Original Article

Amoxicillin for acute lower respiratory tract infection in primary care: subgroup analysis by bacterial and viral aetiology

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ABSTRACT

Objective: We aimed to assess the effects of amoxicillin treatment in adult patients presenting to primary care with a lower respiratory tract infection (LRTI) who were infected with a potential bacterial, viral, or mixed bacterial/viral infection.

Methods: This multicentre randomized controlled trial focused on adults with LRTI not suspected for pneumonia. Patients were randomized to receive either antibiotic (amoxicillin 1 g) or placebo three times daily for 7 consecutive days using computer-generated random numbers (follow-up 28 days). In this secondary analysis of the trial, symptom duration (primary outcome), symptom severity (scored 0–6), and illness deterioration (reconsultation with new or worsening symptoms, or hospital admission) were analysed in pre-specified subgroups using regression models. Subgroups of interest were patients with a (strictly) bacterial, (strictly) viral, or combined infection, and patients with elevated values of procalcitonin, C-reactive protein, or blood urea nitrogen.

Results: 2058 patients (amoxicillin $n = 1036$; placebo $n = 1022$) were randomized. Treatment did not affect symptom duration ($n = 1793$). Patients from whom a bacterial pathogen only was isolated ($n = 207$) benefited from amoxicillin in that symptom severity ($n = 804$) was reduced by 0.26 points (95% CI −0.48 to −0.03). The odds of illness deterioration ($n = 2024$) was 0.24 (95% CI 0.11 to 0.53) times lower from treatment with amoxicillin when both a bacterial and a viral pathogen were isolated (combined infection; $n = 198$).

Conclusions: Amoxicillin may reduce the risk of illness deterioration in patients with a combined bacterial and viral infection. We found no clinically meaningful benefit from amoxicillin treatment in other subgroups. R. Bruyndonckx, Clin Microbiol Infect 2017;■:1

Introduction

Acute lower respiratory tract infection (LRTI) is common in primary care [1]. Antibiotic treatment is of limited benefit both overall and in subgroups at higher risk of an adverse course. Nevertheless, antibiotics are prescribed for most patients with LRTI [2–5]. Primary

analysis of the largest trial to date, the Genomics to combat Resistance against Antibiotics in Community-acquired LRTI (GRACE; http://www.grace-lrti.org) randomized placebo controlled trial (RCT), found no clear evidence of a clinically meaningful benefit from treatment with amoxicillin [2]. A follow-up analysis that examined the benefit of amoxicillin in clinically defined subgroups of patients with LRTI who are most likely to be prescribed antibiotics (i.e. patients with green sputum or those with significant comorbidities) found no clear evidence of meaningful benefit from amoxicillin even

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in these subgroups [3]. Only those patients with evidence of pneumonia on chest X-ray benefited from amoxicillin treatment [6].

However, it is unclear whether patients infected with bacterial pathogens might selectively benefit from antibiotic treatment, and filling this evidence gap could help better target antibiotic prescribing in primary care. This secondary analysis of the GRACE RCT therefore aims to assess whether patients from whom potential bacterial pathogens are isolated receive benefit from amoxicillin treatment. In addition, we aimed to assess whether isolation of a viral pathogen and high levels of C-reactive protein (CRP), blood urea nitrogen (BUN), or procalcitonin (PCT) were associated with benefit from treatment with amoxicillin [7–9].

