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Trend of Use of Quinolone Antibiotics in Community-Acquired Pneumonia

Toplum Kökenli Pnömonide Kinolon Antibiyotik Kullanım Eğilimi

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Abstract

Introduction: Quinolone group antibiotics are frequently used in the treatment of community-acquired pneumonia (CAP). There have also been rising safety concerns related to quinolone usage. In this study, we investigated physicians' tendencies to prescribe quinolones when managing outpatient pneumonia treatment and the factors influencing this decision.
Materials and Methods: Physicians were asked to participate in a survey consisting of 20 questions. They were queried about the antibiotic groups they most frequently prescribe for outpatient treatment in cases of CAP, the specific type of quinolone they most commonly used, their opinions on the effects and side effects of quinolones through Likert-type survey, and the clinical scenarios that lead them to prescribe quinolones. In addition, a comparison was made between pulmonologists and other specialists on these factors.
Results: A total of 16.29% of physicians primarily prescribed quinolones. The most preferred quinolone was moxifloxacin (50%). In cases of treatment failure, physicians were more likely to opt for hospitalization and a broad-spectrum antibiotic treatment approach (78.09%). Pulmonologists were more likely to prescribe quinolones in cases of unresponsiveness to previous beta-lactam therapy and complicated pneumonia than nonpulmonologists (p=0.013, p=0.044, respectively). Pulmonologists placed more importance on the tendinitis side effect compared to nonpulmonologists (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 with 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, the relevant guidelines conflict with each other regarding their first-line of use in CAP. In addition, knowledge about the side effects of quinolones is increasing. The prescription rates of quinolones should therefore be closely monitored and in cases of an increase in the prescription rates, legal regulations should be more strictly adhered to if guideline recommendations are inadequate.
Keywords: Floroquinolones, pneumonia, surveys, questionnaires

Öz

Giriş: Kinolon grubu antibiyotikler, toplum kökenli pnömoni tedavisinde sıkça kullanılmaktadır. Bununla birlikte, kinolonlara ilişkin güvenlik endişeleri de giderek artmaktadır. Bu çalışma, hekimlerin ayaktan tedavi edilen pnömoni yönetiminde kinolon reçeteleme eğilimlerini ve bu kararı etkileyen faktörleri araştırmayı amaçlamıştır.
Gereç ve Yöntem: Hekimler, 20 sorudan oluşturulan ankete davet edildi. Ankette, toplum kökenli pnömoni için ayakta tedavi reçetelemesinde en sık kullandıkları antibiyotik grupları, en çok tercih ettikleri kinolon çeşidi, kinolonların etkileri ve yan etkileri konusundaki görüşleri (Likert tipi sorular ile) ve kinolon reçetelemelerine yol açan klinik senaryolar sorgulandı. Ayrıca, göğüs hastalıkları uzmanları ile diğer uzmanlar karşılaştırıldı.

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Bulgular: Hekimlerin %16,29'u öncelikli olarak kinolon reçetelemekteydi. En çok tercih edilen kinolon moksifloksasin (%50) oldu. Tedavi başarısızlığı durumlarında, hekimlerin hastaları hastaneye yatırmaya ve geniş spektrumlu antibiyotik tedavisine yönelmeye daha yatkın oldukları belirlendi (%78,09). Göğüs hastalıkları uzmanları, önceki beta-laktam tedavisine yanıt alınamayan durumlarda ve komplike pnömoni vakalarında kinolon reçetelemede diğer uzmanlara göre daha fazla eğilim göstermekteydi (sırasıyla p=0,013, p=0,044). Göğüs hastalıkları uzmanları, tendinit yan etkisine diğer uzmanlara göre daha fazla önem vermekteydi (p=0,019). Klinik faktörler arasında, daha önce beta-laktam antibiyotik kullanımı ve hastanın tıbbi geçmişinde kronik hastalık bulunması, kinolonu ilk tercih olarak kullanan hekimlerle kullanmayanlar arasında anlamlı bir farklılık göstermekteydi (sırasıyla p=0,008 ve p=0,006).
Sonuç: Kinolonların tek başına kullanılabilmesi ve iyileşme hızına katkı sağlaması klinisyenler için cazip bir özelliktir. Ancak, kinolonların toplum kökenli pnömonide birinci basamak kullanımı konusunda kılavuzlar birbiriyle çelişmektedir. Ayrıca, kinolonların yan etkilerine ilişkin bilgiler gittikçe artmaktadır. Kinolonların reçeteleme oranları yakından izlenmeli ve reçeteleme oranlarında artış tespit edilirse, kılavuz önerilerinin yetersiz kaldığı durumlarda yasal düzenlemelerin daha etkili olduğu unutulmamalıdır.
Anahtar Kelimeler: Florokinolonlar, pnömoni, anketler, soru formları

Introduction

Microbial etiology varies in community-acquired pneumonia (CAP). In particular, 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 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) 2019 CAP guideline, it was suggested that quinolones can be used in primary care in outpatients with comorbid diseases[2]. Considering the increasing antibiotic resistance and drug side effects, efforts are being made to limit their use in the first-line of pneumonia treatment[3]. In the 2021 CAP guideline, which was created through a consensus of pulmonologists, infectious diseases, internists, and family physicians in Türkiye, it was recommended as an alternative treatment in cases where beta-lactam combinations could not be used or have been used recently[4]. In this study, we evaluated physicians' tendencies to prescribe quinolones in the outpatient treatment of CAP.

Materials and Methods

Approval for this study was obtained from the Hatay Mustafa Kemal University Non-Interventional Ethics Committee (decision number: 20, dated: 04.03.2024). 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 CAP. This study aimed to assess their perspectives and compare these groups to evaluate differences in their prescribing patterns. As this was an exploratory study intended to gather insights into prescribing tendencies, no sample size calculation was performed. To ensure a larger sample size, the study targeted physicians across Türkiye rather than focusing on a specific hospital. To increase the number of participants, physicians in our hospital involved in CAP were asked to share the survey link in the specialty association WhatsApp groups. Data collection was conducted over 3 months, from March to June 2024.

A 20-question survey form was prepared to question the physicians' tendencies toward outpatient CAP treatment and was delivered online to the targeted physician group via social media applications. Antibiotic options were created as multiple choices based on the ATS/IDSA guidelines for CAP[2]. The first four questions of the survey were on expertise, job description, current work institution, and the number of patients with pneumonia diagnosed annually. In the following questions, antibiotic selection and quinolone preference in the outpatient treatment of pneumonia developing in the community, as well as which quinolone was preferred, were inquired. 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. The commonly reported side effects in the literature were used to develop the question items[5-7]. As the last question, alternative treatment tendencies in cases of treatment failure were prepared as a separate question for the participants (See Annex 1 for the survey form).

Statistical Analysis

Categorical variables are presented as numbers and percentages. Comparisons between categorical variables were examined using Pearson's chi-square test or Fisher's exact test. As a result of the evaluation where a significant difference was detected in comparisons of more than two groups, a post-hoc analysis with the Bonferroni method examined the variable that affected 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 the 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-β) of 0.80, and an 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 in the specified effect size. All statistical analyses were performed using SPSS version 25.0 (or other software used).

Results

A total of 178 physicians agreed to participate in the study. The specialty, duty description, organizations, and annual number of patients were recorded as demographic data (Table 1).

First, the tendencies of the physicians participating in the study regarding antibiotic preferences in the outpatient treatment of CAP were evaluated. Participants prioritized quinolones (n=102, 57.30%), amoxicillin + macrolides (90, 50.56%), and macrolides (51, 28.65%) in the first-line of treatment prescription, respectively. Those who prioritized only quinolones as first-line antibiotics in the outpatient treatment of CAP were 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 cites 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 parenchymal lung disease (n=116, 65.17%) (Figure 1).

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 noted in a minority of them (n=40, 22.5%). The fact that the drugs were new-generation agents was important/very important for the majority of clinicians (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 of them 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 the 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 of the clinicians (n=116, 65.2%). About half of the clinicians remained neutral regarding the ease of monitoring (n=90, 50.6%).

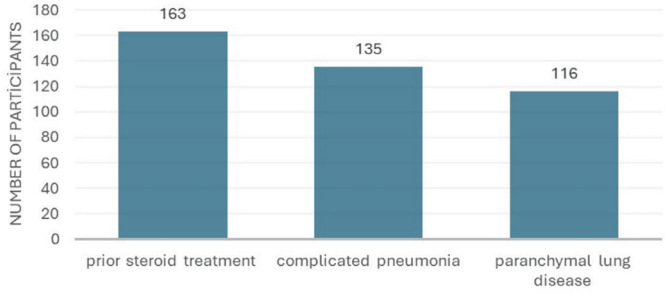

Figure 1. Most common reasons for preferring quinolones

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

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
Organization	**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

noted only among those who prioritized monotherapy in their initial treatment approaches (p=0.01). Clinicians who exclusively selected quinolones as their first choice displayed a significantly greater tendency to prioritize monotherapy compared with those who chose only nonquinolone antibiotics (p=0.045). Those without a clear preference placed more importance on monotherapy than clinicians who chose only nonquinolone 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, the results suggest that the monotherapy advantage of quinolones may influence prescribing habits. No clinical relationship was found between the first choice of antibiotic selection 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. No significant differences were noted between pulmonologists and other specialties in terms of 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 the specialties was in the importance given to tendinitis, with pulmonologists attributing a higher level of importance (p=0.019), although the risk of tendinitis was still not considered insignificant by most nonpulmonologists (Table 2). The difference in views regarding tendinitis likely did not independently influence drug selection as there was a general agreement among clinicians on other efficacy and side effect factors.

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

In addition, both the groups with a preference for quinolones and those without any clear preference placed more importance on the advantage of monotherapy compared to those who prioritized nonquinolone 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 eight physicians chose outpatient alternative quinolone therapy (p=0.032). This report 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 any anti-tuberculosis effect, rather than those with quinolones that do (Table 3).

Participants' opinions regarding the consideration of clinical findings such as underlying parenchymal disease, previous

Table 2. Comparisons of antibiotic 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 nonquinolone	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]	

Means followed by distinct ([a,b]) small letters in the same column are significantly different (p<0.05), *p value obtained from the 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
Clinical recovery speed	Hardly increases at all/ Generally does not increase	1 (3.4)[a,b]	4 (5.3)[a]	2 (2.7)[b]	0.041
	Similar	4 (13.8)[a,b]	30 (40)[a]	17 (23)[b]	
	Mostly faster/Generally faster	24 (82.8)[a,b]	41 (54.7)[a]	55 (74.3)[b]	
The monotherapy advantage	Not at all important/ Not important	0 (0)[a,b]	8 (10.7)[a]	0 (0)[a]	
	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]	0.002
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]	
	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]	0.032

The p value was obtained from the chi-square test. Means followed by distinct ([a,b]) small letters in the same column are significantly different (p<0.05)

unresponsiveness to a 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). Physicians who did not prioritize specific antibiotics group and reported other than quinolone antibiotics as their 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 continuing to increase. The first synthetic quinolone was discovered by George Lesher in the 1960s, and nalidixic acid was the prototype to be used as a drug. After this date, a wide variety of quinolones have been produced, with the 4th-generation being the latest. Currently, there are 2nd-generation ciprofloxacin, 3rd-generation levofloxacin, and 4th-generation moxifloxacin in our country. The latest generation quinolones are used in the treatment of various infections, including pneumonia, by inhibiting bacterial DNA gyrase and topoisomerase IV isoenzyme[8].

Quinolones have 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 CAP 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 because of its serious erythematous rash side effect. The Food and Drug Administration (FDA) has issued serious warnings regarding ciprofloxacin, levofloxacin, and moxifloxacin, which are commonly used in the treatment of pneumonia in our country[11]. The U.S. The FDA and the European Medicines Agency have restricted the use of quinolones due to their side effects, indicating 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 Türkiye. The tendency to prescribe quinolones to 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 prioritized quinolones seemed to avoid quinolones in cases of previous

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			
Only quinolone		**Only non-quinolone**	**No priority**		
		(n=29, 16.29%)	**(n=75, 42,13%)**	**(n=74, 41.57%)**	**p**
Parenchymal 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 the column indicate statistically significant differences (p<0.05) according to the post-hoc test (Bonferroni method)

beta-lactam use or comorbidity, albeit 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 (GPs) about their antibiotic choices in CAP. This study investigated how GPs treat adults with CAP and explored the 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, antibiotic changes were made in 83.3% of cases when the first-line treatment failed. The remaining group preferred "other options" such as reevaluation of the patient and additional tests[13]. In our study, the tendency for hospitalization and the use of broad-spectrum antibiotics in first-line treatment failure was 78.09%. We believe that this difference is due to the predominance of specialist physicians in the study and the tendency of physicians to change in line with the physical facilities in cases 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 cases of mild pneumonia. The statement "quinolones produce inadequate response against pneumococci and are not indicated in pneumonia" in the discussion segment of a past study is probably related to the information at that time[14]. In our study, 16.29% of physicians used quinolones as their first choice, and this rate increased to 34.5% among physicians who cared about the wide spectrum of action. When clinicians were asked about the healing rate of antibiotics, the majority 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 there was no significant difference 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 CAP. This difference may explain why those who initially preferred nonquinolone antibiotics considered monotherapy to be less critical (p=0.002).

In a study conducted in Türkiye, the antibiotics prescribed to the patients referred to the tuberculosis outpatient clinic were examined; it was revealed that 16 (15%) patients had previously been administered quinolone, 5 by pulmonology, and 11 by other specialties. According to our survey results, the importance given to the anti-tuberculosis activity of quinolones by chest disease physicians is consistent with these past data. Meanwhile, the anti-tuberculosis activity of quinolones and macrolides explains the decision of physicians who are alert about this issue in the treatment approaches with broad-spectrum antibiotics with hospitalization in cases of treatment failure due to the lack of oral options. However, behavior changes were encountered with hemoptysis, which is one of the specific findings of tuberculosis. A total of 29 patients had hemoptysis and only one was prescribed moxifloxacin (p=0.04)[16]. We believe 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 reduction in 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. Moreover, a comparison of pulmonologists with other specialties revealed similar perceptions regarding the effects and side effects of antibiotics, except for "tendinitis". Pulmonologists were observed to place greater emphasis on the side effects of tendinitis when compared with other specialties. However, given the similarities in other tendencies, we believe that specialization alone does not significantly influence antibiotic prescribing tendencies.

Study 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 the lack of a calculated sample size limit the generalizability of its findings.

Conclusion

With advancements in quinolone antibiotics, quinolones are expanding their range of applications. As a result, information about the side effects of quinolones is increasingly becoming more available and their use is getting restricted, and some are even getting 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 cases of 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.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the Hatay Mustafa Kemal University Non-Interventional Ethics Committee (decision number: 20, dated: 04.03.2024).

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Concept: K.B.A., Design: M.A.T., Data Collection or Processing: K.B.A., M.K., Analysis or Interpretation: E.C., M.K., Literature Search: M.A.T., Writing: K.B.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT / OLGU SUNUMU

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Subacute Brucellosis-induced Guillain-Barré Syndrome: a Case Report

Subakut Bruselloz ile İlişkili Guillain-Barré Sendromu: Vaka Bildirimi

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Abstract

Guillain-Barré syndrome (GBS) is the most frequent cause of acute flaccid paralysis, and in two-thirds of the patients, antecedent infections have been identified. Brucellosis, a zoonotic disease, rarely leads to GBS. Herein, we present two patients with subacute brucellosis-induced GBS that were diagnosed on the basis of their clinical course and electromyography and nerve conduction velocity study results. There was a 1-month and 5-month interval between the onset of brucellosis and GBS in the two patients. The patients recovered after undergoing plasma exchange, intravenous immunoglobulin administration, and antibiotic therapy. Our findings indicate that physicians should consider brucellosis as a potential etiology of GBS and closely monitor the neurological symptoms of patients with brucellosis.
Keywords: Brucellosis, Guillain-Barré syndrome, electromyography, neurobrucellosis

Öz

Guillain-Barré sendromu (GBS), akut flask felcin en sık görülen nedenidir ve vakaların üçte ikisinde, öncül enfeksiyonlar tanımlanmıştır. Zoonotik bir hastalık olan bruselloz, nadiren GBS'ye yol açar. Burada, klinik seyirleri ve elektromiyografi ve sinir iletim hızı çalışmaları ile teşhis edilen GBS ile ilişkili iki subakut bruselloz vakasını bildiriyoruz. Bruselloz tanısı şikayetler başladıktan 1 ay sonra kondu ve GBS tanısı bruselloz tanısı konduktan 5 ay sonra kondu. Sunulan vakalar, antibiyotik tedavisine ek olarak plazma değişimi ve intravenöz immün globulin uygulandıktan sonra iyileşti. Hekimler brusellozu GBS'nin olası bir etiyolojisi olarak düşünmeli ve brusellozlu hastaların nörolojik semptomlarına dikkat etmelidir.
Anahtar Kelimeler: Bruselloz, Guillain-Barré sendromu, elektromiyografi, nörobruselloz

Introduction

Guillain-Barré syndrome (GBS) is an immune-mediated polyradiculoneuropathy and the most common cause of acute flaccid paralysis worldwide. It typically presents with ascending muscle weakness and diminished deep tendon reflexes following an infection[1]. *Campylobacter jejuni*, *Mycoplasma pneumoniae*, and cytomegalovirus are commonly implicated in its pathogenesis. This condition develops due to cross-reactivity or molecular mimicry between microbial antigens and peripheral nerve structures, which initiates autoantibody production[2].

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Brucellosis, a zoonotic disease caused by intracellular gram-negative coccobacilli bacteria known as *Brucella*, manifests with non-specific symptoms such as undulating fever, asthenia, or musculoskeletal pain. Worldwide, the disease spreads mainly due to direct contact with sick animals or consumption of unpasteurized dairy products. In the case of human infection, the following species are involved: *Brucella melitensis, Brucella abortus, Brucella suis,* and *Brucella canis*[3,4].

In approximately 5% of cases of brucellosis, neurological involvement can be observed in the form of meningovascular disease, cranial nerve (CN) palsies, myelitis, and others[4–6]. However, GBS remains an infrequent manifestation. Thus, herein, we have reported two cases of subacute brucellosis-induced GBS and focused on the clinical course, challenges in diagnosis, and therapeutic outcome of the condition.

Case Report

Case 1

A 64-year-old man presented with musculoskeletal pain, fever, night sweats, weakness, and a weight loss of 6 kg over the past month. At the time of admission, the patient's vital signs were within the normal ranges (blood pressure, 135/90 mmHg; pulse rate, 83 beats/minute; respiratory rate, 19 breaths/minute; and temperature, 37.4 °C). The patient reported a close contact with animals and consumption of unpasteurized dairy products.

Serologic tests revealed a Wright test titer of 1/640 and a 2ME titer of 1/320, confirming a diagnosis of brucellosis. Treatment with doxycycline (100 mg twice daily), rifampin (300 mg twice daily), and intravenous gentamicin (300 mg daily) was administered.

Three days after admission, the patient developed additional symptoms, including paresthesia in the distal extremities, nausea, vomiting, bloating, and odynophagia. Subsequently, severe constipation and urinary retention ensued. Furthermore, muscle strength deteriorated (lower limb power, 3/5 and upper limb power, 4/5). Despite precise consultations, the patient refused to consent to lumbar puncture. Electromyography (EMG) and nerve conduction velocity (NCV), which were conducted on the sixth day, provided evidence of distal symmetric sensorimotor mixed-type peripheral polyneuropathy and acute inflammatory demyelinating polyneuropathy. A diagnosis of GBS was established, and gentamicin was discontinued due to its known neurotoxicity. The patient was subsequently transferred to the neurology department. He underwent ten plasmapheresis sessions and six rehabilitation sessions over a 20-day period.

The patient gradually improved, with full recovery of his ability to walk independently. However, he subsequently developed musculoskeletal pain and chills, which was suggestive of a brucellosis relapse. Outpatient treatment with doxycycline (100 mg) and rifampin (300 mg) every 12 h was administered. The patient was discharged 28 days after admission with normal limb strength. Two months later, there were no signs or symptoms of brucellosis or GBS during the follow-up visit. However, treatment was continued for the next 4 months to prevent the relapse of brucellosis.

Case 2

A 28-year-old male shepherd complained of progressive weakness, pain, and paresthesia in both the upper and lower limbs. Examination revealed bilateral foot drop and diminished deep tendon reflexes (DTRs). The patients had been diagnosed with brucellosis 5 months earlier. Although, the patient had been prescribed doxycycline and rifampin, he was not compliant with his medications.

