primary care. In the Netherlands, where antibiotics are less frequently prescribed than in other European countries<sup>18</sup>, co-morbidity has been found to be taken into account when antibiotics are prescribed for COPD exacerbations<sup>19</sup>.

### *Self- management*

To secure early treatment of exacerbations, many GPs provide their asthma and COPD patient with prescriptions of antibiotics and oral corticosteroids to use during forthcoming exacerbations<sup>11;20</sup>. The patients may thus treat themselves without consulting a GP when their disease worsens. In a Norwegian project<sup>21</sup>, asthma and COPD patients were educated on self-care, including better inhaler technique and regulation of medication by symptoms. The regulation included taking oral prednisolone during exacerbations in patients using inhaled corticosteroids, whereas self-treatment with antibiotics was not incorporated. Patients in the intervention group had significantly less GP visit the following year and better health-related quality of life compared to controls. In a Canadian study, supply of both prednisolone and antibiotics were included in the self-management plan. Increased use of both kinds of medicine was observed, but no change in unplanned medical visits<sup>20</sup>. This indicates that supplying patients with antibiotics may lead to over use. Such self-treatment is not recommended in the GOLD guidelines, neither in those developed by International Primary Care Respiratory Group (IPCRG)<sup>22</sup>. Giving patients the responsibility for diagnosis and treatment of exacerbations may delay help-seeking. Some patients want to avoid bothering their doctor<sup>23</sup>, and with the medication at hand they may feel even more reluctant to "disturb" their GP.

### **Gaps of knowledge**

#### *Epidemiology and use of health care*

Exacerbations of asthma and COPD have mainly been described, as they present in secondary care. More than 50% of those consulting an emergency department in USA are admitted to hospital<sup>24</sup>. Other factors than the severity of the exacerbation influence the consultation rate with GPs in UK as well as at emergency rooms in the U.S<sup>23;25</sup>, such as a missing or poor relationship with a GP. In a Dutch and a Swedish study from primary care 53% and 80% of patients with asthma and COPD exacerbation, respectively, were treated with antibiotics<sup>19;26</sup>. Otherwise, evidence from primary care is sparse.

#### *Assessment of asthma and COPD exacerbations*

Supplying patients with prednisolone and antibiotics may reflect an attitude among GPs that examining the patient during exacerbations is often useless, since the condition usually allows a standard treatment. The relevance of differentiating the treatment on the basis of clinical findings and test results needs to be clarified. The European guidelines for lower respiratory

tract infection express a worry about the validity of the Anthonisens criteria: “ It should be noted that these criteria are subjective and based on only one study. More research in this field is needed”<sup>17</sup>.

#### *The CRP test*

Markers of systemic inflammation, like C-reactive protein (CRP), are often elevated in COPD exacerbations, especially when a bacterial infection is present<sup>27-29</sup>. A CRP value above 50 mg/L in hospitalized patients has been found to be associated with poor outcome<sup>30</sup>. A low CRP value may support a decision not to prescribe antibiotics<sup>28</sup>. It has been suggested to add such a marker to the Anthonisen based diagnostic criteria<sup>31;32</sup>. The CRP test is widely implemented as a near patient test in general practice in Scandinavia, and is already applied in assessing COPD exacerbations<sup>26</sup>. More knowledge is needed about the role of the CRP test in the decision whether or not to treat with antibiotics.

#### *Pulse oximetry*

Availability of pulse oximetry is increasing in primary care<sup>33</sup>. Values  $\leq 92\%$  are associated with severe exacerbations<sup>33</sup>, and a routine use of the test in COPD exacerbations has been recommended<sup>34</sup>. More knowledge about the predictive value of pulse oximetry in asthma and COPD exacerbations is needed.

#### *Spirometry*

Spirometry is now a common examination in Norwegian primary care<sup>35</sup>. Spirometry is not recommended as a routine test in COPD exacerbations in the GOLD guidelines. Sick patients often have difficulties in performing properly<sup>7</sup>, and the predictive value of spirometry in these situations seems to be limited<sup>36</sup>. This recommendation is, however, based on data from emergency departments. The picture may be different in primary care, where patients often are less severely ill. For instance, when considering oral corticosteroids, comparison of current and previous spirometries may prove useful.

#### *Self-treatment and health-seeking behaviour*

Supplying COPD patients with prednisolone and antibiotics may ensure prompt treatment of exacerbations. Self-assessment may also lead to over treatment and delayed doctor visits. We do not know how self-management is applied today. An impression that assessment by a doctor is unnecessary may signal a low status of their disease in the society. Expecting patients to treat themselves may thus foster feelings of shame for having a self-inflicted disease<sup>37</sup>, and more knowledge from the patients point of view could be useful.

