Comparison of amoxycillin and clarithromycin as initial treatment of community-acquired lower respiratory tract infections

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SUMMARY

Background. *Numerous new oral antibiotics have been produced over the last few years with the aims of improving treatment for lower respiratory tract infections.*

Aim. *The aim of the study was to compare the efficacy of an established drug, amoxycillin, with a new macrolide, clarithromycin, for initial treatment of adults with community-acquired lower respiratory tract infection.*

Method. *Consecutive adults fulfilling a standard definition of lower respiratory tract infection presenting to 14 general practitioners in two neighbouring practices were allocated to antibiotic therapy in a random, single-blind manner. The outcome of treatment was assessed by the time taken by the patient to return to normal activities or work, the speed of resolution of symptoms, number of repeat consultations and side effects.*

Results. *The profile of the 221 patients receiving amoxycillin was very similar to that of the 221 receiving clarithromycin. The two groups did not differ greatly in requirement to visit the general practitioner again within either 4 weeks (20% amoxycillin group; 25% clarithromycin group) or 3 months (31% compared with 36%) of the original infection, in time taken to return to normal activities (6 days for group taking amoxycillin; 5 days for those on clarithromycin) or work (5 days for both groups), or in speed of resolution of symptoms. Compliance was good and the side-effects reported were similar for both groups. No increase in gastrointestinal complaints was noted for patients taking the macrolide.*

Conclusion. *Amoxycillin and clarithromycin appear to be equally effective as initial therapy and to be tolerated in similar ways. Use of the newer drug appears to have no advantages over use of the accepted standard treatment.*

Keywords: oral antibiotics; randomized drug trial; lower respiratory tract infections.

Introduction

ACUTE respiratory tract infections are the most common cause of general practitioner consultation, antibiotic prescription and loss of time from work.[1-3] It is generally suggested that atypical pathogens and viruses account for many infections,[4-6] although recent studies have suggested that the spectrum of pathogens causing lower respiratory tract infections is similar to that causing pneumonia.[7,8] Although amoxycillin is the antibiotic chosen by general practitioners for initial treatment of these infections, description of new pathogens and increasing concern about the rise in antibiotic resistance by common respiratory bacteria bring into question the use of this drug.[5,9,10] In a recent study, one-quarter of patients treated with amoxycillin for a lower respiratory tract infection returned for a second consultation, in most cases because of unsatisfactory clinical progress.[7]

This study was set up to compare the efficacy of amoxycillin with a new macrolide (clarithromycin) as a first-line treatment for adults presenting with a lower respiratory tract infection. The outcome was assessed in terms of time taken to return to normal activities, time off work and requirement for further consultation with the general practitioner.

Method

The study was conducted over a period of 30 weeks over the winter period commencing at the beginning of October 1993. Consecutive series of adults aged 16 years and older presenting to 14 general practitioners in two neighbouring practices serving a stable, suburban population in Nottingham were studied.

The definition of lower respiratory tract infection used in the study was as previously described.[7] To be included in the study, the following features were required:

1. The patient presented with a new or increasing cough productive of sputum and associated with at least one other lower respiratory tract feature (including shortness of breath, wheeze, retrosternal soreness, chest pain, new focal or diffuse signs on chest examination)
2. One or more constitutional symptoms including fever, sweats, headache, generalized aches and pains, sore throat, or coryza
3. Antibiotic is prescribed as treatment
4. The patient had received no antibiotics in the 14 days before the trial.

The general practitioner completed a standard clinical data sheet for each patient, including details of past medical history. The study design did not require any investigations to be performed. The patient was asked to complete an initial symptom card and was allocated randomly by the practice nurse to a particular trial therapy.

Patients received either amoxycillin (250 mg three times daily) or clarithromycin (250 mg twice daily) for 7 days. The choice was blinded from both the general practitioner and practice nurse, the antibiotic course being contained within identical numbered boxes.

The patient was asked to fill out a daily symptom diary for 10 days. On the eighth and fifteenth days of the study, the research administrator (JP) conducted a structured interview by telephone with each patient. This interview elicited information about

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symptoms, general and social consequences of the illness and side-effects. A residual antibiotic tablet count was made on the eighth day by the study administrator to assess patient compliance.

Further details on any patients who had to pay a further visit to their general practitioner because of the illness in the following 4 weeks were recorded on the study forms and any visits in the subsequent 2 months were noted.

Levels of statistical significance were computed by a chi-squared test of independence.

