Original Investigation

Prescription Strategies in Acute Uncomplicated Respiratory Infections
A Randomized Clinical Trial

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IMPORTANCE Delayed antibiotic prescription helps to reduce antibiotic use with reasonable symptom control. There are different strategies of delayed prescription, but it is not yet clear which one is the most effective.

OBJECTIVE To determine the efficacy and safety of 2 delayed strategies in acute, uncomplicated respiratory infections.

DESIGN, SETTING, AND PARTICIPANTS We recruited 405 adults with acute, uncomplicated respiratory infections from 23 primary care centers in Spain to participate in a pragmatic, open-label, randomized clinical trial.

INTERVENTIONS Patients were randomized to 1 of 4 potential prescription strategies: (1) a delayed patient-led prescription strategy; (2) a delayed prescription collection strategy requiring patients to collect their prescription from the primary care center; (3) an immediate prescription strategy; or (4) a no antibiotic strategy. Delayed prescription strategies consist of prescribing an antibiotic to take only if the symptoms worsen or if there is no improvement several days after the medical visit.

MAIN OUTCOMES AND MEASURES The primary outcomes were the duration of symptoms and severity of symptoms. Each symptom was scored using a 6-point Likert scale (scores of 3 or 4 were considered moderate; 5 or 6, severe). Secondary outcomes included antibiotic use, patient satisfaction, and patients' beliefs in the effectiveness of antibiotics.

RESULTS A total of 405 patients were recruited, 398 of whom were included in the analysis; 136 patients (34.2%) were men; mean (SD) age, 45 (17) years. The mean severity of symptoms ranged from 1.8 to 3.5 points on the Likert scale, and mean (SD) duration of symptoms described on first visit was 6 (6) days. The mean (SD) general health status on first visit was 54 (20) based on a scale with 0 indicating worst health status; 100, best status. Overall, 314 patients (80.1%) were nonsmokers, and 372 patients (93.5%) did not have a respiratory comorbidity. The presence of symptoms on first visit was similar among the 4 groups. The mean (SD) duration of severe symptoms was 3.6 (3.3) days for the immediate prescription group and 4.7 (3.6) days for the no prescription group. The median (interquartile range [IQR]) of severe symptoms was 3 (1-4) days for the prescription collection group and 3 (2-6) days for the patient-led prescription group. The median (IQR) of the maximum severity for any symptom was 5 (3-5) for the immediate prescription group and the prescription collection group; 5 (4-5) for the patient-led prescription group; and 5 (4-6) for the no prescription group. Patients randomized to the no prescription strategy or to either of the delayed strategies used fewer antibiotics and less frequently believed in antibiotic effectiveness. Satisfaction was similar across groups.

CONCLUSIONS AND RELEVANCE Delayed strategies were associated with slightly greater but clinically similar symptom burden and duration and also with substantially reduced antibiotic use when compared with an immediate strategy.

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Respiratory diseases are one of the most common reasons for consultation with family physicians, the most frequent being rhinitis, pharyngitis, and acute bronchitis.[1] Most respiratory infections are self-limiting, and recent systematic reviews have suggested that antibiotics modify the course of most of these infections only slightly.[2-8] Nevertheless, in the United States, about 60% of patients with a sore throat and 71% of patients with acute uncomplicated bronchitis still receive an antibiotic prescription.[9,10] Overprescription of antibiotics not only increases resistance to these drugs[11,12] but also strains resources, places patients at risk of adverse effects, and increases the number of future consultations for similar episodes.[13-15] In primary care, the availability of diagnostic procedures is generally limited, contributing to diagnostic uncertainty and driving antibiotic prescription even when there is no clear indication of bacterial infection. Antibiotics are also often prescribed because physicians and patients are concerned about the risk of complications and because many patients still expect an antibiotic prescription,[16] an expectation that may be overestimated by physicians.[17]

In cases of uncertainty, when it is difficult to determine whether an infection is caused by a virus or bacteria, the delayed antibiotic prescribing strategy can be a valuable tool to avoid unnecessary antibiotic use. This approach consists of prescribing an antibiotic to take only if the symptoms worsen or if there is no improvement several days after the medical visit. This strategy has been evaluated mainly in acute, uncomplicated respiratory infections.[18] Systematic reviews have suggested that delayed antibiotic strategies could result in poorer symptom control than immediate use of antibiotics.[19-21] Nevertheless, in the largest clinical trial published to date for acute uncomplicated respiratory infections in primary care, Little et al[16] found little difference in symptom control in the short term between delayed antibiotic strategies and no prescription. In a recent British study[22] in patients with sore throat, complications were found in only 1.4% of patients, with the risk of complications being no higher in the delayed antibiotic group than in the immediate antibiotic group.

