

Trend of Use of Quinolone Antibiotics in Community-Acquired Pneumonia

AKGÜN et al. Quinolone Use in CAP

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ABSTRACT

Objectives: Quinolone group antibiotics are used frequently in the treatment of community-acquired pneumonia. In addition, safety concerns regarding quinolones are also on the rise. This study aimed to investigate physicians' tendencies to prescribe quinolones when managing outpatient pneumonia treatment and the factors influencing their decisions.

Methods: Physicians were asked to participate in a survey consisting of 20 questions. They were queried about the antibiotic groups they most frequently use when prescribing outpatient treatment for community-acquired pneumonia, the specific type of quinolone they most commonly use, their opinions on the effects and side effects of quinolones through Likert-type questions, and the clinical scenarios that lead them to prescribe quinolones. Additionally, a comparison was made between pulmonologists and other specialists.

Results: A total of 16.29% of physicians primarily prescribed quinolones. The most preferred quinolone was moxifloxacin (50%). In cases where treatment failed, physicians were more likely to hospitalize patients and approach broad-spectrum antibiotic therapy (78.09%). Pulmonologists were more likely to prescribe quinolones in cases of unresponsiveness to previous beta-lactam therapy and complicated pneumonia than non-pulmonologists ($p=0.013$, $p=0.044$, respectively). Pulmonologists placed more importance on tendinitis side-effect compared to non-pulmonologists ($p=0.019$). Among the clinical factors, the previous use of beta-lactam antibiotics and the presence of chronic disease in the patient's medical history were significantly associated with physicians who preferred quinolones as their first choice compared to those who did not ($p=0.008$ and $p=0.006$, respectively).

Conclusion: The fact that quinolones can be used alone and contribute to the speed of recovery is appealing to clinicians. However, guidelines conflict with each other regarding their first-line use in community-acquired pneumonia. In addition, knowledge about the side effects of quinolones is increasing. The prescription rates of quinolones should be closely monitored, and if an increase in prescription rates is detected, it should be kept in mind that legal regulations are more effective in cases where guideline recommendations are inadequate.

Keywords: fluoroquinolones, pneumonia, surveys and questionnaires

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INTRODUCTION

Microbial etiology varies in community-acquired pneumonia. Especially diseases caused by resistant pathogen microorganisms cause failure in empirical treatments, and as a result, physicians' interest in newly developed

antibiotics is increasing. Quinolone prescription rates have been on an increasing trend in recent decades. (1). In the ATS/IDSA 2019 community-acquired pneumonia guideline, it was suggested that quinolones can be used in primary care in outpatients with comorbid diseases (2). Considering increasing antibiotic resistance and drug side effects, efforts are being made to limit their use in the first-line treatment of pneumonia (3). In the 2021 community-acquired pneumonia guideline, which was created by consensus of pulmonologists, infectious diseases, internists and family physicians in Turkey, it was recommended as an alternative treatment in cases where beta-lactam combinations cannot be used or have been used recently. (4) In this study, we evaluated physicians' tendencies to prescribe quinolones in the outpatient treatment of community-acquired pneumonia.

MATERIALS AND METHODS

Approval for this study was obtained from the Hatay Mustafa Kemal University Non-interventional Ethics Committee, dated 4/3/2024, with decision number 20. The research was conducted as a cross-sectional descriptive survey, including all physicians involved in the diagnosis and treatment of respiratory tract infections, with a focus on pulmonologists and other specialists managing the outpatient treatment of community-acquired pneumonia. The study aimed to assess their perspectives, and a comparison was made between these groups to evaluate differences in prescribing patterns. As this was an exploratory study intended to gather insights into prescribing tendencies, a sample size calculation was not performed. To ensure a larger sample size, the study targeted physicians across Turkey rather than focusing on a specific hospital. To increase the number of participants, physicians in our hospital involved in community-acquired pneumonia were asked to share the survey link in specialty association WhatsApp groups. Data collection took place over a three-month period, from March to June 2024.