Results

During the study period, 442 adults were entered into the study, of whom 221 received amoxycillin (group A) and 221 received clarithromycin (group C). A further 181 patients were excluded from the study for the following reasons: history of relevant antibiotic allergy or side-effects (54); practice too busy (48); patient unwilling to attend or unable to participate (47); severity of infection (13); atypical clinical features (6); and other reasons (13).

The details of the patients in both treatment groups were very similar in terms of previous health and severity of current infection (Table 1). Other findings (not displayed in the table) also demonstrated the similarity between the groups: dyspnoea [group A 125 (56.6%); group C 129 (58.4%)]; wheeze [group A 150 (67.9%); group C 136 (61.5%)]; chest pain [group A 116 (52.5%); group C 113 (51.1%)]; fevers [group A 116 (52.5%); group C 115 (52.0%)]; headaches [group A 141 (63.8%); group C 130 (58.8%)]; sore throat [group A 150 (67.9%); group C 158 (71.5%)] and generalized aches and pains [group A 147 (66.5%); group C 139 (62.9%)].

The outcome of the two groups, as shown by requirement to visit the general practitioner again within 4 weeks or 3 months of the original infection, time taken to return to normal activities or work, or speed of resolution of symptoms (taken from the symptom diaries) did not apparently differ (Table 2).

The response to an open question regarding adverse events that developed while being treated (defined as side-effects) also did not differ between the two groups (Table 3): 11 patients receiving clarithromycin had to cease treatment because of adverse side-effects, compared with five receiving amoxycillin.

Table 1. Comparative findings on presentation for 442 adults treated for a lower respiratory tract infection either amoxycillin or clarithormycin.

	Amoxycillin	Clarithormycin
Number of patients	221	221
Male:female ratio	99:122	94:127
Median age (years) (range)	46 (16–84)	47 (17–85)
Symptom duration (days) (median and range)	7 (1–45)	7 (1–60)
Cough with clear sputum	32 (14.5)	23 (10.4)
Cough with discoloured sputum	189 (85.5)	198 (89.6)
Chest examination:		
chest clear	116 (52.5)	133 (60.2)
generalized signs	80 (36.2)	57 (25.8)
focal signs	24 (10.9)	31 (14.0)
General practitioner severity score assessment:[a]		
1	32 (14.5)	33 (14.9)
2	84 (38.0)	92 (41.6)
3	91 (41.2)	87 (39.4)
4	12 (5.4)	9 (4.1)
Health record:		
previously well	128 (57.9)	120 (54.3)
underlying respiratory disease	66 (29.9)	62 (28.1)
underlying other disease	39 (17.7)	49 (22.2)
Current cigarette smoker	82 (37)	70 (32)

[a]Subjective assessment of illness severity by general practitioner on a scale of 0–5 where 0 is perfectly well and 5 is severe. Unless specified otherwise, values in parentheses are percentages.

Table 2. Outcome for adults treated with amoxycillin or clarithromycin.

Outcome[a]	Amoxycillin (n = 221)	Clarithormycin (n = 221)
Confined to bed	86/191 (45)	93/205 (45)
median (range) duration (days)	3 (1–10)	2 (1–10)
Unable to do normal activities	146/191 (76)	159/204 (78)
median (range) duration (days)	6 (1–10)	5 (1–10)
Off work[b]	59/88 (67)	49/76 (64)
	5 (1–10)	5 (1–10)
Returned to see general practitioner at least once within 28 days for same illness	43/212 (20)	54/214 (25)
Received one or more further courses of antibiotics within 28 days for same illness	21/212 (10)	40/214 (19)
Returned to see doctor only in second or third month for similar symptoms	24/212 (11)	23/214 (11)
Received one or more further course of antibiotics in second or third month	20/212 (9)	19/214 (9)

[a]Expressed as number of patients with that outcome/total number of patients with that information available. [b]For those in full time work. Unless otherwise stated, values in parentheses are percentages.

Table 3. Spontaneously reported potential adverse effects in adults treated with either amoxicillin or clarithromycin.

	Amoxycillin (n = 214[a])	Clarithormycin (n = 214[a])
Any adverse effect	55	57
Change in bowel habit/diarrhoea	18	12
Feeling of sickness	11	16
Stomach pains	7	7
Indigestion	5	1
Headache	6	13
Oral/vaginal thrush	3	3
Sore mouth	3	6
Dizziness/blurred vision	1	6
Paraesthesia	2	2
Rash	2	1
Itchy skin	1	2
Drowsiness	1	2
Itchy eyes	1	0

[a]Data missing on seven patients in each group.