## **Approaches, hypotheses and choice of methods**

### **The four components of the project**

- Study 1:** A clinical study of asthma and COPD exacerbations in primary care, following patients aged 40 years or more with asthma or COPD during their exacerbations.
- Study 2:** In-depth interviews with patients having moderate or severe COPD, about how they experience access to health care, self-treatment, and emotional barriers in their help-seeking.

**Study 3:** Focus group discussions with GPs and pulmonologists from 6 European countries on their views about assessment and medical treatment of patients with asthma- and COPD exacerbations, including self-treatment.

**Study 4:** A survey among patients hospitalized due to asthma or COPD exacerbations about delay, self-treatment and contact with primary care prior to admittance.

### **Aim of the project**

The aim of the project is to gather new knowledge that can contribute substantially to improved guidelines for assessing and treating patients with asthma- and COPD exacerbations in primary care.

### **Main research questions**

- What is the yearly incidence of asthma and COPD exacerbations leading to doctor visits or self-care with oral corticosteroids or antibiotics among adults 40 years or more diagnosed with asthma or COPD? (Study 1)
- How do adult patients with asthma and COPD present, when visiting a GP during acute exacerbation, in terms of symptoms, clinical findings and test results? (Study 1)
- How do symptoms, chest findings and test results change in asthma and COPD exacerbation during the 3 weeks after the first consultation with a GP. (Study 1)
- Which symptoms, clinical findings, and test result are emphasized by GPs when deciding whether or not to treat with antibiotics, oral prednisolone and hospital referral? (Study 1)
- Which factors predict a favourable or poor outcome of asthma and COPD exacerbations presented in primary care? (Study 1)
- How do COPD patients experience access to health care during exacerbations of their disease, and what do they think about self-treatment? (Study 2)
- Which role do feelings like shame and reflections on social identity play in COPD patients help-seeking behaviour, and how can health care be organized to optimize access to medical help? (Study 2)
- How do European GPs and pulmonologists think exacerbations of asthma and COPD in adults should be assessed and treated, and in particular what role do the Anthonisen's criteria play in the decision on antibiotic treatment? (Study 3)
- What do European GPs and pulmonologists think about self-treatment with antibiotics and oral corticosteroids in exacerbations of asthma and COPD? (Study 3)
- Are there differences in the views of GPs and pulmonologists regarding assessment and treatment of exacerbations of asthma and COPD, and between the doctors of the different European countries, and how are such differences reflected in national guidelines? (Study 3)
- How is the health behaviour in patients with asthma and COPD exacerbations prior to acute admittance to hospital? (Study 4)

### **Material and methods**

#### *Study 1*

380 patients 40 years or older diagnosed with asthma or COPD (or both) have been recruited from 7 GP offices between May 2009 and January 2010. They all have taken part in a baseline examination including registration of recent symptoms (CCQ, a validated questionnaire), chest findings, spirometry with reversibility testing, pulse oximetry, and CRP test. The same kind of spirometers (Spirare II) and oximeters (Onyx II) were used, and the

CRP methodology was quality assured at the 7 offices. The year after baseline the participants are asked to visit their GP during exacerbations, within a few days after the onset of symptoms. Like at baseline, symptoms, chest findings, spirometry, pulse oximetry, and CRP value are recorded, as well as the duration of the actual exacerbation and the treatment given. New appointments with their GP are made after one week and three weeks, and the same examinations will be carried out. Predictive factors for prescribing antibiotics and prednisolone will be evaluated by univariate and multivariate methods (logistic regression) and the predictive value of Anthonisen's criteria will be compared with models including baseline chest findings, spirometry, and laboratory tests by Receiver Operating Characteristic (ROC) curve analyses. Given an average prescription rate of antibiotics of 60%, a 20% difference in prescription rate associated with the presence or absence of a predictor, for instance between a prescription rate of 70% and 50%, respectively, can be detected with 90% probability ( $\beta=0.9$ ) and with less than 5% risk of false positive result ( $\alpha=0.05$ ) when 120 exacerbations are included<sup>38</sup>. A material of 150 exacerbations is thus regarded as sufficient. Approximately half of this number has been included so far. Possible predictors of a poor outcome, such as  $PO_2 \leq 92\%$ ,  $CRP > 50$  mg/L, and severe COPD found by spirometry at baseline, will also be evaluated by univariate and multivariate methods. Measures of poor outcome are unplanned re-consultation, lack of recovery after 3 weeks, and hospitalisation.