The use of delayed prescription varies widely from country to country. In the United Kingdom, more than 50% of all prescriptions for acute, uncomplicated respiratory infections are delayed,[23] while in Southern Europe this strategy is not commonly used. No evidence is available for the United States. In addition, most studies on delayed antibiotic strategies have been carried out in the United Kingdom and Scandinavian countries, where the consumption of antibiotics is lower than in Southern Europe or the United States.[24] A previous study[25] in Spain evaluated delayed prescribing in primary care and found a reduction of antibiotic prescribing but did not include clinical outcomes. Therefore, we designed our study to determine the effectiveness of 2 delayed antibiotic strategies compared with immediate antibiotic prescription or no offer of antibiotics.

Methods

Study Design and Participants

We performed a pragmatic, randomized, multicenter, clinical trial (trial protocol available in Supplement 1), the methodology of which has been published elsewhere.[26] Competitive recruitment was performed in 23 primary care centers in 4 regions in Spain from December 2009 to July 2012. Eligible patients were older than 18 years and had 1 of the following acute, uncomplicated respiratory infections: acute pharyngitis, rhinosinusitis, acute bronchitis, or exacerbation of mild-to-moderate chronic obstructive pulmonary disease (COPD) (eAppendix 1 in Supplement 2). In all cases, the physician had reasonable doubt as to whether to treat with an antibiotic. The study was approved by the ethics committee of the Jordi Gol i Gurina Foundation (Barcelona, Spain) and by the clinical research ethics committees in each healthcare area. Approval was also obtained from the Spanish Agency of Medicines and Health Products. Written informed consent was obtained from all participants.

Interventions

Patients were randomized to 1 of 4 strategies, two of which—the patient-led prescription strategy and the prescription collection strategy—were delayed prescription strategies. Patients randomized to the patient-led prescription strategy were given an antibiotic at first consultation, and patients randomized to the prescription collection strategy could collect the antibiotic at their primary care reception desk 3 days after the first consultation.

Patients allocated to the delayed antibiotic strategies received the same instructions from the physician. They were told it was normal to feel worse over the first few days after the visit. If they felt substantially worse in the first few days, however, they were recommended to consider taking the antibiotics or to return to the physician if they considered it necessary. If they noted no improvement after 5 days (in cases of pharyngitis) or after 10 days (in cases of other infections), they were also instructed to consider taking the antibiotics.

Patients randomized to the immediate prescription strategy received an antibiotic at first visit and were instructed to start the medication on the same day, and patients randomized to the no prescription strategy were not offered antibiotics.

Patients allocated to the immediate prescription strategy or to the no prescription strategy were told it was normal to feel worse over the first few days after the visit. However, they were instructed to consider reconsultation if they felt they should see their physician or if there was no improvement after 5 days (in cases of pharyngitis) or after 10 days (in cases of other infections).

In all 4 prescription strategy groups, the choice of antibiotic was made by the physician.

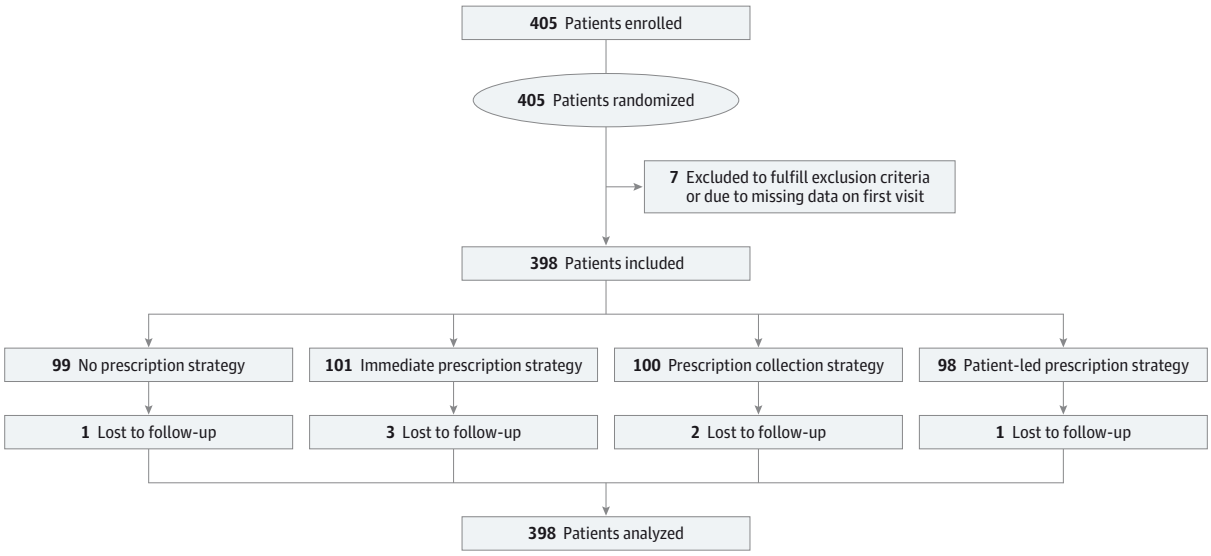
Randomization and Masking

Physicians randomized patients centrally using an electronic online platform. Randomization was performed using permuted block sizes of 4 and stratified by type of infection. Neither patients nor health professionals were blinded.