Methods

Data

The details of the GRACE RCT have been described in detail elsewhere [2]. In summary, non-pregnant adults presenting to primary care with acute cough, in whom pneumonia was not suspected, were recruited between November 2007 and April 2010 by primary care physicians in 16 networks across 12 European countries (Belgium, England, France, Germany, Italy, The Netherlands, Poland, Spain, Slovakia, Slovenia, Sweden, and Wales). Patients who did not consume antibiotics in the month before consultation were randomized to receive either an antibiotic (amoxicillin 1 g) or a placebo three times daily for 7 consecutive days. All patients were asked to complete a symptom diary daily until their symptoms had settled (up to a maximum of 28 days). The diary recorded the severity of cough, phlegm, shortness of breath, wheezing, runny nose, chest pain, muscle ache, headache, disturbed sleep, feeling unwell, fever, and interference with daily activities. Symptoms were scored on a 7-point scale (0: normal/not affected, 1: very little problem, 2: slight problem, 3: moderately bad, 4: bad, 5: very bad, 6: as bad as it could be) [10]. For each patient, a nasopharyngeal swab was taken on the day of presentation. This sample was then analysed using bacterial and viral polymerase chain reaction analysis. We tested for both bacterial pathogens (*Streptococcus pneumoniae*, *Haemophilus influenza*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Bordetella pertussis*, *Legionella pneumoniae*) and viral pathogens (rhinovirus, influenza virus, coronavirus, respiratory syncytial virus, human metapneumovirus, parainfluenza virus, adenovirus, polyomavirus, bocavirus) [11]. Samples with a pathogen present, either bacterial or viral, were referred to as confirmed infections. Samples in which a bacterial pathogen was detected were referred to as bacterial infections. If no viral pathogens were present in these samples, they were referred to as purely bacterial infections. Samples in which a viral pathogen was detected were referred to as viral infections. If no bacterial pathogens were present in these samples, they were referred to as purely viral infections. Samples in which both a bacterial and a viral pathogen were detected were referred to as combined infections. Note that these categorizations are not mutually exclusive. Within 24 hours of presentation to the GP, a venous blood sample was obtained. CRP and BUN were measured using the conventional immunoturbidimetric method. PCT was measured using a rapid sensitive assay [11]. We defined an elevated CRP, PCT, and BUN as the top 25% of measurements in our patient population (referred to as high CRP, high PCT, and high BUN, respectively).

Main outcomes

Symptom duration: The primary outcome was the duration of symptoms rated moderately bad or worse by the patient (score 3 or above) following the initial presentation (in days) [12].

Symptom severity: A secondary outcome was symptom severity, calculated as the mean diary score for all symptoms on days 2–4 (rated by the patient). This time frame was selected because before day 2 antibiotics will have had little chance to provide benefit, and after day 4 the overall symptom severity is less than moderately bad [12].

Illness deterioration: An additional secondary outcome was illness deterioration, defined as a return to the physician with worsening symptoms, new symptoms, new signs or illness requiring admission to hospital within 4 weeks of the initial consultation (documented through a notes review) [13].

Analysis

We fitted a Cox regression model for symptom duration (allowing for censoring), a linear regression model for symptom severity, and a logistic regression model for illness deterioration [14–16]. All analyses controlled for severity of symptoms at baseline and included an interaction term between a particular subgroup (in the studied subgroup or not) and treatment (amoxicillin or placebo). This interaction term was used to assess whether the effectiveness of amoxicillin treatment varied by the subgroup. Similar models, excluding the interaction term, were fitted for patients in the selected subgroup.

The subgroups of interest were patients with a confirmed, bacterial, purely bacterial, viral, purely viral, or combined infection. We were also interested in subgroups with a high CRP, high BUN, or high PCT. Subgroups were not mutually exclusive.

Ethics approval

The study was approved by ethics committees in all participating countries. The competent authority in each country also gave their approval. Patients who fulfilled the inclusion criteria were given written and verbal information on the study and provided written informed consent. The GRACE RCT is registered with EudraCT (2007-001586-15), UKCRN Portfolio (ID 4175), ISRCTN (52261229), and FWO (G.0274.08N).

Results

In total, 2058 patients (out of 2061) that did not consume antibiotics in the month before consultation were randomized. Symptom duration and symptom severity were reported for 87% (1793/2058) and 88% (1804/2024) of patients, respectively. Illness deterioration (or no deterioration) was documented in 98% (2024/2058) of whom 18% (355/2024) experienced illness deterioration. The vast majority of those with illness deterioration represented reconsultation with new or worsening symptoms. Sample size information for subgroup analyses is presented in Fig. 1.

Symptom duration

No subgroups were identified that were significantly more likely to benefit from amoxicillin for the duration of symptoms (in days) rated moderately bad or worse (Table 1).

Symptom severity

Patients with a purely bacterial infection benefitted from amoxicillin treatment (Table 2; interaction term −0.25 (95% CI −0.49 to 0.00); the mean symptom severity score was 0.26 (95% CI −0.48 to −0.03) points lower compared with patients on placebo (Table 2).