doi:10.1093/fampra/cml023 Family Practice Advance Access published on 20 June 2006

Prognostic factors and clinical outcome in acute lower respiratory tract infections: a prospective study in general practice

R M Hopstaken[a,b], S Coenen[c,d], C C Butler[e], P Nelemans[f], J W M Muris[b], P E L M Rinkens[b], A D M Kester[g] and G J Dinant[b]

Hopstaken RM, Coenen S, Butler CC, Nelemans P, Muris JWM, Rinkens PELM, Kester ADM and Dinant GJ. Prognostic factors and clinical outcome in acute lower respiratory tract infections: a prospective study in general practice. *Family Practice* 2006; **23**: 512–519.

Background. Unrealistic expectations about illness duration are likely to result in reconsultations and associated unnecessary antibiotic prescriptions. An evidence-based account of clinical outcomes in patients with lower respiratory tract infection (LRTI) may help avoid unnecessary antibiotic prescriptions and reconsultations.

Objectives. We aimed to identify clinical factors that may predict a prolonged clinical course or poor outcome for patients with LRTI and to provide an evidence-based account of duration of an LRTI and the impact of the illness on daily activities in patients consulting in general practice.

Methods. A prospective cohort study of 247 adult patients with a clinical diagnosis of LRTI presenting to 25 GPs in The Netherlands was carried out. Multivariable Cox regression analysis was used to identify baseline clinical and infection parameters that predicted the time taken for symptoms to resolve. A Kaplan–Meier curve was used to analyse time-to-symptom resolution. Clinical cure was recorded by the GPs at 28 days after the initial consultation and by the patients at 27 days.

Results. Co-morbidity of asthma was a statistically significant predictor of delayed symptom resolution, whereas the presence of fever, perspiring and the prescription of an antibiotic weakly predicted enhanced symptom resolution. The GPs considered 89% of the patients clinically cured at 28 days, but 43% of these nevertheless reported ongoing symptoms. Patient-reported cure was much lower (51%), and usual daily activities were limited in 73% of the patients at baseline, and 19% at final follow-up.

Conclusions. The course of LRTI was generally uncomplicated, but the morbidity of this illness was considerable with a longer duration than generally reported, especially for patients with co-existent asthma. These results underline once again the importance of providing GPs with an evidence-based account of outcomes to share with patients in order to set realistic expectations and of enhancing their communication skills within the consultation.

Keywords. Prognosis, respiratory tract infections, general practice, antibiotics, pneumonia

Introduction

Some patients with an acute lower respiratory tract infection (LRTI) will have evidence of pneumonia and/or infection with certain organisms that may put them at higher risk for a prolonged clinical course or poorer outcome. Accurate identification of these patients in general practice may allow for earlier and

Received 7 June 2005; Accepted 24 April 2006.
[a]Institution of Health Centres Eindhoven, Eindhoven, [b]Department of General Practice, Care and Public Health Research Institute (Caphri), University of Maastricht, Maastricht, The Netherlands, [c]Department of General Practice, University of Antwerp, Antwerp, Belgium, [d]Fund for Scientific Research–Flanders, Brussels, Belgium, [e]Department of General Practice, Cardiff University, Wales, UK, [f]Department of Epidemiology and [g]Department of Methodology and Statistics, University of Maastricht, Maastricht, The Netherlands. Correspondence to RM Hopstaken, Institution of Health Centres Eindhoven, GC Meerhoven, PO Box 8799, 5605 LT Eindhoven, The Netherlands; Email: rogier.hopstaken@hag.unimaas.nl

more appropriate interventions. Similarly, a clinical tool enabling GPs to accurately identify low risk patients could help avoid unnecessary antibiotic prescriptions and reconsultations. Two-thirds of the patients initially treated with an antibiotic, who reconsult, receive another antibiotic, despite the lack of evidence of infection.[1]

Antibiotic overprescribing is associated with diagnostic uncertainty, overestimating the value of abnormal auscultation and various non-medical factors like time and patient pressure, patient expectations and perceived patient expectations.[2–6] An additional potential explanation for unnecessary antibiotic prescribing in LRTI may be a general underestimation of the duration of LRTI.[7]

The aim of the present study was therefore 2-fold. Firstly, we planned to conduct an analysis of the data from our cohort of primary care patients with LRTI to evaluate the contribution of a broad range of patient characteristics, clinical items, infection parameters and antibiotic prescription at presentation on subsequent clinical outcomes. Secondly, we set out to provide an evidence-based account of the duration of an LRTI course and the impact of the illness on daily activities in patients consulting in general practice who were and who were not prescribed an antibiotic, subdivided by radiographic evidence of pneumonia and microbiological aetiology. Such a description of the clinical course of this common condition may help clinicians communicate more effectively with LRTI patients treated with and without an antibiotic to help set realistic expectations about likely duration of symptoms.