Analysis of the cerebrospinal fluid (CSF) revealed a non-inflammatory picture (glucose level, 62 mg/dL; white blood cell count, not detected; protein level, 127 mg/dL; lactate dehydrogenase, 14; and red blood cell count, 20). EMG–NCV results indicated acute motor axonal polyneuropathy, a subtype of GBS associated with a poor prognosis.

The patient was treated with intravenous immunoglobulin (IVIG; 30 g daily) for 5 days. After discharge, outpatient physiotherapy was continued along with supportive care. After 4 weeks, the only residual symptom during the follow-up visit was mild claudication (Table 1).

Discussion

Brucellosis remains a significant threat to both health and economy, particularly in developing countries. Delayed diagnosis and inadequate treatment may lead to chronic, persistent illness, accompanied by notable complications such as central nervous system (CNS) and cardiovascular involvement[7]. Brucellosis can present with various neurological manifestations, such as meningoencephalitis, CN involvement, diffuse CNS involvement, and polyradiculoneuropathy. Additionally, in rare cases, it serves as the antecedent pathology for GBS[8].

In both cases described in this report, the blood and urine cultures and stool examination yielded negative results for other infections. Furthermore, the patients did not report respiratory or gastrointestinal symptoms upon admission. Although testing for *Campylobacter jejuni* or *Mycoplasma pneumoniae* (via polymerase chain reaction) would have provided more definitive evidence, such tests were unavailable. Thus, the evidence is circumstantial. Both of our cases were comparable to those previously reported in which GBS developed either concomitantly with or after brucellosis infection.

Table 1. Characteristics and clinical manifestations of our patients and the interventions performed

Case	Sex/Age	Signs and symptoms	Limb strength	GBS subtype	Lab data	Treatment
1	Male/64 years	Weakness, constipation, pricking, sensation, gastroparesis, urinary retention dysphagia-diminished DTR	Lower: 2/5 Upper: 3/5	AIDP	WBC (cells/μL) count: 16,200; Lymphocyte: 67.8%; Uric acid (mg/dL): 6.1; CRP (mg/dL): 9; ESR (mm/hr): 15	10 sessions of plasmapheresis
2	Male/28 years	Weakness, foot drop, diminished DTR	Lower: 3/5 Upper: 4/5	AMAN	WBC (cells/μL) count: 5,200; Lymphocytes: 58.3%; Uric acid (mg/dL): 5.7; CRP (mg/dL): 8; ESR (mm/hr): 21	IVIG: 30 g/day for 5 days

GBS: Guillain-Barré syndrome, AIDP: Acute inflammatory demyelinating polyneuropathy, AMAN: Acute motor axonal neuropathy, DTR: Deep tendon reflexes, WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, IVIG: Intravenous immunoglobulin

Alanazi et al.[3] reported and reviewed 19 cases of brucellosis-induced GBS that mostly occurred in male patients. They found that the severity of this complication could even lead to death, which implies that its diagnosis and appropriate treatment are important. Although GBS occurred in the setting of subacute brucellosis in our patient, reports demonstrate that GBS could be the initial presentation of this infectious disease. Varol et al.[9] the reported the case of a 5-year-old boy with GBS and brucellosis. Because IVIG (2 g/kg of body weight) was ineffective in the child, plasmapheresis was initiated. After five sessions of plasmapheresis, DTR and strength of the limbs returned to normal[9]. Different therapeutic approaches, including IVIG administration and plasma exchange, have been discussed in the reported cases for dealing with GBS. However, more evidence regarding the efficacy of each approach is required. Nonetheless, physicians should consider treating the underlying infectious diseases in addition to providing rehabilitation[3,4,10].

Although comprehensive and complete information regarding the pathogenesis of GBS is lacking, an infectious disease, usually a respiratory infection or gastroenteritis, is present before the development of GBS in two-thirds of the patients[11]. GBS, the most common cause of acute flaccid paralysis, can occur at any age and has different variants, including those with axonal involvement and nerve demyelination. Furthermore, a combination of both axonal damage and nerve demyelination may occur[12]. The structural similarity of the bacterium antigens causes an autoimmune reaction against the nerve autoantigens. Molecular mimicry is a crucial mechanism via which infectious agents trigger an immune response, leading to GBS[13]. In an animal study, the ganglioside-like molecules expressed on the outer membrane of *Brucella* stimulated the production of autoantibodies against the myelin gangliosides, causing acute paralysis and GBS signs[8]. It has been hypothesized that molecular mimicry between *Brucella* and myelin gangliosides may trigger the cross-reactive immunological response that leads to GBS[14].

Aygul et al.[15] reported the case of a 28-year-old man with brucellosis who was treated with streptomycin and doxycycline. The development of progressive paresis led to a change in treatment to oral trimethoprim-sulfamethoxazole and rifampin for better CNS penetration. After 3 months, the patient was admitted to the intensive care unit with respiratory distress, loss of DTR, and flaccid tetraparesis. EMG-NCV and CSF analysis confirmed the diagnosis of GBS. Therefore, IVIG (0.4 g/kg/day) was administered for 5 days. He was discharged a month later with the ability to walk independently[15]. Early diagnosis of GBS could prevent long-term hospitalization and probable complications. Thus, physicians should pay attention to GBS in patients with brucellosis, especially in endemic areas.

Conclusion

Considering our two patients and similar cases reported globally, it is imperative to consider brucellosis as a potential etiological factor for GBS in endemic areas. Conducting pertinent bacteriological and serological tests, followed by EMG-NCV, is crucial in such scenarios. The presented cases recovered after undergoing plasma exchange, IVIG, and antibiotic therapy, demonstrating the importance of appropriate treatment for a good outcome. The diverse range of presentations and economic ramifications highlights the significance of research and efforts toward preventing and treating brucellosis.

Ethics

Informed Consent: In this case report, informed consent has been taken from the patient, and there is not any specific data in the manuscript identifying the patient.

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Footnotes

Authorship Contributions

Concept: M.M-P., A.M-G., Design: M.M-P., A.M-G., Data Collection or Processing: M.M-P., Analysis or Interpretation: M.M-P., Literature Search: M.M-P., A.M-G., S.M-P., F.R., Writing: M.M-P., A.M-G., S.M-P., F.R.

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LETTER TO THE EDITOR / EDİTÖRE MEKTUP

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Acute Viral Hepatitis-B in a COVID-19 Patient with Respiratory Failure

Solunum Yetmezliği Olan Bir COVID-19 Hastasında Akut Viral Hepatit-B

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Keywords: Acute hepatitis B, COVID-19, liver disease
Anahtar Kelimeler: Akut hepatit B, COVID-19, karaciğer hastalığı

Dear Editor,

Coronavirus Disease of 2019 (COVID-19) is caused by a novel coronavirus, named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). COVID-19 is typically characterized by the presentation of the symptoms of viral pneumonia such as fever, fatigue, dry cough, anosmia, and headache, which may progress to respiratory failure[1]. It causes systemic disease by inducing changes in circulating lymphocytes and the immune system[2]. In addition to the respiratory symptoms, gastrointestinal symptoms such as vomiting, diarrhea, abdominal pain, and elevated liver enzyme and/or bilirubin levels have been reported in association with COVID-19[3]. The frequency of elevated liver enzymes in hospitalized COVID-19 patients, primarily elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and slightly elevated bilirubin, ranges from 14% to 53%[2]. This elevation may be the result of any liver damage occurring during a disease and its treatment or it may occur due to primary liver diseases[4]. We have reported herein a case of COVID-19 with hepatitis-B (HB) virus (HBV) coinfection presenting as an acute symptom.

A 57 year-old woman with a history of diabetes mellitus, asthma, and coronary artery disease, was admitted applied the to emergency department with complaints of nausea, vomiting, dry cough, and fever for 3-4 days. The patient was febrile (38.2 °C), conscious, and displayed orientation cooperation. Her physical examination revealed the following: Glasgow Coma Scale 15, blood pressure 135/84 mm/Hg, heart rate 107/min, respiratory rate 23/min, and oxygen saturation 88% in room air. She also displayed bilateral rales on respiratory examination. Her thorax tomography revealed widespread infiltration.

The initial blood work showed remarkably elevated liver function. Pertinent laboratory findings are presented in Table 1.

In the emergency department, the nasopharyngeal swab was taken and her COVID-19 polymerase chain reaction test result was found positive. Then, she was hospitalized and subjected to symptomatic treatment for SARS-CoV-2. Detailed examinations of her liver function tests were planned in light of previously negative hepatitis serology and no familial hepatitis history. Apart from her recent dental treatment, she had no history of consuming alcohol, drug abuse, or unprotected sexual intercourse. Her serological tests were negative for human immunodeficiency virus, hepatitis A, and hepatitis C. Further liver examination revealed positive HB surface antigen, positive HB core antibody (Ab) immunoglobulin M, positive HBe Ag, and negative HBe antibody (Ab). Her HB-DNA viral load was 171,400,000 IU/mL, confirming the diagnosis of an acute HBV infection. The liver ultrasound did not show any anomalies but showed an echogenic liver without cirrhosis, common bile duct obstruction, or gallstones.

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In the initial days of hospitalization, a reduction in liver function was observed with symptomatic treatment while the bilirubin levels increased. The relation between liver function tests and bilirubin level is presented in Figure 1.

After the 5th day, the patient's respiratory complaints increased and her oxygen saturation started to decrease to 65% in the room air. At this stage, high doses of steroids and immunoplasma had to be supplemented in the treatment for COVID-19. Meanwhile, tenofovir disoproxil fumarate was started for viral HB. After 4 weeks of follow-up, her respiratory symptoms gradually began to improve and the patient's liver function tests also reached the normal level. As the patient's respiratory symptoms started to improve, the steroid dosage was gradually tapered and then discontinued and the patient was discharged from the hospital. After 15 days of discharge, in her polyclinic follow-up examination, her HB surface antigen became negative and her HB surface Ab value was (21.34 mIU/mL) positive. Four months later, this value reached over 1,000 mIU/mL. Her antiviral treatment was also discontinued after 1 year of the HB surface Ab positive result.

Table 1. Laboratory test results for the case patient

Laboratory examination	Result	Reference range
WBC	8.89 mcL	4-10 mcL
Creatine	1.22 mL/dL	0.51-0.95 mL/dL
AST	1,768 u/L	0-50 u/L
ALT	1,903.7 u/L	0-50 u/L
Total bilirubin	1.08 mg/dL	0.20–1.20 mg/dL
Direct bilirubin	0.46 mg/dL	0-2 mg/dL
C-reactive protein	90.89 mg/L	0-5 mg/L
HBsAg	5,802.79 S/CO	0-0.99 S/CO
Anti HBc IgM	42.64	0-0.99
Anti HBc IgG	3.42	0-0.99
Anti HBs	0 mIU/mL	0-10 mIU/mL
Anti HCV	0.05 S/CO	0-0.99 S/CO
HIV Ag/Ab	0.08 S/CO	0-0.99 S/CO
INR	1.61	0.8-1.20
D-dimer	1,550 ng/mL	0-500 ng/mL

HIV: Human immunodeficiency virus, WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HbsAg: Hepatitis B surface antigen, HBc IgM: Hepatitis B core immunoglobulin M antibody, HBc IgG: Hepatitis B core immunoglobulin G antibody, HBs: Hepatitis B, HCV: Hepatitis C virus, HIV Ag/Ab: HIV antigen/antibody, INR: International normalized ratio

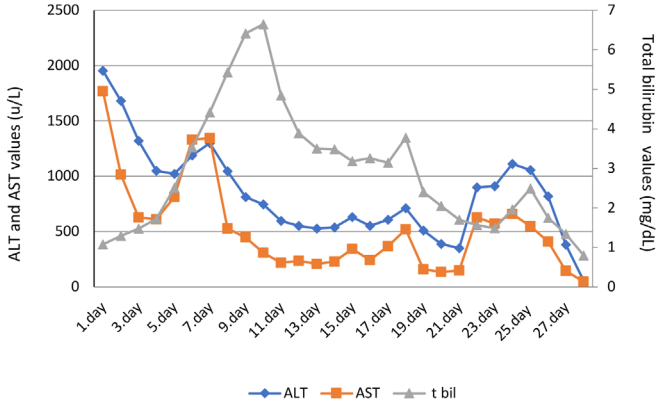

Figure 1. Change chart for the ALT, AST, and bilirubin values
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

COVID-19 caused a pandemic that affected a wide area across the world. Symptomatic SARS-CoV-2 infections are mostly mild to moderate, and not severe. The most common serious manifestation is pneumonia. Chest radiographs are usually normal in the early stages of this disease. At 10–12 days after the onset of symptoms, lung infiltration may increase and the disease may worsen[5]. Our patient showed a tolerable oxygen saturation with oxygen support on room air when she was first admitted to the hospital. In the following days of follow-up, her respiratory complaints increased in line with the course of COVID-19 and her oxygen saturation level began to decrease, as such, high-dose corticosteroids and immune plasma treatment were initiated as supportive treatment.

Elevated liver enzymes are common in COVID-19, as seen in 18.2% of nonsevere cases and up to 39.4% in severe cases[6]. Liver damage in COVID-19 patients may be attributed to the viral infection as well as drug hepatotoxicity. In addition, immune-mediated inflammation and pneumonia-associated hypoxia may contribute to liver injury. Liver disease including chronic-acute viral hepatitis, non-alcohol fatty liver disease, and alcohol-related liver disease represents a major disease burden globally. Although liver enzyme elevation due to COVID-19 is common, its coincidence with acute viral HB is rare. Such rare cases have been reported earlier, and most of these cases were exacerbations of the underlying viral hepatitis disease. Previously, there have been reports of cases showing serological compatibility with acute viral hepatitis but with generally fulminant unknown hepatitis serology[7,8]. Our patient's HB profile showed no history of hepatitis, suggesting an early acute HB infection[9] (Table 1). Treatment for acute HBV is mainly supportive. HBV infection recover clinically and virologically without antiviral therapy in more than 95% of adults. Only patients with severe acute HB, characterized by coagulopathy, and protracted course or signs of acute liver failure should be treated with nucleoside analogs. Past data support the use of tenofovir disoproxil fumarate, entecavir, or lamivudine for such cases[10]. In the present case, as we opted for immunosuppressive treatment for respiratory failure and because the patient's bilirubin levels tended to increase during this period, we planned oral antiviral treatment to prevent liver failure. In the follow-up of our clinically recovered patient, anti HB seroconversion was detected after treatment.

In conclusion, serological tests should be conducted in each patient showing high liver enzymes and the coexistence of the two diseases simultaneously. Such cases should be managed by considering the progression of each disease and the appropriate treatment options.

Footnotes

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Design: S.S.Y., F.K.B., Data Collection or Processing: S.S.Y., F.K.B., Analysis or Interpretation: S.S.Y., F.K.B., Literature Search: S.S.Y., F.K.B., Writing: S.S.Y., F.K.B.

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Effect of Epidermal Growth Factor in a Patient with Diabetic Hand

Diyabetik El Olgusunda Epidermal Büyüme Faktörünün Etkisi

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Abstract

Diabetes mellitus, a multisystemic disease, is associated with microvascular and macrovascular complications in most patients due to the its chronic course. Although diabetic hand infections are rarer than diabetic foot infections, its development is intricate. Herein, we report the case of a 38-year-old man with type 1 diabetes and restless leg syndrome who presented to our out-patient clinic with a necrotic wound on his right thumb. Despite attempts of needle aspiration, surgical procedures, and oral antibiotics, the wound worsened and underwent necrosis. Therefore, surgical debridement was performed by an orthopedist. Upon achieving healing and granulation tissue formation, epidermal growth factor was topically applied twice a day. The patient was discharged with a prescription for doxycycline and topical epidermal growth factor. Follow-up at 1 and 2 months after discharge revealed ongoing wound healing. In conclusion, the treatment and follow-up of diabetic hand infections should involve a comprehensive multidisciplinary approach. Furthermore, conservative treatments such as appropriate antibiotherapy, wound care and blood sugar regulation should be prioritized over amputation. Moreover, epidermal growth factor is a valuable therapeutic option, with its topical application being an advantage.

Keywords: Conservative treatment, diabetic hand infection, epidermal growth factor, prevention of amputation, wound healing

Öz

Diabetes mellitus, multisistemik bir hastalık olup, kronik seyri nedeniyle mikro ve makrovasküler komplikasyonlara yol açmaktadır. Diyabetik el enfeksiyonları, diyabetik ayak enfeksiyonlarına göre daha az sıklıkta görülmekle birlikte, diyabetik el gelişimi de karmaşık bir süreçtir. Bu yazıda, 38 yaşında tip 1 diabetes mellitus ve huzursuz bacak sendromu olan bir erkek hastanın sağ el başparmağındaki nekrotik yara nedeni ile tarafımıza başvurusu sunulmaktadır. Olgumuzun, iğne ile drenaj, cerrahi müdahale ve oral antibiyotik tedavisine rağmen yarası kötüleşmiş ve nekroz gelişmiştir. Ortopedi uzmanları tarafından cerrahi debridman uygulanmıştır. İyileşme ve granülasyon dokusu oluşumu sağlandıktan sonra, hastaya günde iki kez topikal epidermal büyüme faktörü tedavisi başlanmış, doksisiklin ile topikal epidermal büyüme faktörü kullanımı önerilerek taburcu edilmiştir. Taburculuk sonrası birinci ve ikinci ay kontrollerinde yaranın iyileşmeye devam ettiği gözlenmiştir. Bu nedenle, tedavi ve takip sürecinin kapsamlı ve multidisipliner bir yaklaşımla ele alınması gereklidir. Amputasyon düşünülmeden önce uygun antibiyotik tedavisi, yara bakımı ve kan şekeri düzenlemesini içeren konservatif tedavilere öncelik verilmelidir. Topikal uygulama avantajlarıyla epidermal büyüme faktörü, değerli bir tedavi seçeneği olarak öne çıkmaktadır.

Anahtar Kelimeler: Konservatif tedavi, diyabetik el enfeksiyonu, epidermal büyüme faktörü, ampütasyonun önlenmesi, yara iyileşmesi

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Introduction

Prevalence of diabetes mellitus (DM) was 366 million worldwide in 2011, and this figure is expected to increase to 552 million by 2030[1]. Several chronic complications develop due to DM. The development of both microvascular and macrovascular complications is associated with glycemic control. Multiple factors such as endothelial dysfunction, insulin resistance, increased glycation end products, polyol accumulation, and genetic factors are involved in the pathophysiology of DM. Skin and soft tissue infections are observed more frequently in diabetic patients than in healthy individuals. This may be attributed to poor glycemic control, diabetic microangiopathy, and impaired immune system response in diabetic patients[2].

Diabetic foot wounds develop because of various factors such as neuropathy, vasculopathy, abnormal foot biomechanics, and impaired wound healing. Diabetic foot wounds are a leading cause of morbidity in patients with DM[3]. Chronic complications involving the hand may also be observed in such patients. For every hundred diabetic foot infections, there is one case of "diabetic hand" or "diabetic hand syndrome". Diabetic hand syndrome is a multifactorial and complex process, with risk factors similar to those of diabetic foot. If a diabetic hand develops as a result of structural changes in the hand, such as changes in the vascular structure, intrinsic muscles, joint capsule, skin, and subcutaneous tissue, there may be significant limitations in hand movements[4,5].

Wound care, infection control, and debridement are the main treatment approaches for diabetic hand wounds. Finger or hand amputation should be considered as the last option after applying different treatment options, especially for thumb wounds. Herein, we have reported a case of a diabetic wound on the thumb that completely healed with epidermal growth factor (EGF) application after wound debridement.

Case Report

A 38-year-old man with type 1 DM and restless leg syndrome presented to our out-patient clinic with a necrotic wound on his right thumb, which initially appeared as skin redness 15 days ago. Despite interventions such as needle aspiration, surgical procedures, and oral antibiotics (amoxicillin-clavulanic acid, ciprofloxacin, and cefuroxime axetil), the wound worsened and underwent necrosis rapidly. Physical examination revealed a swollen red thumb with a draining wound. Treatment with piperacillin/tazobactam was initiated because of the history of multiple antibiotic use. Routine blood tests at the time of admission yielded unremarkable results (Table 1). A contrast-enhanced hand magnetic resonance imaging was performed to evaluate for osteomyelitis or abscess. However, no pathology was detected. Surgical debridement was performed by an orthopedists on day 10 of antimicrobial therapy (Figure 1A). Intraoperative tissue culture grew extended-spectrum beta-lactamases-negative *Citrobacter freundii*. After achieving healing and granulation tissue formation, topical EGF therapy (twice a day) was initiated. Parenteral antibiotics were discontinued after 21 days, and the patient was discharged. The patients was prescribed doxycycline and topical EGF, considering the absence of osteomyelitis/abscess. Doxycycline, which has good tissue penetration, was chosen because of the patient's history of multiple antibiotic treatments and lack of benefit from previous oral therapies. It was discontinued on the 20th day.