A 20-question survey form was prepared to question the physicians' tendencies towards outpatient community-acquired pneumonia treatment and was delivered online to the targeted physician group via social media applications. Antibiotic options were created as multiple choice based on the ATS/IDSA guideline for community-acquired pneumonia (2). The first four questions of the survey are the field of expertise, job description, institution where one works, and the number of patients with pneumonia diagnosed annually. In the following questions, antibiotic selection and quinolone preference in outpatient treatment of pneumonia developing in the community, as well as which quinolone was preferred, were questioned. In addition, the survey included 12 Likert-scale questions comparing physicians' views on the advantages and disadvantages of quinolones with those of non-quinolone antibiotics. Commonly reported side effects in the literature have been used in formulating the question items (5-7). As the last question, alternative treatment tendencies in case of treatment failure were prepared as a separate question for the participants. (See Annex 1 for the survey form)

Statistics

Categorical variables were presented as numbers and percentages. Comparisons between categorical variables were examined using the Pearson chi-square test or Fisher's exact tests. As a result of the evaluation where a significant difference was detected in comparisons of more than two groups, a post hoc analysis with Bonferroni method was performed to evaluate which variable caused the difference. The hypotheses were accepted as bidirectional.

For statistical clarity, respondents who answered 'not important' and 'less important' were combined into one group, those who answered 'doesn't matter' were placed in a second group, and those who answered 'important' and 'very important' were categorized into a third group for the Likert scale questions.

After data collection, a post hoc power analysis was conducted using G*Power software to assess the adequacy of the sample size. In this study, an independent two-sample t-test (Means: Difference between two independent means) was used to compare the prescription practices of pulmonologists and other specialists. A one-tailed test was applied, as the hypothesis expected a difference in a specific direction. The analysis parameters were set as follows: alpha level of 0.05, desired power ($1-\beta$) of 0.80, and effect size of 0.5.

The post hoc analysis yielded a power of 0.95 with the existing sample size, indicating a 95% probability of detecting a significant difference of the specified effect size. All statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

178 physicians agreed to participate in the study. Specialty, duty description, organisations and annual number of patients were recorded as demographic data. (TABLE-1)

Firstly, the tendencies of the physicians participating in the study regarding antibiotic preferences in the outpatient treatment of community-acquired pneumonia were evaluated. Participants prioritized quinolones ($n=102$, 57.30%), amoxicillin+macrolides (90, 50.56%), and macrolides (51, 28.65%) in first-line treatment prescription, respectively. Those who prioritized only quinolones as first-line antibiotics in outpatient treatment of community-acquired pneumonia are in the minority (16.29%). In the mentioned patients, half of the physicians who preferred quinolones in the first-line treatment reported using moxifloxacin molecule, while levofloxacin was reported to be the second-line treatment with a rate of 32.5%. Figure 1 showed the most common reasons given by physicians for preferring quinolones that are using prior steroid treatment ($n=163$, 91.57%), complicated pneumonia ($n=135$, 75.84%), and paranchymal lung disease ($n=116$, 65.17%).(FIGURE1)

Antibiotic trends of specialty, place of duty and annual patient number data were examined. No statistically significant relationship was found between these demographic data and antibiotic priority, quinolone priority, or clinical approach to treatment failure ($p>0.05$).

The majority of clinicians rated the speed of recovery as important/very important in antibiotic selection ($n=120$, 67.4%). However, the same level of importance given to drug-drug interactions was seen in a minority ($n=40$, 22.5%). The fact that the drugs were new-generation agents was important/very important for the majority ($n=121$, 68.0%). When evaluating whether the drugs could be used as monotherapy, the importance was similarly dominant ($n=155$, 87.1%). The broad-spectrum nature of the drugs was also considered important/very important by most clinicians ($n=167$, 93.8%). A minority considered allergy and arrhythmia to be important/very important ($n=60$, 33.7% and $n=20$, 11.2%, respectively). Nearly half of the clinicians attributed importance to the tendinitis side effect ($n=88$, 49.4%). Although there was no clear majority, gastrointestinal side effects and ease of access to the drug were mostly rated as important ($n=70$, 39.3% and $n=84$, 47.2%, respectively). The effects on the central nervous system were considered important by the majority ($n=116$, 65.2%). About half of the clinicians remained neutral regarding the ease of monitoring ($n=90$, 50.6%).