Methods

Eligibility criteria

Patients aged 18 years and over with a new (i.e. <29 days) or worsening cough—combined with at least one of the following four features: shortness of breath, wheezing, chest pain, auscultation abnormalities; *and* at least one of the following four: reported fever (≥38°C), perspiring, headache, myalgia—were eligible to enter the study, if the GP was convinced of the diagnosis LRTI. Exclusion criteria were pregnancy and lactation, history of hypersensitivity to penicillin or macrolide antibiotics, concomitant treatment with ergot alkaloids and/or terfenadine during the study period, other severe clinical disease, treatment with an antibiotic within the preceding 14 days and hospital stay for respiratory complaints in the previous 4 weeks. Some of the exclusion criteria were relevant to a randomised clinical trial, which was running in parallel to the present study.[8]

Baseline characteristics

The GPs performed and recorded an extensive, standardised medical history, physical examination and clinical diagnosis. GPs then decided on the basis of their own assessment whether or not to prescribe an antibiotic for the patient. If a decision was made to prescribe an antibiotic, the patient was entered into a randomised controlled trial in which the efficacy of amoxicillin was compared with that of a macrolide antibiotic (roxithromycin).[8] Additional management decisions were at the GPs' discretion. Other eligible patients who were not prescribed an antibiotic were included for this study as well.

Infection parameters

GPs measured and recorded body temperature. Venous blood samples were taken for white cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and for determination of sero-conversion for the viral pathogens Influenza A, Influenza B, Parainfluenza 1/2/3, Adenovirus and Respiratory syncytial virus, and the bacteria *Mycoplasma pneumoniae* and *Legionella pneumophila.*[9] The GPs were informed of the haematology results if ESR was >80.

Sputum samples and oral washings were taken for standard microbiological analysis for all patients. Isolation of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and other bacteria as predominant microorganisms was considered indicative of a laboratory diagnosis of infection. Nasopharyngeal swabs were taken for detection of *Chlamydia pneumoniae* using PCR.[10] Susceptibilities of the cultured bacteria for the antibiotic prescribed were recorded. If no viral or bacterial pathogens were isolated, the infection was considered of unexplained aetiology.

Chest radiographs (lateral and postero–anterior) were performed on the third day after inclusion to increase the chance of detection of infiltrates.[11] The radiographs were assessed for the presence or absence of infiltrates by two independent radiologists in a blinded fashion.[12] If there was disagreement between the findings of the two radiologists, a third radiologist conducted an independent assessment that was considered definitive. The conclusive finding of a pulmonary infiltrate was regarded as evidence of pneumonia.

Follow-up and outcome measures

The final follow-up point was at 28 days after entry into the study. GPs took a history and conducted a physical examination at this point and made a decision regarding whether or not the patient was cured. Patient assessment of cure, defined as the absence of self-reported symptoms, was obtained the night before, at 27 days after entry into the study. Patients had to fill-out a symptom score on days 1–10, 21 and 27 after the initial consultation. They also had to register whether or not the complaints of LRTI had worsened, had remained the same, were less or were resolved compared with the day before. We calculated the proportion of patients whose symptoms had resolved

and the proportion of patients whose symptoms still affected their usual daily activities for days 1–10, 21 and 27 after the initial consultation. Data on patients who were not cured according to the GPs at 28 days were followed-up until cure or another outcome was established.

Statistical analysis

We used Cox regression analysis [calculated in hazard ratio's, expressed as relative risks (RRs) and 95% confidence intervals (95% CIs)] to identify the contribution that all patient characteristics, symptoms and physical signs recorded at the initial assessment made to predicting the time taken for symptoms to resolve. Variables with a *P*-value <0.10 were used for the multivariable analysis. Backward elimination with $P > 0.05$ was then used for exclusion of the variables. The remaining variables represented the final prognostic factors for clinical cure.