Follow-up at 1- and 2-months after discharge revealed ongoing wound healing (Figure 1B, C). At the 2-month follow-up, EGF therapy was discontinued. During both follow-up visits, the wound edges had merged. The HbA1c level was 11.5% in June 2023 and 13.2% in September 2023. Because the patient's blood glucose levels remained uncontrolled despite the high doses of insulin, he was referred to an endocrinologist. His insulin regimen and diet were revised, and lifestyle modifications were recommended.

Discussion

DM, a multisystemic disease, results in microvascular and macrovascular complications in most patients due to the chronic course of the disease. Although diabetic hand infections are less common than diabetic foot infections, the development of diabetic hand is intricate. Infections may occur more frequently and may be more severe in diabetic patients than in healthy individuals. This may be attributed to hyperglycemia, phagocytic system disorders, decreased cellular immunity, and decreased vascularity that are the results of a chronic process in patients with DM.

Table 1. Routine blood test results at the time of presentation

Parameter	Value	Parameter	Value
Leukocytes	6.56 (10^3/μL)	AST	56 (U/L)
Neutrophils	72.6 (%)	ALT	18 (U/L)
Lymphocytes	1.11 (10^3/μL)	Creatinine	0.8 (mg/dL)
Hemoglobin	13.1 (g/dL)	C-reactive protein	15.94 (mg/L) (0-5)
Platelet	197 (10^3/μL)	INR	1.06

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, INR: International normalized ratio

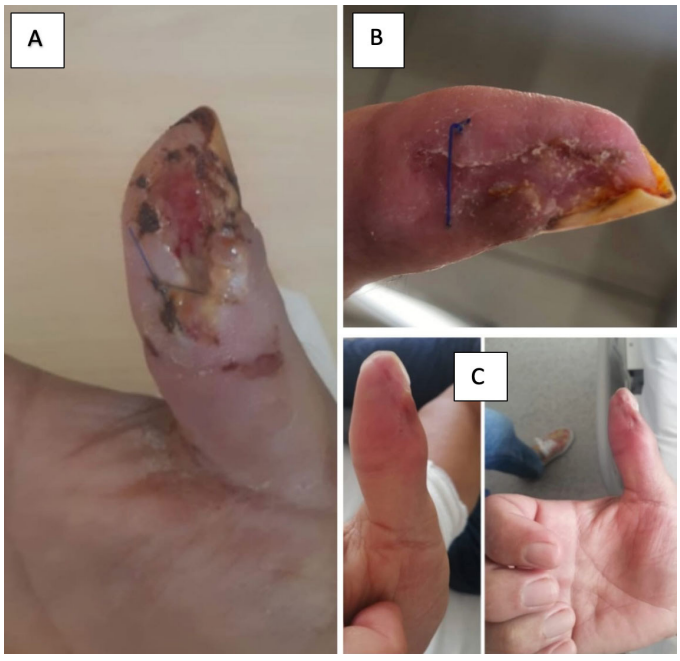

Figure 1. Wound image obtained A) immediately following surgical debridement, B) at the 1-month follow-up, and C) at the 2-month follow-up

Diabetic hand infections are as serious as diabetic foot infections. However, because they are rarer than diabetic foot infections, studies on them are limited[6]. The clinical presentation of diabetic hand infections ranges from cellulitis to ulcerated and gangrenous lesions. It usually occurs following a minor trauma to the hand, and are mostly observed in tropical regions. In the rural areas of Africa, most of the patients with diabetic hand infections were women because they are more frequently engaged in agriculture and exposed to agriculture-associated trauma than men. However, in urban areas, hand ulcers are more commonly encountered in men[7], which is consistent with our case finding. Although *Staphylococcus aureus* is the most common causative organism of diabetic hand infections, polymicrobial agents have also been reported[7,8]. However, no previous study has reported *Citrobacter spp.* as the causative organism. Because diabetic hand infections are less common than diabetic foot infections, the number of studies on EGF use in hand infections are limited. Given its proven benefits in diabetic foot infections, it may be effective in hand infections. Although it is not a novel treatment approach, EGF can be beneficial in appropriate indications.

Amputations are more frequently performed for diabetic foot infections than for hand infections. This may be attributed to the fact that hands are frequently used to perform activities of daily living, which raises the question of how much these complications affect hand function and activities of daily living in diabetic patients.

The development of the diabetic hand is complex and multifactorial, which is similar to that of diabetic foot. The treatment and follow-up of patients with diabetic hand should be a multidisciplinary approach. Initially, primary and secondary preventive methods and optimal medical treatment should be sought. Conservative treatments such as wound care and blood sugar regulation should be prioritized before amputation because they affect daily functioning. If possible, patients and their relatives or care providers should be involved in the process, and adequate training should be provided for the prevention and treatment of diabetic hand and its complications[4,6]. It is crucial to prioritize conservative treatments such as appropriate antibiotherapy, wound care, and blood sugar regulation over amputation. EGF appears to be a valuable option, with its topical application being an advantage. In patients with abscess and osteomyelitis, debridement or amputation is required. In the study by Wang et al.[5], healing was achieved without amputation in 76% of patients with diabetic hand infections. In osteomyelitis, treatment should last at least 42 days. However, 5 days of treatment is sufficient if no residual tissue remains postoperatively. Furthermore, without osteomyelitis or abscess, 14-21 days of treatment is sufficient. In our patient, the treatment duration was prolonged due to the use of multiple antibiotics and a delayed response. There are several studies on the use of EGF in diabetic foot. However, because diabetic hand is rare, there are no studies on EGF use in diabetic hand.

Conclusion

In conclusion, our case report demonstrates that a multidisciplinary care framework for managing diabetic hand infections, which advocates for a judicious balance between conservative measures and surgical interventions, is crucial. By leveraging a collaborative and patient-centric approach, clinicians can navigate the complexities inherent to diabetic hand infections and facilitate favorable outcomes. This further highlights the pivotal role of comprehensive care in diabetic limb salvage initiatives.

Ethics

Informed Consent: Informed consent was obtained.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: D.K., G.V., M.C.S., M.I.T., Concept: M.C.S., M.I.T., Design: M.C.S., M.I.T., Data Collection or Processing:

D.K., G.V., Analysis or Interpretation: D.K., G.V., M.C.S., M.I.T., Literature Search: D.K., G.V., Writing: D.K., G.V.

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A Case of Lumbar Spondylodiscitis and Psoas Abscess Caused by *Candida albicans*

Candida albicans'a Bağlı Lomber Spondilodiskit ve Psoas Apsesi Olgusu

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Abstract

Bone and joint infections due to candidiasis are rare. The simultaneous occurrence of lumbar spondylodiscitis and psoas abscess is rare. Furthermore, although *Candida albicans* remains the most common causative agent, recent reports have indicated a rise in non-albicans *Candida* species. In this report, we have presented a case of lumbar spondylodiscitis and psoas abscess that was associated with *C. albicans*-induced candidemia.
Keywords: *Candida albicans*, spondylodiscitis, psoas abscesses

Öz

Kandidozlara bağlı kemik ve eklem enfeksiyonları nadirdir. *Candida* kökenlerine bağlı lomber spondilodiskit ve psoas apsesi birlikteliği ise oldukça nadir görülen bir klinik tablodur. Etken olarak en sık *Candida albicans* görülmekle birlikte son yıllarda albicans dışı kandida sıklığının da arttığı bildirilmektedir. Burada *C. albicans* kandidemisine bağlı bir lomber spondilodiskit ve psoas apsesi olgusu sunulmuştur.
Anahtar Kelimeler: *Candida albicans*, spondilodiskit, psoas absesi

Introduction

Spondylodiscitis and psoas abscess that are caused by *Candida* species are rare clinical conditions. Although the infection often occurs as a result of hematogenous spread, it can also develop via direct extension and contiguity. In adults, skeletal involvement, particularly vertebral involvement, is common. However, other bone structures can also be affected. *Candida albicans* is the most common pathogen. However, in recent years, the incidence of spondylodiscitis caused by non-albicans *Candida* species has increased. Because the clinical and radiological findings of spondylodiscitis and psoas abscess caused by *Candida* species are non-specific, the disease can be frequently overlooked[1]. Herein, we have presented a case of lumbar spondylodiscitis and psoas abscess that was associated with candidemia due to *C. albicans*.

Case Report

A 33-year-old female presented to our clinic with complaints of lower back pain. Her medical history included hemophilia

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A and recurrent vulvovaginitis. Eight months prior to her visit, her pregnancy was terminated at 3 months of gestation due to placenta previa. Furthermore, a hysterectomy with salpingooophorectomy was performed. Five days postoperatively, she developed deep vein thrombosis of the right lower extremity and pulmonary embolism. During her hospital stay, a nephrostomy catheter was placed for a right-sided hydronephrosis. Following the development of pyelonephritis, *C. albicans* was detected in both blood cultures and urine cultures obtained from the nephrostomy. After 20 days of treatment, she was discharged. Subsequently, she developed vision loss in her right eye and was diagnosed with *Candida* endophthalmitis. She underwent a surgical intervention, and voriconazole treatment was initiated. However, the patient was noncompliant with the treatment regimen. Four months after the hysterectomy and nephrostomy, she developed lower back pain. The patient reported that despite physical therapy, the pain persisted. Thus, she was admitted to our department for further treatment.

A physical examination revealed a good general condition and stable vital signs. Furthermore, her lower back movements were painful. The gynecological examination revealed vulvovaginitis, which was treated. No active inflammation was detected during the eye examination. Laboratory tests revealed a C-reactive protein level of 36 mg/dL and an erythrocyte sedimentation rate of 55 mm/h. Other laboratory findings were within the normal ranges.

The patient was hospitalized. No growth was detected in the blood and urine cultures. The Brucella standard tube agglutination test yielded a negative result. Transthoracic echocardiography and orbital magnetic resonance imaging (MRI) did not reveal any abnormalities. The lumbar MRI revealed spondylodiscitis at the L2, L3, and L4 levels, with intense contrast enhancement in the psoas muscle, indicating an abscess (Figure 1). A percutaneous transpedicular biopsy of the lumbar vertebrae and disks was performed by a neurosurgeon. Bacterial and tuberculosis (TB) cultures of the tissue samples did not yield any growth, and the TB polymerase chain reaction (PCR) test yielded a negative result. Pathological examination of the specimen showed no evidence of malignancy. *C. albicans*, susceptible to treatment, was isolated from the fungal culture of the tissue sample. The patient was discharged with oral fluconazole (400 mg once daily) for 6-12 months. From the 15th day of treatment, significant clinical and laboratory improvement was observed. By the 8th month of follow-up, the clinical, laboratory, and radiological test results demonstrated a good response to fluconazole. The follow-up MRI at the 6th month revealed significant regression of the psoas muscle abscess and spondylodiscitis findings (Figure 1). Fluconazole was discontinued at the 9th month follow-up.

Discussion

In Türkiye, some studies have focused on osteoarticular infections and psoas abscesses. However, no study or case report has specifically documented the co-existence of spondylodiscitis and psoas abscess caused solely by *Candida* species[1]. Therefore, the epidemiology of such cases in Türkiye is not well understood. Thus, our case findings contribute to the limited national literature.

In a PRISMA-based review, the PubMed, Web of Science, Embase, Scopus, and OVID Medline databases were searched from their inceptions to November 30, 2022, using terms related to *Candida spondylodiscitis*. The search yielded 625 studies. Of these, 72 studies met the inclusion criteria and were included in the review. The number of patients with Candida spondylodiscitis was 89. Furthermore, *C. albicans* accounted for 62% of the cases, while non-albicans *Candida* species (e.g., *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, and *Candida krusei*) accounted for 32% of the cases.

In our patient, although there was no known immunosuppression other than the pregnancy, the clinical condition developed following a history of recurrent vulvovaginitis, placenta previa, and *C. albicans*-associated pyelonephritis, which had led to candidemia. Additionally, there are studies on psoas abscesses caused by *Candida* species (e.g., *C. albicans, C. glabrata,* and

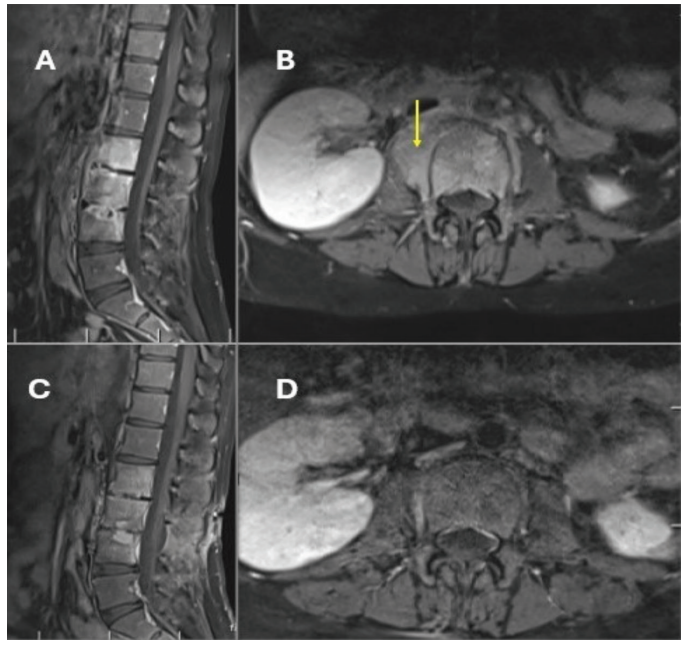

Figure 1. (A, B) Pre-treatment, contrast-enhanced, T1-weighted, sagittal and axial MRI showing spondylitis at the L2, L3, and L4 vertebrae and an abscess in the right psoas muscle (yellow arrow). (C, D) Post-treatment MRI showing regression of spondylitis and the abscess

MRI: Magnetic resonance imaging

C tropicalis)[3-5]. However, our patient appears to be the first to present with both a psoas abscess and lumbar spondylodiscitis. The most significant clinical finding in *Candida*-associated spondylodiscitis and psoas abscess is lower back pain, in addition to restricted movements of the lower back and extremities[1]. Our patient presented with lower back pain.

Laboratory findings such as C-reactive protein level, sedimentation rate, beta-D-glucan level, procalcitonin level, and leukocyte count, as well as imaging modalities such as computed tomography and MRI, are not sufficient for making a definitive diagnosis[1,2]. Ultrasound-guided biopsy, computed tomography-guided biopsy, and tissue sampling via open surgery are the current standard methods for identifying the causative pathogen and determining the differential diagnoses[6,7]. In our patient, an open surgical biopsy was performed as a minimally invasive procedure for diagnostic purposes. Subjecting the biopsy specimen to bacterial and fungal cultures, TB culture, PCR, and pathological examination is essential for establishing a definitive diagnosis. In our patient, *C. albicans* was isolated from the fungal culture. For the treatment of Candida-associated spondylodiscitis and psoas abscess, fluconazole at a dose of 6 mg/kg/day for 6-12 months has been strongly recommended as an empirical antifungal therapy. A regimen consisting of 2 weeks of echinocandin (e.g., caspofungin, micafungin, and anidulafungin) or liposomal amphotericin B at 3-5 mg/kg/day, followed by fluconazole at 6 mg/kg/day for 6–12 months, has also been suggested. Another important aspect of treatment is surgery. Surgical intervention should be considered in appropriate candidates on the basis of patient-specific findings [8].

Conclusion

In conclusion, *Candida* species should be considered as potential pathogens in patients presenting with spondylodiscitis and a psoas abscess.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.Y., Y.Z.D., H.A., H.İ.S., Concept: H.Y., Y.Z.D., T.A., Design: H.Y., Y.Z.D., H.A., Data Collection or Processing: H.Y., Y.Z.D., H.A., T.A., Analysis or Interpretation: H.Y., Y.Z.D., H.A., T.A., Literature Search: H.Y., Y.Z.D., Writing: H.Y., Y.Z.D.

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Predictive Value of Procalcitonin and Lymphocyte Count for Secondary Infection Risk in Patients Hospitalized with Influenza Pneumonia

İnfluenza Pnömonisi Nedeniyle Hastaneye Yatırılan Hastalarda Prokalsitonin ve Lenfosit Sayımının Sekonder Enfeksiyon Riski İçin Öngörücü Değeri

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Abstract

Introduction: The primary complications of influenza are secondary infections, particularly pneumonia, which contribute to increased morbidity and mortality. Currently, no reliable methods exist to differentiate secondary infections occurring alongside influenza. This study aimed to evaluate the role of procalcitonin (PCT) and lymphocyte count in predicting mortality and diagnosing secondary infections in patients hospitalized with influenza pneumonia.

Materials and Methods: Patients with confirmed influenza and radiological evidence of lung infiltration on chest X-ray or computed tomography were included. Medical records were reviewed retrospectively. Patients were classified into two groups: those with influenza alone and those with influenza and a secondary infection. The highest PCT level and the lowest lymphocyte count recorded during hospitalization were analyzed for their association with secondary infection risk and mortality.

Results: Among 66 patients, 30 (45%) were treated in the intensive care unit (ICU), while 36 (55%) received care in the general ward. Secondary infections were identified in 29 patients (43.9%). Although ICU admission rates did not differ between groups, mortality was 38.4% in patients with secondary infections and 3% in those with influenza alone. During the 5-day influenza treatment period, C-reactive protein and PCT levels showed no significant differences between groups. The highest median PCT levels in discharged and deceased patients were 1.63 and 9.8 µg/L, respectively (p=0.005). The mean lowest lymphocyte count in discharged and deceased patients were 300 cells/mL and 100 cells/mL, respectively (p=0.008). Among patients with a lowest lymphocyte count below 200 cells/mL, the secondary infection rate was 73% compared to 35.3% (p=0.031) in those with a count above 200 cells/mL. Additionally, mortality was 46% vs. 9.8% (p=0.001), and hospital stay was longer at 20 (13-40) days vs. 15 (9-19) days (p=0.047), respectively.

Conclusion: Patients hospitalized with influenza frequently develop secondary infections, which are linked to higher mortality. A lymphocyte count below 200 cells/mL is associated with an risk of secondary infection, prolonged hospitalization, and higher mortality. Although elevated PCT levels were also linked to an increased risk of secondary infections and mortality, this association was not statistically significant.

Keywords: Influenza, secondary infection, lymphopenia, procalcitonin, pneumonia, mortality

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Öz

Giriş: İnfluenzanın başlıca komplikasyonları, mortalite ve morbiditede artışa neden olan sekonder enfeksiyonlar, özellikle de pnömonidir. Mevcut yöntemler influenzaya eşlik eden sekonder enfeksiyonları güvenilir bir şekilde ayırt edememektedir. Bu çalışmada, influenza pnömonisi nedeniyle hastaneye yatırılan hastalarda prokalsitonin (PCT) ve lenfosit değerlerinin mortalite ve sekonder enfeksiyon tanısı üzerindeki etkisini araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya influenza polimeraz zincir reaksiyonu testi pozitif olan ve akciğer grafisinde veya bilgisayarlı tomografisinde akciğer infiltrasyonu bulguları olan hastalar dahil edildi. Hastaların tıbbi kayıtları retrospektif olarak incelendi. Hastalar iki gruba ayrıldı: sadece influenza enfeksiyonu olanlar ve influenza ile birlikte sekonder enfeksiyonu olanlar. Hastanede yatış sırasında ölçülen en yüksek PCT düzeyi ve en düşük lenfosit sayısı sekonder enfeksiyon ve mortalite riski açısından araştırıldı.

Bulgular: Çalışmaya dahil edilen 66 hastanın 30'u (%45) yoğun bakım ünitesinde (YBÜ), 36'sı (%55) serviste tedavi edildi. Toplamda 29 hastada (%43,9) eşlik eden sekonder enfeksiyon gelişti. YBÜ'ye yatış oranı gruplar arasında farklılık göstermemekle birlikte, ölüm oranı influenzaya sekonder enfeksiyonun eşlik ettiği hastalarda %38,4, sadece influenza enfeksiyonu olan hastalarda ise %3'tü. İnfluenza tedavisinin 5 günü boyunca, C-reaktif protein ve PCT düzeylerinin takibi gruplar arasında önemli farklılıklar göstermedi. Taburcu edilen ve ölen hastalarda en yüksek medyan PCT konsantrasyonları sırasıyla 1,63 ve 9,8 µg/L idi (p=0,005). Taburcu edilen ve ölen hastalarda ortalama en düşük lenfosit seviyeleri sırasıyla 300 hücre/mL ve 100 hücre/mL idi (p=0,008). Yatış sırasında ölçülen en düşük lenfosit sayısı 200 hücre/mL'nin altında olan hastalarda, en düşük lenfosit sayısı 200 hücre/mL'nin üzerinde olan hastalara kıyasla, sekonder enfeksiyon oranı sırasıyla %73'e karşı %35,3 (p=0,031), ölüm oranı %46'ya karşı %9,8 (p=0,001) ve hastanede kalış süresi 20 (13-40) güne karşı 15 (9-19) gündü (p=0,047).