The relationship between clinicians' perspectives on antibiotic efficacy and side effects and the antibiotic groups they chose as their first option was examined. A significant difference was found only among those who prioritized monotherapy in their initial treatment approaches ($p=0.01$). Clinicians who exclusively selected quinolones as their first choice showed a significantly greater tendency to prioritize monotherapy compared to those who chose only non-quinolone antibiotics ($p=0.045$). Those without a clear preference also placed more importance on monotherapy compared to clinicians who chose only non-quinolone antibiotics ($p<0.001$). However, there was no difference between those who exclusively chose quinolones and those without a clear preference ($p=0.548$). Since individuals without a clear preference also prescribed quinolones as their first choice, these results suggest that the monotherapy advantage of quinolones may influence prescribing habits. No clinical relationship was found between the first-choice antibiotic selections and the importance given to recovery speed, drug-drug interactions, generation differences, spectrum of activity, ease of monitoring, accessibility, anti-tuberculosis activity, allergy risk, arrhythmia side effects, tendinitis risk, gastrointestinal side effects, or central nervous system effects ($p>0.05$).

Clinicians' perspectives on the efficacy and side effects of drugs were largely similar. There were no significant differences between pulmonologists and other specialties in the importance attributed to drug efficacy, drug-drug interactions, generation differences, spectrum of activity, ease of monitoring, drug accessibility, or anti-tuberculosis activity; nor were there any disagreements regarding allergy, arrhythmia, gastrointestinal, and central nervous system side effects ($p>0.05$). The only difference observed between specialties was in the importance given to tendinitis, with pulmonologists attributing a higher level of importance ($p=0.019$), though tendinitis risk was still not considered insignificant by most non-pulmonologists. Pulmonologists also tended to prescribe quinolones more frequently than other specialists in cases of unresponsiveness to previous beta-lactam therapy and complicated pneumonia ($p=0.013$ and $p=0.044$, respectively) (Table 2). The difference in views regarding tendinitis likely did not independently influence drug selection, as there was general agreement among clinicians on other efficacy and side effect factors.

Groups were analyzed based on their antibiotic preferences, and their views on drug efficacy and side effects were examined. In the group with a preference for quinolones, the importance given to recovery speed was significantly higher compared to others ($p=0.041$). This suggests that physicians may be prescribing quinolones more frequently due to the perception that they lead to faster recovery compared to other antibiotics.

Additionally, both the group with a preference for quinolones and those without any clear preference placed more importance on the advantage of monotherapy compared to those who prioritized non-quinolone antibiotics ($p=0.002$). The ability to use quinolones as monotherapy may explain why clinicians who prioritize monotherapy tend to prescribe quinolones, or at least why they do not hold a strict stance against them.

When analyzing groups based on their approach to treatment failure, those who opted for hospitalization or broad-spectrum antibiotics placed more importance on the anti-tuberculosis effect of the drugs, while only 8 physicians chose outpatient alternative quinolone therapy ($p=0.032$). This indicates that tuberculosis is often considered in cases of resistant pneumonia, and as an alternative, treatment is continued with broad-spectrum antibiotics that do not have an anti-tuberculosis effect, rather than with quinolones that do (Table – 3).