Compliance was good, with 91% of patients receiving amoxycillin taking at least 75% of their tablets and 93% of those receiving clarithromycin doing so.

Discussion

Traditionally, comparative studies of antibiotics have assessed microbiological efficacy in terms of clearance of bacterial pathogens from sputum and 'cure' of the infection. This has little practical relevance to most patients treated in general practice as, firstly, almost all patients will be 'cured', and secondly, such studies usually include only patients with positive sputum cultures, who in practice make up a very small proportion of the patients treated empirically by general practitioners for such infections.[7,11,12] Additionally, general practitioners rarely have the results of investigations to hand when deciding on initial antibiotic therapy. In this study, a more pragmatic approach was chosen, and the outcome assessed by time taken for resolution of symptoms, return to normal activities and the associated morbidity and social implications of the infection for each treatment group, together with the need to return to the general practitioner for further treatment.

Descriptions of lower respiratory tract infection, chest infection or acute bronchitis in the community are notoriously variable, making it difficult to make between-study comparisons. Extensive discussions with general practitioners, a pilot study and two previously published studies[7,8] resulted in the definition used here, which should include almost all patients treated by general practitioners with antibiotics for lower tract infections while excluding those with upper respiratory tract infections only. This definition appears simple and applicable to the 'real life' situation in general practice and the observer is able to see how such patients fall within the spectrum of cases seen with acute respiratory illness.

Recovery from lower respiratory tract infections is variously reported as taking from 5 days to one month or more.[4,5] A recent detailed community study of such infections in adults, based on a similar practice population, demonstrated moderate morbidity in terms of time in bed, time taken to resume normal activities and time off work.[7] One-quarter of the patients in this study returned for a second consultation, in most cases because of unsatisfactory clinical progress. Of these, 10% returned because of side-effects, resulting in an extra burden for both the patient and the general practitioner.

This study reinforces the earlier findings: 23% of all patients returned to see the general practitioner within a month and a further 11% in the following 2 months. Of the patients in full-time employment, two-thirds lost a median of 5 days off work and half of the patients studied spent 2 or more days in bed.

The argument for use of newer antibiotics as first-line therapy could be strengthened if the increased cost per patient of these newer antibiotics, compared with a drug such as amoxycillin, could be offset by greater efficacy and lower side-effects, reducing the time to recovery and need for repeat visits. However, Davey, *et al* have argued that universal use of more expensive antibiotics is not cost-effective and that strategies for careful targeting of these agents may be more appropriate.[13] In addition, widespread use of different broad-spectrum antibiotics contributes to the increasing problem of resistance of common respiratory pathogens in the community.

The present study was unable to demonstrate any difference in outcome for the two groups even when subgroups were analysed for characteristics that would be useful in guiding the general practitioner towards the appropriate antibiotic choice: underlying chronic respiratory disease, significant other underlying disease, age of 60 years or more, presentation with clear or discoloured sputum, signs on chest examination or presence of symptoms for over seven days.

This study does not address the important issues of which patients with acute lower respiratory symptoms and infection actually require antibiotics,[14] and what action should be taken when a patient reconsults following an initial course of antibiotics. The potential causes of such 'relapses' are many,[15] but the fact that further courses of antibiotics are prescribed for most of these patients suggests that infection is still perceived to be present.[7] It is hoped that ongoing research will help to clarify these points.

This study was performed at a time of low background *Mycoplasma pneumoniae* activity. Infection with this organism occurs in epidemics every 4 years. The latest epidemic started early in 1995.[16] At such times, a macrolide might be expected to confer some advantages that were not apparent when we performed this study.

Of the side-effects usually associated with antibiotics, skin rash was very uncommon in both groups, being seen in only three patients. A popular oral antibiotic for treating lower respiratory tract infections is erythromycin, but this has the significant disadvantage of gastrointestinal side-effects in up to 20% of patients.[17–19] The incidence of spontaneously reported gastrointestinal side-effects in this study was similar for amoxycillin and clarithromycin, and in this respect, clarithromycin appears to be better than erythromycin.

Conclusion

The use of clarithromycin has no apparent advantage over the currently accepted standard antibiotic treatment, amoxycillin, for the initial therapy of lower respiratory tract infection in adults.

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