Sonuç: İnfluenza nedeniyle hastaneye yatırılan hastalarda sıklıkla daha yüksek ölüm ile ilişkili olan sekonder enfeksiyonlar gelişir.
Lenfosit sayısının <200 hücre/mL olması sekonder enfeksiyon gelişme riski, uzamış hastanede kalış süresi ve yüksek mortalite ile ilişkilidir. Artmış PCT konsantrasyonu istatistiksel anlamlı olmamakla birlikte, sekonder enfeksiyon ve mortalite riskinde artışa yol açmaktadır.

Anahtar Kelimeler: Grip, sekonder enfeksiyon, lenfopeni, prokalsitonin, pnömoni, ölüm oranı

Introduction

Influenza viruses, which primarily circulate during winter, have historically caused pandemics approximately every decade. Secondary infections, particularly pneumonia[1,2], are the most common complications of influenza and are associated with increased morbidity and mortality[3,4]. Since influenza strains responsible for pandemics generally cause self-limiting illnesses, the accurate diagnosis and treatment of concurrent bacterial infections are essential to reducing mortality and morbidity. During the 2009 H1N1 influenza outbreak, the incidence of secondary infections among intensive care unit (ICU)-admitted influenza patients was reported to be 18-34%, significantly contributing to increased mortality[5,6].

Currently, no reliable method exists to differentiate viral from bacterial lower respiratory tract infections in patients with influenza. The 2019 American Thoracic Society-Infectious Diseases Society of America Guidelines recommend empirical antibiotic therapy for patients with influenza pneumonia[7]. However, ruling out secondary infections could help reduce unnecessary antibiotic use, lower healthcare costs, minimize adverse effects, and prevent the emergence of multidrug-resistant infections.

In infection management, procalcitonin (PCT) is not recommended for initiating antibiotic therapy but is advised for guiding antibiotic discontinuation[8]. However, data on the role of PCT in predicting secondary infections in H1N1 patients are limited, and findings remain inconsistent[9-12].

Lymphopenia frequently occurs in viral infections, and leukocytosis with relative lymphopenia has been widely used for diagnosing influenza A H1N1 in emergency settings[13-16]. Prolonged lymphopenia has been linked to respiratory failure and increased mortality in patients with influenza pneumonia[17]. However, its role in diagnosing secondary infections in influenza patients remains uncertain.

This study aimed to assess the impact of PCT and lymphocyte levels on diagnosing secondary infections and predicting mortality in patients hospitalized with influenza pneumonia.

Materials and Methods

This study was approved by the Marmara University Ethics Committee (approval number: 09.2020.969, dated: 02.10.2020). Due to the retrospective, observational, cross-sectional design of the study, written informed consent was not obtained from the patients. The study included patients who were monitored in the ICU or inpatient ward following a diagnosis of influenza pneumonia between October 2018 and January 2020. Influenza pneumonia was diagnosed based on a positive influenza quantitative reverse transcription polymerase chain reaction test from a nasal swab, along with evidence of lung infiltration on chest X-ray or computed tomography. Patients younger than 18 years were excluded.

Patient medical records were reviewed retrospectively using hospital information management systems and patient files. Data collected included demographic characteristics, comorbidities, coexisting viral infections, empirical antibiotic

and antiviral treatment (dose and duration), daily C-reactive protein (CRP), PCT, leukocyte (white blood cell) count for the first 5 days, highest PCT and lowest lymphocyte levels recorded during hospitalization, length of stay in the inpatient ward, ICU severity scores [Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment], use of mechanical ventilation (invasive and non-invasive), vasopressor therapy, ICU and total hospitalization duration, and in-hospital mortality.

A total lymphocyte counts of <1000 cells/mL (<1x10^9/L) in adults is defined as lymphopenia[18]. In our laboratory, the reference range for PCT is 0-0.5 µg/L, while the normal range for CRP is 0-5 mg/L.

Patients were categorized into two groups: those with influenza infection only and those with influenza accompanied by a secondary infection. Bacteremia was diagnosed in patients with infection symptoms based on bacterial growth in aerobic and anaerobic cultures from two sets of blood samples collected from separate venous sites. Cases of contamination and colonization were excluded by assessing clinical findings consistent with bacteremia and elevated inflammatory markers. However, the infection source was not recorded for patients diagnosed with bacteremia. Patients with secondary infections were further classified into two groups: those with concurrent infection (developing a secondary infection within 72 hours of influenza diagnosis) and those who developed secondary infection after completing influenza treatment (occurring between 5 days and 1 month of continued hospitalization). No patients developed secondary infection between the third and fifth days of treatment. All groups were compared based on recorded data, including secondary infectious agents and antibiotic use. The highest PCT level and lowest lymphocyte count during hospitalization were analyzed for their association with secondary infection risk and mortality. Additionally, the relationship between secondary infection development and mortality was examined based on the presence and duration of lymphopenia. Patients were classified into three groups: those without lymphopenia, those with lymphopenia lasting ≤5 days, and those with lymphopenia lasting >5 days.

Statistical Analysis

Statistical analysis was conducted using Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA) and Stata version 15.1, year 2017 (StataCorp 4905, Texas, USA). The independent t-test was used to compare descriptive statistical measures (mean, standard deviation, median, and interquartile range) and normally distributed binary variables. The Mann-Whitney U test was applied for comparing binary groups of non-normally distributed variables, while the Kruskal-Wallis test was used for comparisons involving three groups of non-normally distributed variables. Qualitative data were analyzed using the chi-squared test and Fisher's exact test. A p-value of <0.05 was considered statistically significant.

Results

General Characteristics of Patients

A total of 66 patients diagnosed with influenza pneumonia and hospitalized between October 2018 and January 2020 were included in the study. Of these, 54 patients presented to the emergency department due to influenza, while 12 were diagnosed during hospitalization for other conditions. Among the patients, 30 (45%) received treatment in the ICU, and 36 (55%) were treated in the inpatient clinic.

The mean age of the patients was 69 years (ranging from 51 to 76 years). Hypertension (53.3%) and diabetes mellitus (31.8%) were the most common comorbidities. Additionally, 50% of the patients had chronic respiratory diseases, including chronic obstructive pulmonary disease, restrictive lung disease, and lung malignancies (Table 1).

It was noted that 90% of patients received antibiotic therapy, with 50% starting antibiotics on the first day of hospitalization.

Relationship Between Influenza and Secondary Infection

A total of 29 patients (43.9%) developed a secondary infection. Among these, bacteremia was identified in 12 patients (41.3%),

Table 1. General characteristics of patients with an influenza diagnosis

Number of patients	**66**
Sex: Female[a]	39 (59.1%)
Age (years)[b]	69 (51-76)
Chronic disease[a]	65 (98.5%)
Hypertension	35 (53.1%)
Diabetes mellitus	21 (31.8%)
Ischemic heart disease, congestive heart failure	28 (42.4%)
Prior cerebrovascular event, dementia	8 (12.1%)
Chronic renal failure	8 (12.1%)
Immunosuppression	7 (10.6%)
Malignancy (solid organ)	14 (21.2%)
Malignancy (hematologic)	6 (9.1%)
Chronic obstructive pulmonary disease	15 (22.7%)
Other respiratory diseases	14 (21.2%)
Complainta	
Cough-phlegm	23 (42.5%)
Dyspnea	33 (61.1%)
Runny nose	5 (9.2%)
Fever	7 (12.9%)

[a]Values are presented as n (%), [b]values are presented as median (25-75%)

bacterial pneumonia in 19 patients (65.5%), and urinary tract infection in 15 patients (51.72%).

Across 57 secondary infections in 29 patients, 10 different infectious agents were detected. The most common pathogens were *Acinetobacter baumannii* (7 cases, 12.2%), *Klebsiella pneumoniae* (5 cases, 8.7%), *Escherichia coli* (4 cases, 7%), *Pseudomonas aeruginosa* (2 cases, 3.5%), other *Gram-negative bacteria* (4 cases, 7%), *Staphylococcus aureus* (6 cases, 10.5%), *Enterococcus* species (9 cases, 15.7%), *Corynebacterium* species (3 cases, 5.2%), *Candida albicans* (10 cases, 17.5%), and non-*albicans Candida* species (7 cases, 12.2%).

Secondary infections were observed in 12 out of 36 patients (33%) in the inpatient clinic and in 17 out of 30 patients (56%) in the ICU. Among ICU patients, the APACHE II score was significantly higher in those with secondary infection [median, 20 (17-26)] compared to those without [median, 15 (12-17), p=0.007].

Although ICU admission rates did not differ significantly between groups, mortality was higher in patients with secondary infections (10/29, 34.4%) compared to those without (2/37, 5.4%) (p=0.001). The median hospital stay was longer in patients with secondary infections [22 days (14-40)] than in those without [13 days (7-16)] (p=0.001) (Table 2).

No significant differences were observed in CRP, PCT, or WBC values at admission between patients with and without secondary infections (Table 3).

Association of PCT with Secondary Infection and Clinical Outcomes

During the 5-day course of influenza treatment, CRP and PCT levels showed no significant difference between groups (Figure 1).

Although the highest PCT levels recorded during hospitalization were higher in patients with secondary infections compared to those without (2.77 µg/L vs. 1.71 µg/L), the difference was not statistically significant. In patients with secondary infections, PCT levels stopped declining after day 3.

When patients were grouped based on PCT levels, there were no significant differences in mortality or length of hospitalization (Table 4). However, the mean highest PCT levels were 1.63 µg/L in discharged patients and 9.8 µg/L in deceased patients (p=0.005). The median highest PCT concentrations were significantly higher in ICU patients (6.05 µg/L) compared to those in the inpatient clinic (1.25 µg/L) (p = 0.001).

Table 2. The comparison of clinical characteristics between patients with influenza only and those with accompanying secondary infection

Patients followed up in the ICU (n=30)	**With secondary infection (n=17)**	**Without secondary infection (n=13)**	**p-value**
APACHE II score during ICU stay[b]	20 (17-26)	15 (12-17)	0.0073
SOFA score during ICU stay[b]	6 (3-10)	5 (3-7)	(0.05)
Length of ICU stay, day[b]	6 (4-10)	5 (4-5)	>0.05
Length of service hospitalization before ICU[b]	3 (1-5)	1 (0-2)	>0.05
Mechanical ventilation needed[a]	9 (60.0%)	6 (40.0%)	>0.05
Mechanical ventilation duration[b]	6 (2-10)	4 (2-4)	>0.05
Non-invasive mechanical ventilation needed[a]	5 (50.0%)	5 (50.0%)	>0.05
Vasopressor needed[a]	7 (58.33%)	5 (41.67%)	>0.05
Mortality[a]	10 (58.8%)	0 (0.0%)	(0.001)
Patients followed up in the service (n=36)	**With secondary infection (n=12)**	**Without secondary infection (n=24)**	**p-value**
H1N1 diagnosis location			
Admission to the emergency department caused by influenza[a]	6 (22.22%)	21 (77.28%)	(0.036)
Diagnosed with influenza during hospitalization[a]	6 (66.67%)	3 (33.3%)	
Need for non-invasive mechanical ventilator[a]	3 (33.33%)	6 (66.67%)	>0.05
Non-invasive mechanical ventilation duration[b]	10 (8-19)	3.5 (2-10)	>0.05
Length of Service Stay, days[b]	20 (14-40)	11 (6.5-14.5)	**0.0033**
Mortality[a]	**0 (0%)**	**2 (8.3%)**	**>0.05**

[a]Values are presented as n (%), [b]values are presented as median (25-75%)

Relationship Among Lymphopenia, Secondary Infection, and Clinical Outcomes

At the time of influenza diagnosis, 51 patients (77%) had a lymphocyte count of <1000 cells/mL. Among the patients, 6 (0.9%) did not experience lymphopenia during hospitalization, 16 (24%) had lymphopenia lasting ≤5 days, and 44 (66%) had lymphopenia lasting >5 days. No significant differences in mortality rates or secondary infection development were found between these groups.

The mean lowest lymphocyte count in discharged patients was 300 cells/mL, compared to 100 cells/mL in deceased patients (p=0.008). ICU patients had a mean lowest lymphocyte count of 200 cells/mL, while those in the inpatient clinic had a mean of 350 cells/mL (p=0.03).

Patients with the lowest lymphocyte count below 200 cells/mL during hospitalization had a significantly higher rate of secondary infection (73% vs. 35.3%, p=0.031), higher mortality rate (46% vs. 9.8%, p=0.001), and longer hospital stays [20 days (13-40) vs. 15 days (9-19), p=0.047)] compared to those with counts above 200 cells/mL (Table 4).

Table 3. Comparison of patients with influenza based on secondary infection groups

	Secondary infection			p-value
	None (n=37)	Concurrent (n=15)	After (n=14)	
The unit where H1N1 was diagnosed[a]				>0.05
Emergency room	33 (61.11%)	10 (18.51%)	11 (20.37%)	
Service	4 (33.33%)	5 (41.67%)	3 (25.0%)	
Empirical antibiotics[a]	34 (59.65%)	12 (21.05%)	11(19.3%)	>0.05
The unit where H1N1 treatment was administered[a]				
ICU	13 (43.33%)	6 (20%)	11 (36.66%)	>0.05
Service	24 (66.66%)	9 (25%)	3 (8.33%)	
The highest level of procalcitonin[b]	1.71 (0.17%-6.6%)	1.58 (0.21-2.95)	9 (1.23-23)	>0.05
The lowest lymphocyte count[b]	300 (200-500)	300 (100-500)	300 (100-400)	>0.05
At the time of diagnosis				
CRP (mg/L)[b]	112 (51-156)	51 (37-117)	79 (41-102)	>0.05
PCT (µg/l)[b]	0.2 (0.11-1.47)	0.14 (0.1-0.7)	0.18 (0.13-0.29)	>0.05
Leukocyte, (x103 mL)[b]	9.6 (7%-12.3%)	11.1 (7.5-16.4)	9.4 (6.2%-17.5%)	>0.05
The length of ICU stay days[b]	5 (4-5)	5 (5-12)	7 (4-10)	>0.05
The length of service stay days[b]	10 (6-14)	20 (14-38)	43.5 (19-68)	**0.0061**
The length of hospital stay days[b]	13 (7-16)	17 (14-32)	33 (18-68)	**0.0001**
Mortality[a]	**1 (0.02%)**	**4 (0.26%)**	**7 (50.0%)**	**0.0003**

[a]Values are presented as n (%), [b]values are presented as median (25-75%). CRP : C-reactive protein, PCT: Procalcitonin, ICU: Intensive care unit

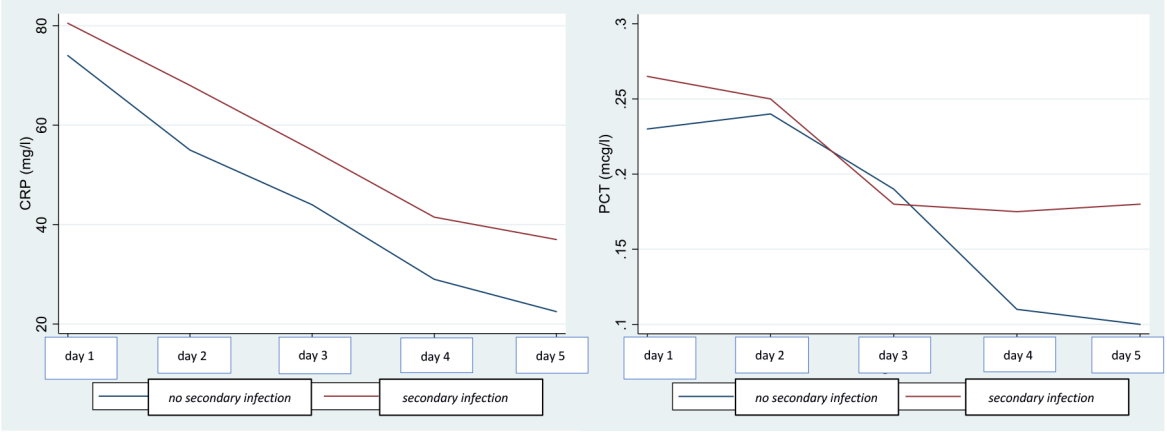

Figure 1. CRP and PCT levels during 5-day influenza treatment in patients with and without secondary infection
CRP: C-reactive protein, PCT: Procalcitonin

Table 4. The relationship between the highest PCT value and the lowest lymphocyte count with secondary infection, mortality, and length of hospitalization

	Groups according to highest PCT level				p-value	Groups according to lowest lymphocyte count		p-value
	0-0.5 µg/L (n=22)	0.5-2 µg/L (n = 11)	2-10 µg/L (n=16)	>10 µg/L (n=17)		<200 (n=15)	>200 (n=51)	
Secondary infection[a]	7 (31.8%)	5 (45.4%)	8 (50%)	9 (52.9%)	0.562	11 (73 %)	18 (%35)	0.031
Mortality	1 (4.5%)	1 (10%)	4 (26.6%)	6 (35.3%)	0.057	7 (46%)	5 (9.8)	0.001
The length of hospitalization[b]	15 (12-18)	14.5 (9-20)	16 (7.5-24.5)	17 (10-32)	0.965	20 (13-40)	15 (9-19)	0.047

[a]Values are presented as n (%), [b]values are presented as median (25-75%), PCT: Procalcitonin

Discussion

In this study, patients with influenza pneumonia and a lymphocyte count below 200 cells/mL had significantly higher rates of secondary infections, longer hospital stays and increased mortality. Although higher PCT levels tended to correlate with an increased frequency of secondary infections and mortality, the differences were not statistically significant.

The risk of secondary infection is higher in influenza pneumonia compared to other viral pneumonias, likely due to influenza A's ability to target alveolar macrophages via the PB1-F2 protein[19,20]. The pooled prevalence of influenza bacterial co-infection was 20.3% (95% confidence interval =16.0-25.4) in a meta-analysis including 63 articles; however, in our study, the rate was 43.9%[21].

The link between secondary infections and increased mortality remains controversial[5,6,10,22,23]. In our study, patients with secondary infections had significantly longer hospital stays and higher mortality rates (p<0.0001).

Lymphopenia is commonly seen in viral infections and is frequently used to help diagnose influenza A H1N1 in emergency settings[13-15]. Hage et al.[16] found that relative lymphopenia occurred in all patients with influenza A H1N1, with the lowest lymphocyte count typically reached by day 3.5.

The role of lymphopenia in the development of secondary infections in influenza remains unclear, although it has been associated with poor prognosis. In hospitalized influenza A H1N1 patients, a lymphocyte count <800 cells/mL at admission was identified as an independent risk factor for respiratory failure[24]. Cui et al.[25] found that persistent lymphopenia after 5 days was a risk factor for mortality, with ICU patients having a lymphocyte count of 580 cells/mL and non-ICU patients having 1065 cells/mL. In our study, ICU patients had a lymphocyte count of 200 cells/mL, while those in the inpatient clinic had 350 cells/mL. Similarly, Cui et al.[25] reported lymphocyte count of 580 cells/mL in deceased patients and 790 cells/mL in survivors. In our study, the lowest lymphocyte count in discharged and deceased patients were 300 cells/mL and 100 cells/mL, respectively. Although lymphopenia is not a definitive risk factor for mortality, most surviving patients (93.1%) showed improvement in lymphocyte count within approximately 5 days. Lymphopenia lasting longer than 5 days was observed in 70% of deceased patients and 6.8% of survivors[25]. In our study, no statistically significant differences in secondary infection or mortality were found between patients with no lymphopenia, lymphopenia lasting <5 days, or lymphopenia lasting >5 days.

In the study by Lalueza et al.[17], 59% of patients had lymphopenia (<1000 cells/mL) at hospitalization, with the rate increasing to 71.7% during the hospital stay. Lymphopenia (<500 cell/mL) at admission was linked to respiratory failure, while the lowest lymphocyte value (<300 cell/mL) was associated with both respiratory failure and poor prognosis[17]. In our study, no statistically significant correlation was found between secondary infection development and lymphocyte level at the time of diagnosis.