Differences in clinical cure rate between patients with and without antibiotic treatment were tested with two-sided chi-square analysis ($\alpha = 0.05$) and expressed in RR and 95% CI. Time-to-symptom resolution was analysed using a Kaplan–Meier curve. The statistical analyses were performed with (SPSS) version 11.0.

Results

Patients and characteristics at baseline

A total of 25 GPs in The Netherlands recruited 247 patients with a mean age of 52 (range 18–89) years. Clinical data from the initial assessment were not available for one patient who was prescribed an antibiotic. Most patients suffered from acute cough (92%) and dyspnoea (78%) and showed abnormalities on auscultation (84%; Table 1). Patients suffered from LRTI symptoms for an average of nine (range 1–28) days before consulting. An antibiotic was prescribed for 196 patients (80%). Conservative treatment or reassurance was given to the remaining 51 patients. Nine of these 51 patients did however receive a prescription for an antibiotic at a subsequent consultation, which took place at a mean of 10.8 (range 4–21) days after the first presentation. Evaluation of GP reported outcome was missing in eight patients. Five of these patients did not attend the scheduled consultation at 28 days; two patients were admitted to hospital at the time of this assessment, one for heart failure and the other for exacerbation of COPD, and in one other patient the outcome measure reported by the GP was missing. A complete dataset for both assessment and outcome was thus available for 239 patients. Patient-reported cure and the analysis of prognostic factors were assessed in 240 patients, since patient-reported data were available for one extra patient.

Infection parameters

Recorded fever, presence of a bacterial or a viral infection, mean ESR, mean leucocytes and radiographic pneumonia were not significantly different between those for whom an antibiotic was prescribed and those who were not prescribed an antibiotic. However, the mean CRP level was significantly higher in the group who was prescribed an antibiotic ($P = 0.03$).

A total of 51 patients with a positive bacterial culture, including 57 bacterial strains, received an antibiotic. *In vitro* resistance to the antibiotic prescribed was found in 22 (39%) strains: 12/28 *H. influenzae*, 1/11 *S. pneumoniae*, 2/7 *H. parainfluenzae*, 4/6 *M. catarrhalis* and 3/5 (various) other bacteria.

Radiographic pneumonia was identified in 32 patients (13%). Five pneumonia patients did not receive an antibiotic prescription at baseline. One of them received a prescription for amoxicillin 5 days later.

Predicting outcomes

Based on univariate analysis, the following clinical variables were eligible for multivariable testing in Cox regression analysis: co-morbidity of asthma, present smoking, reported fever, perspiring, cough <2 days, crackles, pneumonia, ESR, CRP and antibiotic prescribed. CRP and ESR, both measuring inflammation, were sequentially tested with identical results. Fever, perspiring and antibiotic prescribed were statistically significant predictors of enhanced symptom resolution (Table 1). Co-morbidity of asthma was a statistically significant predictor of delayed symptom resolution.

Cure: GP assessment and self report

GPs considered 213/239 (89%) of the patients cured at complete follow-up (28 days), although 76 of these 213 (36%) patients considered to be cured by their GPs still reported symptoms to their GP at this point, and physical signs were identified in 13 (6%) of these 213 patients. Sixteen of the 26 patients not clinically cured at 28 days recovered shortly after and did not reconsult their GP. Ten patients with an exacerbation of COPD slowly returned to their baseline clinical condition. Four patients, all clinically cured for the LRTI episode, were found to have concomitant pulmonary cancer. Curative lobectomy was performed in one of the patients. The others received palliative treatment.

The patient-reported cure rate gradually increased (days 1–10, 21 and 27), but only 123/240 (51%) of the patients reported themselves cured at 27 days (Fig. 1). Cough ($n = 82$; 74%) and shortness of breath ($n = 59$; 53%) were the most common remaining symptoms in the patients who considered themselves not cured (Table 2). Moreover, 37 (34%) patients were limited in terms of performing usual daily activities, and 12 (11%) had abandoned their