All data will be recorded on separate forms marked with the case number, not including name or date of birth, and will be stored in a quality assured computerized storing system (EUTRO) at the University of Tromsø. The study has been approved by the Regional committee for health research ethics.

### *Study 2*

Patients with moderate or severe COPD who have experienced at least one exacerbation last year, will be invited to take part, for instance participants in Study 1 or patients at a local rehabilitation unit. The interviews will be based on the methods described by S Kvale<sup>39</sup>. Grounded theory will be used as the basic methodology and the analytic strategy will follow GT's approach to theoretical sampling, coding and constant comparisons<sup>40</sup>. In the final analysis Nvivo 8 will be used as software tool.

We aim at interviewing 20 patients with exacerbations of COPD, and following the GT approach sampling will be made to obtain theoretical saturation of data.

The interviews will be recorded on MP3 recorders and transcribed before analysis. The transcribed version will be marked with case numbers and stored in an unidentifiable form. The interviews will be carried out after the study has been approved by the Regional committee for health research ethics.

### *Study 3*

GPs and pulmonologists from 6 European countries (Wales, The Netherlands, Germany, Poland, Russia (Arkhangelsk region), Sweden and Norway) will be sampled based on a purposeful and stratified approach<sup>41</sup>. In all countries GPs from both urban and rural practices and pulmonologists from both university hospitals (where possible) and regional hospitals will be invited to participate in a FGD (focus group discussion). One FGD with GPs, one with pulmonologists and one with a mix of the two specialties (a total of 3 FGDS for each country) will be conducted, aiming at 5-8 doctors in each group. The FGDs will follow a prepared interviewguide<sup>42</sup>, the same for all three interviews. The guide will be developed on a common basis to be used in all countries though admitting exceptional variations if there is a need to discuss country/culture specific items.

All FGDs will be recorded on MP3 recorders and transcribed verbatim. The transcribed version will be marked with case numbers and stored in an unidentifiable form. In the final

analysis Nvivo 8 will be used as software tool. Grounded theory will be used as the basic methodology and the analytic strategy will follow GT's approach to theoretical sampling, coding and constant comparisons as in study 2<sup>40</sup>.

Analysis will be based on translated transcripts (to English) and take into account differences in terminology and both social and cultural context of each country when developing final theories from the data. Analytic comparisons will be made within each country's data and also across countries. This requires internal agreement on aims and methods, e.g. equivalent methods in all countries and frequent meetings (Skype or live) among researchers in all phases of the project. The project's organisational structure will be developed to support this. The study needs approval from the ombudsman for personal security in Norway and corresponding bodies in the cooperating countries.

The effort to involve 6 countries in this study is made to provide knowledge on different attitudes and practices among health professionals towards treatment of COPD and to assess their ideas as possible input to improved guidelines for clinical practice. Drawing on more than one country the study will demonstrate possible professional and contextual variations. This may prove fruitful for instructions, teaching and implementation of future guidelines and inspiration for organisation of treatment. Moreover, the approach will create or strengthen networks across professions and countries.

#### *Study 4*

A questionnaire is distributed to patients hospitalized with asthma or COPD exacerbation. Questions are asked about what happened between onset of symptoms and admittance to hospital.. Contacts with health care and self-treatment will be described and whether or not GPs are involved before hospitalization. The GPs actions in terms of treatment and referral will add to the data collected in Study 1. The collection of data will be coordinated by two hospital doctors. The study started 1. January 2010, and during one year it will be possible to include 100 patients from the University hospital and 100 patients from three district hospitals

The methodologies in all four studies represent altogether an interdisciplinary approach to the overall aim of the project. This approach is connected closely to the variation in research questions and hence represents the methodological implication of these. Basically the aim and problems concerning COPD exacerbations call for investigations of different kinds and each methodological approach will be carried out on its own disciplinary premises. It is also the ambition to carry out joint analyses across the four studies in order to let the chosen studies inform each other and obtain rich and robust knowledge on the overall project aim.

### **The project plan, project management, organisation and cooperation**

The project period will start September 1. 2010, and last for three years (see the time schedule in the application scheme). The project period may be extended if the ph.d students work part time general practice in periods. Hasse Melbye, head of AFE Tromsø, will be project leader and involved in all four studies. The project team of Study 1 will also consist of Professor Jørund Straand, head of AFE Oslo, Mette B Risør will be included in the research team of Study 2, whereas Mark Spigt and Mette B. Risør will both be involved in Study 3. In addition to the ph.d. students in the project, ph,d, student at AFE Oslo will take part in preparation of the Study 1 manuscripts, and the two hospital doctors coordinating Study 4 will be involved writing manuscripts as well. The cooperation between the European researchers in Study 3, builds on networking since 1998 through the annual meetings of General Practice Respiratory infection (GRIN) network and through GRACE, a network of excellence study in EU 6<sup>th</sup> framework on lower respiratory tract infections.