Consistent previous studies, we observed that increased mortality was associated with longer hospitalization in patients with a lymphocyte count <200 cells/mL during hospitalization. Additionally, the secondary infection rate was significantly higher in the group with a lymphocyte count <200 cells/mL.

In a meta-analysis of six studies examining the relationship between PCT and secondary infection, the area under the curve (AUC) value for PCT was 0.68 for detecting secondary infection, with a sensitivity of 84% and a specificity of 64%. The AUC value was 0.73 in the subgroup of ICU patients[26]. In our study, the PCT value at admission was not significantly predictive of secondary infection. The AUC value for mortality in our study was 0.61.

Another study emphasized that the course of PCT, rather than a single measurement, is important. It reported that high baseline

PCT levels decreased over time in both ICU patients with isolated influenza and those with secondary infection, with significantly lower PCT levels at 24, 48, and 120 hours in the isolated H1N1 group compared to the secondary infection group[27]. In our study, PCT values were high at baseline and decreased over time in both groups. When comparing PCT values at 0, 24, 48, 72, 96, and 120 hours, the rate of decline in PCT levels after 72 hours in the group with secondary infection tended to decrease, but no statistical significance was found. Additionally, the frequency of secondary infections was 31.8% in those with the highest PCT values below 0.5 and 53% in those with values over 10. Thus, a tendency for increased secondary infection frequency was observed with higher PCT values ($p>0.05$). Mortality was 4.5% in those with the highest PCT values below 0.5, 10% in those with values between 0.5 and 2, 26.5% in those with values between 2 and 10, and 35.5% in those with values above 10. As PCT values increased, mortality also tended to increase ($p=0.057$). The lack of statistical insignificance may be due to the small sample size.

Study Limitations

The primary limitation of our study is its retrospective, single-center design. Only patients with microbiologically confirmed secondary infections were included, while those with clinically suspected secondary infection were excluded. However, the lack of culture growth results could influence the findings. Additionally, the empirical antibiotic therapy administered to most patients might have impacted the results.

This, however, remains debatable, as some studies suggest that excluding patients receiving empirical antibiotic therapy does not alter the results[28]. While lymphopenia was considered, another limitation is that other potential causes of lymphopenia were not explored.

Conclusion

Patients hospitalized with influenza had high rates of secondary infections, which were linked to increased mortality. A lymphocyte count of <200 cells/mL was found to be an indicator of the risk for secondary infections, prolonged hospitalization, and higher mortality. Although higher PCT levels were associated with a tendency for increased secondary infections and mortality, this relationship was not statistically significant.

Ethics

Ethics Committee Approval: This study was approved by the Marmara University Ethics Committee (approval number: 09.2020.969, dated: 02.10.2020).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., Concept: S.K., Design: S.S.İ., Data Collection or Processing: E.T., Analysis or Interpretation: C.I., Literature Search: S.S.İ., Writing: S.S.İ.

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CASE REPORT / OLGU SUNUMU

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Listeria monocytogenes Bacteremia in Immunocompromised Patients: A Report of Two Cases

Listeria monocytogenes Bakteremisi: İki Olgunun Sunumu

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Abstract

Listeria monocytogenes is a Gram-positive, rod-shaped bacterium that can cause outbreaks through contaminated food. This report describes two cases of *L. monocytogenes* bacteremia successfully treated with a combination of meropenem and gentamicin. Both patients had underlying malignancies-multiple myeloma and breast cancer. Neither reported consuming unpasteurized milk or food from external sources. No relapse occurred in either case during a 6-month follow-up period. In conclusion, while *L. monocytogenes* bacteremia without associated meningitis or gastroenteritis is uncommon, it can occur in immunocompromised individuals. To our knowledge, these are the first reported cases of *L. monocytogenes* bacteremia in Bahrain.
Keywords: Glucose-6-phosphate dehydrogenase deficiency, central line-associated bloodstream infections, clabsi, transtuzumab, listeriosis

Öz

Listeria monocytogenes, kontamine gıdalar aracılığıyla salgınlara neden olabilen Gram-pozitif basillerdir. Bu yazıda meropenem ve gentamisin ile başarılı bir şekilde tedavi edilen iki *L. monocytogenes* bakteremi vakası sunuldu. Her iki vakanın da altta yatan maligniteleri vardı (multiple myeloma ve meme kanseri). Her iki olgu da pastörize edilmemiş süt ya da, dışarıdan gıda kullanımı yoktu. Her iki vakada da altı aylık takip süresince nüks olmadı. Sonuç olarak, menenjit veya gastroenterit ile ilişkili olmayan *L. monocytogenes* izole bakteremi vakaları çok yaygın olmasa da, immün yetmezliği olan bireylerde görülebilmektedir. Bildiğimiz kadarıyla, bu iki olgu Bahrain'den bildirilen ilk *L. monocytogenes* bakteremi vakalarıdır.
Anahtar Kelimeler: Glikoz-6-fosfat dehidrojenaz eksikliği, ateter ilişkili kan dolaşımı enfeksiyonu, kikde, transtuzumab, listeryoz

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Introduction

Listeria monocytogenes is a Gram-positive, rod-shaped bacterium that can cause outbreaks through contaminated food. It can lead to severe infections, including meningitis, bacteremia, and gastroenteritis, particularly in elderly and immunocompromised individuals[1-8]. This report describes two cases of *L. monocytogenes* bacteremia successfully treated with a combination of meropenem and gentamicin.

Case Report

Case 1

A 60-year-old Bahraini female was admitted to the Hematology-Oncology ward at Bahrain Oncology Centre with fever. She was referred to an Infectious Diseases consultant for antibiotics optimization. The patient had a diagnosis of Stage III multiple myeloma and a history of treated colon cancer (diagnosed in April 2016). She also had severe glucose-6-phosphate dehydrogenase deficiency. Her past medical history was otherwise unremarkable. Empirical treatment with piperacillin-tazobactam [4.5 g intravenous (IV) every 6 h] was initiated by the primary team while awaiting septic workup results. Blood cultures were obtained upon admission in the Emergency Department. Peripheral blood cultures (from both arms) grew *L. monocytogenes*, which was sensitive to meropenem but resistant to penicillin and cotrimoxazole. The patient did not have a central line. Following consultation with the Infectious Diseases team, piperacillin-tazobactam was discontinued after 6 days, and meropenem (1 g IV every 4 h) plus gentamicin (3 mg/kg IV once daily) were initiated. The patient exhibited no clinical signs of meningitis, presenting only with fever and flu-like symptoms. She denied consuming unpasteurized milk, food from external sources, or unregulated water. Blood cultures were repeated on the same day the antimicrobial regimen was modified and again 72 h later (two sets obtained 1 h apart). All follow-up blood cultures were negative. Inflammatory markers showed significant improvement, with C-reactive protein decreasing from 61 mg/l to 14 mg/l and procalcitonin from 25 ng/ml to 0.03 ng/ml. The patient remained afebrile after starting piperacillin-tazobactam. She completed a 14-day antibiotic course and was discharged in stable condition. There was no relapse during the 6-month follow-up.

Case 2

A 61-year-old Bahraini female was admitted to the Hematology-Oncology ward at Bahrain Oncology Centre due to poor oral intake and electrolyte imbalance (hypokalemia). She had metastatic breast cancer (with brain, liver, and bone involvement) and was receiving active treatment with monoclonal antibodies (trastuzumab emtansine). Her medical history also included diabetes mellitus, hypertension, and dyslipidemia. She had a central line (port-a-cath). She presented to the Emergency Department with poor oral intake and nausea. She denied consuming unpasteurized milk, food from external sources, or unregulated water. Routine urinalysis revealed white blood cell>100 and large leukocytes. C-reactive protein was elevated at 50 mg/l, and procalcitonin was 14 ng/ml. Empirical treatment with ceftriaxone (2 g IV every 24 h) was initiated, and a urine culture was sent. Twelve hours after admission, she developed hypotension (blood pressure 90/50), prompting a full septic workup and fluid resuscitation. Ceftriaxone was escalated to piperacillin-tazobactam (4.5 g IV every 8 h). Two days later, empirical vancomycin (1 g IV every 12 h) was added after preliminary blood culture results showed Gram-positive rods in both peripheral and port-a-cath samples. The Infectious Diseases team was consulted 3 days later following positive blood culture results. *L. monocytogenes* was isolated from both peripheral blood and port-a-cath cultures, with susceptibility to penicillin and meropenem but resistance to cotrimoxazole. The Infectious Diseases team recommended discontinuing piperacillin-tazobactam and vancomycin and initiating meropenem (1 g IV every 4 h) plus gentamicin (3 mg/kg IV once daily). They also advised port-a-cath removal and repeat blood cultures. A peripheral blood culture repeated 3 days after starting gentamicin and meropenem showed no growth. However, the port-a-cath sample grew *Pseudomonas luteola*, which was pan-sensitive. By that time, the port-a-cath had already been removed, and the patient was clinically improving, remained afebrile, and had decreasing inflammatory markers. C-reactive protein decreased from 50 mg/l to 28 mg/l, and procalcitonin dropped from 14 ng/ml to 0.28 ng/ml, with no leukocytosis. A subsequent peripheral blood culture grew methicillin-resistant *Staphylococcus epidermidis*, which later returned negative, and advised initiating linezolid IV only if the patient developed a fever. The port-a-cath had already been removed. During follow-up, the patient left the hospital against medical advice on day 11 of meropenem and gentamicin treatment. There was no relapse during the 6-month follow-up period.

Discussion

L. monocytogenes is a Gram-positive, non-spore-forming, motile, facultatively anaerobic, rod-shaped bacterium. It is catalase-positive and oxidase-negative and produces a beta-hemolysin that lyses red blood cells[1-3]. *L. monocytogenes* is naturally found in moist environments, including soil, water, and decaying vegetation and animals. It is challenging to eradicate from food processing facilities, as it can spread to food through contact with contaminated equipment or surfaces and continue

to grow in refrigerated conditions. However, it is easily destroyed by heating food to sufficiently high temperatures[1-3,8].

Human listeriosis is commonly transmitted through unpasteurized milk, soft cheese (due to their high moisture, low salt content, and low acidity), and raw meats such as cold cuts, hot dogs, and fermented or dry sausages. Additionally, cold-smoked fish, melons, and sprouts have been implicated in *Listeria* outbreaks[1-3,8]. *L. monocytogenes* can cause meningitis in neonates, the elderly, and immunocompromised individuals. In contrast, healthy individuals typically experience a self-limiting gastrointestinal illness with symptoms such as fever and diarrhea[5]. Among the elderly, *L. monocytogenes* is the third most common cause of bacterial meningitis, following *Streptococcus pneumoniae* and *Neisseria meningitidis*[9,10]. Cases of complications from bacteremia in central nervous system (CNS) listeriosis are relatively common, occurring in approximately 40% of cases, and are associated with a high mortality rate. Patients with *Listeria* infections affecting the CNS may present with symptoms such as altered mental status, fever, seizures, focal neurological deficits, and nuchal rigidity in about 60% of cases. According to the literature, the classic triad of fever, neck stiffness, and altered mental status is observed in 43% of cases, and nearly all patients exhibit at least two of the four hallmark symptoms: headache, fever, neck stiffness, and altered mental status[9,10]. Neither of our patients had an epidemiological link, nor did they exhibit signs of altered mental status or nuchal rigidity. Consequently, CNS listeriosis was deemed unlikely, and lumbar puncture was not performed due to the absence of classic meningitis symptoms. Both patients were immunocompromised and had no recent history of gastroenteritis. Nonetheless, they were treated as if they had CNS listeriosis[6]. Penicillin, ampicillin, and amoxicillin are the primary treatment options for *Listeria* infections. Combination therapy, such as adding gentamicin to ampicillin, has demonstrated the highest efficacy against the bacterium *in vitro*; however, gentamicin is ineffective against intracellular bacteria. Alternative treatment options include rifampin, vancomycin, linezolid, carbapenems, and quinolones, while trimethoprim is used in cases of beta-lactam intolerance[1-3,6,7]. Skogberg et al.[11] conducted a study on 74 patients with listeriosis, including immunocompromised individuals. In nine cases, cephalosporins-antibiotics with limited efficacy against *L. monocytogenes*-were administered. Among these, four patients died, including three with meningitis and one with bacteremia. In contrast, patients treated with antibiotics demonstrating strong in vitro activity against *L. monocytogenes*, such as penicillin G, ampicillin, or piperacillin-either alone or in combination with aminoglycosides-had better outcomes ($p<0.05$)[11]. In our study, both patients were treated with a combination of meropenem and gentamicin due to their underlying malignancies and immunocompromised status. As a result, both exhibited a significant and durable clinical response to this treatment regimen.

Conclusion

In summary, although isolated cases of *L. monocytogenes* bacteremia without associated meningitis or gastroenteritis are uncommon, they can occur in immunocompromised individuals. To the best of our knowledge, there are no previously reported cases of *L. monocytogenes* bacteremia in Bahrain.

Ethics

Informed Consent: Consent form was filled out by all participants.

Footnotes

Authorship Contributions

Concept: N.J., U.E., O.R.S., Design: N.J., U.E., O.R.S., Data Collection or Processing: N.J., U.E., A.K., N.B., A.R., S.H., O.R.S., Analysis or Interpretation: N.J., U.E., A.K., N.B., A.R., S.H., O.R.S., Literature Search: N.J., U.E., O.R.S., Writing: N.J., O.R.S.

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Is *Papillotrema (Cryptococcus) laurentii* an Emerging Concern? A Literature Review and Case Series from a Tertiary Hospital

Papillotrema (Cryptococcus) laurentii Giderek Artan Bir Sorun mu Oluyor? Üçüncü Basamak Bir Hastanede Olgu Serisi Eşliğinde Literatür Derlemesi

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Abstract

Introduction: Cryptococcosis is a significant opportunistic fungal infection, particularly affecting immunocompromised individuals. *Papillotrema laurentii* has been increasingly reported in recent years, especially in immunosuppressed patients. This study aims to provide guidance on the diagnosis and treatment of *P. laurentii*-related infections or colonization, along with a review of the existing literature.
Materials and Methods: Patients with *P. laurentii* isolated in any culture sample between 2017 and 2022 were included in this study. A literature search was conducted using the electronic databases Scopus, Web of Science, MEDLINE (PubMed), and Google Scholar.
Results: Over the past 5 years, *P. laurentii* was identified in culture samples from nine patients in our hospital. A literature review revealed 35 publications reporting a total of 40 cases of *P. laurentii* infection between 1998 and 2022. The most common risk factors included the use of broad-spectrum antibiotics and the presence of invasive devices or catheters.
Conclusion: Although *P. laurentii* is considered a rare pathogen, it can cause infections of various organ systems. Therefore, clinicians should be aware that this uncommon fungal species may act as an infectious agent, particularly in patients receiving broad-spectrum antibiotics or steroid therapy.
Keywords: Papiliotrema laurentii, fungal diseases, Cryptococcosis

Öz

Giriş: Kriptokokozis, özellikle immün sistemi baskılanmış hastalarda görülen önemli bir fırsatçı mantar enfeksiyonudur. *Papillotrema laurentii* son yıllarda özellikle immün sistemi baskılanmış hastalarda bildirilmiştir. Bu makalede literatür derlemesi yapılarak *Papillotrema laurentii* ile ilişkili enfeksiyonların veya kolonizasyonların tanı ve tedavisine rehberlik etmek amaçlanmıştır.
Gereç ve Yöntem: Çalışmamıza, 2017-2022 yılları arasında herhangi bir kültür örneğinde *Papillotrema laurentii* izolasyonu saptanan hastalar dahil edilmiştir. Literatür taramaları, Scopus, Web of Science, MEDLINE (PubMed) ve Google Scholar gibi elektronik veri tabanlarında gerçekleştirilmiştir.
Bulgular: Son beş yıl içerisinde hastanemizde kültür örneklerinde *Papillotrema laurentii* izole edilen dokuz hasta tespit edilmiştir. Yapılan literatür taramasında, 1998-2022 yılları arasında *Papillotrema laurentii* enfeksiyonu gelişen toplam kırk olguyu içeren otuz beş yayın bulunmuştur. Geniş spektrumlu antibiyotik kullanımı ile invaziv araç veya kateter varlığı en sık karşılaşılan risk faktörleri olarak belirlenmiştir.
Sonuç: Nadir bir etken olarak bildirilen *Papillotrema laurentii*, birçok sistemi tutarak çeşitli enfeksiyonlara yol açabilmektedir. Bu nedenle, özellikle geniş spektrumlu antibiyotik ve steroid tedavisi kullanan hastalarda, bu tür nadir etkenlerin enfeksiyon etkeni olarak karşımıza çıkabileceği akılda tutulmalıdır.
Anahtar Kelimeler: *Papiliotrema laurentii*, mantar hastalıkları, Kriptokokkoz

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Introduction

Papillotrema laurentii, formerly known as *Cryptococcus laurentii*, is an encapsulated basidiomycetous yeast. Cryptococcosis is a major opportunistic fungal infection, primarily affecting immunocompromised patients[1]. However, in approximately 30% of cases, no identifiable predisposing factors are present[2]. The most common pathogenic species associated with Cryptococcosis are *C. neoformans* and *C. gattii*. Notably, around 80% of reported cases of non-*neoformans* or non-*gattii* Cryptococcosis have been attributed to *C. laurentii* and *C. albidus*[3].

Although *P. laurentii* is generally considered a saprophytic and rare yeast, reports of invasive infections have increased in recent years[4,5]. Documented infections caused by *P. laurentii* include involvement of the lungs, central nervous system, bloodstream, urinary tract, and musculoskeletal system[6]. While this species is typically regarded as non-pathogenic to humans, such infections have been reported.

This study aims to investigate *P. laurentii* infections or colonization detected in our hospital and review the existing literature to emphasize the clinical relevance of *C. laurentii*-related infections and provide guidance for their diagnosis and treatment.

Materials and Methods

Patients with *P. laurentii* isolated from any culture sample between 2017 and 2022 were included in this study. Demographic and clinical data were obtained from the hospital database. Infection was defined as the proliferation of the microorganism in the host leading to disease symptoms due to invasion, whereas colonization was characterized by the presence of the microorganism without causing a disease response. Sputum samples were assessed using the Bartlett classification. According to this method, active inflammation was defined by the presence of 10-25 or more leukocytes at 10x magnification and fewer than 10 epithelial cells in the same field. A literature search was conducted using the electronic databases Scopus, Web of Science, MEDLINE (PubMed), and Google Scholar. Among the identified studies, 3 were retrospective cohort studies, 7 were systematic reviews, and 31 were case reports. No restrictions were placed on language or publication date. Both pediatric and adult populations were included, and reference lists of the retrieved studies were manually reviewed. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols guidelines.

Ethical Approval

The study protocol was approved by the Ethics Committee of Kocaeli University Faculty of Medicine (approval number: GOKAEK-2023/11.27, dated: 16.06.2023).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the normality of data distribution. Continuous variables were presented as mean ± standard deviation, while categorical variables were expressed as frequency (percentage). Since the assumption of normal distribution was not met, the Wilcoxon signed-rank test was used for comparisons between pretreatment and posttreatment values. Relationships between categorical variables were analyzed using the chi-squared test. A p-value of <0.05 was considered statistically significant.

Results

Over the past 5 years, *P. laurentii* was identified in culture samples from nine patients in our hospital. Of these, seven patients exhibited clinical findings indicative of infection, while two were classified as cases of colonization. A literature review identified 35 publications reporting a total of 40 cases of *P.* laurentii infection between 1998 and 2022 (Table 1). Among the infected patients, 66% were male, with a mean age of 48.3±7.085 years (range, 15-77 years). A summary of cases identified in our hospital and those reported in the literature is presented in Table 1.

Case Presentations

Case 1

A 42-year-old female patient with a history of asthma and hypothyroidism was admitted with fever and shortness of breath. She was started on ceftriaxone, clarithromycin, and treatment for an asthma attack. Chest computed tomography (CT) revealed several pulmonary nodules. Gram staining of a bronchoalveolar lavage (BAL) sample showed active inflammation based on Bartlett classification, with leukocytes and yeast cells present. *P.* laurentii was isolated in the BAL fungal culture. After 3 months of fluconazole treatment, follow-up CT showed a reduction in nodule size.

Case 2

A 34-year-old female patient with a history of cryoglobulinemic vasculitis was admitted to the clinic with pneumonia, presenting with a 10 day history of cough and sputum production. She had been using prednisolone intermittently for 2 years. Chest CT showed pleural effusion adjacent to consolidation in the lower lobe of the right lung, along with a cavitary lesion. Additionally, tree-in-bud nodules and ground-glass opacities were observed in the lower lobe of the left lung. Fluconazole was added to her antibiotic regimen. Gram staining of sputum

samples showed numerous leukocytes but no microorganisms. *P.* laurentii was isolated in the sputum culture. After 6 months of fluconazole therapy, follow-up chest CT revealed the resolution of the ground-glass opacities, consolidation, cavity, and pleural effusion.