Outcomes

The primary outcome measure was the duration and severity of symptoms. Patients filled out a daily questionnaire for a maximum of 30 days.[27] Each symptom was scored using a 6-point Likert scale. Symptoms scoring 3 or 4 were considered moderate, and those scoring 5 or 6 were considered se-

Figure. Patient Randomization Flowchart



Flowchart following the randomization of patients to different prescription strategies to final analysis.

vere. We included common symptoms such as fever, discomfort or general pain, cough, difficulty sleeping, changes in everyday life in all patients, and specific symptoms according to the condition. Our secondary outcomes were antibiotic use, satisfaction with health care, belief in the effectiveness of antibiotics, and absenteeism (absence from work or doing their daily activities). We also determined the risk of complications (eg, pneumonia, abscesses, or cellulitis) and the need for unscheduled health care (eAppendix 2 in Supplement 2).

Procedures

All family physicians received training before recruitment began. Family physicians personally informed the patients during consultation at the primary care centers, using a structured script about: (1) the expected duration and the self-limiting natural history of the corresponding respiratory infection; (2) the marginal benefits and potential adverse effects of antibiotics; and (3) the study purpose and procedure. This information was also provided to patients in writing. After signing the consent form, those who agreed to participate were randomized to 1 of the 4 prescription strategies. All patients received recommendations according to the strategy assigned that included advice about nonantibiotic medication use. They also received a diary with a validated symptom questionnaire to be filled out daily.[27] Baseline data were collected by the family physician and/or a nurse. A central telephone follow up was conducted on days 2, 7, 15, and 22 if symptoms persisted. All patients were visited 30 days after randomization at their surgery.

Statistical Analyses

Sample Size Calculation

We calculated a sample size of 150 patients per arm (600 patients) considering a mean (SD) of 12 (6) days as the average duration of an acute uncomplicated respiratory infection without treatment.[27] We considered a difference of 2 days in the duration of symptoms in the immediate antibiotic strategy, compared with a delayed strategy, as a clinically relevant result. For our statistical analyses, we used an α error of 5% (α = .05) and a power of 80% (β = 0.2).

Main Analyses

Characteristics of the study population were described using frequencies for categorical variables, and mean (SD) for quantitative variables. To compare the included strategies, we used a χ^2 test or Fisher exact test for categorical variables and analysis of variance (ANOVA) for continuous variables. To compare the duration of symptoms across strategies, we used a negative binomial regression model per symptom with symptom duration (ie, number of days with the symptom) as the dependent variable and both the prescription strategy and antibiotic consumption as independent variables. For severity of symptoms, we used an ordered logistic regression model per symptom with severity of symptom as the dependent variable and both the prescription strategy and antibiotic consumption as independent variables. Both regression models were adjusted by reported antibiotic consumption. Intention-to-treat guided all the analyses. The level of significance was 5% (α = .05). We used STATA statistical software version 13.1 (StataCorp) for all statistical analyses.

Results

Characteristics of the Study Participants

A total of 405 patients were recruited, 398 of whom were included in the analysis (**Figure**). Overall, 136 patients (34.2%) were men, mean (SD) age was 45 (17) years, and 265 patients (72%) had at least a secondary education level. The most common infection was pharyngitis (n = 184; 46.2%), followed by acute

Table 1. Baseline Patient Characteristics[a]

Characteristic	Prescription Strategy, No. (%)				
	Immediate (n = 101)	Collection (n = 100)	Patient-Led (n = 98)	No Prescription (n = 99)	Total (n = 398)
Men	39 (38.6)	29 (29.0)	33 (33.7)	35 (35.3)	136 (34.2)
Age, mean (SD), y	48 (17)	42 (17)	45 (17)	45 (16)	45 (17)
Educational level					
Primary or less	26 (28.3)	19 (21.1)	32 (34.8)	26 (27.7)	103 (28.0)
Secondary	32 (34.8)	42 (46.7)	35 (38.0)	33 (35.1)	142 (38.6)
Higher	34 (36.9)	29 (32.2)	25 (27.2)	35 (37.2)	123 (33.4)
Respiratory comorbidity[b]	7 (6.9)	5 (5.0)	4 (4.1)	10 (10.1)	26 (6.5)
Smoking status					
Nonsmoker	53 (54.1)	50 (50.5)	61 (62.2)	51 (52.6)	215 (54.8)
Smoker	22 (22.4)	25 (25.3)	11 (11.2)	20 (20.6)	78 (19.9)
Former smoker	23 (23.5)	24 (24.2)	26 (26.5)	26 (26.8)	99 (25.3)
Uncomplicated acute respiratory infection					
Rhinosinusitis	20 (19.8)	20 (20.0)	19 (19.4)	19 (19.2)	78 (19.6)
Pharyngitis	47 (46.5)	46 (46.0)	45 (45.9)	46 (46.5)	184 (46.2)
Acute bronchitis	32 (31.7)	32 (32.0)	32 (32.7)	32 (32.3)	128 (32.2)
Exacerbation of mild-to-moderate COPD	2 (2.0)	2 (2.0)	2 (2.0)	2 (2.0)	8 (2.0)
Severity of symptoms, mean (SD)[c]					
Fever	2.2 (1.8)	1.8 (1.7)	2.0 (1.9)	2.2 (1.8)	2.0 (1.8)
Discomfort or general pain	2.8 (1.7)	3.0 (1.6)	2.9 (1.8)	3.5 (1.6)	3.0 (1.7)
Cough	2.4 (2.0)	2.5 (2.0)	2.6 (2.0)	2.9 (2.1)	2.6 (2.0)
Difficulty sleeping	2.1 (1.9)	2.2 (2.1)	2.0 (2.1)	2.4 (1.9)	2.2 (2.0)
Changes in everyday life	2.3 (1.9)	1.9 (2.0)	2.1 (1.9)	2.4 (2.0)	2.2 (2.0)
Days with symptoms prior to the visit, mean (SD)	6 (6)	5 (5)	6 (7)	6 (8)	6 (6)
General health status, mean (SD)[d]	53 (21)	55 (20)	56 (19)	53 (19)	54 (20)