TABLE 1 *Findings on presentation for 246 patients presenting to the GP with LRTI, followed by the clinical predictors of enhanced symptom resolution in 240[a] patients with LRTI. Univariate and multivariate Cox regression analysis*

	n (%)[b]	Possible predictors of enhanced symptom resolution (*P*-value)[c]	Independent predictors of enhanced symptom resolution
Male	117 (47.6)	0.617	
Mean age in years (SD)	52 ± 16	0.214	
Acute cough (new or increasing)	226 (91.9)	0.217	
Dry cough	58 (23.6)	0.735	
Cough <2 days	11 (4.5)	0.016[d]	NS
Dyspnoea	191 (77.6)	0.175	
Fever	85 (34.6)	0.001[d]	RR 1.5, 95% CI 1.1–2.2
Perspiring	184 (74.8)	0.047[d]	RR 1.7, 95% CI 1.0–2.8
Myalgia	151 (61.4)	0.653	
Chills	124 (50.4)	0.899	
Headache	153 (62.2)	0.695	
Nausea	39 (15.9)	0.856	
Confusion	8 (3.3)	0.210	
Current smoking	83 (33.7)	0.090[d]	NS
Co-morbidity			
Asthma	48 (19.5)	0.015[d]	RR 0.5, 95% CI 0.3–0.9
COPD	32 (13.0)	0.112	
General impression: moderate/severe illness	65 (26.4)	0.737	
Respiration rate >20/minute	9 (3.7)	0.268	
Wheezing	105 (42.7)	0.956	
Crackles	50 (20.3)	0.088[d]	NS
Rhonchi	154 (62.6)	0.651	
Body temperature ⩾ 38.0°C	58 (23.6)	0.403	
Antibiotic prescription	196 (79.7)	0.036[d]	RR 1.7, 95% CI 1.0–2.8
C-reactive protein, median (range)[e]	22.5 (2–312)	0.003[d]	NS
Erythrocyte sedimentation rate, median (range)[e]	19.0 (1–121)	0.076[d]	NS
Leucocytes, median (range)	8.3 (3.8–19.7)	0.630	
Bacterial infection	47 (19)	0.679	
Viral infection	49 (19.8)	0.101	
Mixed bacterial-viral infection	16 (6.5)	0.217	
Pneumonia	32 (13.2)	0.029[d]	NS

NS = non-significant; RR = relative risk; CI = confidence interval.
[a]Patient-reported cure was missing in six patients.
[b]Percentage based on number of patients for each variable (valid percentage).
[c]*P*-value <0.1 to be selected for multivariate Cox regression analysis.
[d]Variable selected for multivariate Cox regression analysis.
[e]Analysis once performed with ESR and once with CRP resulting in the same RR and CIs.

usual daily activities, while 30 (29%) patients still performed no significant physical activity whatsoever.

Table 3 provides an overview of the cure rates according to GPs' assessment and patient self-report for patients who were prescribed an antibiotic, for patients who received a radiographic diagnosis of pneumonia and for patients with a microbiological diagnosis of viral or bacterial infection. Rates for GP assessment of cure were similarly high [168/187 (90%) versus 42/49 (89%); RR 1.33, 95% CI 0.67–2.65] for patients who were and who were not prescribed an antibiotic. However, patient-reported cure was statistically significantly higher for those that were prescribed an antibiotic [102/187 (55%) versus 18/49 (37%); RR 1.87, 95% CI 1.11–3.14]. This difference was confined to and explained by the higher cure rate in patients with a radiographic diagnosis of pneumonia who were prescribed an antibiotic [20/26 (77%) versus 0/5 (0%); $P = 0.003$].

Limited and abandoned usual daily activities

Usual daily activities at baseline were limited by the illness in 164 (73%, valid %) patients, while 95 (42%) had abandoned all usual daily activities (Fig. 2). These numbers gradually decreased to 42 (19%) and 13 (6%), respectively, by day 27. The same pattern was found for both the patients prescribed an antibiotic and those who were not prescribed an antibiotic, although the proportion of the latter group was somewhat lower at baseline.