Case 3

A 77-year-old male patient with no known comorbidities was hospitalized with Coronavirus Disease 2019 (COVID-19), confirmed by a Severe Acute Respiratory Syndrome Coronavirus 2 Polymerase Chain Reaction, tests. Chest CT showed diffuse bilateral ground-glass opacities, and his oxygen saturation was 75% on room air. He was started on antibiotics and pulse steroid therapy (250 mg for 3 days, followed by 40 mg of prednisolone). On the seventh and eighth days of hospitalization, he received two doses of tocilizumab. *P.* laurentii was isolated in a blood culture 8 days after pulse steroid therapy and 1 day after tocilizumab administration. The patient died on the same day.

Case 4

A 43-year-old male patient with no known medical conditions underwent surgery for a duodenal perforation. He was started on meropenem and tigecycline. On the second day of hospitalization, *Enterococcus faecalis* and *P. laurentii* were isolated from the culture of the fluid collected from the surgical drain. Gram staining of the fluid showed numerous leukocytes and yeast cells. Fluconazole was added to his treatment regimen. The surgical drain was removed after 28 days of treatment, and the patient was discharged in full recovery.

Case 5

A 67-year-old female patient with a history of diabetes mellitus, hypertension, and coronary artery disease was admitted to the Nephrology Department with postrenal acute kidney injury and required hemodialysis. She presented with dysuria, fatigue, and nausea. A pigtail catheter had been inserted approximately 1 year earlier. Urine culture from the patient, who had pyuria, revealed *P. laurentii* at a concentration of 10^5 colony-forming units (CFU) . The pigtail catheter was replaced, and the patient completed a 7 day course of fluconazole before being discharged. Follow-up urine culture was negative, and pyuria was no longer present.

Case 6

A 47-year-old male patient with hypertension was admitted to the intensive care unit with fever, shortness of breath, and cough. He developed acute kidney injury and required hemodialysis. A renal biopsy confirmed acute tubulointerstitial nephritis, for which he received 60 mg of prednisolone for 3 days. Two days later, *P.* laurentii was isolated in a sputum culture. However, as there was no evidence of active inflammation based on the Bartlett classification and no microorganisms detected in Gram staining, the isolate was considered a case of colonization. The patient was discharged after completing antibiotic treatment.

Case 7

A 15-year-old male patient with Duchenne muscular dystrophy underwent surgery in the Orthopedics Department for fractures of the right femur and humerus. On the sixth day of hospitalization, *P.* laurentii was isolated from a wound culture obtained from the surgical site. However, as leukocytes were absent in the sample, the isolate was considered a case of colonization rather than infection.

Case 8

A 77-year-old male patient with a history of mitral valve replacement and a previous cerebrovascular stroke was admitted with a 45 day history of fever. Transesophageal echocardiography revealed an oscillating mass on the mitral valve. He was started on broad-spectrum antibiotics and was managed with a urinary catheter. One month later, after catheter removal, urine analysis showed 55 leukocytes, and urine culture yielded *P. laurentii* at a concentration of 10^5 CFU. The patient reported worsening fatigue and reduced oral intake, and his C-reactive protein level was elevated to 33 mg/l (normal upper limit: 5 mg/l). He was diagnosed with cystitis and started on fluconazole. Follow-up urine culture was negative. However, the patient died during surgical intervention for endocarditis.

Case 9

A 33-year-old male patient with nasopharyngeal cancer was hospitalized with pneumonia. *P.* laurentii was isolated from a BAL sample. Gram staining of the BAL sample revealed leukocytes, yeast cells, and Gram-positive cocci. The patient was initially treated with amphotericin B for 5 days, followed by fluconazole. His treatment was completed in 14 days, leading to a full recovery.

Systematic Review

The first documented case of *P.* laurentii-associated infection was a cutaneous infection reported in 1977. Between 1977 and 2023, 43% of all identified cases were recorded. Among 40 reported cases of *P.* laurentii infection, 65.7% occurred in male patients, with a mean age of 39.4±3.928 years (age range, 0-88 years). The most frequently reported infection was fungemia, followed by meningitis and pneumonia. Less common infections included enteritis, skin ulcers, septic arthritis, endophthalmitis, lung abscesses, peritonitis, and mucositis. Notably, two cases of enteritis, one case of septic arthritis, and one case of endophthalmitis were newly reported in recent years (Figure 1). Broad-spectrum antibiotic use and the presence of invasive devices or catheters were frequently identified as risk factors in the literature[7,8]. Treatment primarily involved fluconazole and

amphotericin B. Among the 39 patients with available prognosis data, 33 (84.6%) recovered, while 5 (12.8%) died due to *P.* laurentii infection, and 1 (2.6%) succumbed to an underlying condition. Of the five patients who died from *P.* laurentii infection, two had fungemia, one had both meningitis and cutaneous infection, one had meningitis, and one had mucositis (Figure 2).

Comparison of Our Cases with Published Data

The average age of our patients was 48.3 years, while the mean age of cases reported in the literature was 39.4 years. This difference was not statistically significant (p=0.302). Male predominance was observed in both our study and the literature, with no significant difference between the two groups (p=0.641).

In our study, pneumonia was the most frequently observed clinical manifestation, whereas fungemia was the most common presentation in the literature. Consistent with previous findings, broad-spectrum antibiotic use and the presence of invasive devices or catheters were identified as key risk factors for Cryptococcosis. A comparison of our hospital data with published cases is provided in Table 2.

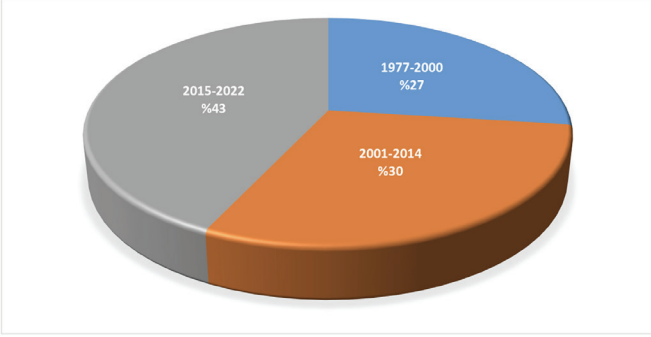

Figure 1. *Cryptococcus laurentii* cases reported in the literature over the years

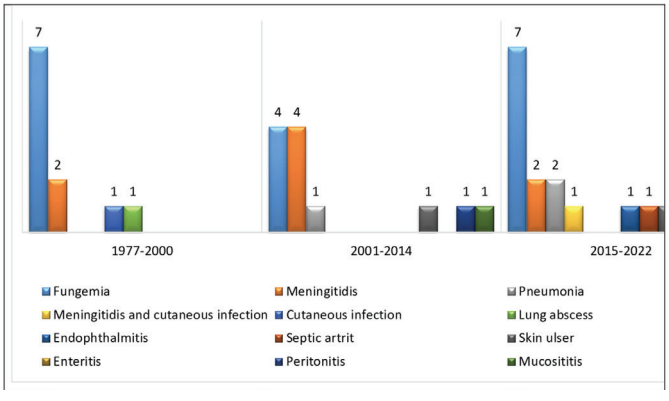

Figure 2. *Cryptococcus laurentii* infections reported in the literature over the years and the number of cases

Discussion

This study presents seven cases of infection and two cases of colonization caused by *P. laurentii,* a rare human pathogen. To the best of our knowledge, this is the first report documenting *P. laurentii* cases in Türkiye. While immunocompromised individuals are generally considered at higher risk for *P. laurentii* infections, cases can also occur in immunocompetent patients.

Although *P.* laurentii has traditionally been regarded as a saprophyte and an uncommon human pathogen, reports of invasive infections have increased in recent years[9]. This rise may be linked to the growing number of immunocompromised individuals and the widespread use of immunosuppressive therapies[1]. Similarly, our findings align with the literature, as our cases also involved invasive infections.

Non-*neoformans* cryptococci are capable of infecting various organ systems. A study by Khawcharoenporn et al.[1] reported that bloodstream infections (39%) were the most common, followed by central nervous system infections (32%). In our study, one patient (14%) developed a bloodstream infection after receiving corticosteroids and cytokine blockers for COVID-19. Priscilla et al. also reported *P.* laurentii isolation from sputum culture under similar clinical conditions[10]. Additionally, a study of 30 COVID-19 patients found that corticosteroid and cytokine blocker therapy (e.g., tocilizumab) increased the risk of opportunistic cryptococcal infections[10].

In our study, pulmonary Cryptococcosis was identified in three cases (42%). Cryptococcal lung disease can present in various forms, ranging from asymptomatic colonization to severe pneumonia with respiratory failure. Radiological findings may include pulmonary nodules, masses, segmental or lobar consolidation, reticulonodular infiltrates, mediastinal or hilar lymphadenopathy, and, less commonly, pleural effusion[9]. However, individuals with advanced HIV tend to exhibit more severe imaging abnormalities. Most case series have reported interstitial infiltrates as the predominant finding, while pleural effusions, cavitary lesions, adenopathy, and alveolar opacities are less frequently observed[11]. Additionally, endobronchial colonization has been documented in patients with chronic pulmonary disease, as seen in one case from our study[12]. The presence of yeast in urine cultures of asymptomatic individuals is typically regarded as colonization.

Current guidelines recommend that treatment for asymptomatic candiduria should focus on eliminating risk factors and should only be considered for patients at risk of disease progression[10].

Invasive device use was identified as a risk factor in our study. Similarly, a review highlighted the presence of invasive devices as a significant risk factor for *P.* laurentii infection. One case report described *P.* laurentii as the causative agent of peritoneal

dialysis-associated peritonitis[13]. However, in our study, peritonitis developed in one patient, and the isolation of the pathogen after surgery may have been influenced by broad-spectrum antibiotic use or the presence of an invasive device.

Table 1. Summary of our cases and systematically reviewed reported cases

References	Country	Age/sex	Underlying condition	PAE/PSE	C-D/PN	Sample	Diagnosis	Manifestation	Treatment	Outcome
Our study	Türkiye	42/F	Asthma	No/inhale steroid	No/No	BAL	Pneumonia	Fever, dyspnea	F for 3 months	Cured
		34/F	Cryoglobulinemic vasculitis	No/Yes	No/No	Sputum	Pneumonia	Cough, sputum	F for 6 months	Cured
		77/M	COVID-19	Yes/Yes	No/No	Blood	Fungemia	NR	-	Died
		47/M	None	Yes/No	Yes/No	Peritoneal drainage catheter	Intraabdominal infection	NR	F for 1 month	Cured
		67/F	DM, hypertension, coronary artery disease	No/No	Yes/No	Urine	Urinary tract infection	NR	F for 7 days	Cured
		47/M	Hypertension	Yes/Yes	No/No	Sputum	Colonization	Fever, dyspnea, cough	-	Cured
		15/M	Duchenne muscular dystrophy	No/No	No/No	Skin	Colonization	Discharge in the wound	-	Cured
		77/M	Mitral valve replacement, cerebrovascular stroke	Yes/No	Yes/No	Urine	Urinary tract infection	NR	F for 2 weeks	Cured
		33/M	Nasopharyngeal cancer	Yes/No	No/No	BAL	Pneumonia	Dyspnea	Amp B for 5 days followed by F for 9 days	Cured
Deepa et al.[14]	India	50/M	DM, COVID-19	Yes/Yes	No/No	Vitreous	Endophthalmitis	6 weeks of progressive blurred vision	Topical V for 9 months, oral F for 1 month	Cured
Al-Otaibi et al.[7]	Kuwait	Newborn	Very low birth weight	Yes/No	Yes/No	Blood	Fungemia	Abdominal distension and weight loss	Amp B for 14 days	Cured
Huang et al.[6]	China	29/M	History of plant-related scratches	Yes/Yes	No/No	Joint fluid	Septic arthritis	Knee pain and limited activity	A month of treatment with topical V and knee irrigation with Amp B. The treatment continued with F for nearly 7 months	Cured
Castro-Lainez et al.[15]	USA	59/M	DM	Yes/NR	No/No	CSF	Meningitidis	Headache, blurred vision, disequilibrium, and photophobia	Amp B and F for 6 weeks	Cured
Londero et al.[8]	Brazil	68/F	DM, breast cancer with radical mastectomy	Yes/No	Yes/No	Catheter and peripheral blood	Fungemia	Fever and abdominal pain	Catheter removed and Amp B and F for 2 weeks	Cured
Zhang et al.[16]	China	50/M	HIV	No/NR	NR/No	Skin and CSF	Meningitis and cutaneous infection	Skin lesions	Amp B and F	Died
		64/F	HIV	Yes/NR	NR/No	BAL	Pneumonia	Mild fever, productive cough, dyspnea	F	Cured
Gupta et al.[17]	India	6 days/M	Premature	Yes/No	Yes/No	Blood	Fungemia	Worsening of the clinical condition	IV Amp B for 8 days followed by F for 24 days	Cured

Table 1. Continued

References	Country	Age/sex	Underlying condition	PAE/PSE	C-D/PN	Sample	Diagnosis	Manifestation	Treatment	Outcome
Ding et al.[18]	Malaysia	35/F	Hodgkin's lymphoma	Yes/No	No/No	Blood	Fungemia	Supraclavicular mass, fever	F for 2 weeks	Cured
Park et al.[19]	Korea	47/F	Refractory AML after allogenic HSCT	Yes/NR	NR/Yes	Blood and skin	Fungemia	Fever and erythematous papules	Amp B for 3 weeks	Cured
Martinez et al.[20]	Mexico	65/M	Cutaneous leishmaniosis	No/No	No/No	Skin biopsy	Skin ulcer	Ulcer	Itraconazole	Cured
Bhat et al.[21]	India	26/F	Hodgkin's lymphoma autologous HSCT	No/NR	NR/No	Stool	Enteritis	Diarrhea	V for 4 weeks	Cured
Calista et al.[22]	Italy	74/M	Hepatitis B, colorectal cancer on chemotherapy	Yes/NR	NR/Yes	Stool	Enteritis	Diarrhea	Amp B for 10 days	Cured
Cheng et al.[23]	Taiwan	88/F	Right breast cancer (postmastectomy), diffuse large B-cell lymphoma	Yes/Yes	NR/Yes	Blood	Fungemia	Fever	Amp B and flucytosine for 2 weeks	Cured
Conti et al.[24]	Italy	47/F	SLE and Sjogren syndrome treated with cyclosporine A and corticosteroids	Yes/Yes	NR/No	BAL	Pneumonia	Cough, fever	Initially Amp B, switched to F for 8 months due to toxicity	Cured
Mittal et al.[25]	India	30/F	Recent C-section due to fetal distress	Yes/NR	NR/No	CSF	Meningitidis	Postpartum headache and drowsiness	Amp B	Died
Neves et al.[26]	Brazil	42/M	Cervical cancer treated with chemotherapy and radiotherapy	Yes/NR	NR/No	Blood	Fungemia	Fever and abdominal pain	F for 22 weeks	Cured
Asano et al.[13]	Japan	32/M	IgA neuropathy in PD	No/No	Yes (PD)/ No	Peritoneal fluid	Peritonitis	Fever	Removal of the PD catheter and V for 3 months	Cured
Banerjee et al.[27]	India	76/M	Hypertension, coronary artery disease, and previous hemorrhagic stroke	Yes/No	Cardiac defibrillator implantation 2 weeks before fungemia/ No	Blood	Fungemia	Fever, shortness of breath, heart failure	Amp B for 2 weeks followed by F for 2 weeks	Cured
Molina-Leyva et al.[28]	Spain	8/F	None	No/No	No/No	Skin biopsy	Skin ulcer	Skin lesion in the right forearm	F for 2 weeks	Cured
Rodríguez et al.[29]	Colombia	3 months/M	Premature baby with down syndrome	Yes/No	Yes/No	Blood	Fungemia	Respiratory failure	Amp B	Died
Furman-Kuklinska et al.[30]	Polonia	39/M	Type I membranoproliferative glomerulonephritis,	No/Yes	No/No	Blood	Fungemia	Fever	Itraconazole for 4 weeks due to persistent fungemia	Cured
Khawcharoenporn et al.[31]	Thailand	35/M	HIV	NR/NR	NR/NR	Blood and CSF	Meningitidis	Fever, headache	Amp B for 14 days followed by F for 3 months	Cured
Manfredi et al.[32]	Italy	34/M	HIV, IV drug user, previous *C. neoformans* meningitis	No/No	No/No	CSF	Meningitidis	Fever, headache	F for 46 days	Cured
Shankar et al.[33]	India	35/F	HIV, DM	Yes/No	No/No	Pleural fluid	Pneumonia	Fever, night sweats, pleuritic chest pain, and dyspnea	F for 5 weeks	Cured

Table 1. Continued

References	Country	Age/sex	Underlying condition	PAE/PSE	C-D/PN	Sample	Diagnosis	Manifestation	Treatment	Outcome
Simon et al.[34]	Hungary	9/M	X- linked hyperimmunoglobulin M syndrome	Yes/No	No/Yes	CSF	Meningitidis	Headache, nausea, and somnolence	F for 9 months with tittering of dosage	Cured
Vlchkova-Lashkoska et al.[35]	Slovakia	51/M	Alcoholism	No/No	No/No	Skin and CSF	Meningitidis	Skin lesion on the back	NR	NR
Averbuch et al.[36]	Israel	16/M	Metastatic ganglioneuroblastoma	Yes/No	Yes/No	Blood	Fungemia	Fever	Amp B for 3 weeks	Cured
Bauters et al.[36]	Belgium	45/M	Erythroleukemia	Yes/NR	NR/Yes	Oropharynx	Mucositis	Fever	Amp B for 18 days	Died
Kunova and Krcmery et al.[38]	Slovakia	NR	Neutropenia	Yes/NR	Yes/Yes	Blood	Fungemia	Fever	F for 10 days	Cured
		NR	Neutropenia	Yes/NR	Yes/Yes	Blood	Fungemia	Fever	Amp B for 14 days	Cured
		NR	Neutropenia	Yes/NR	No/Yes	Blood	Fungemia	Fever	NR	Died
Kordosis et al.[39]	Greece	34/M	HIV and Kaposi's sarcoma	No/No	No/No	CSF	Meningitidis	Fever, headache, and diplopia	Amp B and flucytosine for 2 weeks followed by F as a maintenance therapy	Cured
Kunova and Krcmery et al.[38]	Slovakia	NR/M	Solid tumor	Yes/No	Yes/Yes	Blood	Fungemia	NR	F	Cured
		NR/M	nonHodgkin's lymphoma	Yes/Yes	Yes/Yes	Blood	Fungemia	NR	Amp B	Died due to underlying disease
Johnson et al.[40]	USA	27 days/M	Premature	Yes/No	Yes/No	Blood	Fungemia	NR	Amp B and flucytosine	Cured
		27/F	IV drug use, bacterial endocarditis, and bipolar disorder	Yes/No	NR/No	Blood	Fungemia	Fever and painful cutaneous nodules	F	Cured
Lynch et al.[41]	USA	55/F	Adenocarcinoma, dermatomyositis	No/Yes	NR/No	NR	Lung abscess	Asymptomatic right upper lobe cavitary lesion	Amp B	Cured
Kamalam et al.[42]	India	40/M	Mycobacterial skin infection	NR/NR	NR/NR	Skin	Cutaneous infection	Cutaneous granulomas in the leg and foot	Amp B	Cured

PAE: Prior antibiotic exposure, PSE: Prior steroid exposure, C-D: Catheter device, PN: Prior neutropenia, BAL: Bronchoalveolar lavage, DM: Diabetes mellitus, Amp B: Amphotericin B, F: Fluconazole, V: Voriconazole, IV: Intravenous, PD: Peritoneal dialysis, HSCT: Hematopoietic stem cell transplantation, SLE: Systemic lupus erythematosus, CSF: Cerebrospinal fluid, NR: Not reported, HIV: Human immunodeficiency virus, AML: Acute myeloid leukemia

Table 2. Comparison of patient data with literature case reports

Characteristics	Case series (n=9)	Literature cases (n=40)	p-value
Age, mean years	48.3 + 7.085 (15–77)	39.4+3.928 (0-88)	0.302
Male, sex	6 (66%)	23 (65.7%)	0.641
Risk factors, n (%)			
• Invasive devices or catheter	2 (22%)	12 (30%)	
• Prior steroid exposure	3 (33%)	7 (17.5%)	
• Anti-interleukin	1 (11%)	1 (2.5%)	
• Broad-spectrum antibiotic	2 (22%)	27 (67%)	
• Solid tumor	1 (11%)	7 (17%)	
• HIV	0	6 (15%)	
• Lymphoma or leukemia	0	4 (10%)	
• DM	1 (11%)	4 (10%)	
Clinical manifestations, n (%)			
• Blood stream infection	1 (11%)	18 (45%)	
• Pulmonary infection	4 (44%)	3 (7%)	
• Peritonitis	1 (11%)	1 (2.5%)	
• Urinary tract infection	2 (22%)	-	
• Meningitidis		8 (20%)	
• Meningitis and cutaneous infection		1 (2.5%)	
• Enteritis		2 (5%)	
• Skin ulcer		2 (5%)	
• Cutaneous infection		1 (2.5%)	
• Endophthalmitis	1 (11%)	1 (2.5%)	
• Lung abscess		1 (2.5%)	
• Septic arthritis		1 (2.5%)	
• Mucositis		1 (2.5%)	
Treatment, n (%)			
• Fluconazole	6 (66%)	20 (50%)	
• Amphotericin B	1 (11%)	22 (55%)	
• No treatment	2 (22%)	-	
• Voriconazole	-	4 (10%)	
• Flucytosine	-	3 (7%)	
• Itraconazole	-	2 (5%)	
Outcome, n (%)			
• Cured	8 (88%)	35 (87%)	
• Died	1 (11%)	5 (13%)	

DM: Diabetes mellitus, HIV: Human immunodeficiency virus

Conclusion

In summary, an evaluation of these nine cases indicates that *P.* laurentii, though considered a rare pathogen, can cause infections in multiple organ systems. Successful treatment can be achieved with appropriate antifungal therapy initiated based on thorough clinical evaluation and culture results. However, delays in treating systemic infections may result in fatal outcomes. Therefore, it is important to recognize that this rare pathogen can act as an infectious agent, particularly in patients receiving broad-spectrum antibiotics or steroid therapy.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Kocaeli University Faculty of Medicine (approval number: GOKAEK-2023/11.27, dated: 16.06.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.T.D., Design: S.A., Data Collection or Processing: M.T.D., Analysis or Interpretation: S.A., Literature Search: S.A., Writing: M.T.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Do Obstetricians' Knowledge and Approaches to HIV and Pregnancy Reflect the State-of-the-Art Literature in the Era of Contemporary ARTs, U=U, and PrEP?