Abbreviation: COPD, chronic obstructive pulmonary disease.

[a] Data presented are the frequency (percentage) or mean (SD).

[b] Only cardiovascular comorbidity (P = .12) and diabetes (P = .19).

[c] Score based on a Likert scale from 0 (no problem) to 6 (as bad as it could be), and common symptoms are characteristic of the 4 pathologies studied (rhinosinusitis, pharyngitis, acute bronchitis, and exacerbation of mild-to-moderate COPD).

[d] Score based on a visual analog scale from 0 (worst health status) to 100 (best health status) on first visit.

bronchitis (n = 128; 32.2%). Mean severity of symptoms ranged from 1.8 to 3.5 points on a Likert scale from 0 to 6, and the mean (SD) duration of symptoms described on the first visit was 6 (6) days. The mean (SD) general health status at the first visit was 54 (20), with 0 corresponding to the worst health status and 100 to the best status. Most patients were nonsmokers (n = 314; 80.1%) and did not have respiratory comorbidity (n = 372; 93.5%) (**Table 1**). The presence of symptoms at the first visit was similar among the 4 groups (**Table 2**).

Primary Outcomes

The mean (SD) duration of severe symptoms was 3.6 (3.3) days for the immediate prescription group and 4.7 (3.6) days for the no prescription group (P = .002). The median (IQR) duration of severe symptoms was 3 (1-4) days for the prescription collection group and 3 (2-6) days for the patient-led prescription group. Patients randomized to the immediate prescription strategy showed shorter durations of severe symptoms, ranging from 0.4 days less than the prescription collection strategy to 1.5 days less than the patient-led prescription strategy. The duration of moderate symptoms was mean (SD) 4.7 (4.0) days for the immediate prescription group; 5.2 (4.3) days for the prescription collection group; 6.0 (5.5) days for the patient-led prescription group; and 6.5 (5.2) days for the no prescription group (P < .001). The duration of moderate symptoms was significantly shorter for the prescription collection group than for the no prescription group (P = .008) (**Table 3**).

The duration of common symptoms (ie, fever, discomfort, cough, difficulty sleeping, and difficulty performing daily activities) in the immediate prescription group compared with the no prescription group was shorter for 3 out of 5 symptoms (P < .05 for all). For the immediate prescription group compared with the prescription collection and patient-led prescription groups, the duration was significantly different for only discomfort or general pain (prescription collection strategy, P = .003; patient-led prescription strategy, P = .05). Compared with the no prescription group, the duration of 2 common symptoms was shorter for the patient-led prescription group and shorter for 1 symptom in the prescription collection group (P < .05 for all) (Table 3).

The maximum severity for any symptom was median (interquartile range [IQR]) 5 (3-5) points for the immediate prescription group; 5 (3-5) points for the prescription collection group; 5 (4-5) points for the patient-led prescription group; and 5 (4-6) points for the no prescription group (P = .009). The severity of the specific symptoms and general health statuses was similar among the 4 strategies (**Table 4**).

