Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial

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Summary

Background Lower-respiratory-tract infection is one of the most common acute illnesses managed in primary care. Few placebo-controlled studies of antibiotics have been done, and overall effectiveness (particularly in subgroups such as older people) is debated. We aimed to compare the benefits and harms of amoxicillin for acute lower-respiratory-tract infection with those of placebo both overall and in patients aged 60 years or older.

Methods Patients older than 18 years with acute lower-respiratory-tract infections (cough of ≤28 days' duration) in whom pneumonia was not suspected were randomly assigned (1:1) to either amoxicillin (1 g three times daily for 7 days) or placebo by computer-generated random numbers. Our primary outcome was duration of symptoms rated "moderately bad" or worse. Secondary outcomes were symptom severity in days 2–4 and new or worsening symptoms. Investigators and patients were masked to treatment allocation. This trial is registered with EudraCT (2007-001586-15), UKCRN Portfolio (ID 4175), ISRCTN (52261229), and FWO (G.0274.08N).

Findings 1038 patients were assigned to the amoxicillin group and 1023 to the placebo group. Neither duration of symptoms rated "moderately bad" or worse (hazard ratio 1·06, 95% CI 0·96–1·18; p=0·229) nor mean symptom severity (1·69 with placebo *vs* 1·62 with amoxicillin; difference –0·07 [95% CI –0·15 to 0·007]; p=0·074) differed significantly between groups. New or worsening symptoms were significantly less common in the amoxicillin group than in the placebo group (162 [15·9%] of 1021 patients *vs* 194 [19·3%] of 1006; p=0·043; number needed to treat 30). Cases of nausea, rash, or diarrhoea were significantly more common in the amoxicillin group than in the placebo group (number needed to harm 21, 95% CI 11–174; p=0·025), and one case of anaphylaxis was noted with amoxicillin. Two patients in the placebo group and one in the amoxicillin group needed to be admitted to hospital; no study-related deaths were noted. We noted no evidence of selective benefit in patients aged 60 years or older (n=595).

Interpretation When pneumonia is not suspected clinically, amoxicillin provides little benefit for acute lower-respiratory-tract infection in primary care both overall and in patients aged 60 years or more, and causes slight harms.

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Introduction

Acute uncomplicated lower-respiratory-tract infection is the most common acute illness managed in primary care in developed countries; most patients receive antibiotics, even in low-antibiotic-prescribing countries.[1–4] Many patients worry about severe symptoms,[5] and clinicians are keen to appropriately treat acute bacterial infections to avoid medicolegal consequences, provide symptomatic benefit, and avoid complications (especially community-acquired pneumonia).[3,6–8] However, the prescription of antibiotics has costs, including the purchase of the drugs themselves, dispensing costs, and costs associated with increased reconsultation because of the medicalisation of self-limiting illness.[9,10] Primary care prescribing of antibiotics is one of the main drivers of resistance, which is also a major threat.[11]

Consensus opinion has been to restrict antibiotic use in acute lower-respiratory-tract infections.[12–15] However, a Cochrane review[16] of the use of antibiotics for acute bronchitis showed moderate benefits—eg, a number needed to treat of 6 for cough, almost halving the number of patients not improving, and no significant short-term harms. Thus, the debate about the balance of benefit and harm continues, especially because of the scarcity of data from placebo-controlled trials for important symptomatic outcomes for patients, such as the number of days feeling ill (fewer than 500 patients were included in the Cochrane review[16]). Which subgroups of patients will probably benefit from treatment, and particularly the effects in older patients (in whom most complications occur), are also debated.[3] Most clinicians tend to prescribe antibiotics for older people with severe illness and major comorbidities, but the role of drugs in fitter older patients is unclear.

We aimed to provide robust estimates of the benefits and harms of amoxicillin in acute uncomplicated community-

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acquired lower-respiratory-tract infections, particularly for important symptomatic outcomes for patients, both overall and in older patients.