Günümüz ART, U=U ve PrEP Döneminde Obstetrisyenlerin HIV ve Gebeliğe Yönelik Bilgi ve Yaklaşımları Güncel Literatürü Yansıtıyor mu?

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Abstract

Introduction: Obstetricians are very important intermediaries for reaching and engaging with women living with Human Immunodeficiency Virus (HIV) or women at risk for acquiring HIV. Thus, they should acquire up-to-date HIV knowledge for them to make clinical decisions in prepregnancy counseling and follow-up of HIV-positive pregnant women.

Materials and Methods: This study assessed obstetricians' knowledge about HIV and pregnancy and their behaviors regarding the follow-up of HIV-positive pregnant women using a 54-item face-to-face and online questionnaire administered to physicians working in Türkiye between February and May 2023. This cross-sectional study questionnaire consists of four sections including following up of HIV+ pregnancies, knowledge of HIV, undetectable=untransmittable (U=U) pre-exposure prophylaxis (PrEP), and patient management or treatment approaches.

Results: A total of 133 obstetricians and gynecologists, comprising 15 (11.3%) academic members, 43 (32.3%) specialists, and 75 (56.4%) residents, participated in this study. A significant proportion of respondents felt that they knew nothing (2.2%) or little (34.6%) about HIV/Acquired Immunodeficiency Syndrome. A substantial proportion of respondents with <5 years of experience (40.5%, p=0.001) stated they had never attended a scientific meeting on HIV and had never read a guideline or article, whereas 34.6% had never followed up an HIV-positive pregnancy, and 43.6% reported having followed up only one to five HIV-positive pregnancies. Of the participants, 49.6% believed that HIV is an infection that will continue to progress and lead to death despite treatment, 74.4% reported they had never heard of the term U=U, and only 18.8% stated they had some knowledge on PrEP. Knowledge regarding the use of semen preparation techniques and indications for cesarean section and intravenous zidovudine in pregnant women with HIV was reportedly lacking.

Conclusion: The knowledge level on HIV, the disease course, the efficacy of antiretroviral drugs, and the use of these drugs in pregnancy among obstetricians participating in our study is insufficient. Considering that the incidence and prevalence of HIV will continue to increase significantly in the coming years and that a significant proportion of this increase will be young women of childbearing age, obstetricians and gynecologists must keep themselves up-to-date on HIV and pregnancy.

Keywords: HIV-positive pregnant woman, undetectable=untransmittable, U=U, preexposure prophylaxis, obstetricians' knowledge

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Öz

Giriş: Kadın doğum uzmanları, İnsan Bağışıklık Yetmezliği Virüsü (HIV) ile yaşayan ya da HIV bulaşma riski taşıyan kadınlara ulaşma ve onlarla iletişim kurma konusunda çok önemli aracılardır. Kadın doğum uzmanlarının güncel HIV bilgisi, gebelik öncesi danışmanlık ve HIV pozitif gebe kadınların takibinde klinik kararlar alabilmeleri için de önemlidir.

Gereç ve Yöntem: Kadın doğum uzmanlarının HIV ve gebelik hakkındaki bilgilerini ve HIV pozitif gebelerin takibine ilişkin davranışlarını değerlendirmek amacıyla katılımcılara 54 soruluk yüz yüze ve çevrimiçi bir anket uygulanmıştır. Anketimiz demografik bilgiler, HIV, belirlenemeyen=bulaştırmayan (B=B), maruziyet öncesi profilaksi (PrEP), hasta yönetimi ve tedavi yaklaşımları ile ilgili soruları içeren beş bölümden oluşmaktadır.

Bulgular: Çalışmaya 15'i (%11,3) öğretim üyesi, 43'ü (%32,3) uzman ve 75'i (%56,4) asistan olmak üzere toplam 133 kadın hastalıkları ve doğum uzmanı katılmıştır. Katılımcıların önemli bir kısmı HIV/Edinilmiş Bağışıklık Yetmezliği Sendromu (AIDS) hakkında hiçbir şey bilmediğini (%2,2) veya çok az şey bildiğini (%34,6) düşünmektedir. Beş yıldan az deneyime sahip katılımcıların önemli bir kısmı (%40,5) HIV ile ilgili hiçbir bilimsel toplantıya katılmadıklarını ve hiçbir kılavuz ya da makale okumadıklarını belirtmiştir. Katılımcıların %34,6'sı hiç HIV pozitif gebelik takip etmemişken, %43,6'sı sadece bir ila beş HIV pozitif gebelik takip ettiğini bildirmiştir. Katılımcıların %49,6'sı HIV'in tedaviye rağmen ilerlemeye devam edecek ve ölüme yol açacak bir enfeksiyon olduğuna inanırken, %74,4'ü U=U terimini hiç duymadığını ve sadece %18,8'i PrEP hakkında biraz bilgi sahibi olduğunu söylemiştir. HIV'li gebe kadınlarda sperm hazırlama teknikleri, sezaryen endikasyonları ve intravenöz zidovudin kullanımı hakkında bilgi eksikliği vardı.

Sonuç: Türkiye'de kadın doğum uzmanları arasında HIV virüsü, hastalığın seyri, antiretroviral ilaçların etkinliği ve bu ilaçların gebelikte kullanımı konusunda bilgi düzeyi yeterli değildir. HIV insidansının ve prevalansının önümüzdeki yıllarda önemli ölçüde artmaya devam edeceği ve bu artışın önemli bir bölümünü doğurganlık çağındaki genç kadınların oluşturacağı düşünüldüğünde, kadın hastalıkları ve doğum uzmanlarının HIV ve gebelik konusunda kendilerini güncel tutmaları büyük önem taşımaktadır.

Anahtar Kelimeler: HIV pozitif gebe kadın, belirlenemeyen=bulaştırmayan, U=U, maruziyet öncesi profilaksi, kadın doğum uzmanlarının bilgisi

Introduction

Recent advances in antiretroviral therapies (ART) for the Human Immunodeficiency Virus (HIV) have developed treatments that are resistant to the occurrence of resistance, are easy to use, and have a better short- and long-term side-effect profile. Consequently, global treatment coverage has increased, and the life expectancy of people living with HIV (PLWH) has improved. Virological suppression achieved with treatment has contributed to a reduction in HIV incidence at the community level, in addition to its positive contribution to health at the individual level[1]. Reducing new infections among adolescents and young women, as well as other key populations such as sex workers and men who have sex with men, and injecting drug users and transgender people, are key to eliminating HIV infection and achieving the Joint United Nations Programme on HIV/Acquired Immune Deficiency Syndrome (UNAIDS) 95-95-95 targets by 2030[2].

As the life expectancy of PLWH approaches that of the general population, issues such as living without social exclusion, avoiding stigma and discrimination, and preventing comorbidities associated with aging, which were not priorities a few decades ago, can be addressed. Some authorities referred this as the fourth target, but not officially adopted by UNAIDS, to improve HIV health-related quality of life (HrQoL) by addressing comorbidities and other psychosocial challenges[3]. The desire to have children is one of the most important components of HrQoL.

The treatment concepts such as prevention based on ART (TasP) and pre-exposure prophylaxis (PrEP), which have emerged in the last decade, have resulted in very important innovations in pregnancy management about HIV and the approach to PLWH. TasP refers to the use of ART in decreasing transmission in PLWH. Undetectable=untransmittable (U=U) is defined as people with suppressed HIV viral loads who cannot transmit HIV sexually with effective treatment as a result of scientific evidence from TasP. Converely, PrEP involves the use of ART by HIV-uninfected individuals to reduce the risk of potential transmission through sexual intercourse. Accumulating evidence supports the key role of U=U and PrEP in decreasing HIV transmission and incidence[4]. Furthermore, provided the above conditions are met, HIV serodiscordant couples who want to have a child can have a safe sexual intercourse without using a condom in terms of the risk of HIV transmission[5].

When HIV infection is considered in women and reproductive health, historical evidence suggests that the risk of HIV transmission from an ART-naive HIV-positive pregnant woman to her baby is 25-30%, which increases by 5-20% with breastfeeding. This risk can be reduced by increasing the frequency of HIV diagnostic testing, starting treatment as early as possible, planning cesarean sections, and preventing breastfeeding[6]. Screening all pregnant women for HIV infection, providing sexual health information to HIV-positive women, and raising their awareness are critical for achieving the goal of eliminating HIV[7].

All this points to obstetricians as very important intermediaries for reaching and engaging with women. Therefore, they should acquire up-to-date HIV knowledge for them to make clinical decisions in pre-pregnancy counseling and follow-up of HIV-positive pregnant women. Furthermore, the fact that vertical transmission from mother to child is one of the most important routes of transmission following sexual intercourse, especially in developing countries, obstetricians are among the most critical physicians in ending the HIV epidemic. The low level of HIV knowledge among obstetricians negatively affects their management approach to pregnant women and HIV-positive pregnant women who want to become pregnant, and this contributes negatively to the stigma and discrimination faced by PLWH. In other words, obstetricians are one of the most important clinical specialties for HIV, following HIV specialists and infectious disease specialists, who are clinicians who provide primary HIV care, and thereby, the level of knowledge and awareness of these clinicians about HIV and HIV-positive pregnancy care should be increased.

This study aimed to determine the level of experience of obstetricians in Türkiye in following up HIV-positive pregnant women, their level of awareness of this issue, their level of knowledge, and their level of competence in the follow-up of HIV-positive pregnant women.

Materials and Methods

The study population consisted of obstetricians and obstetric assistants caring for pregnant women in Türkiye. A 54-item questionnaire was designed to assess obstetricians' and gynecologists' knowledge of HIV and pregnancy and their behaviors about the care of HIV-positive pregnant women. The questionnaires were administered both face-to-face in the hospitals where the doctors worked and as an online questionnaire that the doctors forwarded to their colleagues. Sample selection was made with "snowball sampling." In the study, different groupings were considered to determine differences in knowledge level at each category, as well as differences in secondary and tertiary care hospitals. After obtaining informed consent, a total of 133 participants were included in the study. This is a multicentre study conducted in both secondary and tertiary hospitals. Our questionnaire is a cross-sectional study consisting of four sections: "Questions to assess obstetricians' general attitudes toward following up HIV+pregnancies," "Questions to assess obstetricians' general knowledge of HIV," "Questions to assess obstetricians' general knowledge of U=U and PrEP," and "Questions to assess how obstetricians manage and treat HIV-positive pregnancies."

The questionnaire was conducted face-to-face and online by medical students. After the survey, results were evaluated separately by two infectious diseases and clinical microbiology specialists. The evaluating experts were blinded on the information about the participants. Furthermore, peer assessment was obtained when formulating the questions. It was not aimed to obtain any total or average score from the questionnaire used in the study. Furthermore, the questionnaire items were evaluated separately. Considering these situations, no analysis related to the validity-reliability processes was needed, and the items were evaluated as questionnaire questions.

Our questions were divided into four different groups. Questions in the first group allow us to assess the obstetricians' perspectives on HIV and PLWH in general. We tried to understand whether they followed up with HIV-positive pregnant women. If not, was this because of fear of HIV transmission or lack of knowledge or experience? We also tried to measure whether obstetricians had attended a scientific meeting or read an article on pregnancy with HIV and their level of interest in HIV (Table 1).

Table 1. Questions to assess obstetricians' general attitudes toward following up HIV+pregnancies

What is your level of knowledge regarding HIV/AIDS?		No	Little	Enough	Advanced	p-value
Total		3 (2.2%)	46 (34.6%)	**67 (50.4%)**	17 (12.8%)	
By hospital type	Secondary hospitals	3.1%	25.0%	**46.9%**	25.0%	0.099
	Tertiary hospitals	2.0%	37.6%	**51.5%**	8.9%	
By years of experience	0-5 years	4.0%	**47.3%**	41.9%	6.8%	**0.004**
	6-10 years	0.0%	**38.9%**	**38.9%**	22.2%	
	11-20 years	0.0%	15.4%	**65.4%**	19.2%	
	>20 years	0.0%	0.0%	**80.0%**	20.0%	
By types of professional degree	Residents	4.0%	**46.7%**	41.3%	8.0%	**0.008**
	Specialists	0.0%	22.7%	**56.8%**	20.5%	
	Academics	0.0%	7.1%	**78.6%**	14.3%	

Table 1. Continued

What is your level of knowledge regarding HIV/AIDS?		**No**	**Little**	**Enough**	**Advanced**		**p-value**
How confident are you in providing follow-up care for HIV-positive pregnancies?		**Unconfident**	**Partially confident**	**Totally confident**			**p-value**
Total		20 (15%)	**81 (60.9%)**	32 (24.1%)			
By hospital type	Secondary hospitals	9.3%	**71.9%**	18.8%			0.329
	Tertiary hospitals	16.9%	**57.4%**	25.7%			
By years of experience	0-5 years	13.5%	**55.4%**	31.1%			0.545
	6-10 years	16.7%	**72.2%**	11.1%			
	11-20 years	19.2%	**65.4%**	15.4%			
	>20 years	13.3%	**66.7%**	20.0%			
By types of professional degree	Residents	14.7%	**53.3%**	32.0%			0.065
	Specialists	11.4%	**75.0%**	13.6%			
	Academics	28.6%	**57.1%**	14.3%			
When did you last attend a talk, symposia, etc., about HIV and pregnancy and hear from an expert?		**Never**	**Within a year**	**Within 1-5 years**	**Within 6-10 years**	**>10 years**	**p-value**
Total		33 (24.8%)	17 (12.8%)	**45 (33.9%)**	24 (18%)	14 (10.5%)	
By hospital type	Secondary hospitals	15.6%	3.1%	31.3%	**34.4%**	15.6%	**0.021**
	Tertiary hospitals	27.7%	15.8%	**34.7%**	12.9%	8.9%	
By years of experience	0-5 years	**40.5%**	14.9%	36.5%	6.8%	1.3%	**0.001**
	6-10 years	0.0%	16.7%	**38.9%**	**38.9%**	5.5%	
	11-20 years	7.7%	11.5%	26.9%	**34.7%**	19.2%	
	>20 years	6.6%	0.0%	26.7%	20.0%	**46.7%**	
By types of professional degree	Residents	**40.0%**	16.0%	33.4%	9.3%	1.3%	**0.001**
	Specialists	6.8%	4.6%	**31.8%**	**31.8%**	25.0%	
	Academics	0.0%	21.4%	**42.9%**	21.4%	14.3%	
When did you last read an article or guideline about HIV and pregnancy?		**Never**	**Within a year**	**Within 1-5 years**	**Within 6-10 years**	**>10 years**	**p-value**
Total		34 (25.6%)	42 (31.6%)	37 (27.8%)	10 (7.5%)	10 (7.5%)	
By hospital type	Secondary hospitals	12.5%	25.0%	37.5%	6.2%	18.8%	**0.019**
	Tertiary hospitals	29.7%	33.7%	24.7%	7.9%	4.0%	
By years of experience	0-5 years	**41.9%**	28.4%	23.0%	6.7%	0.0%	**0.001**
	6-10 years	5.6%	33.3%	50.0%	11.1%	0.0%	
	11-20 years	7.7%	38.5%	19.2%	7.7%	26.9%	
	>20 years	0.0%	33.3%	40.0%	6.7%	20.0%	
By types of professional degree	Residents	**42.7%**	28.0%	21.3%	8.0%	0.0%	**0.001**
	Specialists	4.5%	25.0%	40.9%	9.1%	20.5%	
	Academics	0.0%	71.5%	21.4%	0.0%	7.1%	
Under what conditions do you provide follow-up care for HIV-positive pregnant women?		**I do not**	**With a multidisciplinary team of experts in my hospital**	**Consultation with specialists from other hospitals if required**	**I do not have experts to consult, I do it myself**		**p-value**
Total		33 (24.8%)	79 (59.4%)	13 (9.8%)	8 (6.0%)		

Table 1. Continued

What is your level of knowledge regarding HIV/AIDS?		**No**	**Little**	**Enough**	**Advanced**	**p-value**
By hospital type	Secondary hospitals	37.5%	28.1%	21.9%	12.5%	**0.001**
	Tertiary hospitals	20.8%	69.3%	5.9%	4.0%	
By years of experience	0-5 years	29.7%	63.5%	4.1%	2.7%	**0.13**
	6-10 years	16.7%	44.4%	16.7%	22.2%	
	11-20 years	26.9%	50.0%	15.4%	7.7%	
	>20 years	6.7%	73.3%	20.0%	0.0%	
By types of professional degree	Residents	28.0%	64.0%	4.0%	4.0%	0.013
	Specialists	27.3%	45.4%	15.9%	11.4%	
	Academics	0.0%	78.6%	21.4%	0.0%	
In comparison to normal pregnancies, what would be your approach to the follow-up of HIV-positive pregnant women?		**I follow-up with HIV-positive pregnant women as I would with HIV-negative pregnancies**	**I would definitely involve other specialties like infectious diseases and internal medicine and follow patients with a multidisciplinary team**	**If additional interventions such as assisted reproductive techniques are not available, I would refer the pregnant woman to a more advanced center**	**I would refer the patient to a more advanced hospital; I do not follow up with HIV-positive pregnant women**	**p-value**
Total		14 (10.5%)	**108 (81.2%)**	6 (4.5%)	5 (3.8%)	
By hospital type	Secondary hospitals	12.4%	**75.0%**	6.3%	6.3%	0.594
	Tertiary hospitals	9.9%	**83.2%**	4.0%	3.0%	
By years of experience	0-5 years	14.9%	**79.7%**	4.0%	1.4%	0.107
	6-10 years	5.6%	**94.4%**	0.0%	0.0%	
	11-20 years	3.8%	**73.1%**	11.6%	11.5%	
	>20 years	6.7%	**86.7%**	0.0%	6.6%	
By types of professional degree	Residents	14.7%	**81.3%**	2.7%	1.3%	0.076
	Specialists	4.6%	**81.8%**	4.5%	9.1%	
	Academics	7.1%	**78.6%**	14.3%	0.0%	
How many HIV-positive pregnant women have you seen to date?		**None**	**1-5**	**6-10**	**>10**	**p-value**
Total		46 (34.6%)	58 (43.6%)	21 (15.8%)	8 (6.0%)	
By hospital type	Secondary hospitals	34.4%	46.9%	15.6%	3.1%	0.876
	Tertiary hospitals	34.7%	42.6%	15.8%	6.9%	
By years of experience	0-5 years	44.6%	35.1%	16.2%	4.1%	0.059
	6-10 years	27.8%	55.5%	11.1%	5.6%	
	11-20 years	15.4%	65.4%	15.4%	3.8%	
	>20 years	26.7%	33.3%	20.0%	20.0%	
By types of professional degree	Residents	45.4%	33.3%	16.0%	5.3%	**0.004**
	Specialists	27.3%	54.5%	15.9%	2.3%	
	Academics	0.0%	64.3%	14.3%	21.4%	