Secondary Outcomes

In the immediate prescription group, 92 patients (91.1%) used antibiotics, compared with 12 patients (12.1%) in the no prescription group, 23 patients (23.0%) in the prescription collection group, and 32 patients (32.6%) in the patient-led prescription group. No differences were observed for

Table 2. Presence of Patient Symptoms on First Visit[a]

Characteristic	Prescription Strategy, No. (%)				Overall *P* Value
	Immediate (n = 101)	Collection (n = 100)	Patient-Led (n = 98)	No Prescription (n = 99)	
Moderate symptoms (3 or 4)[b]	80 (93.0)	76 (89.4)	88 (97.8)	80 (92.0)	.13
Severe symptoms (5 or 6)[b]	47 (54.7)	45 (52.9)	47 (52.2)	53 (60.9)	.65
Common symptoms[c]					
Fever	66 (65.4)	63 (63.0)	64 (65.3)	67 (67.7)	.92
Discomfort or general pain	90 (89.1)	92 (92.0)	87 (88.8)	85 (85.9)	.59
Cough	77 (76.2)	82 (82.0)	78 (80.0)	83 (83.8)	.56
Difficulty sleeping	72 (71.3)	67 (67.0)	61 (62.2)	68 (68.7)	.58
Changes in everyday life	77 (76.2)	67 (67.0)	71 (72.5)	69 (69.7)	.51
Rhinosinusitis					
Spontaneous facial pain	12 (13.5)	12 (13.2)	13 (14.3)	13 (14.8)	.99
Facial pain on touch	12 (13.5)	13 (14.3)	11 (12.1)	13 (14.8)	.96
Pharyngitis					
Swallowing difficulties	46 (48.4)	41 (45.1)	38 (40.0)	31 (33.0)[d]	.16
Rhinosinusitis and pharyngitis					
Headache	58 (59.2)	51 (52.6)	52 (54.2)	48 (50.5)	.66
Nasal mucosity	50 (51.0)	49 (50.5)	53 (55.2)	51 (53.7)	.90
Sore throat	57 (58.2)	59 (60.8)	50 (52.1)	52 (54.7)	.63
Acute bronchitis and exacerbation of mild-to-moderate COPD					
Expectoration or phlegm	28 (31.5)	28. (31.8)	28 (30.4)	31 (34.1)	.96
Breathlessness	22 (24.7)	26 (29.6)	29 (31.5)	29 (31.9)	.70
Chest pain on breathing	25 (28.1)	17 (19.3)	21 (22.8)	23 (25.3)	.57
Chest noises on breathing	26 (29.2)	23 (26.1)	19 (20.7)	22 (24.2)	.60

Abbreviation: COPD, chronic obstructive pulmonary disease.

[a] Data presented are the frequency (percentage) of patients with symptoms. Statistical significance was calculated by adjusting a negative binomial regression model per symptom, with the number of days with the symptom as dependent variable and both strategy and antibiotic consumption as independent variables.

[b] Score based on a Likert scale from 0 (no problem) to 6 (as bad as it could be).

[c] Common symptoms are characteristic of the 4 pathologies studied (rhinosinusitis, pharyngitis, acute bronchitis, and exacerbation of mild-to-moderate COPD).

[d] *P* = .03 compared with the immediate prescription strategy.

complications, adverse effects, or the need for unscheduled care among the strategy groups, and no differences were observed in the perception of general health statuses assessed at 30 days. The majority of patients that collected the antibiotic reported that they finally took them (**Table 5**).

Rates of absenteeism were lower in the delayed strategy groups (prescription collection, 18 patients [21.4%]; patient-led prescription, 23 patients [25.8%]) than in the immediate prescription group (28 patients [33.3%]) and the no prescription group (33 patients [39.8%]) (*P* = .05). Patient satisfaction was high and similar among the 4 groups (*P* = .14). Belief that antibiotics had no effect or were not very effective was higher for patients in the 2 delayed antibiotic strategies (prescription collection, 12 patients [15.6%]; patient-led prescription, 16 patients [19.0%]) and the no antibiotic strategy (15 patients [19.7%]) than the immediate prescription strategy (7 patients [8.2%]) (*P* = .02). Finally, more patients randomized to the immediate prescription strategy (n = 72 [85.7%]) reported that they would return to their physician for a similar episode than patients in the no prescription (n = 59 [70.2%]), prescription collection (n = 58 [69.1%]), and patient-led prescription strategies (n = 60 [69.0%]) (*P* = .06).

Discussion

To our knowledge, this is the largest study to date outside Northern Europe to evaluate the effect of 2 delayed antibiotic strategies in acute, uncomplicated respiratory infections on symptom control. We found that the delayed strategy groups had slightly greater symptom burden and duration than the immediate prescription group, although the differences were not clinically relevant. Delayed prescription and no prescription strategies notably reduced antibiotic use compared with the immediate prescription group.

Our results are comparable with a previous Cochrane systematic review[21] and a recent trial by Little et al[16] studying delayed prescription in acute uncomplicated respiratory infections. With respect to the duration of symptoms, the Cochrane review of 3157 patients with respiratory infections reported that the duration of symptoms in the delayed antibiotic strategy groups was similar to that in the immediate prescription approach, particularly in those with a sore throat and acute otitis media.[21,22] This was consistent with our study, which showed that the duration of severe symptoms was quite similar in the immediate prescription group and in the 2 delayed prescription groups.

