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Amoxicillin for clinically unsuspected pneumonia in primary care: subgroup analysis

To the Editor:

Antibiotic treatment is recommended for pneumonia [1, 2]. However, some studies have suggested that the milder spectrum of pneumonia in primary care does not have important adverse consequences if missed and, therefore, managed without antibiotics [3–5]. Better insight in the effects of antibiotics for pneumonia in primary care could improve patient information and management.

The aim of our study was to assess whether antibiotic treatment influenced outcome in patients presenting with acute lower respiratory tract infection (LRTI) with a radiologically proven, but clinically unsuspected, pneumonia compared to those without pneumonia.

This was a secondary analysis of a randomized, placebo controlled trial of amoxicillin for acute LRTI in 16 primary research networks in 12 European countries from October 2007 until April 2010. More details on this GRACE-10 study (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe, www.gracelrti.org) have been reported elsewhere [6]. Eligible patients were aged ⩾18 years who consulted their general practitioner (GP) for the first time with an acute cough (duration of ⩽28 days) as the main symptom. Exclusion criteria were clinically suspected pneumonia [7], based on focal chest signs (focal crepitations and bronchial breathing) and systemic features (high fever, vomiting and severe diarrhoea); pregnancy, allergy to penicillin, treatment with antibiotics in the previous month and immunodeficiency. The study was approved by ethics committees in all participating countries and all participants provided written informed consent.

Patients who agreed to randomisation were allocated to receive amoxicillin (1 g three times daily for 7 days) or placebo, by the GP dispensing sequentially numbered randomised containers.

GPs recorded patients' clinical signs, and comorbidities on a case report form. They also registered 14 baseline symptoms (cough, phlegm, shortness of breath, wheeze, runny nose, fever, chest pain, muscle aching, headache, disturbed sleep, feeling generally unwell, interference with normal activities/work, confusion/disorientation and diarrhoea) on a 4-point Likert-scale from "no problem" to "severe problem". Baseline symptom severity was calculated by summing the scores of the symptoms and rescaling them to make them range between 0 and 100. Patients filled in a daily symptom diary during their illness for up to 28 days for the same symptoms on a 7-point Likert scale (0=no problem, 1=very little problem, 2=slight problem, 3=moderately bad, 4=bad, 5=very bad and 6=as bad as it could be). This diary was previously validated and shown sensitive to change [8]. If the diary was not returned after 4 weeks, brief information about symptom duration and severity were collected with either a short questionnaire or a standardised telephone call.

Chest radiographs were taken for each patient within 7 days of first presentation, but preferably within 3 days. Pneumonia was determined by radiologists, who were blind to all other information when they judged chest radiographs. In analysis reported here we defined pneumonia as all patients in whom the radiologist diagnosed pneumonia based on the chest radiograph [9].

Outcomes were duration of symptoms rated by patients as "moderately bad or worse" after initial presentation, symptom severity on days 2–4 after the index consultation, and worsening of illness, defined as a revisit to the GP with worsening symptoms, new symptoms, new signs, or illness necessitating admission to hospital within 4 weeks after the first consultation [6].

The effectiveness of the antibiotics was compared in patients with radiologically proven pneumonia compared to those without pneumonia for all three outcomes. Data were analysed using linear regression models. Cox regression was used for the duration of symptoms allowing for censoring, simple linear regression for symptom severity and logistic regression for worsening of illness. Interaction terms were used to estimate differences in effectiveness of antibiotics in those with radiologically proven pneumonia compared to those without pneumonia for all three outcomes. To assess whether the effect of antibiotics in patients with radiologically proven pneumonia was modified by illness duration before index consultation and baseline symptom severity, we used interaction terms for each outcome. Number needed to harm was calculated.

A total of 2055 patients with acute cough were recruited in the randomised controlled trial (RCT), of which 1905 (93%) underwent a chest radiograph. Patients with a chest radiograph of insufficient quality (n=20) were excluded, resulting in 1885 subjects for analysis. Patients without chest radiograph results were younger and had a higher baseline symptom severity. The mean±SD age of the 1885 subjects was 49 ±16 years and 41% (n=769) were male. Radiologically proven pneumonia was present in 56 (3%) out of 1885. Baseline characteristics did not differ significantly between those with and without pneumonia nor in patients with pneumonia between those allocated to amoxicillin (n=23) and to those allocated to placebo (n=33).