### **Relevant resources at the applicant institution**

The project leader has more than 20 years experience in research on respiratory illness in primary care, and Mette Bech Risør is an experienced researcher in the field of health anthropology. Department of Community Medicine, University of Tromsø, hosting AFE Tromsø, has a good reputation in epidemiological research. AFE Tromsø has since 2006 been engaged in GRACE (see over) , The research unit has been responsible for respiratory topics, including spirometry, in the Tromsø Study, a population based health survey.

### **Budget**

Shown in the application scheme

### **Perspectives and compliance with strategic documents**

#### **Compliance with strategic documents and relevance to society**

The study may prepare for better cooperation between primary and secondary care regarding patients with COPD, which has been called for in several documents from health authorities the last years. See the introductory comments on relevance.

#### **Environmental perspectives**

The results of the project may contribute to a decrease in unnecessary use of antibiotics. Over use of antibiotics brings about bacterial resistance, which is a threat for our future health. Better care in rural GP practices may reduce patient travels to hospital.

#### **Ethical aspects**

The participant in Study one will undergo more examinations than usual care, but not examinations considered to be associated with increased health risk. All study participants give written consents, and it will be impossible to recognize any of them when the data are analysed and stored.

#### **Gender equality and gender perspectives**

Both genders will be well represented among study participants and among the researchers.

### **Communication with users and utilisation of results**

#### **Communication with users**

Results will be communicated to GPs and pulmonologist through courses and conferences. The National advisory for COPD, at the National Directory of Health, will also be informed.

#### **Dissemination plan**

Scientific papers addressing the research questions above will be published in international peer-reviewed journals. National coordinators of Study 3 can publish results from a national point of view as soon as the common papers are accepted for publication.

### Reference List

- (1) Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007; 370(9589):765-773.

- (2) Arif AA, Delclos GL, Lee ES, Tortolero SR, Whitehead LW. Prevalence and risk factors of asthma and wheezing among US adults: an analysis of the NHANES III data. *Eur Respir J* 2003; 21(5):827-833.
- (3) Guerra S. Asthma and chronic obstructive pulmonary disease. *Curr Opin Allergy Clin Immunol* 2009; 9(5):409-416.
- (4) Grootendorst DC, Rabe KF. Mechanisms of bronchial hyperreactivity in asthma and chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2004; 1(2):77-87.
- (5) Hoogendoorn M, Feenstra TL, Schermer TR, Hesselink AE, Rutten-van Molken MP. Severity distribution of chronic obstructive pulmonary disease (COPD) in Dutch general practice. *Respir Med* 2006; 100(1):83-86.
- (6) Volla TT, Kopperud GS. [Maintenance treatment of chronic obstructive pulmonary disease]. *Tidsskr Nor Laegeforen* 2008; 128(7):826-828.
- (7) Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176(6):532-555.
- (8) Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359(22):2355-2365.
- (9) Dougherty RH, Fahy JV. Acute exacerbations of asthma: epidemiology, biology and the exacerbation-prone phenotype. *Clin Exp Allergy* 2009; 39(2):193-202.
- (10) Niewoehner DE. The impact of severe exacerbations on quality of life and the clinical course of chronic obstructive pulmonary disease. *Am J Med* 2006; 119(10 Suppl 1):38-45.
- (11) O'Reilly JF, Williams AE, Holt K, Rice L. Defining COPD exacerbations: impact on estimation of incidence and burden in primary care. *Prim Care Respir J* 2006; 15(6):346-353.
- (12) Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 169(12):1298-1303.
- (13) Calverley PM. Effect of corticosteroids on exacerbations of asthma and chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2004; 1(3):161-166.
- (14) Dekhuijzen PN, Broeders ME, Tuut MK, Grol MH. [Practice guideline 'Medical treatment of COPD']. *Ned Tijdschr Geneesk* 2008; 152(26):1465-1468.
- (15) Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106(2):196-204.

