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

secondary analysis of a multicentre European trial

Abstract

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

Aim
To determine the illness course of infections with resistant bacteria in adults presenting to primary care with acute cough.

Design and setting
Secondary analysis of a multicentre European trial in primary care.

Method
A total of 2061 adults with acute cough (lasting ≤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 = 1021) 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 4 weeks. Patients with and without resistant bacterial infection were compared with regards to symptom severity, duration of symptoms, worsening of illness, and duration of interference with normal activities or work.

Results
Of the 834 patients with diary records, 104 showed *S. pneumoniae* and/or *H. influenzae* infection. Of this number, 54 (52%) were resistant to antibiotics, while seven (7%) were resistant to penicillin. For the duration of symptoms rated 'moderately bad or worse' (hazard ratio 1.27, 95% confidence interval [CI] = 0.67 to 2.44), mean symptom severity (difference −0.48, 95% CI = −1.17 to 0.21), and worsening of illness (odds ratio 0.31, 95% CI = 0.07 to 1.41), there was no statistically significant difference 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 antibiotic-sensitive bacteria.

Keywords
antimicrobial drug resistance; cough; lower respiratory tract infection; primary care; prognosis.

INTRODUCTION

Lower respiratory tract infection (LRTI) is one of the leading reasons for consulting in primary care and for 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 on respiratory tract infections (RTIs) 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, higher mortality rates, and increased 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 including RTIs are often self-limiting and not treated by antibiotics, resistance of bacteria in itself is not likely to provoke worse outcomes, but data in this domain are lacking. The authors hypothesise that, for outpatients with LRTIs, there is no relevant difference in outcome between those with, and without, antibiotic-resistant bacteria in the absence of antibiotic treatment in primary care.

A few studies have reported on the effects of antibiotic resistance in primary care;[7–9] they show that antibiotic resistance is associated with increased duration and severity of symptoms, along with a higher chance that a patient will re-consult. However, those studies focused on urinary tract infections and, often, did not include the interaction between antibiotic type and bacterial resistance. To the authors' knowledge, no study has explored the impact of antibiotic resistance on the natural course of disease in primary care patients with RTIs. Improved knowledge of the consequences of resistance in RTIs 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 using antibiotics in an attempt to treat these highly common infections. Therefore, the aim of this study was to evaluate the illness

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How this fits in

This study demonstrated 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, in terms of antimicrobial resistance, outpatients who do not require antibiotics are a different domain from patients who are hospitalised or outpatients who have already been treated with antibiotics.

course of patients presenting in primary care with LRTI in whom antibiotic-resistant bacteria were isolated, and to compare their illness course with that of patients with LRTI and no antibiotic-resistant bacteria.

METHOD

Design and study population

This was a secondary analysis of a randomised, placebo-controlled trial of amoxicillin for LRTI conducted in 16 primary care networks in 12 European countries from October 2007 until April 2010. More details on this study (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe [GRACE-10]; 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 those aged at least 18 years, who consulted with their GP for the first time with an acute cough (duration of ≤28 days) as their main symptom, or for whom the GP considered an acute LRTI as the main diagnosis, although cough was not the most prominent symptom. Exclusion criteria were:

- clinically suspected pneumonia[11] based on focal chest signs (focal crepitation and bronchial breathing) and systemic features (high fever, vomiting, or 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 those who did not return their follow-up diary were excluded. Patients in whom infection with *Streptococcus pneumoniae* and/or *Haemophilus influenzae* was present were included.