Discussion

Summary of main findings

Our first aim was to identify findings available to clinicians at the initial assessment of patients consulting with LRTI that would predict an abnormal or prolonged clinical course. We found that co-morbidity

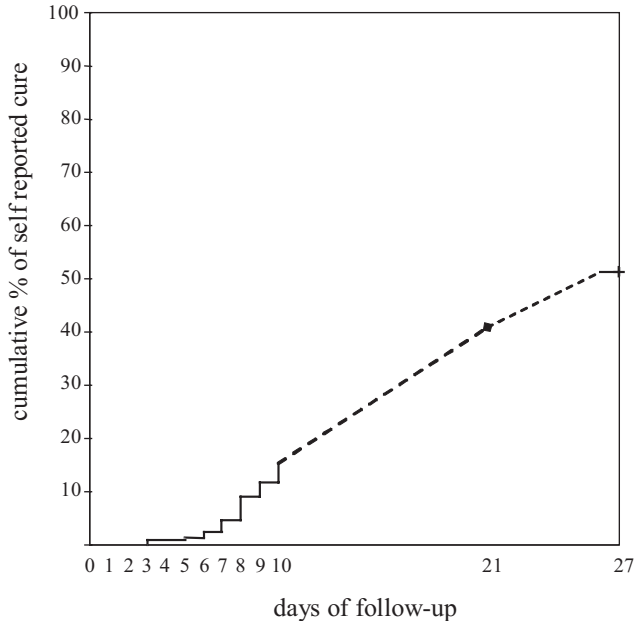


FIGURE 1 *Cumulative percentage of self reported cure for 240 LRTI patients during 27 days of follow-up (Kaplan–Meier curve)*

TABLE 2 *Persisting symptoms and influence on daily activities for 117 patients not cured after 27 days of follow-up*

	n (%)[a]
Number of patients	117 (49)[b]
Symptoms	
Cough	82 (74)
Shortness of breath	59 (53)
Sleeping problems	20 (18)
Chest pain	32 (29)
Feeling ill	15 (14)
Headache	25 (23)
Myalgia	21 (19)
Perspiring	22 (20)
Chills	8 (7)
Fever	5 (5)
Nausea	6 (5)
Diarrhoea	5 (5)
Stomach ache	6 (6)
Daily activities	
Impaired	37 (34)
Abandoned	12 (11)
No physical activities	30 (29)
Stays in bed	4 (4)

[a]Valid percentage.
[b]No data available for seven patients.

with asthma was correlated with a slow resolution of symptoms, whereas the presence of fever, perspiring and the prescription of an antibiotic at the initial assessment weakly predicted symptom resolution by day 27.

Our second aim was to describe the (natural) history of LRTI for patients who were and were not prescribed an antibiotic at the initial consultation. Most patients (89%) were clinically cured according to the GPs 28 days after first consulting, irrespective of whether or not they were prescribed an antibiotic. However, 43% of the patients GPs considered cured nevertheless reported ongoing symptoms (mainly cough and dyspnoea) to their GPs at this point. Self-reported cure was much lower (51%) and usual daily activities were limited according to 19% of the patients at the 27 day follow-up. Self-reported cure was not achieved for the five pneumonia patients who were not prescribed an antibiotic at the initial assessment.

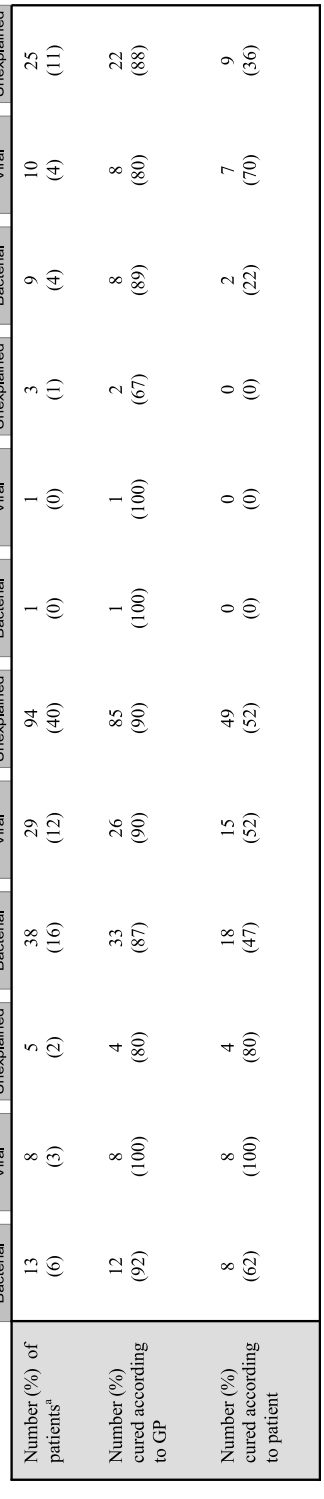
Duration of symptoms and the considerable impact of the LRTI course on daily activities lasted much longer than has thus far been suggested. The difference in assessment of cure between GPs and patients underlines the importance of communication in managing LRTI in general practice in appropriately modifying patient's help seeking behaviour.[13,14] If, for example, GPs reassure patients that the illness is 'just a self-limiting viral bronchitis that will disappear in a week or so', this may trigger the patient to reconsult if the illness lasts longer or if a bothersome cough remains present. Expectations for antibiotic treatment may be higher in a second consultation.