Methods

Study design and patients

We did a parallel, randomised, placebo-controlled trial. Patients were recruited between Nov 15, 2007, and April 14, 2010 (the predefined cutoff defined by the trial steering committee), at primary care practices in 16 networks in 12 European countries (Belgium, England, France, Germany, Italy, the Netherlands, Poland, Slovakia, Slovenia, Spain, Sweden, and Wales). Recruitment rates were low because of time pressures during the first winter season, so further networks in France, Poland, Slovakia, and Slovenia were recruited; these networks joined during the winter of 2008–09. Additionally, two of the original networks had difficulty obtaining approval from the competent authority, so did not start recruting until the second winter. Trial procedures were all shown to be feasible and thus no changes in documentation or process were necessary.

Eligible patients were aged 18 years or older and consulting for the first time with either an acute cough (≤28 days' duration) as their main symptom, for which non-infective diagnoses were judged very unlikely, or an illness in which cough was not the most prominent symptom but the clinician thought acute lower-respiratory-tract infection the most probably diagnosis.

We excluded patients in whom the initial clinical diagnosis was community-acquired pneumonia[17] (ie, complicated lower-respiratory-tract infection) on the basis of focal chest signs (focal crepitations, bronchial breathing) and systemic features (high fever, vomiting, severe diarrhoea). We did not use a formal clinical prediction rule for the diagnosis of pneumonia because of the absence of consensus about which rule to use.[18–21] Patients were excluded pragmatically when the working diagnosis was cough of non-infective cause (eg, pulmonary embolus, left ventricular failure, oesophageal reflux, allergy); antibiotics had been used in the previous month; they were unable to provide informed consent or complete a diary (eg, if they had dementia, psychosis, or severe depression); or they were pregnant, allergic to penicillin, or had immunological deficiencies. Previous diagnoses of asthma, chronic obstructive pulmonary disease, and other comorbid disorders were not exclusion criteria, and thus acute infective exacerbations were included.

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.

Randomisation and masking

Trial drugs were block randomised by Scott Harris, a statistician in our research group who is independent of the GRACE consortium. The random code was sent as a password-protected list and as a hardcopy to the manufacturer, Almac (Armagh, UK). Both clinicians and patients were masked to the randomisation sequence, and all outcome data were gathered masked to allocation status.

Almac prepared containers with the contents (amoxicillin or placebo) determined by a computer-generated random number list provided by a statistician who was independent of the trial statisticians. The amoxicillin and placebo were manufactured to be identical in appearance, taste, and texture. The randomisation codes for amoxicillin or placebo were kept by the manufacturer and the designated pharmacist at the University Medical Center, Utrecht. A 24 h unmasking service also had access to the list to break the code in an emergency. Unmasking was acceptable when requested by clinicians for clinical reasons, such as adverse events—eg, anaphylaxis, hospital admission with life-threatening illness (such as severe sepsis, meningitis, severe pneumonia necessitating admission to intensive-care unit), death.

Procedures

Patients were recruited consecutively by clinicians in each practice (to the extent possible within the time constraints of daily practice). Those who agreed to randomisation were allocated (1:1) to receive three times daily either 1 g amoxicillin or placebo for 7 days by the clinician, who dispensed sequentially numbered randomised containers. Recruiting health-care professionals had to keep non-recruitment logs and record reasons for not screening patients. The dose was based on a Monte Carlo simulation; we aimed to reach a minimum inhibitory concentration of roughly 1·5 mg/L to cover *Haemophilus influenzae* and intermediately resistant pneumococci for 90% of the intended population (taking into account countries with high rates of antibiotic use and well documented pneumococcal resistance). We estimated that, to achieve bacterial eradication, concentrations needed to be higher than the minimum inhibitory concentration for at least 5 days. We chose a 7 day course for acceptability to clinicians and to allow for poor compliance.

The responsible clinician recorded comorbidities, clinical signs, and the severity of baseline symptoms reported by the patient on a case report form. Each symptom was rated as "no problem", "mild problem", "moderate problem", or "severe problem". Clinical characteristics were compared with a recent observational study[1] that used the same clinical pro forma but was much less time intensive, and so recruited eligible patients more quickly.