Measurements

Patient follow-up. GPs recorded patients' clinical signs and comorbidities on a case report form (available from the authors on request), and registered 14 baseline symptoms — cough, phlegm, shortness of breath, wheeze, blocked/runny nose, fever, chest pain, muscle ache, headache, disturbed sleep, feeling generally unwell, interference with normal activities or work, confusion or disorientation, and diarrhoea — on a 4-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 range between 0 and 100. Patients completed a daily symptom diary during their illness for a period of up to 28 days, grading 13 symptoms — cough, phlegm, shortness of breath, wheeze, blocked/runny nose, fever, chest pain, muscle ache, headache, disturbed sleep, feeling generally unwell, interference with normal activities or work, and interference with social activities — on a 7-point Likert scale ranging from 'normal/not affected' to 'as bad as it could be' (further details are available from the authors on request). This diary was previously validated and showed sensitivity to change.[12]

All patients underwent chest radiography within 7 days of their first visit, preferably within 3 days. Pneumonia was determined by radiologists who were blinded to all other information and examined chest radiographs using a uniform procedure (further details are available from the authors on request).[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 (further details are available from the authors on request). Nasopharyngeal swabs, stored in Universal Transport Medium (Copan Diagnostics) and in skimmed milk medium, were sent to the laboratory of the University of Antwerp, Belgium, 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 — *Mycoplasma pneumoniae*, *Bordetella pertussis*, and *Legionella pneumophila* — were also identified; methods and results have been reported elsewhere.[14,15]

After frozen transport, undertaken by the laboratory of the University of Antwerp, susceptibility testing to a uniform panel of antimicrobial agents was performed for *S. pneumoniae* and *H. influenzae* only, using the Etest or agar dilution method at Karolinska Institutet in Stockholm, Sweden, and at the University of Oxford, UK, respectively. Minimum inhibitory concentrations of *H. influenzae* to ampicillin and tetracycline were performed; the same was done 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 system of species-related breakpoints set by the European Committee on Antimicrobial Susceptibility Testing.[16]

Bacterial resistance was defined as the presence of infection with *S. pneumoniae* and/or *H. influenzae* that 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 according to five outcomes, similar to other analyses of this trial:

- time to resolution, after initial presentation, of symptoms rated by patients as 'moderately bad or worse';
- symptom severity score on days 2–4 after the index consultation;
- duration of symptoms until complete resolution;
- worsening of illness, defined as a return visit to the GP with worsening symptoms, new symptoms, new signs, or illness necessitating admission to hospital within 4 weeks of the first consultation;[10]
- 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 disease course of antibiotic-resistant LRTI in adults with acute cough was compared with that of patients with LRTI that was not resistant to antibiotics. Data were analysed using regression analyses. Linear regression was used for symptom severity and 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, all outcomes were controlled for the potentially confounding factors of age, current smoking status, comorbidity (for example, pulmonary or cardiac comorbidity, or diabetes mellitus), and cough duration before index consultation. Adjustments were made for bacteria (*S. pneumoniae* or *H. influenzae*) because of the unequal distribution of resistance among the two species. Data were analysed using SPSS (version 20.0) for Windows.

RESULTS

In total, 1021 patients were randomised to placebo. Of those, 834 patients (82%) returned the diary. There was evidence of infection in 104 participants: 48 participants with *S. pneumoniae*, 48 participants with *H. influenzae*, and eight participants with both. With the exception of age and baseline symptom severity scores, the baseline characteristics of these 104 patients were similar to the characteristics of those who did not return the diary or had no evidence of infection with *S. pneumoniae* or *H. influenzae* (further details are available from the authors on request).

Antibiotic-resistant LRTI was present in 54 (52%) of the 104 patients. Resistance to amoxicillin, ampicillin, or penicillin (penicillins) was present in seven (7%) of the 104 patients. The proportion of resistance was much higher in patients infected with *S. pneumoniae* (42/48 [88%]) than in those infected with *H. influenzae* (5/48 [10%]). Resistance of *S. pneumoniae* to specific antibiotics was as follows:

- amoxicillin 0/56 (0%);
- penicillin G 1/56 (2%);
- erythromycin/clindamycin 13/56 (23%);
- tetracycline 13/56 (23%);