In their trial, Little et al[16] found minimal differences in symptom severity. The authors compared the effectiveness of 4 delayed antibiotic strategies (recontact for a prescription, post-dated prescription, prescription collection, and patient-led prescription) with no antibiotics in patients with acute uncomplicated respiratory infections. However, the study did not include an immediate antibiotic randomization strategy. Our findings are concurrent with their results.

The Cochrane review[21] raised debate about whether a no prescription strategy is more suitable than a delayed strategy because it results in lower antibiotic use.[21] In line with these results, our study showed that the delayed prescription groups also reported a lower antibiotic use. Just over one-tenth of patients not initially prescribed antibiotics ended up using them, as opposed to 23.0%

Table 3. Duration of Patient Symptoms After First Visit[a]

Characteristic	Duration of Symptoms per Prescription Strategy, d, Mean (SD)				Overall *P* Value
	Immediate	Collection	Patient-Led	No Prescription	
Any until disappearance	11.7 (8.4)	12.3 (7.3)	13.1 (8.5)	14.4 (8.1)[b]	.02
Moderate (3 or 4)[c]	4.7 (4.0)	5.2 (4.3)[b,d]	6.0 (5.5)[b]	6.5 (5.2)[b]	<.001
Severe (5 or 6)[c]	3.6 (3.3)	4.0 (4.2)[b]	5.1 (6.3)[b]	4.7 (3.6)[b]	.002
Common symptoms					
Fever	3.7 (4.2)	3.8 (3.2)[d]	3.8 (3.7)[d]	5.4 (6.3)[b]	.004
Discomfort or general pain	6.7 (5.7)	8.7 (7.0)[b]	7.9 (7.1)[b,d]	10.2 (7.1)[b]	.002
Cough	10.0 (6.6)	9.6 (6.7)	11.1 (8.0)	12.3 (8.1)[b]	.03
Difficulty sleeping	6.0 (6.2)	6.5 (5.2)	8.3 (7.1)	7.6 (6.2)	.11
Changes in everyday life	6.4 (6.4)	6.6 (5.5)	6.9 (6.3)	8.4 (6.6)	.14
Rhinosinusitis					
Spontaneous facial pain	7.1 (6.6)	5.4 (3.6)	6.1 (5.5)	8.6 (7.7)	.48
Facial pain on touch	7.6 (5.2)	11.6 (9.7)	9.0 (9.7)	9.2 (8.4)	.15
Pharyngitis					
Swallowing difficulties	5.1 (3.8)	6.1 (4.3)	5.6 (3.1)	6.8 (4.9)	.71
Rhinosinusitis and pharyngitis					
Headache	4.1 (3.8)	7.0 (5.9)[b]	6.3 (6.1)	9.0 (8.0)[b]	.03
Nasal mucosity	8.3 (7.2)	10.1 (7.8)	9.8 (7.5)	11.0 (7.4)	.47
Sore throat	5.9 (4.7)	7.0 (4.7)	6.7 (4.6)	8.1 (6.3)	.22
Acute bronchitis and exacerbation of mild-to-moderate COPD					
Expectoration or phlegm	12.1 (8.7)	13.1 (8.2)	14.6 (9.5)	13.4 (7.6)	.88
Breathlessness	11.8 (9.1)	6.7 (5.6)	9.7 (9.0)	10.3 (6.7)	.43
Chest pain on breathing	7.5 (6.4)	5.5 (3.4)	9.2 (8.4)	9.6 (6.9)	.22
Chest noises on breathing	7.2 (4.8)	5.3 (5.3)	11.9 (10.2)	10.9 (8.4)	.24

Abbreviation: COPD, chronic obstructive pulmonary disease.

[a] Data presented are mean (SD) of the number of days with symptoms. Only patients who had symptoms for 1 or more days were included. Statistical significance was calculated by adjusting a negative binomial regression model per symptom, with the number of days with the symptom as dependent variable and both prescription strategy and antibiotic use as independent variables.

[b] $P < .05$ compared with the immediate prescription strategy.

[c] Score based on a Likert scale from 0 (no problem) to 6 (as bad as it could be).

[d] $P < .05$ compared with the no prescription strategy.

Table 4. Severity of Patient Symptoms After First Visit[a]