Participants' opinions regarding the consideration of clinical findings such as underlying parenchymal disease, previous unresponsiveness to beta-lactam group, previous steroid use, underlying chronic diseases, use of broad-spectrum beta-lactam antibiotics in the last 3 months, and complicated pneumonia in the decision to choose a quinolone as the first antibiotic are given in Table 4. Among the clinical factors, the rates of previous use of beta lactam antibiotics and the presence of a chronic disease in their past medical history were found to be different between those who reported quinolone as their first choice and those who reported non-quinolone as their first choice or those who did not report a first choice ($p=0.008$ and $p=0.006$, respectively). It was observed that physicians who did not prioritize specific antibiotics group and reported other than quinolone antibiotics as a

first-choice antibiotic had a significantly higher rate of prescriptions due to non-response to beta lactam (54, 73%; 43, 57.3%, respectively).

DISCUSSION

Quinolones are frequently used in pneumonia and their usage rates are increasing. The first synthetic quinolone was discovered by George Leshner in the 1960s, and nalidixic acid was the first prototype to be used as a drug. After this date, a wide variety of quinolones have been produced and the 4th generation has now been reached. Currently, there are 2nd generation ciprofloxacin, 3rd generation levofloxacin and 4th generation moxifloxacin in our country. Latest generation quinolones are used in the treatment of various infections, including pneumonia, by inhibiting bacterial DNA gyrase and topoisomerase IV isoenzyme (8).

Quinolones had a broad spectrum of use, covering not only respiratory infections but also urinary and digestive system infections (9). With the introduction of new-generation quinolones, the tendency to prescribe them had increased significantly, and at one point, they became the most commonly prescribed antibiotic group in the U.S., with expectations at the time that this trend would continue (1,10). According to the ATS/IDSA 2019 community-acquired pneumonia guideline, respiratory quinolones (levofloxacin, moxifloxacin, gemifloxacin) can be used alone as a first-line treatment option in patients with comorbidities (2). Although quinolones have strong activity against many infectious agents, they can cause serious side effects and many quinolones are withdrawn after being introduced to the market. Gemifloxacin, recommended in the guideline, has been withdrawn from the market in our country due to its serious erythematous rash side effect. The FDA has issued serious warnings regarding ciprofloxacin, levofloxacin, and moxifloxacin, which are commonly used in pneumonia treatment in our country (11). The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have restricted the use of quinolones due to their side effects, indicating that the risks associated with their use as first-line therapy. Following this restriction, a decrease in the prescription rate of quinolones was observed, suggesting that health policies may be more effective than guidelines in influencing prescribing habits (12). In our study, no obvious differences were detected in the clinical conditions affecting the first antibiotic choice, probably because there are no restrictions in Turkey. The tendency to prescribe quinolones in those who do not have an antibiotic group priority in case of previous beta-lactam use may be due to the scarcity of alternative antibiotic groups. Those who only prioritize quinolones seem to avoid quinolones in case of previous beta-lactam use or comorbidity, but the fact that this group consisted of fewer people compared to the other groups may have affected the results.

A study conducted in Denmark surveyed 108 general practitioners about their antibiotic choices in community-acquired pneumonia (CAP). The study aimed to investigate how general practitioners (GPs) treat adults with CAP and explore associations between GP characteristics and treatment duration. In this study, quinolones were not included among the options and were probably considered among the 'other options' by the participants. In the study, it was reported that antibiotic changes were made in 83.3% of cases when there was no response to first-line treatment. The remaining group preferred 'other options' such as re-evaluation of the patient and additional tests (13). In our study, the tendency for hospitalization and broad-spectrum antibiotics in first-line treatment failure was 78.09%. We think that this difference is due to the predominance of specialist physicians in the study and the tendency of physicians to change in line with physical facilities in case of treatment failure. An old survey of 288 internal medicine clinicians in West Germany in 1989 found that quinolones were used very rarely (2.5%) in mild pneumonia. The statement "quinolones produce inadequate response against pneumococci and are not indicated in pneumonia" in the discussion part of the study is probably related to the information at that time (14). In our own study, 16.29% of physicians used quinolones as their first choice, and this rate increased to 34.5% in physicians who cared about the wide spectrum of action. When clinicians were asked about the healing rate of antibiotics, a significant portion of them thought that quinolones had a 'faster' healing rate ($p=0.041$). However, studies comparing quinolones with other antibiotics in terms of clinical recovery rate are limited, and no significant difference was found in the meta-analysis of studies conducted with tetracyclines (15).