Strength and limitations of the study

The eligibility criteria for our LRTI study were adapted from the first prospective study on LRTI in the community by Macfarlane *et al.*[15] Our definition required the presence of acute cough, together with at least one focal and one general symptom and sign of LRTI. The wide inclusion criteria reflect the variety and complexity of clinical presentations that characterize daily general practice and ensured inclusion of patients with co-morbidity of asthma and chronic obstructive pulmonary disease with an infectious exacerbation. This study is therefore likely to have included important numbers of patients in whom clinical doubt and lack of evidence on diagnosis, management and prognosis is most profound.

In this pragmatic study, the process of diagnosis and deciding whether or not to prescribe an antibiotic for LRTI was left up to the GPs analogous to usual care. Despite this diagnostic reasoning and the effort to accurately select only those patients on clinical grounds who are likely to benefit from antibiotic treatment, microbiological, haematological and radiographic findings indicative of infection were almost evenly distributed among patients who received a prescription for an antibiotic and those who did not. Two retrospective studies suggest that reducing antibiotic treatment may be associated with more complicated respiratory tract infections, but the sizes of the effects were modest,[16] and possibly confounded by other (unidentified) factors.[17] However, the need for finding

TABLE 3 *Cure rates for 236 patients according to the GPs and the patients, differentiated for patients with and without antibiotic treatment, as well as for type of LRTI (pneumonia or no pneumonia) and aetiology(bacterial, viral, or unexplained).*



	Antibiotic						No antibiotic					
	Pneumonia			No pneumonia			Pneumonia			No pneumonia		
	Bacterial	Viral	Unexplained	Bacterial	Viral	Unexplained	Bacterial	Viral	Unexplained	Bacterial	Viral	Unexplained
Number (%) of patients[a]	13 (6)	8 (3)	5 (2)	38 (16)	29 (12)	94 (40)	1 (0)	1 (0)	3 (1)	9 (4)	10 (4)	25 (11)
Number (%) cured according to GP	12 (92)	8 (100)	4 (80)	33 (87)	26 (90)	85 (90)	1 (100)	1 (100)	2 (67)	8 (89)	8 (80)	22 (88)
Number (%) cured according to patient	8 (62)	8 (100)	4 (80)	18 (47)	15 (52)	49 (52)	0 (0)	0 (0)	0 (0)	2 (22)	7 (70)	9 (36)

[a] $n = 236$ patients; chest radiographs missing ($n = 3$); outcome missing ($n = 7$).

better methods of targeting antibiotics to patients at risk for poor outcome is confirmed by the results of these studies.

The results of the prognostic analysis need to be carefully interpreted. The prescription of an antibiotic was a (weak) factor predicting enhanced symptom resolution. Antibiotic treatment in a large number of these patients may have affected outcome and thus limited the power of this study to identify clinical factors associated with outcome. The analysis could therefore have been subject to confounding by treatment.[18] However, systematically studying the natural course of untreated LRTI, including pneumonia, is not possible for ethical reasons. The modest prognostic value of 'antibiotic prescribed' to enhanced resolution of symptoms turned out to be confined to the patients with radiographic evidence of pneumonia.

To explore possible selection bias, we compared the actual numbers of patients presenting with LRTI in three of the participating practices (with a total of nine GPs and a combined patient list of 13 269) with the numbers recruited to the cohort from those practices during one of the study years. Of the 463 potentially eligible patients, 43(9%) were actually recruited. This proportion is not unusual for studies in primary care.[19] Recruited patients did not differ from eligible patients who were not recruited for age, clinical diagnosis, severity of illness and GPs' decisions about the need for antibiotic treatment.

Comparison with other studies

Prospective studies on the outcome and prognosis of LRTI in primary care are rare and have generally been medication trials on acute bronchitis. Hospital studies generally focus on the biomedical evaluation of pneumonia and do not usually capture outcome that are important to patients, other than mortality,[20,21] Pneumonia is a subdiagnosis of LRTI, and so studies of pneumonia alone do not reflect the complexity of clinical presentation in daily general practice.

