Author's response to reviews

Title: Usefulness of C-reactive protein testing in acute cough: an open cluster-randomised clinical trial with CRP testing in the intervention group

Authors:

Elena A Andreeva (klmn.69@mail.ru)
Hasse Melbye (hasse.melbye@uit.no)

Version: 2 Date: 22 September 2013

Author's response to reviews: see over
Dear Mr. Editor

Below we are given responses to the reviewers.

Response to Michael Moore

Title:
We would like to keep the old title: Usefulness of C-reactive protein testing in acute cough: an open cluster-randomized clinical trial with CRP testing in the intervention group.

We specified in Methods section that patients with LRTI could be included in the absence of cough. Cough was pointed as one of the main symptoms (59% of participants in the intervention group and 62% in the control group were pointed it as a severe or moderate problem).

A power calculation:
The sample sizes were based on a hypothesis of 20% reduction in antibiotic prescribing in the intervention group, compared to the control group. Differences in referral to chest X-ray between intervention and control group and within each group before and after the intervention were also calculated. Based on Chi-square statistic the required sample size in each group was 72 participants (with a power of 90% and a risk of false positive difference less than 5%).

Method:
Cluster randomization was performed with GPs as units with the use of a computer program. All participants worked in separate out-patient departments (polyclinics), some of them in single GP offices, others within GP partnership (but with doctors, who did not participate in this study). Two months before the trial a baseline study without CRP testing was conducted that included 13 of the 18 participating GPs, using the same case report form (CRF) and examination. All GPs (participating in the baseline study and/or in the trial) were trained in CRP method before the baseline study and randomization.

Results:
The difference in numbers of recruitment between intervention and control was due to practice size. Initially 98 patients were recruited in the control group. During analysis, it became clear that there were incomplete registrations in the CRFs from two GPs, and follow-up data was frequently missing, as was patient consent forms. To assure quality all patients from these two GPs were excluded from the analysis, and we ended up with 78 patients in the control group from.

We compute severity score (similar to that made in the GRACE study. Symptom severity scores calculated with scores for 13 symptoms. The categories for clinicians to rate the severity of each symptom as “no problem,” “mild problem,” “moderate problem,” or “severe problem” were scored 1, 2, 3, and 4, respectively. Scores were calculated for patients with a minimum of 85% (that is, 12 out of 14 symptoms) of their symptoms recorded. This score was scaled to range between 0 and 100 so that it could be interpreted as a percentage of maximum symptom severity. The severity scores were similar in the two groups.
High rate of chest radiography can be explained by the definite recommendation for physicians in RF (as was listed in the background).

The prevalence of pneumonia in our study was somewhat higher than in the study by van Vugt et al and GRACE study (which includes also patients with cough as a dominant symptom or suspected LRTI). This can possibly be explained by season variation in morbidity (winter-spring). The geographical location of the participating GPs (northern part of Russia) and absence of vaccination against pneumococcal infections in this area can probably also be taking into account. All pneumonia cases were confirmed by performing chest radiography which made and reviewed by specialists from radiology departments according to routine.

Discussion
Initially 98 patients were recruited in the control group and we ended up with 78 patients in the control group from. The antibiotic prescribing rate in the inclusion day was lower in the intervention group (37.6%) than in the control group (58.9%) (p = 0.006). The antibiotic prescribing rate in total (during the two weeks) was 40.6% in the intervention group and 71.8% in the control group (p = 0.0001). 12 of the excluded patients from the control group were treated with antibiotics at first visit. When these prescribing are included in the analysis, the prescribing rate in the control group at first visit was 60%, significantly higher than in the intervention group (p = 0.002).

The severity scores were similar in the two groups.

Russian guidelines indicate that chest radiography is mandatory when pneumonia is suspected by symptoms and clinical findings. It can be confirmed for example by the high rate of any abnormal lung sounds among those referred to X-ray (67.8% and 76.6% in intervention and control groups, correspondently). In our study there were more pneumonia in the control group and this strengthens our results.

Recovery rates were evaluated both by a GP and a patient during a follow-up consultation after two weeks of a first consultation. Evaluation was based on the same CRF form (with the same complains, clinical symptoms and findings). Due to the open design this was evaluation was not blinded, and the results should be interpreted with caution. Regretfully we miss data on the duration of illness.

Response to Matthias Briel
Major:

1.) Ch-squared test was used as a statistical method. As long as we have randomized patients we decided to use chi-squared test. Table 1 can justify our method (no difference between groups in the severity score).

2.) The duration of illness at the time of the index consultation did not mentioned in the CRF form. We used the same CRF form as the GRACE study, but regretfully we miss data on the duration of illness. The main inclusion criteria were an acute or worsened cough as the main or dominant symptom, or a clinical presentation suggesting LRTI, < 28 days duration and first consultation for this illness episode.

3.) Recovery rates were evaluated both by a GP and a patient during a follow-up consultation after two weeks of a first consultation. Evaluation was based on the same CRF form (with the same complains, clinical symptoms and findings). Due to the open design this was evaluation was not blinded, and the results should be interpreted with caution. Regretfully we miss data on the duration of illness.
GPs could prescribe any treatment, including antibiotics and other drugs if deemed necessary. They were told that medication should be prescribed after the clinical examination (and after the CRP test in the intervention group), without waiting for chest radiography results.

Minor:
4.) We included this reference in the Discussion section. van Vugt SF, Broekhuizen BD, Lammens C, Zuithoff NP, de Jong PA, Coenen S, leven M, Butler CC, Goossens H, Little P, Verheij TJ; GRACE consortium. Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: diagnostic study. BMJ. 2013 Apr 30;346:f2450. doi: 10.1136/bmj.f2450.

5.) “The authors expressed, however, some doubts regarding the validity of the Cals study, suggesting that the difference between antibiotic prescribing rates in cases and controls was connected with a higher frequency of chest abnormalities among controls [26]” This is related to the severity discussion. In our study there were more pneumonias in the control group and this strengthens our results.

6.) A study by Gonzales and co-workers also indicated that the CRP test provided no additional value beyond clinical decision support in terms of reducing antibiotic use in adults with acute cough [19]. In this study patients with CRP levels between 10 and 20 mg/L should be treated according to the algorithm in the CRP group, which may be one reason for the increased prescribing rate in those tested with CRP test. Another reason was probably less informed doctors, nothing is written in the paper about attending a course on how to interpret CRP values.

7.) The sample sizes were based on a hypothesis of 20% reduction in antibiotic prescribing in the intervention group, compared to the control group. Differences in referral to chest X-ray between intervention and control group and within each group before and after the intervention were also calculated. Based on Chi-square statistic the required sample size in each group was 72 participants (with a power of 90% and a risk of false positive difference less than 5%).

We invited in our study all GPs who participated in the postgraduate program for GP in 2 regions of RF. Cluster randomization was performed with GPs as units with the use of a computer program. All participants worked in separate out-patient departments (polyclinics), some of them in single GP offices, others within GP partnership (but with doctors, who did not participate in this study).

8.) The trial was registered in the ClinicalTrials.gov Protocol Registration System (identification number: NCT01794819

9.) All GPs for each patient fulfilled the CRF after 2 weeks from the first consultation. This form included number of reconsultation, antibiotics taken after inclusion, changing antibiotics and reasons for this. So, GP had opportunity to check if patient took antibiotics or not, changed antibiotics. We could not know whether or not the patient actually took the pills.

Sincerely,
Elena Andreeva, Hasse Melbye.