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

Characteristic	All patients, *n* = 104	Resistant to antibiotic, *n* = 54[a]	Sensitive to antibiotic, *n* = 50	Missing
Age, mean (SD)	53 (17)	54 (15)	53 (19)	0 (0)
Male sex, *n* (%)	47 (45)	22 (41)	25 (50)	0 (0)
Current smoker, *n* (%)	34 (33)	18 (33)	16 (32)	0 (0)
Comorbidity: pulmonary, cardiac, diabetes mellitus, *n* (%)[b]	30 (29)	18 (33)	12 (24)	0 (0)
Cough duration in days before index consultation, mean (SD)	9 (6)	8 (6)	10 (7)	0 (0)
Symptom severity score (14 symptoms), mean (SD)[c]	35 (14)	33 (12)	38 (16)	1 (1)
Infiltrate on chest radiograph, *n* (%)	7 (7)	3 (6)	4 (8)	5 (5)

[a]Defined as resistant to at least one tested antibiotic. [b]Pulmonary comorbidity = history of chronic obstructive pulmonary disease, asthma, or other lung disease; cardiac comorbidity = history of heart failure, ischaemic heart disease, or other heart disease. [c]Score for 14 physician-recorded symptoms, summed and scaled to range between 0 and 100 on day 1. SD = standard deviation.

- chloramphenicol 4/56 (7%);
- trimethoprim/sulfamethoxazole 48/56 (86%);
- levofloxacin 0/56 (0%); and
- cefotaxime 0/56 (0%).

For *H. influenzae*, resistance was as follows:

- ampicillin 6/56 (11%); and
- tetracycline 1/56 (2%).

The baseline characteristics did not differ greatly between patients with and without antibiotic-resistant LRTIs (Table 1); this was also the case for the subgroups of infection with *S. pneumoniae* (further details are available from the authors on request) and infection with *H. influenzae* (further details are available from the authors on request).

Disease course

For all outcomes, the illness course for patients with antibiotic-resistant LRTI tended to be slightly more favourable than that for patients with sensitive bacteria. However, after adjustment for confounders there were no significant differences in illness course between those with and without antibiotic-resistant LRTIs (Table 2).

Only one patient from the entire cohort required hospital admission within 4 weeks after their first consultation and that patient was from the non-antibiotic-resistant group. No study-related deaths were noted.

DISCUSSION

Summary

Over half of the *S. pneumoniae* and

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

Outcome	Resistant to antibiotic, *n* = 54[a]	Sensitive to antibiotic, *n* = 50	Crude analysis	Adjusted analysis[b]	Adjusted analysis *P*-value
Time to resolution, in days, of symptoms rated 'moderately bad or worse'	7 (5–11)[c]	9 (5–19)[c]	1.24 (0.82 to 1.88)[d]	1.27 (0.67 to 2.44)[d]	0.464
Patient recorded symptom severity score on days 2–4 after consultation (7-point scale from 0 = 'normal/not affected', 6 = 'as bad as it could be'	1.75 (0.94)[e]	2.18 (1.21)[e]	−0.43 (−0.85 to −0.01)[f]	−0.48 (−1.17 to 0.21)[f]	0.172
Duration of symptoms until complete resolution in days	14 (10–24)[c]	15 (9–28)[c]	1.15 (0.70 to 1.88)[d]	1.32 (0.61 to 2.90)[d]	0.483
Worsening of illness (new or worsening symptoms, hospital admission)	9/54 (17)[g]	18/50 (36)[g]	0.36 (0.14 to 0.89)[h]	0.31 (0.07 to 1.41)[h]	0.129
Duration of interference with normal activities or work, in days	6 (2–8)[c]	7 (3–12)[c]	1.46 (0.97 to 2.21)[d]	1.67 (0.85 to 3.28)[d]	0.136

[a]Defined as resistant to at least one tested antibiotic. [b]Adjusted for age (for each year increase), current smoking status, comorbidity, cough duration before index consultation, and bacteria (Streptococcus pneumoniae *or* Haemophilus influenzae). *[c]Median (interquartile range). [d]Hazard ratio (95% CI). [e]Mean (standard deviation). [f]Difference (95% CI). [g]n (%). [h]Odds ratio (95% CI). CI = confidence interval.*