In an important series of UK studies on lower respiratory tract illness, treatment was at the GPs' discretion, as in our study.[1,22,23] Reconsultations for the same illness within a month was also common in these studies (16–20%) and not influenced by microbiological evidence of infection or antibiotic use. However, reconsultations were more common in those with persisting cough and functional impairment. Cough was present in 58% of the patients and 29% had not resumed normal activities after 10 days of follow-up.[23] Two-thirds of the patients who reconsulted received another antibiotic.[1] Our study provides longer-term follow-up. However, the general pattern we found at 28 days (frequent, ongoing symptoms, regardless of microbiological diagnosis and antibiotic treatment) is similar to the findings of other researchers at 10 days.

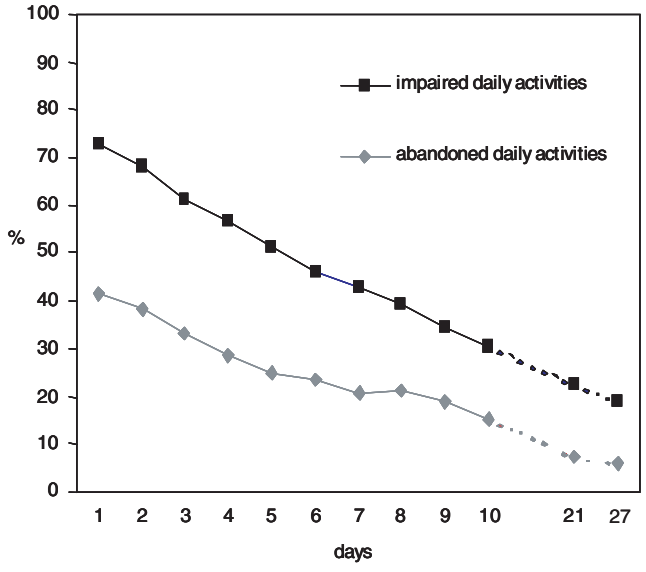


FIGURE 2 *Percentage of patients with impaired and abandoned daily activities for 240 LRTI patients during 27 days of follow-up. Average decrease in impaired and abandoned daily activities per day*

A large prospective study on LRTI, including possible pneumonia, in primary care is needed to confirm the results of our study and to narrow the gap to a possible next phase in LRTI research: a placebo-controlled study design on outcome and prognosis of community-acquired LRTI, including (mild) pneumonia cases, under the safety net of multiple clinical evaluation moments and proper monitoring of the illness with repeated near-patient CRP testing.[24] Furthermore, strategies for changing physician and patient behaviour regarding the limited value of antibiotics in self-limiting diseases like most respiratory tract infections need to be systematically studied to increase chances of successful implementation.[13] The effect of providing a clear, evidence-based account of expected duration of symptoms to patients with LRTI also needs prospective evaluation.

Conclusion

The course of LRTI was generally uncomplicated, but the morbidity of this illness was considerable with a longer duration than generally reported, in particular in patients with co-morbidity of asthma. Although the GPs considered most patients cured at 28 days, considerable numbers of patients had remaining symptoms and/or limited usual daily activities, thus focusing attention once again on the importance of enhancing GPs' communication skills within the consultation. With this evidence-based account of outcomes in patients with LRTI, GPs may be able to set realistic expectations about illness duration and thus help avoid reconsultations and associated unnecessary antibiotics.

Acknowledgements

We wish to thank the patients, GPs and their assistants for their participation in the study. The study was supported by a grant from the Research Institute for Extramural and Transmural Health Care, Maastricht.

References

[1] Macfarlane J, Prewett J, Rose D *et al*. Prospective case–control study of role of infection in patients who reconsult after initial antibiotic treatment for lower respiratory tract infection in primary care. *BMJ* 1997; **315:** 1206–1210.

[2] Melbye H, Straume B, Aasebo U, Dale K. Diagnosis of pneumonia in adults in general practice. Relative importance of typical symptoms and abnormal chest signs evaluated against a radiographic reference standard. *Scand J Prim Health Care* 1992; **10:** 226–233.