- (16) Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;(2):CD004403.
- (17) Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortqvist A et al. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; 26(6):1138-1180.
- (18) Goossens H, Ferech M, Vander SR, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; 365(9459):579-587.
- (19) Bont J, Hak E, Hoes AW, Macfarlane JT, Verheij TJ. Predicting death in elderly patients with community-acquired pneumonia: a prospective validation study reevaluating the CRB-65 severity assessment tool. *Arch Intern Med* 2008; 168(13):1465-1468.
- (20) Beaulieu-Genest L, Chretien D, Maltais F, Pelletier K, Parent JG, Lacasse Y. Self-administered prescriptions of oral steroids and antibiotics in chronic obstructive pulmonary disease: are we doing more harm than good? *Chron Respir Dis* 2007; 4(3):143-147.
- (21) Gallefoss F, Bakke PS. Impact of patient education and self-management on morbidity in asthmatics and patients with chronic obstructive pulmonary disease. *Respir Med* 2000; 94(3):279-287.
- (22) Bellamy D, Bouchard J, Henrichsen S, Johansson G, Langhammer A, Reid J et al. International Primary Care Respiratory Group (IPCRG) Guidelines: management of chronic obstructive pulmonary disease (COPD). *Prim Care Respir J* 2006; 15(1):48-57.
- (23) Shipman C, White S, Gysels M, White P. Access to care in advanced COPD: factors that influence contact with general practice services. *Prim Care Respir J* 2009; 18(4):273-278.
- (24) Tsai CL, Clark S, Cydulka RK, Rowe BH, Camargo CA, Jr. Factors associated with hospital admission among emergency department patients with chronic obstructive pulmonary disease exacerbation. *Acad Emerg Med* 2007; 14(1):6-14.
- (25) Tsai CL, Griswold SK, Clark S, Camargo CA, Jr. Factors associated with frequency of emergency department visits for chronic obstructive pulmonary disease exacerbation. *J Gen Intern Med* 2007; 22(6):799-804.
- (26) Andre M, Vernby A, Odenholt I, Lundborg CS, Axelsson I, Eriksson M et al. [General practitioners prescribed less antibiotics but used the CRP test more. Diagnosis-prescription studies in 2000-2005]. *Lakartidningen* 2008; 105(41):2851-2854.
- (27) Dev D, Wallace E, Sankaran R, Cunniffe J, Govan JR, Wathen CG et al. Value of C-reactive protein measurements in exacerbations of chronic obstructive pulmonary disease. *Respir Med* 1998; 92(4):664-667.

- (28) Weis N, Almdal T. C-reactive protein--can it be used as a marker of infection in patients with exacerbation of chronic obstructive pulmonary disease? *Eur J Intern Med* 2006; 17(2):88-91.
- (29) Hurst JR, Donaldson GC, Perera WR, Wilkinson TM, Bilello JA, Hagan GW et al. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 174(8):867-874.
- (30) Ruiz-Gonzalez A, Lacasta D, Ibarz M, Martinez-Alonso M, Falguera M, Porcel JM. C-reactive protein and other predictors of poor outcome in patients hospitalized with exacerbations of chronic obstructive pulmonary disease. *Respirology* 2008; 13(7):1028-1033.
- (31) Stolz D, Tamm M. Discriminate use of antibiotics for exacerbation of COPD. *Curr Opin Pulm Med* 2009; 15(2):126-132.
- (32) Makris D, Bouros D. COPD exacerbation: lost in translation. *BMC Pulm Med* 2009; 9:6.
- (33) Schermer TR, Jacobs JE, Chavannes NH, Hartman J, Folgering HT, Bottema BJ et al. Validity of spirometric testing in a general practice population of patients with chronic obstructive pulmonary disease (COPD). *Thorax* 2003; 58(10):861-866.
- (34) Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23(6):932-946.
- (35) Joensen L, Melbye H. [Spirometry in general practice in Northern Norway.]. *Tidsskr Nor Laegeforen* 2010; 130(1):33-35.
- (36) Bach PB, Brown C, Gelfand SE, McCrory DC. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. *Ann Intern Med* 2001; 134(7):600-620.
- (37) Arne M, Emtner M, Janson S, Wilde-Larsson B. COPD patients perspectives at the time of diagnosis: a qualitative study. *Prim Care Respir J* 2007; 16(4):215-221.
- (38) Friedman LM. Fundamentals of clinical trials. PSG Publishing Company Inc., Littleton 1985; 10 A.D.
- (39) Kvale S. Interviews. Brinkmann S, editor. Sage publications, Los Angeles 2009.  
Ref Type: Generic
- (40) Strauss A. Basics of qualitative research: techniques and procedures for developing grounded theory. Corbin J, editor. Thousands Oaks, California, Sage 1998.  
Ref Type: Generic
- (41) Patton MQ. Qualitative research & evaluation methods. Sage publications 2002.  
Ref Type: Generic
- (42) Krueger. Focus groups: a practical guide for applied research. Richard A, editor. Thousand Oaks, California, Sage 2000.  
Ref Type: Generic