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Ethical approval

Ethical approval for the Netherlands was granted by the Medisch Ethische Toetsingscommissie [Medical Research and Ethics Committee] of the University Medical Center Utrecht (ref: 07-179/O). Competent authority approval for the Netherlands was granted by De Centrale Commissie Mensgebonden Onderzoek [Central Committee on Research Involving Human Subjects]. 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. All other research sites obtained ethical and competent authority approval from their local organisations. Patients who fulfilled the inclusion criteria were given written and verbal information on the study and gave their informed consent to participate.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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H. influenzae isolates from adults presenting to primary care with LRTI were resistant to at least one tested antibiotic, but resistance to penicillins was present in 7%. Patients with antibiotic-resistant LRTI did not have a vastly different illness course than those with antibiotic-susceptible infections.

Strengths and limitations

To the authors' knowledge, this is the first study of the illness course of antimicrobial-resistant LRTI in primary care; the illness course of antibiotic-resistant and antibiotic-sensitive LRTIs could be described and compared.

One potential limitation is the misclassification of bacterial LRTI by airway bacterial colonisation or carriership, due to which it may have been erroneously concluded in this study that there are no differences in disease course between those with, and those without, antibiotic-resistant LRTI. It is expected that this misclassification is limited, because colonisation of the lower airways is unlikely in symptomatic ambulatory outpatients. In studies in which *H. influenzae* and *S. pneumoniae* were identified using conventional methods in healthy individuals — for example, by Lieberman *et al*[17] and Gunnarsson *et al*[18] — prevalence of colonisation was 10% at most. Patients with chronic obstructive pulmonary disease (COPD) are different in that they are more likely to be colonised with *H. influenzae* (17%);[19] however, only a few patients with COPD ($n = 6/104$, 6%) were included in the study presented here.

Another possible limitation is that the authors defined bacterial resistance as resistance to at least one tested antibiotic, and the overall prevalence of bacterial resistance was mainly driven by the resistance of *S. pneumoniae* to trimethoprim/sulfamethoxazole (86%). The number of patients with resistance to penicillins was too small ($n = 7$) to evaluate the course of disease in this subgroup separately, but it could be claimed that resistance to penicillins is more clinically relevant, as penicillins are the recommended antibiotic for LRTI in Europe. Moreover, antibiotic resistance does not appear to be a relevant issue for individual patients with LRTI in the study presented here; it is likely to be more relevant for patients with pneumonia, in which antibiotics have been shown to have a relevant effect.[20]

As LRTIs are common, many more eligible patients consulted their clinicians during the recruitment period than were invited to participate in this study; as a result, the authors did not achieve the goal of recruiting all consecutive, eligible patients. Nevertheless, it has been assumed 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]

The authors studied outpatients who had LRTI and few comorbidities, in whom pneumonia or the need for hospitalisation were not suspected during their initial assessment; as such, the findings might not be generalisable to more vulnerable patients or those with more-severe illness.

Finally, the power calculation of the GRACE trial did not formally include analyses on the subgroup of patients with antibiotic-resistant bacteria; as such, there is a risk of false negative results (type II error).

Comparison with existing literature

In the study presented here, antibiotic-resistant LRTIs are not associated with a different illness course than susceptible infections. The impact of bacterial resistance in LRTIs in primary care has, to the authors' knowledge, never been studied; in urinary tract infections, however, a few studies found that antibiotic resistance is associated with prolonged symptoms and frequent return visits.[7–9] One explanation for this difference may be treatment failure caused by resistance of the causal uropathogen to the prescribed antibiotics. This was not taken into account in the study conducted by McNulty *et al*,[9] while Butler *et al* found that infections caused by *Escherichia 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 females with uncomplicated urinary tract infection.[8]

Implications for practice

The results of the study presented here show that, when bacteria are present, LRTIs generally have a mild, uncomplicated, and self-limiting disease course, irrespective of the presence of antimicrobial resistance. This study confirms that, in terms of antimicrobial resistance, outpatients who do not require antibiotics are a different domain from patients who are hospitalised or outpatients who have already been treated with antibiotics.

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