**TITLE PAGE**

Title: Clinical relevance of bacterial resistance in lower respiratory tract infection in primary care

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**Abstract**

**Background:**

The impact of antimicrobial resistance on clinical outcomes in patients with lower respiratory tract infection in primary care is largely unknown.

**Aim:**

We determined the illness course of infections with resistant bacteria in adults presenting with acute cough to primary care.

**Design and setting:**

Secondary analysis of a multicentre European trial in primary care.

**Method:**

2,061 adults with acute cough (≤ 28 days) were recruited from primary care and randomised to amoxicillin or placebo. To reflect the natural course of disease, only patients in the placebo group (n = 1,021) were eligible. Nasopharyngeal flocked swabs and/or sputa (when available) were analysed at baseline and *Streptococcus pneumoniae* and *Haemophilus influenzae* isolates underwent susceptibility testing. Patients recorded their symptoms in a diary every day for four weeks. Patients with and without resistant bacterial infection were compared with regards to symptom severity, duration of symptoms and a return consultation.

**Results:**

Of the 834 patients with diary records, 104 showed *S. pneumoniae* and/or *H. influenzae* infection. Of this number, 54/104 (52%) were antibiotic-resistant, while 7/104 (7%) were resistant to penicillin. Neither duration of symptoms rated “moderately bad or worse” (hazard ratio 1.27, 95% CI 0.67-2.44) nor mean symptom severity (difference -0.48, 95% CI -1.17-0.21) nor worsening of illness (odds ratio 0.31, 95% CI 0.07-1.41) differed significantly between the antibiotic resistant and antibiotic sensitive groups.

**Conclusion:**

The illness course of antibiotic-resistant lower respiratory tract infection does not differ from that caused by sensitive bacteria.

**Keywords:**

antimicrobial resistance, lower respiratory tract infection, cough, prognosis, primary care

**Introduction**

Lower respiratory tract infection is one of the leading reasons for consulting in primary care and antibiotic prescription, which drives antibiotic resistance.[1,2] Despite growing concerns about antibiotic-resistant bacteria, there is a lack of information about the impact of antibiotic resistance in respiratory tract infections in primary care. There is an abundance of data on the impact of antibiotic resistance in hospital settings which shows that antimicrobial-resistant organisms are associated with increased length of hospital stay, mortality and costs. The underlying pathophysiology for worse outcomes as presented in secondary care studies in antibiotic-resistant bacteria is however unclear and could largely be explained by confounding.[3-6] In primary care, where infections and also respiratory tract infections are often self-limiting and not treated by antibiotics, resistance of bacteria in itself is not likely to provoke worse outcomes. However, data on this domain are lacking. Our hypothesis is that there is no relevant difference in outcome in outpatients with lower respiratory tract infections between those with and without antibiotic-resistant bacteria in the absence of antibiotic treatment in primary care.

A few studies reported on the effects of antibiotic resistance in primary care.[7-9] These studies show that antibiotic resistance is associated with increased duration and severity of symptoms and a higher chance that a patient will re-consult. These studies focused on urinary tract infections and often did not include the interaction between type of antibiotic and bacterial resistance. No study has explored the impact of antibiotic resistance on the natural course of disease in primary care patients with respiratory tract infections. Improved knowledge of the consequences of resistance in respiratory tract infections in primary care could contribute to discussions on first- and second-choice agents and help physicians and their patients consider the risks and benefits of antibiotic use in these highly common infections.

The aim of this study was therefore to evaluate the illness course of patients presenting in primary care with lower respiratory tract infection in whom antibiotic-resistant bacteria were isolated and to compare their illness course with that of patients with lower respiratory tract infection with no antibiotic-resistant bacteria.

**Method**

*Design and study population*

This was a secondary analysis of a randomised, placebo-controlled trial of amoxicillin for lower respiratory tract infection in 16 primary care 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 lower respiratory tract infection in Europe; www.grace-lrti.org/portal/en-gb/homepage) have been reported elsewhere.[10] Recruited networks had access to a minimum of 20,000 patients.