After consultation with the responsible clinician, patients completed a daily symptom diary for the duration of the illness (to a maximum of 28 days). The diary items recorded the severity of cough, phlegm, shortness of breath, wheeze, blocked or runny nose, chest pain,

muscle aches, headaches, disturbed sleep, general feeling of being unwell, fever, and interference with normal activities. Each symptom was scored on a scale from 0 to 6 (0=no problem, 1=very little problem, 2=slight problem, 3=moderately bad, 4=bad, 5=very bad, 6=as bad as it could be). Patients also recorded non-respiratory symptoms, such as diarrhoea, skin rash, and vomiting. This diary has previously been validated and is sensitive to change and internally reliable (Cronbach's α 0·75).[9,22] All study materials were translated into relevant local languages. Back translations were checked to ensure consistency of meaning between networks.[1]

Members of the research team telephoned participants after 4 days to offer support and answer any questions about completion of the diary. If the diary was not returned after 4 weeks, we collected brief information with either a short questionnaire or a standardised telephone call about symptom duration and severity. Participating clinicians registered all contacts with patients for 4 weeks after the initial consultation, including referral to hospitals and out-of-hours contacts.

Outcomes

We specified three key outcomes, which were intended to capture important symptomatic outcomes for patients, before the trial. These outcomes did not change when the trial began. Our primary outcome was the duration of symptoms rated by patients as "moderately bad" or worse after initial presentation. We chose this endpoint because it was easy for patients and physicians to understand.

Symptom severity and new or worsening symptoms were secondary endpoints. Symptom severity was measured as the mean diary score for all symptoms during days 2–4 after the index consultation.[9]

We defined new or worsening symptoms as a return to the physician with worsening symptoms, new symptoms, new signs, or illness necessitating admission to hospital within 4 weeks after the first consultation (established from reviews of patients' notes).

Statistical analysis

For symptom duration and severity, our priority was to estimate the probable benefit of antibiotics. The null hypothesis was that antibiotics provide no benefit for important symptomatic outcomes for patients, neither overall nor for people aged 60 years or older. We assumed an α of 0·01 (for multiple outcomes), 80% power, and 20% loss to follow-up, and estimated that 544 patients would be needed in each age group to detect a 0·33 standardised difference between groups (equivalent to 1·5 days of symptoms rated "moderately bad", or one patient in three rating the diary components "a slight problem" instead of "a moderately bad problem"). For the total cohort we estimated that 1110 patients overall would detect a 0·23 standardised difference between groups, equivalent to a day of symptoms labelled "moderately bad". Differences much smaller than this cutoff are

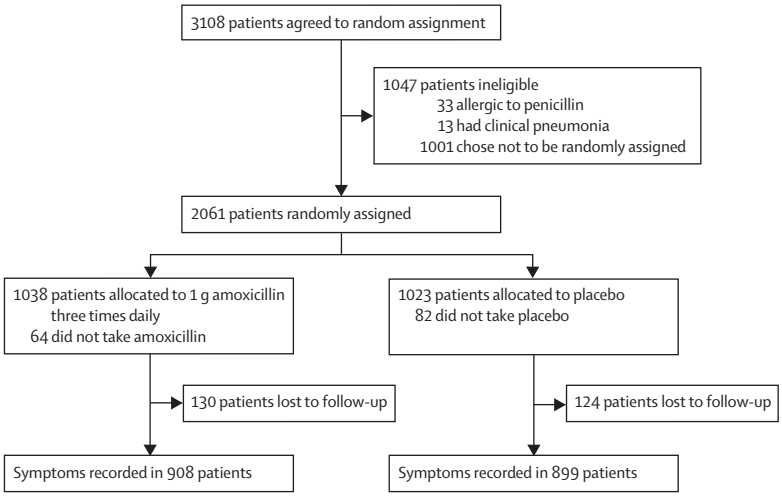

Figure 1: **Trial profile**

	Amoxicillin	Placebo
Women	624/1038 (60·1%)	600/1023 (58·7%)
Age (years)	48·6 (16·7)	49·3 (16·4)
Non-smoker (past or present)	477/1037 (46·0%)	483/1022 (47·3%)
Illness duration before index consultation (days)	9·5 (8·0)	9·3 (7·2)
Respiratory rate (breaths per min)	16·9 (3·3)	16·9 (3·3)
Body temperature (°C)	36·7 (3·3)	36·8 (3·3)
Lung disease*	163/1037 (15·7%)	147/1023 (14·4%)
Mean severity score (all symptoms)†	2·1 (0·5)	2·1 (0·5)
Mean severity score (cough)†	3·1 (0·7)	3·2 (0·7)
Sputum production	814/1036 (78·6%)	824/1021 (80·7%)
Discoloured sputum‡	481/968 (49·7%)	468/957 (48·9%)

Data are n/N (%) or mean (SD). *Chronic obstructive pulmonary disease or asthma. †Severity of symptoms: 1=no problem; 2=mild problem; 3=moderate problem; 4=severe problem. ‡Green, yellow, or bloodstained.