Characteristic	Prescription Strategy, Median (IQR)				Overall *P* Value
	Immediate	Collection	Patient-Led	No Prescription	
Maximum severity of any symptom[b]	5 (3-5)	5 (3-5)[c]	5 (4-5)[c,d]	5 (4-6)[d]	.009
Common symptoms					
Fever	2 (2-3)	2 (1-3)	2 (1-3)	2 (1-3)	.49
Discomfort or general pain	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-4)	.54
Cough	2 (1-3)	2 (1-3)	2 (1-3)	3 (1-4)	.30
Difficulty sleeping	2 (1-4)	2 (1-3)	2 (1-4)	2 (1-3)	.54
Changes in everyday life	2 (1-3)	2 (1-3)[c]	2 (1-4)[c]	3 (1-4)[d]	.03
Rhinosinusitis					
Spontaneous facial pain	2 (1-3)	3 (2-3)	3 (2-4)	2 (1-4)	.33
Facial pain on touch	1 (1-2)	3 (3-4)	3 (2-4)	3 (1-5)	.08
Pharyngitis					
Swallowing difficulties	3 (2-4)	2 (1-4)	2 (1-4)	3 (1-4)	.41
Rhinosinusitis and pharyngitis					
Headache	2 (1-3)	2 (2-4)	3 (2-3)	2 (1-4)	.75
Nasal mucosity	2 (1-4)	2 (1-4)	3 (1-3)	3 (1-4)	.30
Sore throat	3 (2-4)	2 (1-4)	3 (2-4)	3 (2-4)	.49
Acute bronchitis and exacerbation of mild-to-moderate COPD					
Breathlessness	1 (1-2)	1 (1-2)	2 (1-2)	2 (1-3)	.46
Chest pain on breathing	2 (1-3)	1 (1-2)	2 (1-4)	2 (1-3)	.10
Chest noises on breathing	2 (1-3)	1 (1-2)[c]	2 (1-3)	2 (1-4)	.05

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

[a] Only patients with symptoms for 1 or more days were included. Statistical significance was calculated by adjusting an ordered logistic regression model per symptom, with severity of symptom as the dependent variable and both prescription strategy and antibiotic use as independent variables.

[b] Scores based on a Likert scale from 0 (no problem) to 6 (as bad as it could be).

[c] $P < .05$ compared with the no prescription strategy.

[d] $P < .05$ compared with the immediate prescription strategy.

(n = 23) of patients randomized to the prescription collection strategy. Conversely, the use of antibiotics in the immediate antibiotic group was very high as expected (n = 92 [91.1%]).

Although still unclear, several patterns in the delayed prescription approach seem to be emerging. Earlier studies[21] comparing delayed prescription strategies showed variability in antibiotic use rates, with higher use in patient-led strategies than in the prescription collection strategies. Later studies,[16] like our own, show a similar pattern. The hassle of having to return to a clinic for a prescription likely plays a role in this difference.

Table 5. Secondary Outcomes

Characteristic	Prescription Strategy							Total	
	Immediate (n = 101)	Collection (n = 100)	*P* Value[a]	Patient-Led (n = 98)	*P* Value[a]	No Prescription (n = 98)	*P* Value[a]	(n = 398)	Overall *P* Value
Antibiotic collected, No. (%)	90 (89.1)	26 (26.0)	<.001	34 (34.7)	<.001	NA	NA	150 (50.2)	<.001
Antibiotic used, No. (%)	92 (91.1)	23 (23.0)	<.001	32 (32.6)	<.001	12 (12.1)		159 (39.9)	<.001
Nonantibiotic medication use, No. (%)	75 (74.3)	75 (75.0)	.90	79 (80.6)	.29	81 (81.8)	.20	310 (77.9)	.46
Need for unscheduled health care, No. (%)	4 (4.0)	4 (4.0)		6 (6.1)		6 (6.1)		20 (5.0)	.84
General health status, mean (SD)[b]	95 (90-100)	91 (85-100)	.86	95 (90-100)	.98	95 (90-100)	.77	95 (90-100)	.87
Adverse effects, No. (%)	1 (1.0)	0		1 (1.0)		3 (3.0)		5 (1.3)	.27
Referral to the emergency department, No. (%)	0	0		1 (1.0)		1 (1.0)		2 (0.5)	.37

Abbreviation: NA, not applicable.

[a] Immediate antibiotic strategy was the reference category.

[b] Score based on a visual analog scale from 0 (worst health status) to 100 (best health status).

The low use of antibiotics observed in clinical trials should be considered with caution because they may not reflect real use. As opposed to observational studies, research participants receive structured advice and are typically more motivated than in usual practice.[25]

The Cochrane review[21] did not find any evidence that delayed antibiotics are safer or more harmful than a no antibiotic approach, but as in our study, this outcome was underpowered.[16] With respect to patient satisfaction in the Cochrane review, immediate antibiotics had slightly higher levels of patient satisfaction than delayed antibiotics, although the clinical significance was marginal (92% vs 87%, respectively).[21] Our results did not reveal any significant differences between groups.

Limitations and Strengths of Our Study

The first limitation of our study is that we did not achieve the target sample size. This was mainly because we ran out of funding since recruitment was slow as a result of clinicians' time limitations.[28] Despite the smaller sample size, however, the variability observed in the duration of symptoms was 2.8 instead of 6 standard deviations, which was lower than expected. With these new data our study was overpowered. Second, most patients had pharyngitis and bronchitis, limiting the inferences for patients with rhinosinusitis or exacerbation of mild-to-moderate COPD. Third, it could be argued that the open nature of the study may have caused a placebo effect favoring antibiotics. However, this effect was minimized by the similar structured information all patients received about the self-limiting nature of respiratory infections and the advice about nonantibiotic medication use. Furthermore, the open design allowed us to study the perceptions of patients in a situation similarly to usual practice.[29]

The strengths of our study are its pragmatic design and that our study, as far as we know, is the largest trial to assess delayed prescription strategies outside Northern Europe by directly comparing delayed prescription strategies with an immediate prescription arm in a randomized fashion.