Eligible patients were at least 18 years old who consulted their general practitioner for the first time with an acute cough (duration of ≤ 28 days) as their main symptom or where cough was not the most prominent symptom, but where the general practitioner considered an acute lower respiratory tract infection as the main diagnosis. Exclusion criteria were clinically suspected pneumonia[11] based on focal chest signs (focal crepitation and bronchial breathing) and systemic features (high fever, vomiting, severe diarrhoea), pregnancy, allergy to penicillin, treatment with antibiotics in the previous month and immunodeficiency disorders. The study was approved by ethics committees in all participating countries and all participants provided written informed consent. For the present analysis, patients allocated to amoxicillin or patients who did not return their follow-up diary were excluded. Furthermore, we included patients in whom infection with *Streptococcus pneumoniae* and/or *Haemophilus influenzae* was present.

*Measurements*

*Patient follow-up*. General practitioners recorded patients’ clinical signs and comorbidities on a case reportform (appendix 1).They also registered 14 baseline symptoms (cough, phlegm, shortness of breath, wheeze, runny nose, fever, chest pain, muscle ache, headache, disturbed sleep, feeling generally unwell, interference with normal activities/work, confusion/disorientation and diarrhoea) on a four-point Likert-scale that ranged 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 out a daily symptom diary during their illness for a period of up to 28 days, grading the same symptoms on a seven-point Likert scale ranging from “no problem” to “severe problem” (appendix 2). This diary was previously validated and shown sensitivity to change.[12] All patients underwent chest radiography within seven days of their first visit, preferably within three days. Pneumonia was determined by radiologists who were blinded to all other information and examined chest radiographs using a uniform procedure (appendix 3).[13]

*Laboratory analysis*. A sputum sample from a productive cough (not available for all) and a nasopharyngeal swab sample were collected from each patient on the day of presentation, before any antibiotic therapy was prescribed. Sputum samples were sent to the local laboratory for immediate processing. Direct microscopy, gram stain and culture were performed according to a standardised protocol (appendix 4). Nasopharyngeal swabs, stored in Universal Transport Medium (Copan Diagnostics) and in skim milk medium, were sent to the laboratory of the University of Antwerp for bacterial and viral polymerase chain reaction analysis. Infection with *S. pneumoniae* or *H. influenzae* was defined by isolation of a predominant microorganism in the sputum (using a ratio of one or more leukocytes to epithelial cells as the criterion for good quality) or from the nasopharyngeal swab. Other bacterial pathogens were also identified (*Mycoplasma pneumoniae*, *Bordetella pertussis* and *Legionella pneumophila*); methods and results have been reported elsewhere.[14] Susceptibility testing to a uniform panel of antimicrobial agents, only for *S. pneumoniae* and *H.* *influenzae,* was performed with Etest or agar dilution method at the Karolinska Institute in Stockholm, Sweden and at Oxford University in Oxford, United Kingdom, respectively, after frozen transport by the laboratory of the University of Antwerp. Minimum inhibitory concentrations of *H. influenzae* to ampicillin and tetracycline were performed and for *S. pneumoniae* to penicillin G, amoxicillin, erythromycin/clindamycin, tetracycline, chloramphenicol, trimethoprim/sulfamethoxazole, levofloxacin and cefotaxime. Isolates were classified as sensitive, intermediate or resistant according to the EUCAST system of species-related breakpoints.[15]

Bacterial resistance was defined as the presence of infection with *S. pneumoniae* and/or *H. influenzae* which was classified as resistant to at least one tested antibiotic. All other isolates that were classified as sensitive and/or intermediate were defined as ‘sensitive to antibiotics’. Isolates with intermediate resistance were classified as ‘sensitive to antibiotics’, because the most commonly used dosages of amoxicillin are high enough to overcome intermediate resistance.

*Main outcomes*

The disease course was defined in five ways, similar to other analyses of this trial: 1. Duration of symptoms rated by patients as “moderately bad or worse” after initial presentation; 2. Symptom severity on days 2-4 after the index consultation; 3. Worsening of illness, defined as a return visit to the general practitioner with worsening symptoms, new symptoms, new signs or illness necessitating admission to hospital within four weeks of the first consultation[10]; 4. Duration of symptoms until complete resolution; 5. Duration of interference with normal activities or work. The duration of symptoms was reported in days. Symptom severity was defined as the mean diary score for all symptoms during days 2–4 after the index consultation.