Table 1: **Baseline characteristics**

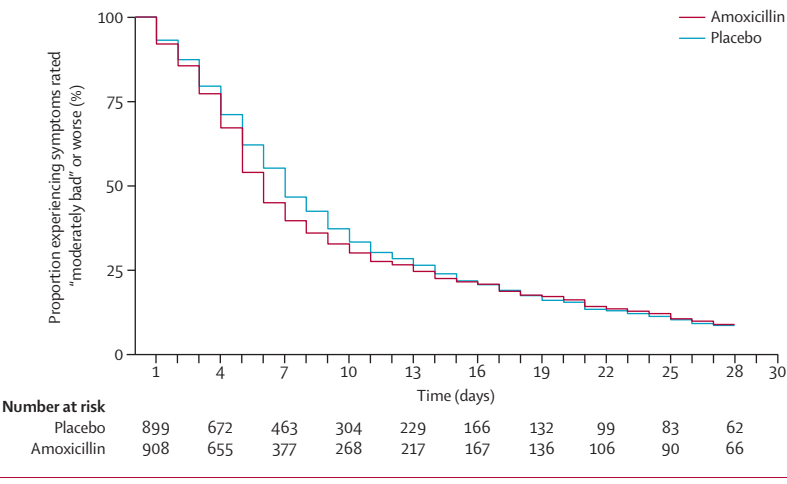

Figure 2: **Kaplan-Meier estimates for duration of symptoms rated "moderately bad" or worse**

	n	Hazard ratio (95% CI)	p
Whole cohort	1799	1·06 (0·96–1·18)	0·229
Age 60 years or older	550	0·95 (0·79–1·14)	0·555
Age younger than 60 years	1249	1·12 (0·98–1·24)	0·071

Table 2: **Resolution of symptoms rated "moderately bad" or worse in amoxicillin group versus placebo group**

	n	Placebo	Amoxicillin	Difference (95% CI)	p
Whole cohort	1789	1·69 (0·84)	1·62 (0·84)	–0·07 (–0·15 to 0·007)	0·074
Age 60 years or older	547	1·50 (1·02)	1·47 (0·94)	–0·03 (–0·17 to 0·11)	0·676
Age younger than 60 years	1242	1·78 (0·85)	1·69 (0·85)	–0·08 (–0·18 to 0·01)	0·073

Data are mean (SD) unless otherwise specified. Each symptom was scored from 0 to 6 (0=no problem, 1=very little problem, 2=slight problem, 3=moderately bad, 4=bad, 5=very bad, 6=as bad as it could be).

Table 3: **Mean symptom severity score on days 2–4 after consultation (controlling for baseline symptom severity)**

	Amoxicillin	Placebo	Odds ratio (95% CI)	p	Number needed to treat (95% CI)
Whole cohort	162/1021 (15·9%)	194/1006 (19·3%)	0·79 (0·63 to 0·99)	0·043	30 (16 to 811)
Age 60 years or older	54/285 (18·9%)	58/299 (19·4%)	0·97 (0·64 to 1·47)	0·890	222 (17 to –15)
Age younger than 60 years	108/736 (14·7%)	136/707 (19·2%)	0·72 (0·55 to 0·95)	0·021	22 (13 to 128)

Data are n/N (%) unless otherwise specified.

Table 4: **Worsening of illness in the amoxicillin group versus placebo group**

unlikely to be clinically significant.[9] For new or worsening symptoms, we assumed an α of 0·05, 80% power, 5% loss to follow-up, and that 15% of patients suffer new or worsening symptoms, and estimated that 586 patients in each age group could detect a 50% reduction as a result of antibiotics, and a total cohort of 1500 could detect a 33% reduction (ie, from 15% to 10%). Thus, our minimum sample size target was 586 patients in each age group and 1500 for the total cohort; our maximum target was 1500 patients in each age group.