Once-daily dosing can be particularly important for the geriatric population, who often take multiple medications. While moxifloxacin and levofloxacin offer the convenience of once-daily administration, most beta-lactam antibiotics require multiple doses per day and are often used in combination with macrolides for treating community-acquired pneumonia. This difference may explain why those who initially prefer non-quinolone antibiotics consider monotherapy to be less critical ($p=0.002$).

In a study conducted in Turkey, the antibiotics prescribed to the patients referred to the tuberculosis outpatient clinic were examined. 16 patients (15%) had previously been given quinolone treatment, 5 by pulmonology and 11 by other specialties. According to our survey results, the high importance given to the anti-tuberculosis activity of quinolones by chest diseases physicians is consistent with these data. At the same time, considering the anti-tuberculosis activity of quinolones and macrolides, it explains the decision of physicians who are alert about this issue to treat with broad-spectrum antibiotics with hospitalization in case of treatment failure - due to the lack of oral options. However, behavior changes when hemoptysis is encountered, which is one of the specific findings for tuberculosis. Twenty-nine patients had hemoptysis and only one was prescribed

moxifloxacin ($p=0.04$) (16). We think that the determining factor here is the experience of tuberculosis among clinicians, considering the difference between pulmonology and other branches. Gemifloxacin was also found to be prescribed in this study. Because of its low anti-tuberculosis effectiveness and reducing the delay in tuberculosis treatment, it may affect physician behavior in pulmonology, especially in areas with high tuberculosis prevalence (17). However, it could not be examined in our study because it was removed from the market and there were no quinolones with similar properties. Additionally, when comparing pulmonologists with other specialties, the perceptions regarding the effects and side effects of antibiotics were found to be similar, except for “tendinitis.” Pulmonologists were observed to place greater emphasis on the side effect of tendinitis compared to other specialties. However, given the similarities in other tendencies, we believe that specialization alone does not significantly influence antibiotic prescribing tendencies.

CONCLUSION

With developments in quinolone antibiotics, quinolones are expanding their range of applications. As a result, information about the side effects of quinolones increases and their use is restricted, and some are even withdrawn from the market. Considering that the side effects of quinolones outweigh their benefits, it should be kept in mind that they are not recommended for use in first-line treatment, except for contraindications to other antibiotics. Although it is known that antibiotic guidelines influence physicians' opinions, it should be noted that restrictions imposed by local health authorities are more effective. For this purpose, while the annual number of antibiotics, the number of antibiotics per outpatient clinic, and the annual distribution of antibiotic groups are regularly recorded in some countries, it is clear that these data should be tracked more rigorously in our country.

Limitations

The primary limitation of this study is the relatively small and heterogeneous sample size, which may not fully represent broader trends. Moreover, the study's exploratory nature and lack of a calculated sample size limit the generalizability of its findings.

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Table-1: Demographic data		
Specialty	n	%
Pulmonology	88	49.4
Emergency room	17	9.6
Internal medicine	11	6.2
Family medicine	45	25.3
Infectious diseases	8	4.5
Other specialties	9	5.1
(Non-pulmonology)	(90)	(50.6)
Duty description	n	%
General practitioner	11	6.2
Research assistant doctor	60	33.7
Specialist physician	80	44.9
Academician	27	15.2
Organisation	n	%
1st level health services	27	15.2
2nd level health services	43	24.2
Tertiary health services	62	34.8
University health services	46	25.8
Annual number of pneumonia cases	n	%
<100	55	30.9
100-250	56	31.5
250-500	36	20.2
500-1000	20	11.2
>1000	11	6.2
Total	178	100.0