*Data analysis*

The course of disease of antibiotic-resistant lower respiratory tract infection in adults with acute cough was compared to that of patients without antibiotic-resistant lower respiratory tract infection for all five outcomes. Data were analysed using regression analyses. Linear regression was used for symptom severity, Cox regression for the duration of symptoms allowing for censoring and logistic regression for return visits for new or worsened symptoms. In the multivariable analyses, we controlled all outcomes for the potentially confounding factors age, current smoking, comorbidity (pulmonary, cardiac, diabetes mellitus) and cough duration before index consultation. Moreover, we adjusted for bacteria (*S. pneumoniae* or *H. influenzae*), because of the unequal distribution of resistance among the two bacteria species. Data was analysed using SPSS (version 20.0) for Windows.

**Results**

In total, 1,021 patients were randomised to placebo. Of that number, 834 patients (82%) returned the diary. There was evidence of infection in 104 participants: with *S. pneumoniae* (48 participants), *H. influenzae* (48 participants) or both (8 participants). The baseline characteristics of these 104 patients were similar to those who did not return the diary or had no evidence of infection with *S. pneumoniae* or *H. influenzae,* except for age and baseline symptom severity scores (appendix 5). Antibiotic-resistant lower respiratory tract infection was present in 54 (52%) out of 104 patients. Resistance to amoxicillin, ampicillin or penicillin (penicillins) was present in 7/104 patients (7%). The proportion of resistance was much higher in patients infected with *S. pneumoniae* (42 of 48) than in those infected with *H. influenzae* (5 of 48). Resistance of *S. pneumoniae* to specific antibiotics were as follows: amoxicillin 0/56 (0%), penicillin G 1/56 (2%), erythromycin/clindamycin 13/56 (23%), tetracycline 13/56 (23%), chloramphenicol 4/56 (7%), trimethoprim/sulfamethoxazole 48/56 (86%), levofloxacin 0/56 (0%) and cefotaxime 0/56 (0%). For *H. influenzae*, the numbers were as follows: ampicillin 6/56 (11%) and tetracycline 1/56 (2%). The baseline characteristics did not differ between patients with and without antibiotic-resistant lower respiratory tract infections (table 1); this was also the case for the subgroups of infection with *S. pneumoniae* (appendix 6) and infection with *H. influenzae* (appendix 7).

*Disease course*

For all outcomes, the illness course of patients with antibiotic-resistant lower respiratory tract infection tended to be slightly more favourable than that of patients with sensitive bacteria. After adjustment for confounders, however, there were no significant differences in illness course between those with and those without antibiotic-resistant lower respiratory tract infections (table 2). Only one patient from the non-antibiotic-resistant lower respiratory tract infection group required hospital admission within four weeks after their first consultation. No study-related deaths were noted.

**Discussion**

*Summary*

Over half of the *S. pneumoniae* and *H. influenzae* isolates from adults presenting to primary care with lower respiratory tract infection were resistant to at least one tested antibiotic, but resistance to penicillins was present in less than 10%. Patients with antibiotic-resistant lower respiratory tract infection did not have a different illness course than those with susceptible infections.

*Strengths and limitations*

To our knowledge, this is the first study of the illness course of antimicrobial-resistant lower respiratory tract infection in primary care. We were able to describe and compare the illness course of antibiotic-resistant and antibiotic-sensitive lower respiratory tract infections.

A first potential limitation is misclassification of bacterial lower respiratory tract infection by airway bacterial colonisation or carriership, due to which we may have erroneously concluded that there are no differences in disease course between those with and without antibiotic-resistant lower respiratory tract infections. In studies where *H. influenzae* and *S. pneumoniae* were identified using conventional methods in healthy individuals, prevalence of colonisation was 10% at most.[16,17] Patients with chronic obstructive pulmonary disease are different in the sense that they are more likely to be colonised with *H. influenzae* (17%),[18] but only a few patients with chronic obstructive pulmonary disease (n = 6/104, 6%) were included in our study. In our study population of symptomatic patients with acute lower respiratory tract infection, we expect misclassification by carriership to be far less than 10% because we assume there to be a high chance that detected bacteria were actually the cause of current complaints, rather than a sign of carriership.