We did all analyses masked to treatment allocation. We did not do an interim analysis. Subgroup analyses of patients aged 60 years or older were specified in advance. We decided to do a secondary analysis for patients aged 70 years or older after completion of data collection. We used linear regression models that controlled for the severity of baseline symptoms—specifically, Cox regression for the duration of symptoms allowing for censoring, simple linear regression for symptom severity, and logistic regression for deterioration of illness. We assessed any evidence of a difference in benefit for patients aged 60 years or older versus the younger group by estimating interaction terms for each outcome. Separate estimates were made for participants aged 60 years or older and for those aged 70 years or older. Our primary analyses included patients for whom we had outcome data (ie, complete cases) on an intention-to-treat basis. We assessed the possible effects of loss to follow-up by estimating the change in hazard ratio (HR) for several assumptions about resolution of symptoms in patients with missing data. Number needed to treat and number needed to harm were calculated. No per-protocol analysis was done. We checked that the groups were balanced by country, practice, and network.

We used Stata (version 11.2) for all analyses. For interpretation we used a significance threshold of 5% for the primary outcome and 1% for the secondary outcomes to minimise the chance of type I error with multiple outcomes. The trial was registered with EudraCT (Eudract-CT 2007-001586-15) in November, 2007, and in January, 2009, we obtained an ISRCTN number (ISRCTN52261229). Trial procedures did not change between the two registrations.

Role of the funding source

The funding sources had no roles in data collection, analysis, or interpretation; report writing; or submission. PL, MM, and BS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had responsibility for the final decision to submit for publication.

Results

3108 patients agreed to participate during recruitment; 2061 were randomly assigned—1038 to the amoxicillin group and 1023 to the placebo group (figure 1). Recruitment took more than 30 min. Because of time pressures during winter, not all potentially eligible patients were screened, and completion of non-recruitment logs was poor (data not shown). Lack of time was the main reason given for not screening, and was reported by 44 (92%) of 48 health-care professionals. Only three (6%) health-care professionals reported that patients' clinical state restricted recruitment. 595 (28·9%) of the trial population were aged 60 years or older; 310 (15·0%) had asthma or chronic obstructive pulmonary disease; and 1966 (95·8%) of 2052 had dyspnoea, sputum, or fever (nine patients had missing data). Table 1 shows the baseline clinical characteristics of the amoxicillin and placebo groups.

Symptom duration was documented in 1799 (87·3%) participants and symptom severity in 1789 (86·8%). New or worsening symptoms were measured in 2027 (98·3%) participants; 356 (17·6%) had new or worsening symptoms. 778 (92·4%) of 842 participants in the amoxicillin group and 746 (90·1%) of 828 in the placebo group reported taking study drug at day 5 in their diaries (by which stage bacteria should have been eradicated).

Symptoms rated "moderately bad" or worse lasted a median of 6 days in the amoxicillin group (IQR 3–11) and 7 days (4–14) in the placebo group; the difference between

	n	Original model with missing data		All patients with missing data resolved on day 1		All patients with missing data resolved on day 28		All patients with missing data unresolved on day 28	
		Effect	p	Effect	p	Effect	p	Effect	p
Whole dataset	1799	1·06	0·229	1·06	0·237	1·05	0·316	1·05	0·311
Age 60 years or older	550	0·95	0·555	0·96	0·637	0·97	0·720	0·96	0·638
Age younger than 60 years	1249	1·12	0·071	1·11	0·101	1·08	0·163	1·10	0·130

Table 5: **Effect of different assumptions about missing data on hazard ratios of amoxicillin versus placebo for resolution of symptoms rated "moderately bad" or worse**

the groups was not significant (HR 1·06, 95% CI 0·96–1·18; p=0·229; figure 2, table 2, appendix). Duration of symptoms rated "moderately bad" or worse did not differ significantly between the older age group and the younger age group (interaction term 0·86; p=0·116) and and no selective benefit was noted in the older age group. Symptom severity did not differ between treatment groups (table 3), and no selective benefit was detected in the older age group (interaction term 0·06; p=0·47). In the 266 participants aged 70 years or older, the differences between treatment groups for symptom severity (–0·04, 95% CI –0·21 to 0·12; p=0·614) and symptom duration (HR 0·96, 95% CI 0·94–1·16; p=0·432) were not significant (data not shown). Exclusion of patients with asthma or chronic obstructive pulmonary disease made little difference to the estimates of duration of symptoms rated "moderately bad" or worse (HR 1·04).