[3] Hopstaken RM, Muris JWM, Knottnerus JA, Kester ADM, Rinkens PELM, Dinant GJ. Contributions of symptoms, signs, erythrocyte sedimentation rate and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection. *Br J Gen Pract* 2003; **53:** 358–364.

[4] Coenen S, Van Royen P, Vermeire E, Hermann I, Denekens J. Antibiotics for coughing in general practice: a qualitative decision analysis. *Fam Pract* 2000; **17:** 380–385.

[5] Butler CC, Rollnick S, Pill R, Maggs Rapport F, Stott N. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *BMJ* 1998; **317:** 637–642.

[6] Coenen S, Michiels B, Van Royen P, Van Der Auwera JC, Denekens J. Antibiotics for coughing in general practice: a questionnaire study to quantify and condense the reasons for prescribing. *BMC Fam Pract* 2002; **3:** 16.

[7] Little P. Where next with antibiotics and respiratory tract infections? *J Fam Pract* 2002; **51:** 337–338.

[8] Hopstaken RM, Nelemans P, Stobberingh EE, Muris JWM, Rinkens PELM, Dinant GJ. Is roxithromycin better than amoxicillin in the treatment of acute lower respiratory tract infections in primary care? A double-blind randomized controlled trial. *J Fam Pract* 2002; **51:** 329–336.

[9] Hopstaken RM, Stobberingh EE, Knottnerus JA *et al*. Clinical items not helpful in differentiating viral from bacterial lower respiratory tract infections in general practice. *J Clin Epidemiol* 2005; **58:** 175–183.

[10] Tong CY, Sillis M. Detection of *Chlamydia pneumoniae* and *Chlamydia psittaci* in sputum samples by PCR. *J Clin Pathol* 1993; **46:** 313–317.

[11] Bartlett JG, Mundy LM. Community-acquired pneumonia. *N Engl J Med* 1995; **333:** 1618–1624.

[12] Hopstaken RM, Witbraad T, van Engelshoven JMA, Dinant GJ. Interobserver variation in the interpretation of chest radiographs for pneumonia in community-acquired lower respiratory tract infections. *Clin Radiol* 2004; **59:** 743–752.

[13] Butler CC, Rollnick S, Kinnersley P, Jones A, Stott N. Reducing antibiotics for respiratory tract symptoms in primary care: consolidating 'why' and considering 'how'. *Br J Gen Pract* 1998; **48:** 1865–1870.

[14] Butler CC, Rollnick S, Kinnersley P, Tapper-Jones L, Houston H. Communicating about expected course and re-consultation for respiratory tract infections in children: an exploratory study. *Br J Gen Pract* 2004; **54:** 536–538.

[15] Macfarlane JT, Colville A, Guion A, Macfarlane RM, Rose DH. Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. *Lancet* 1993; **341:** 511–514.

[16] Little P, Watson L, Morgan S, Williamson I. Antibiotic prescribing and admissions with major suppurative complications of respiratory tract infections: a data linkage study. *Br J Gen Pract* 2002; **52:** 187–190.

[17] Price DB, Honeybourne D, Little P *et al*. Community-acquired pneumonia mortality: a potential link to antibiotic prescribing trends in general practice. *Respir Med* 2004; **98:** 17–24.
[18] Doust J, Del Mar C. Diagnosing coughs and colds. *Br J Gen Pract* 2004; **54:** 5–6.
[19] Wilson S, Delaney BC, Roalfe A *et al*. Randomised controlled trials in primary care: case study. *BMJ* 2000; **321:** 24–27.
[20] Barlow GD, Lamping DL, Davey PG, Nathwani D. Evaluation of outcomes in community-acquired pneumonia: a guide for patients, physicians, and policy-makers. *Lancet Infect Dis* 2003; **3:** 476–488.
[21] BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. *Thorax* 2001; **56 (Suppl 4):** 1–64.
[22] Macfarlane J, Holmes W, Gard P *et al*. Prospective study of the incidence, aetiology, outcome of adult lower respiratory tract illness in the community. *Thorax* 2001; **56:** 109–114.
[23] Holmes WF, Macfarlane JT, Macfarlane RM, Hubbard R. Symptoms, signs, and prescribing for acute lower respiratory tract illness. *Br J Gen Pract* 2001; **51:** 177–181.
[24] Pepys MB, Berger A. The renaissance of C reactive protein. *BMJ* 2001; **322:** 4–5.