Another possible limitation is that we defined bacterial resistance as resistance to at least one tested antibiotic. In our study, the overall prevalence of bacterial resistance was mainly driven by the resistance of *S. pneumoniae* to trimethoprim/sulfamethoxazole (86%). One might claim, however, that resistance to penicillins is more clinically relevant, since penicillins are the recommended antibiotic for lower respiratory tract infection in Europe. However, the number of patients with resistance to penicillins was too small (n = 7) to evaluate the course of disease in this subgroup separately. Moreover, antibiotic resistance does not appear to be a relevant issue for the individual patient with lower respiratory tract infection in our study. It is probably more relevant for patients with pneumonia where antibiotics were shown to have a relevant effect.[19]

Because lower respiratory tract infections are common, far more eligible patients consulted their clinicians during the recruitment period than were invited to participate in this study. As a result, we did not achieve the goal of recruiting all consecutive, eligible patients. Nevertheless, we assume that this study sample resulted in limited selection bias, because participating clinicians reported that the main reason not to include all eligible patients was due to time constraints.[13]

Regarding generalisability, we studied outpatients with lower respiratory tract infection with little comorbidity in whom pneumonia or the need for hospitalisation were not suspected during their initial assessment. Our findings might not be generalizable to more vulnerable or more severely ill patients. Finally, the power calculation of the GRACE trial did not formally include analyses on the subgroup of patients with antibiotic-resistant bacteria and therefore there is a risk of false negative results (Type II error).

*Comparison with existing literature*

In our study, antibiotic-resistant lower respiratory tract infections are not associated with a different illness course than susceptible infections. The impact of bacterial resistance in lower respiratory tract infections in primary care was never studied. However, in urinary tract infections a few studies found that antibiotic resistance is associated with prolonged symptoms and frequent return visits.[7-9] One of the explanations for this difference may be treatment failure caused by resistance of the causal uropathogen to the prescribed antibiotics, which was not taken into account in the study conducted by McNulty.[9] Butler et al. found that infections caused by *E. coli* resistant to trimethoprim lasted longer even when treated with an appropriate antibiotic[7] and Little et al. showed that both treating with an antibiotic to which the infection is resistant and not prescribing antibiotics at all are associated with a longer duration of more severe symptoms in women with uncomplicated urinary tract infection.[8]

*Implications for research and/or practice*

Our results show that when bacteria are present, lower respiratory tract infections generally have a mild, uncomplicated and self-limiting disease course, irrespective of the presence of antimicrobial resistance. This study confirms that regarding antimicrobial resistance, outpatients who do not require antibiotics are a different domain than hospitalised patients, or outpatients who have already been treated with antibiotics.

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**Ethical approval**

Ethical approval for the Netherlands was granted by the Medisch Ethische Toetsing Commissie (METC) of the University Medical Center Utrecht (ref 07-179/O). Competent authority approval for the Netherlands was granted by De Centrale Commissie Mensgebonden Onderzoek (CCMO). For the UK ethical approval was granted by Southampton and South West Hampshire Local Research Ethics Committee (B) (ref 07/H0504/104). Competent authority approval for the UK was granted by the Medicines and Healthcare Products Regulatory Agency. Also the other research sites obtained ethical and competent authority approval from their local organizations. Patients who fulfilled the inclusion criteria were given written and verbal information on the study and gave informed consent.

**Competing interests**

All authors declare that we have no relevant conflicts of interest.

**Authors' contributions**

Chris Butler, Margareta Ieven, Samuel Coenen, Maciek Godycki-Cwirko, , Herman Goossens, Paul Little, and Theo Verheij conceived and designed the study. Katherine Loens and Christine Lammens were responsible for testing all samples for bacterial infection. Birgitta Henriques was responsible for reidentification and further testing of all pneumococcal strains. Patricia Hordijk reviewed the literature critically. Jolien Teepe and Lidewij Broekhuizen interpreted the data and performed the analyses. Jolien Teepe, Lidewij Broekhuizen, and Theo Verheij wrote the first draft of the manuscript, and all of the coauthors critically revised the manuscript. The guarantor is Theo Verheij.