Significantly fewer individuals experienced new or worsened symptoms in the amoxicillin group overall than in the placebo group (table 4), but the number needed to treat was high (30). No significant differences were noted in the older age group.

Controlling for network did not significantly affect findings. Between groups, the HR for duration of symptoms was 1·06 (95% CI 0·96–1·18; p=0·229), difference in symptom severity was –0·07 (–0·15 to 0·01; 0·085), and odds ratio for new or worsening symptoms was 0·80 (0·63–1·02; 0·067).

Nausea, rash, or diarrhoea was recorded by 249 (28·7%) of 867 participants in the amoxicillin group and 206 (24·0%) of 860 in the placebo group (number needed to harm 21, 95% CI 11–174; p=0·025). No study-related deaths were noted. Three patients (two in the placebo group and one in the amoxicillin group) were acutely admitted to hospital for respiratory or cardiovascular issues during the month after randomisation. One patient in the amoxicillin group had documented anaphylaxis.

Assumptions about missing study data did not significantly affect our results and thus our inferences remain acceptable (table 5).

Discussion

To our knowledge, this trial is the largest multicentre randomised placebo-controlled study of antibiotics for acute, uncomplicated lower-respiratory-tract infection (panel). We noted that amoxicillin did not significantly reduce the duration of symptoms rated "moderately bad" or worse or symptom severity compared with placebo. Our cohort had similar clinical characteristics to the previous observational cohort recruited in these networks[1] and other cohorts of people with lower-respiratory-tract infections.[1,9,27,28]

See Online for appendix

The applicability of our findings is strengthened by the international nature of the trial and the broad, pragmatic inclusion criteria. These properties could mean that our population is heterogeneous, but such demographics represent the diagnostic realities of daily practice because no accepted diagnostic algorithm to identify patients with infection is available, and no universally agreed definition exists for the diagnosis of uncomplicated lower-respiratory-tract infection.[16] We used criteria consistent with consensus exercises[29] and similar to those of previous pragmatic trials, large cohorts, and observational studies.[1,28,30,31]

Most patients in our study had acute cough with sputum. When we excluded key groups such as patients with asthma or chronic obstructive pulmonary disease or those aged 60 years or older, our results were little affected, suggesting that our findings can probably be generalised to most patients with clinically defined acute lower-respiratory-tract infection in primary care (where nearly all such infections are managed). Recruitment was slow, and feedback during and after the study clarified that this rate of recruitment was because of time pressures, which were very intensive for the acute setting. Although roughly a third of patients chose not to be randomly assigned, we noted no evidence of recruitment bias compared with the observational studies done in the same recruiting network, which used very similar baseline clinical pro forma and had patients with very similar characteristics (80% had sputum and 15% had other lung disease).[1] Our choice of antibiotic might have restricted efficacy, but the chosen dose of amoxicillin effectively treated more than 90% of all isolates in Europe. The size of the older age group restricted the power to assess a reduction in deterioration in illness. Similarly, some other clinical subgroups might benefit from amoxicillin. Poor adherence could have diminished efficacy, but more than 90% of patients in both groups reported taking the study drugs by day 5, and adherence is probably better in a trial than in routine care.[32]

Our study provides further evidence for the long natural history of lower-respiratory-tract infections. In previous studies,[1,9] most people had clinically significant symptoms