Implications for Practice and Research

Delayed prescription strategies are a useful approach to management in patients with acute uncomplicated respiratory infections. When patients or physicians are concerned about the risk of complications, or when patients expect to be prescribed antibiotics, a delayed antibiotic strategy may be particularly helpful compared with a no prescription strategy. Delayed prescription strategies show high potential for clinical benefit not only in Spain but in other countries, including the United States, where antibiotic use is often inappropriate.[9,10]

Further studies are required to identify subgroups in which delayed prescription strategies may be most useful. Likewise, delayed strategies should be evaluated in larger populations that include older patients, participants with a lower educational level, exacerbations of mild-moderate COPD, or acute sinusitis and otitis. Finally, more qualitative research is called for to better understand the contextual use of delayed prescription strategies.

Conclusions

In this pragmatic, open-label, randomized trial of antibiotic treatment strategy for acute, uncomplicated respiratory infections, delayed strategies were associated with slightly greater, but clinically similar, symptom burden and duration, as well as substantially reduced antibiotic use when compared with an immediate prescription strategy. In case of uncertainty, delayed strategies should become standard practice as they reduce antibiotic use and patient belief in antibiotic effectiveness.

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Invited Commentary

Delayed Antibiotic Prescribing Strategies—Time to Implement?

Amanda R. McCullough, PhD; Paul P. Glasziou, PhD

Despite growing concern over antibiotic resistance, global antibiotic use continues to rise.[1] Outpatients in the United States used more than 30 million antibiotics for acute respiratory infections in 2010,[2] yet those prescriptions offered minimal or no benefits for most patients.[3] Since antibiotic use drives the development of antibiotic resistance, simple and effective interventions to curb antibiotic use and slow the development of resistance are urgently needed. A delayed prescription strategy is an intervention that may offer an acceptable compromise between immediate and no antibiotic prescription.

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Cates[4] first used a delayed prescribing strategy for parents of children with acute otitis media by providing them with an antibiotic prescription and instructions to wait for 1 or 2 days before filling it. At 1 year, amoxicillin use fell by 32% (95% CI, 25%-39%) compared with a 12% (95% CI, 4%-20%) reduction in controls.[4] This reduction in antibiotic use was sustained even after 3 years.[5] A systematic review of subsequent randomized clinical trials[6] confirmed that delayed prescribing reduces antibiotic use compared with immediate prescribing and causes only minor reductions in patient satisfaction without increasing rates of complications or consultations. Fewer patients (28%) used antibiotics if they had to return to collect a delayed prescription from the clinic reception compared with 40% of patients when a delayed prescription was given during the consultation.[6] The lowest rate of antibiotic prescription was achieved by not prescribing antibiotics (14% of patients) and the highest rate was achieved by providing an immediate antibiotic prescription (93% of patients).[6] There has been no direct comparison of these 4 strategies in a single trial, and the sustainability of delayed prescription outside of the study by Cates[5] has not been explored.

In this issue of *JAMA Internal Medicine*, de la Poza Abad and colleagues[7] test delayed prescribing in a 4-arm randomized clinical trial for adults with uncomplicated acute respiratory infections in primary care clinics in Spain. This is the first study in a Spanish setting and the first to directly compare 4 different prescription strategies: (1) a patient-led strategy where physicians prescribe an antibiotic and advise patients to take it only if symptoms worsen or do not improve within several days; (2) a collection strategy where patients could collect an antibiotic prescription on day 3 postconsultation; (3) an immediate prescription strategy; or (4) a no prescription strategy without reconsultation.

Among patients allocated to the immediate prescribing strategy, 91% used antibiotics.[7] Rates of antibiotic use in the patient-led, prescription collection, and no prescription strategies were significantly lower: 33%, 23%, and 12%, respectively (absolute reductions in antibiotic use of 58%, 68%, and 79%).[7] Compared with the immediate prescribing strategy, severe symptoms lasted 0.4 to 1.5 days longer in the patient-led, prescription collection, and no prescription strategies, but patient satisfaction did not differ. Importantly, fewer patients randomized to the patient-led, prescription collection, or no prescription strategies intended to reconsult for the same illness (69%, 70%, and 69%, respectively) compared with the immediate prescription strategy (86%).[7] Overall, more patients randomized to the patient-led, prescription collection, and no prescribing strategies believed that antibiotics were ineffective for acute respiratory infections (19%, 16%, and 20%, respectively) compared with the immediate prescribing strategy (8%).[7]

These findings should be interpreted in light of the study's limitations. The risk of allocation bias is unclear because the authors do not report the allocation concealment procedures at randomization. Participants self-reported their symptom burden and antibiotic use leading to a high risk of measure-