Table – 2: Comparisons of antibiotics preferences according to the specialty				
		Pulmonologists (n=88)	Non-pulmonologists (n=90)	p
		n (%)	n (%)	
First choice antibiotic group	Only quinolone	17 (19,3)	12 (13,3)	0,263
	Only non-quinolone	32 (36,4)	43 (47,8)	
	No priority	39 (44,3)	35 (38,9)	
Prior beta lactam treatment	No	26 (29,5)	43 (47,8)	0,013
	Yes	62 (70,5)	47 (52,2)	
Complicated pneumonia	No	61 (69,3)	74 (82,2)	0,044
	Yes	27 (30,7)	16 (17,8)	
Tendinitis	Not at all important/Not important	19 (21,59) ^{a, b}	24 (26,66) ^{a, b}	0,019
	Somewhat important	16 (18,18) ^a	31 (34,44) ^a	
	Important/very important	53 (60,22) ^b	35 (38,88) ^b	

*p value obtained by chi-square test

Table – 3: Comparison of drug effect-side effect opinions according to antibiotic priority					
First choice antibiotic group		Only quinolone	Only non-quinolone	No priority	p
	Hardly increases at all/Generally does not increase	1(3,4) ^{a,b}	4(5,3) ^a	2(2,7) ^b	
	Similar	4(13,8) ^{a,b}	30(40) ^a	17(23) ^b	

Clinical recovery speed	Mostly faster/Generally faster	24(82,8) ^{a,b}	41(54,7) ^a	55(74,3) ^b	0,041
Monotherapy advantage	Not at all important/Not important	0 (0) ^{a,b}	8 (10,7) ^a	0 (0) ^a	0,002
	Somewhat important	2 (6,9) ^a	10 (13,3) ^a	3 (4,1) ^a	
	Important/very important	27 (93,1) ^{a,b}	57 (76) ^b	71 (95,9) ^a	
Approach to treatment failure		Follow-up with non-quinolone treatment	Follow-up with alternative quinolone treatment	Hospitalization and broad spectrum treatment	p
Anti-tuberculosis activity	Not at all important/Not important	1 (3,2) ^a	2 (25) ^a	9 (6,5) ^a	0,032
	Somewhat important	11 (35,5) ^a	0 (0) ^a	24 (17,3) ^a	
	Important/very important	19 (61,3) ^a	6 (75) ^b	106 (76,3) ^b	

p value was obtained by Chi Square test. Means followed by distinct (^{a,b}) small letters in the same column, are significantly different ($p < 0.05$).

Table – 4: Comparisons of the importance of clinical problems in antibiotic selection between groups formed according to first-line antibiotic preference

		First choice antibiotic group			p
		Only quinolone (n=29, 16,29%)	Only non-quinolone (n=75, 42,13%)	No priority (n=74, 41,57%)	
Parachymal lung disease (n, %)	Yes	12 (41,4)	22 (29,3)	28 (37,8)	0,398
	No	17 (58,6)	53 (70,7)	46 (62,2)	
Prior beta-lactam treatment (n, %)	Yes	^a 12 (41,4)	^a 43 (57,3)	^b 54 (73)	0,008
	No	^b 17 (58,6)	^a 32 (42,7)	^a 20 (27)	
Prior steroid treatment (n, %)	Yes	1 (3,4)	7 (9,3)	7 (9,5)	0,573
	No	28 (96,6)	68 (90,7)	67 (90,5)	
Chronic diseases (n, %)	Yes	^a 12 (41,4)	^b 23 (30,7)	^a 42 (56,8)	0,006
	No	^a 17 (58,6)	^b 52 (69,3)	^b 32 (43,2)	
Broad-spectrum beta-lactamase treatment in the last 3 months (n, %)	Yes	15 (51,7)	45 (60)	43 (58,1)	0,744
	No	14 (48,3)	30 (40)	31 (41,9)	
Complicated pneumonia (n, %)	Yes	4 (13,8)	20 (26,7)	19 (25,7)	0,359
	No	25 (86,2)	55 (73,3)	55 (74,3)	

p value Chi square test. Different superscript letters (^{a,b}) in column indicate statistically significant differences ($p < 0.05$) according to post hoc test (Bonferroni method).