Panel: Research in context

Systematic review

The authors of a Cochrane review[16] searched the Cochrane Central Register of Controlled Trials (including the Acute Respiratory Infections Group's specialised register), Medline (for studies published between 1966, and week 4 of August, 2010), and Embase (for studies published between 1974, and September, 2010) for randomised controlled trials of antibiotics in patients with acute bronchitis (including acute cough with or without sputum production). The main search terms used were "exp bronchitis", "bronchit*.tw.", "(bronchial adj2 infect*).tw", "exp respiratory tract infections", and "exp anti-bacterial agents"; the appendix contains a full list of terms used. The placebo-controlled studies identified in the review provide little evidence of important symptomatic outcomes; at follow-up, patients given antibiotics were less likely to have a cough than were those given placebo (risk ratio 0·64, 95% CI 0·49–0·85; number needed to treat 6), but these results came from only four studies[23–26] with 275 participants in total. Patients given antibiotics were also less likely to have a night cough (0·67, 0·54–0·83; 7), but this finding was noted in a population of only 538 participants. Numbers of patients were small for the outcomes of feeling unwell (n=435) or activity limitation (393). The review provided no data about the role of antibiotics in subgroups of patients—particularly the fit elderly.

Interpretation

Our trial is the largest study so far of the use of antibiotics in acute lower-respiratory-tract infection, and adds much to the placebo-controlled evidence noted in the Cochrane review, especially data for patients aged 60 years or older.[16] Compared with placebo, amoxicillin did not significantly affect the duration of symptoms rated "moderately bad" or worse in the first few days of infection, neither overall nor in patients older than 60 years. Symptom severity also did not differ significantly between treatment groups. Amoxicillin prevented some patients from developing new or worse symptoms but the number needed to treat was high and matched by a similarly sized number needed to harm for side-effects. Our data suggest, if anything, a smaller benefit from antibiotics for symptoms and a clearer estimate of harms than did the Cochrane review. Thus, unless pneumonia is suspected, antibiotics should not be prescribed for patients with acute lower-respiratory-tract infection.

for more than a week before presentation and severe symptoms for about 7 days afterwards (and milder symptoms for even longer).

Neither duration of symptoms nor symptom severity was significantly affected by amoxicillin. Symptom severity was measured as the mean diary score for all symptoms during days 2–4 after the index consultation because this period is when symptoms are rated as the worst problem by patients. Before day 2, antibiotics will have had little chance to provide benefit and after day 4, although some symptoms remain "moderately bad" or worse, mean diary scores for all symptoms tend to be rated less than "moderately bad".

Although new or worsening symptoms developed significantly less often in the amoxicillin than in the placebo group, the number needed to treat was high, and three patients only had to be admitted to hospital. The definition of new or worsening symptoms used was useful and workable in previous studies of respiratory-tract infection in the community.[33] Because so few patients needed to be admitted to hospital, the outcomes effectively represent symptom control. Our findings are consistent with those of a Cochrane review of antibiotics for acute bronchitis[16] and consensus guidance,[15] but suggest that amoxicillin is even less beneficial than was noted in the placebo-controlled trials in the Cochrane review (possibly because of differences in setting and spectrum bias). Any moderate benefits need to be balanced against the probable slight harms from treatment (number needed to harm was about 20 for rash, nausea, or diarrhoea in the amoxicillin group). The restricted benefit of antibiotics might partly be because, for most acute lower-respiratory-tract infections in primary care, bacterial pathogens can only be identified in a few patients.[28,30] In view of the small numbers of patients who benefit from antibiotic treatment, the challenge is to identify these individuals.

Previous estimates of benefit of antibiotics in older patients have varied; one study of doxycycline showed a benefit,[33] but another of amoxicillin did not.[9] However, the numbers of patients included in these studies were small, and the CIs for the estimates of effect were wide.

Our results suggest strongly that for older patients in whom pneumonia is not suspected, amoxicillin has very little effect. However, severely ill older patients with several comorbidities are unlikely to have been approached to participate in the trial, so these findings should be interpreted cautiously and not extrapolated to a generally unwell older population.[15]

In conclusion, amoxicillin provides little symptomatic benefit for patients presenting in primary care who are judged to have clinically uncomplicated lower-respiratory-tract infections. Any mild, short-term benefits of antibiotic treatment should be balanced against the risks of side-effects and, in the long-term, of fostering resistance.

Contributors

PL, TV, CCB, SC, and HG proposed the initial idea for the study. All authors contributed to the development of the protocol and study management. GO'R and CB led the day-to-day management of the study (supervised by PL and TV, respectively). HG led the funding application and coordinated the GRACE consortium overall. PL, BS, and MM analysed the data; all authors interpreted the data and contributed to the write-up.

Conflicts of interest

We declare that we have no conflicts of interest.

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