Patients with radiologically proven pneumonia who were allocated to antibiotics had faster resolution of symptoms rated "moderately bad or worse" than those allocated to placebo (median 5 days *versus* 11 days, HR 2.20, 95% CI 1.18–4.08, p=0.013; interaction term for the difference in effect between those with and without pneumonia 2.04, p=0.024) and lower mean (95% CI) symptom severity on days 2–4 were −0.68 (−1.28– −0.08) (p=0.027), although the interaction term was of borderline significance (interaction term −0.63; p=0.050) (table 1). Development of new or worsening symptoms was not different in those allocated to antibiotics as compared to those allocated to placebo (OR 0.33, 95% CI 0.10–1.11; p=0.074) and the effect of antibiotics between those with and without pneumonia was not different (interaction term 0.38; p=0.125). In patients with radiologically proven pneumonia the effect of antibiotics was not modified by illness duration before index consultation and baseline symptom severity for all three outcomes (results not shown) In patients without pneumonia amoxicillin showed no effect (table 1). Nausea, rash, or diarrhoea was recorded by 239 (29%) out of 822 patients in the amoxicillin group and 196 (24%) out of 811 in the placebo group (number needed to harm 21, 95% CI 11–159; p=0.025). Two patients in the placebo group and one in the amoxicillin group needed to be admitted to hospital. No study-related deaths were noted.

Our findings are consistent with recommendations in current guidelines [1, 2] that those with radiologically proven pneumonia appear to derive beneficial effect from antibiotics on symptom duration and symptom severity. The findings from our placebo-controlled study will compliment trials of head to head comparisons between antibiotic classes summarised in the Cochrane review of antibiotics for pneumonia in primary care [10].

In this analysis only patients with clinically unsuspected pneumonia were studied that represent likely the somewhat milder end of the clinical spectrum. In these patients we saw a clear and relevant effect of antibiotics. In addition, power calculation of the original RCT did not include this subgroup analysis of patients with pneumonia, which is another reason why we could have missed some true effects of the intervention. Finally, stratifying all trial patients according to the presence or absence of radiologically proven pneumonia makes it uncertain whether confounders were still randomly distributed between these two groups. However, baseline characteristics did not differ significantly between those allocated to amoxicillin and those allocated to placebo in this subgroup.

Radiologically proven pneumonia which is not clinically suspected at presentation does benefit from antibiotic treatment in terms of symptom duration and symptom severity. This suggests that efforts to detect even the milder and less clear cases of pneumonia in primary care are worthwhile. Since it is not

TABLE 1 Prognostic outcomes for radiologically proven pneumonia in amoxicillin *versus* placebo group compared to those without pneumonia

	Amoxicillin	Placebo	Interaction term (95% CI)	p-value	Analysis	p-value	Missing n (%)
Time to resolution of symptoms rated moderately bad days							
Pneumonia present	5 (2–9)	11 (7–20)	2.04 (1.10–3.80)	0.024	2.20 (1.18–4.08)[¶]	0.013	8 (14.3)
Pneumonia absent	6 (3–12)	7 (4–13)			1.05 (0.95–1.16) [¶]	0.363	182 (9.7)
Symptom severity score on days 2–4 after consultation							
Pneumonia present	1.48±0.95	2.16±1.02	−0.63 (−1.27–0.00)	0.050	−0.68 (−1.28–−0.08)[+]	0.027	10 (17.9)
Pneumonia absent	1.82±1.05	1.87±1.08			−0.05 (−0.15–0.06)[+]	0.365	232 (12.3)
Worsening of illness							
Pneumonia present	5/23 (22)	15/33 (46)	0.38 (0.11–1.30)	0.125	0.33 (0.10–1.11)[§]	0.074	0 (0.0)
Pneumonia absent	149/934 (16)	160/895 (18)			0.87 (0.68–1.11)[§]	0.272	0 (0.0)

Data are presented as median (interquarile range (IQR)), mean±SD, or n/N (%) unless otherwise stated. [#]: interaction addresses the comparison of the effects of amoxicillin between those with and without pneumonia.[¶]: data presented as hazard ratio (95% CI); [+]: data presented as difference (95% CI); [§]: data presented as odds ratio (95% CI).

feasible or cost-effective to perform a chest radiograph in all patients with signs and symptoms of a LRTI in primary care, diagnostic models and the use of point-of-care tests could be useful in improving diagnostic strategies in these patients.

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Clinically unsuspected pneumonia does benefit from antibiotic treatment in terms of duration and severity of symptoms http://ow.ly/T46up

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