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Table 1. Baseline characteristics of patients with and without antibiotic-resistant lower respiratory tract infection

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All patients****N=104 (%)** | **Resistant to antibiotic§****N=54 (%)** | **Sensitive to antibiotic****N=50 (%)** |  | **Missing** **N (%)** |
| Age, mean (SD) | 53 (17) | 54 (15) | 53 (19) |  | 0 (0.0) |
| Male gender | 47 (45) | 22 (41) | 25 (50) |  | 0 (0.0) |
| Current smoker | 34 (33) | 18 (33) | 16 (32) |  | 0 (0.0) |
| Comorbidity (pulmonary, cardiac, diabetes mellitus)\* | 30 (29) | 18 (33) | 12 (24) |  | 0 (0.0) |
| Cough duration before index consultation, mean (SD)† | 9 (6) | 8 (6) | 10 (7) |  | 0 (0.0) |
| Severity score (all symptoms), mean (SD)‡ | 35 (14) | 33 (12) | 38 (16) |  | 1 (1.0) |
| Infiltrate on chest radiograph | 7 (7) | 3 (6) | 4 (8) |  | 5 (4.8) |

Numbers represent number (%), unless stated otherwise. SD = standard deviation.

\* Pulmonary comorbidity = history of chronic obstructive pulmonary disease, asthma or other lung disease.

Cardiac comorbidity = history of heart failure, ischemic heart disease or other heart disease.

† Presented in days.

‡ Score for 14 patients’ physician-recorded symptoms summed and scaled to range between 0 and 100 on day 1.

§ Resistant to antibiotic is defined as resistant to at least one tested antibiotic.

Table 2. Prognostic outcomes in patients with and without antibiotic-resistant lower respiratory tract infection

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **Resistant to antibiotic\*****N=54** | **Sensitive to antibiotic****N=50** | **Crude analysis** | **Adjusted analysis†** | **P value‡** |  |
| Time to resolution of symptoms rated  “moderately bad or worse”, days | 7 (5-11) | 9 (5-19) | 1.24 (0.82 to 1.88)§ | 1.27 (0.67 to 2.44)§ | 0.464 |  |
| Symptom severity score on day 2-4 after consultation|| | 1.75 ± 0.94 | 2.18 ± 1.21 | -0.43 (-0.85 to -0.01)\*\* | -0.48 (-1.17 to 0.21)\*\* | 0.172 |  |
| Duration of symptoms until  complete resolution, days | 14 (10-24) | 15 (9-28) | 1.15 (0.70 to 1.88)§ | 1.32 (0.61 to 2.90)§ | 0.483 |  |
| Worsening of illness†† | 9/54 (17) | 18/50 (36) | 0.36 (0.14 to 0.89)‡‡ | 0.31 (0.07 to 1.41)‡‡ | 0.129 |  |
| Duration of interference with normal  activities or work, days | 6 (2-8) | 7 (3-12) | 1.46 (0.97 to 2.21)§ | 1.67 (0.85 to 3.28)§ | 0.136 |  |

Numbers represent median (interquartile range), mean ± SD, or n/N (%), unless stated otherwise.

\* Resistant to antibiotic is defined as resistant to at least one tested antibiotic.

†Adjusted for age (for each year increase), current smoking, comorbidity, cough duration before index consultation and bacteria (*S. pneumoniae* or *H. influenzae)*.

‡ For adjusted analysis.

§ Data presented as hazard ratio (95% CI).

|| Each symptom was scored by the patient 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).

\*\* Data presented as difference (95% CI).

†† The vast majority of these represent return visits with new or worsening symptoms and only one patient required hospital admission (with an *H. influenzae* infection sensitive to antibiotics) within four weeks after their first consultation. No study-related deaths were noted.

‡‡ Data presented as odds ratio (95% CI).

No missing data.