Table 1. Continued

What is your level of knowledge regarding HIV/AIDS?		**No**	**Little**	**Enough**	**Advanced**	**p-value**
How does caring for HIV-positive pregnant women make you feel as a doctor?		**I have no idea because I do not follow them up**	**I feel very comfortable, just like an HIV-negative pregnant woman**	**I feel worried that I might lack the skills to manage the patient**	**I feel worried about myself, whether I will get HIV**	**p-value**
Total		40 (30.1%)	46 (34.6%)	34 (25.5%)	13 (9.8%)	
By hospital type	Secondary hospitals	21.9%	46.9%	18.7%	12.5%	0.276
	Tertiary hospitals	32.7%	30.7%	27.7%	8.9%	
By years of experience	0-5 years	40.5%	18.9%	33.8%	6.8%	**0.001**
	6-10 years	22.2%	44.4%	22.2%	11.2%	
	11-20 years	15.4%	50.0%	15.4%	19.2%	
	>20 years	13.3%	73.3%	6.7%	6.7%	
By types of professional degree	Residents	42.7%	18.7%	32.0%	6.6%	**0.001**
	Specialists	18.2%	45.5%	20.4%	15.9%	
	Academics	0.0%	85.7%	7.2%	7.1%	
How many HIV-positive deliveries have you had to date?		**None**	**1-5**	**6-10**	**>10**	**p-value**
Total		55 (41.4%)	59 (44.4%)	14 (10.4%)	5 (3.8%)	
By hospital type	Secondary hospitals	25.0%	59.4%	15.6%	0.0%	0.061
	Tertiary hospitals	46.5%	39.6%	8.9%	5.0%	
By years of experience	0-5 years	62.2%	27.0%	8.1%	2.7%	**0.001**
	6-10 years	5.6%	77.8%	11.1%	5.5%	
	11-20 years	19.2%	69.2%	11.6%	0.0%	
	>20 years	20.0%	46.7%	20.0%	13.3%	
By types of professional degree	Residents	61.3%	26.7%	8.0%	4.0%	**0.001**
	Specialists	15.9%	68.2%	13.6%	2.3%	
	Academics	14.3%	64.3%	14.3%	7.1%	
What kind of problems do you experience during the follow-up of HIV-positive pregnancies and the delivery?		**I have no idea because I do not follow them up**	**I do not experience any problems**	**I am experiencing both medical and administrative difficulties**		**p-value**
Total		41 (30.8%)	**67 (50.4%)**	25 (18.8%)		
By hospital type	Secondary hospitals	28.1%	**40.6%**	31.3%		0.112
	Tertiary hospitals	31.6%	**53.5%**	14.9%		
By years of experience	0-5 years	41.9%	**43.2%**	14.9%		**0.004**
	6-10 years	22.2%	**50.0%**	27.8%		
	11-20 years	11.5%	**53.8%**	34.7%		
	>20 years	20.0%	**80.0%**	0.0%		
By types of professional degree	Residents	42.7%	**42.7%**	14.6%		**0.002**
	Specialists	20.4%	**52.3%**	27.3%		
	Academics	0.0%	**85.7%**	14.3%		

HIV/AIDS: Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

The second set of questions consisted of general information about HIV. It aimed to measure the general knowledge level regarding screening, diagnosis, clinic, transmission, and treatment of HIV infection (Table 2). The third set of questions aimed to measure the level of knowledge about U=U and PrEP, whereas the fourth set of questions consisted of questions about approaching HIV-positive pregnant women and HIV-positive pregnancy management (Tables 3 and 4). Ethics committee approval was graded by University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee (approval number: 27/33, dated: 30.12.2022). The consent form was filled out by all participants.

Table 2. Questions to assess obstetricians' general knowledge of HIV

HIV testing should be routinely included in antenatal screening		**Agree**	**Disagree**
Total		**129 (97.0%)**	4 (3.0%)
By hospital type	Secondary hospital	**96.9%**	3.1%
	Tertiary hospital	**97.0%**	3.0%
By years of experience	0-5 years	**95.9%**	4.1%
	6-10 years	**94.4%**	5.6%
	11-20 years	**100.0%**	0.0%
	>20 years	**100.0%**	0.0%
By types of professional degree	Residents	**96.0%**	4.0%
	Specialists	**97.7%**	2.3%
	Academics	**100.0%**	0.0%
I perform an HIV test at my first antenatal visit; there is no need for a repeat test later in pregnancy		**Agree**	**Disagree**
Total		44 (33.1%)	**89 (66.9%)**
By hospital type	Secondary hospital	37.5%	**62.5%**
	Tertiary hospital	31.7%	**68.3%**
By years of experience	0-5 years	32.4%	**67.6%**
	6-10 years	27.8%	**72.2%**
	11-20 years	**50.0%**	**50.0%**
	>20 years	13.3%	**86.7%**
By types of professional degree	Residents	33.3%	**66.7%**
	Specialists	27.3%	**72.7%**
	Academics	**50.0%**	**50.0%**
I perform an anti-HIV test at the first pregnancy visit and repeat it in the last trimester		**Agree**	**Disagree**
Total		**100 (75.2%)**	33 (24.8%)
By hospital type	Secondary hospital	**81.2%**	18.8%
	Tertiary hospital	**73.3%**	26.7%
By years of experience	0-5 years	**73.0%**	27.0%
	6-10 years	**77.8%**	22.2%
	11-20 years	**65.4%**	34.6%
	>20 years	**100.0%**	0.0%
By types of professional degree	Residents	**74.7%**	25.3%
	Specialists	**79.5%**	20.5%
	Academics	**64.3%**	35.7%
HIV is a sexually transmitted viral infection		**Agree**	**Disagree**
Total		**125 (94.0)**	8 (6.0%)
By hospital type	Secondary hospital	**87.5%**	12.5%
	Tertiary hospital	**96.0%**	4.0%

Table 2. Continued

HIV testing should be routinely included in antenatal screening		**Agree**	**Disagree**
By years of experience	0-5 years	**97.3%**	2.7%
	6-10 years	**94.4%**	5.6%
	11-20 years	**88.5%**	11.5%
	>20 years	**86.7%**	13.3%
By types of professional degree	Residents	**97.3%**	2.7%
	Specialists	**88.6%**	11.4%
	Academics	**92.9%**	7.1%
HIV causes opportunistic infections within weeks to months because it rapidly destroys the immune system		**Agree**	**Disagree**
Total		**69 (51.9%)**	64 (48.1%)
By hospital type	Secondary hospital	**56.2%**	43.8%
	Tertiary hospital	**50.5%**	49.5%
By years of experience	0-5 years	**58.1%**	41.9%
	6-10 years	**50.0%**	**50.0%**
	11-20 years	34.6%	**65.4%**
	>20 years	**53.3%**	46.7%
By types of professional degree	Residents	**58.7%**	41.3%
	Specialists	47.7%	**52.3%**
	Academics	28.6%	**71.4%**
HIV can be asymptomatic for many years after infection		**Agree**	**Disagree**
Total		**128 (96.2%)**	5 (3.8%)
By hospital type	Secondary hospital	**100.0%**	0.0%
	Tertiary hospital	**95.0%**	5.0%
By years of experience	0-5 years	**93.2%**	6.8%
	6-10 years	**100.0%**	0.0%
	11-20 years	**100.0%**	0.0%
	>20 years	**100.0%**	0.0%
By types of professional degree	Residents	**93.3%**	6.7%
	Specialists	**100.0%**	0.0%
	Academics	**100.0%**	0.0%
HIV can be transmitted from an HIV-positive mother to her baby during pregnancy and childbirth		**Agree**	**Disagree**
Total		**128 (96.2%)**	5 (3.8%)
By hospital type	Secondary hospital	**96.9%**	3.1%
	Tertiary hospital	**96.0%**	4.0%
By years of experience	0-5 years	**94.6%**	5.4%
	6-10 years	**100.0%**	0.0%
	11-20 years	**96.2%**	3.8%
	>20 years	**100.0%**	0.0%
By types of professional degree	Residents	**96.0%**	4.0%
	Specialists	**95.5%**	4.5%
	Academics	**100.0%**	0.0%

Table 2. Continued

HIV testing should be routinely included in antenatal screening		**Agree**	**Disagree**
Hugging, eating in the same place, and using a shared pool or toilet can all transmit HIV		**Agree**	**Disagree**
Total		11 (8.3%)	**122 (91.7%)**
By hospital type	Secondary hospital	9.4%	**90.6%**
	Tertiary hospital	7.9%	**92.1%**
By years of experience	0-5 years	10.8%	**89.2%**
	6-10 years	0.0%	**100.0%**
	11-20 years	11.5%	**88.5%**
	>20 years	0.0%	**100.0%**
By types of professional degree	Residents	10.7%	**89.3%**
	Specialists	4.5%	**95.5%**
	Academics	7.1%	**92.9%**
HIV is an infection that keeps progressing despite treatment and can lead to death		**Agree**	**Disagree**
Total		66 (49.6%)	**67 (50.4%)**
By hospital type	Secondary hospital	46.9%	**53.1%**
	Tertiary hospital	**50.5%**	49.5%
By years of experience	0-5 years	**60.8%**	39.2%
	6-10 years	38.9%	**61.1%**
	11-20 years	42.3%	**57.7%**
	>20 years	20.0%	**80.0%**
By types of professional degree	Residents	**61.3%**	38.7%
	Specialists	43.2%	**56.8%**
	Academics	7.1%	**92.9%**
Although there is no cure for HIV, treatment can stop its progression		**Agree**	**Disagree**
Total		**128 (96.2%)**	5 (3.8%)
By hospital type	Secondary hospital	**96.9%**	3.1%
	Tertiary hospital	**96.0%**	4.0%
By years of experience	0-5 years	**93.2%**	6.8%
	6-10 years	**100.0%**	0.0%
	11-20 years	**100.0%**	0.0%
	>20 years	**100.0%**	0.0%
By types of professional degree	Residents	**93.3%**	6.7%
	Specialists	**100.0%**	0.0%
	Academics	**100.0%**	0.0%
With effective treatment, people with HIV have almost the same life expectancy as the general population		**Agree**	**Disagree**
Total		**112 (84.2%)**	21 (15.8%)
By hospital type	Secondary hospital	**81.3%**	18.8%
	Tertiary hospital	**85.1%**	14.9%
By years of experience	0-5 years	**85.1%**	14.9%
	6-10 years	**77.8%**	22.2%
	11-20 years	**80.8%**	19.2%
	>20 years	**93.3%**	6.7%

Table 2. Continued

HIV testing should be routinely included in antenatal screening		**Agree**	**Disagree**
By types of professional degree	Residents	**84.0%**	16.0%
	Specialists	**84.1%**	15.9%
	Academics	**85.7%**	14.3%
HIV/AIDS is a disease that can be cured with medicines that are available today		**Agree**	**Disagree**
Total		19 (14.3%)	**114 (85.7%)**
By hospital type	Secondary hospital	18.8%	**81.3%**
	Tertiary hospital	12.9%	**87.1%**
By years of experience	0-5 years	8.1%	**91.9%**
	6-10 years	16.7%	**83.3%**
	11-20 years	15.4%	**84.6%**
	>20 years	40.0%	**60.0%**
By types of professional degree	Residents	8.0%	**92.0%**
	Specialists	27.3%	**72.7%**
	Academics	7.1%	**92.9%**
HIV medicines should never be used during pregnancy, as they can be toxic/ teratogenic to the baby		**Agree**	**Disagree**
Total		25 (18.8%)	**108 (81.2%)**
By hospital type	Secondary hospital	12.5%	**87.5%**
	Tertiary hospital	20.8%	**79.2%**
By years of experience	0-5 years	28.4%	**71.6%**
	6-10 years	0.0%	**100.0%**
	11-20 years	3.8%	**96.2%**
	>20 years	20.0%	**80.0%**
By types of professional degree	Residents	26.7%	**73.3%**
	Specialists	11.4%	**88.6%**
	Academics	0.0%	**100.0%**
HIV can be transmitted to the baby through breastfeeding		**Agree**	**Disagree**
Total		**109 (82.0%)**	24 (18.0%)
By hospital type	Secondary hospital	**78.1%**	21.9%
	Tertiary hospital	**83.2%**	16.8%
By years of experience	0-5 years	**83.8%**	16.2%
	6-10 years	**77.8%**	22.2%
	11-20 years	**76.9%**	23.1%
	>20 years	**86.7%**	13.3%
By types of professional degree	Residents	**84.0%**	16.0%
	Specialists	**79.5%**	20.5%
	Academics	**78.6%**	21.4%

HIV: Human İmmunodeficiency Virus

Statistical Analysis

Data were analysed using IBM SPSS 25 (IBM Corp. 2017 IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.) software package programme. The frequency and percentage values were presented for qualitative variables. The chi-square test was used for comparisons between the two qualitative variables. The type I error rate was taken as 0.05 in the study.

The number of observations to be included in the sample was calculated using the formula: $n = \frac{\varepsilon_\alpha^2 . P . Q}{d^2}$. Based on the result of the calculations, 97 observations should be included in the sample *(p = 0.5; q = 0.5; d = 0.10; α = 0.05)*[8].

Table 3. Questions to assess obstetricians' general knowledge of U=U and PrEP

Have you ever heard of U=U or B=B (in Turkish)?		**No**	**Yes, but I have no idea**	**Yes, and I have some knowledge**
Total		**99 (74.4%)**	29 (21.8%)	5 (3.8)
By hospital type	Secondary hospitals	**65.6%**	31.3%	3.1%
	Tertiary hospitals	**77.2%**	18.8%	4.0%
By years of experience	0-5 years	**83.8%**	12.2%	4.1%
	6-10 years	**61.1%**	33.3%	5.6%
	11-20 years	**69.2%**	30.8%	0.0%
	>20 years	**53.3%**	40.0%	6.7%
By types of professional degree	Residents	**82.7%**	13.3%	4.0%
	Specialists	**70.5%**	25.0%	4.5%
	Academics	42.9%	**57.1%**	0.0%
If people living with HIV take their treatment regularly and achieve viral suppression (effective treatment), even unprotected sex will not lead to HIV transmission		**Agree**	**Disagree**	**No idea**
Total		33 (24.8)	46 (34.6%)	**54 (40.6)**
By hospital type	Secondary hospitals	21.9%	37.5%	**40.6%**
	Tertiary hospitals	25.7%	33.7%	**40.6%**
By years of experience	0-5 years	20.3%	**40.5%**	39.2%
	6-10 years	38.9%	16.7%	**44.4%**
	11-20 years	30.8%	30.8%	**38.5%**
	>20 years	20.0%	33.3%	**46.7%**
By types of professional degree	Residents	22.7%	37.3%	**40.0%**
	Specialists	22.7%	29.5%	**47.8%**
	Academics	**42.9%**	35.7%	21.4%
If one of the partners who wants to have children is HIV-positive, unprotected sex may be allowed without further counseling if the partner is on effective HIV treatment		**Agree**	**Disagree**	**No idea**
Total		24 (18%)	66 (49.6%)	43 (32.3%)
By hospital type	Secondary hospitals	21.9%	**46.9%**	31.2%
	Tertiary hospitals	16.8%	**50.5%**	32.7%
By years of experience	0-5 years	18.9%	**52.7%**	28.4%
	6-10 years	16.7%	38.9%	**44.4%**
	11-20 years	15.4%	**50.0%**	34.6%
	>20 years	20.0%	**46.7%**	33.3%
By types of professional degree	Residents	20.0%	**50.7%**	29.3%
	Specialists	13.6%	**45.5%**	40.9%
	Academics	21.4%	**57.2%**	21.4%
Even if it is accepted that people living with HIV on effective treatment do not transmit HIV, this does not convince me that other assisted reproductive techniques, such as sperm washing and intrauterine insemination, need not be used		**Agree**	**Disagree**	**No idea**
Total		**54 (40.6%)**	36 (27.1%)	43 (32.3%)
By hospital type	Secondary hospitals	**59.3%**	18.8%	21.9%
	Tertiary hospitals	34.7%	29.7%	**35.6%**
By years of experience	0-5 years	**36.5%**	27.0%	**36.5%**
	6-10 years	**38.9%**	22.2%	**38.9%**
	11-20 years	**50.0%**	26.9%	23.1%
	>20 years	**46.7%**	33.3%	20.0%

Table 3. Continued

Have you ever heard of U=U or B=B (in Turkish)?		**No**	**Yes, but I have no idea**	**Yes, and I have some knowledge**
By types of professional degree	Residents	**38.7%**	26.7%	34.7%
	Specialists	**38.6%**	25.0%	36.4%
	Academics	**57.1%**	35.7%	7.1%
Have you heard of PrEP?		**No**	**Yes, but I have no idea**	**Yes, and I have some knowledge**
Total		25 (18.8%)	**83 (62.4%)**	25 (18.8%)
By hospital type	Secondary hospitals	9.4%	**81.2%**	9.4%
	Tertiary hospitals	21.8%	**56.4%**	21.8%
By years of experience	0-5 years	18.9%	**64.9%**	16.2%
	6-10 years	22.2%	**61.1%**	16.7%
	11-20 years	15.4%	**61.5%**	23.1%
	>20 years	20.0%	**53.3%**	26.7%
By types of professional degree	Residents	21.3%	**62.7%**	16.0%
	Specialists	18.2%	**65.9%**	15.9%
	Academics	7.1%	**50.0%**	42.9%
PrEP is the use of certain HIV medicines to prevent the spread of HIV in high-risk groups, such as people who have an HIV-positive sex partner, people who have multiple sex partners, or people who inject drugs		**Agree**	**Disagree**	**No idea**
Total		**85 (63.9%)**	6 (4.5%)	42 (31.6%)
By hospital type	Secondary hospitals	**78.1%**	6.3%	15.6%
	Tertiary hospitals	**59.4%**	4.0%	36.6%
By years of experience	0-5 years	**59.5%**	1.4%	39.1%
	6-10 years	**72.2%**	0.0%	27.8%
	11-20 years	**65.4%**	11.5%	23.1%
	>20 years	**73.3%**	13.3%	13.4%
By types of professional degree	Residents	**58.7%**	1.3%	40.0%
	Specialists	**63.6%**	11.4%	25.0%
	Academics	**92.9%**	0.0%	7.1%
The idea that drugs that are used to treat HIV can be used by healthy people for prevention seems to me to be unnecessary/ absurd		**Agree**	**Disagree**	**No idea**
Total		25 (18.8%)	**80 (60.2%)**	28 (21.0%)
By hospital type	Secondary hospitals	15.6%	**62.5%**	21.9%
	Tertiary hospitals	19.8%	**59.4%**	20.8%
By years of experience	0-5 years	20.3%	**58.1%**	21.6%
	6-10 years	22.2%	**72.2%**	5.6%
	11-20 years	11.5%	**65.4%**	23.1%
	>20 years	20.0%	**46.7%**	33.3%
By types of professional degree	Residents	21.3%	**58.7%**	20.0%
	Specialists	18.2%	**59.1%**	22.7%
	Academics	7.1%	**71.5%**	21.4%
PrEP use should also be recommended for pregnant women at risk of HIV transmission		**Agree**	**Disagree**	**No idea**
Total		**61 (45.9%)**	18 (13.5%)	54 (40.6%)
By hospital type	Secondary hospitals	37.5%	21.9%	**40.6%**
	Tertiary hospitals	**48.5%**	10.9%	40.6%

Table 3. Continued

Have you ever heard of U=U or B=B (in Turkish)?		**No**	**Yes, but I have no idea**	**Yes, and I have some knowledge**
By years of experience	0-5 years	39.2%	14.9%	**45.9%**
	6-10 years	**61.1%**	11.1%	27.8%
	11-20 years	**46.2%**	7.6%	**46.2%**
	>20 years	**60.0%**	20.0%	20.0%
By types of professional degree	Residents	**42.7%**	14.6%	**42.7%**
	Specialists	**47.7%**	15.9%	36.4%
	Academics	**57.1%**	0.0%	42.9%
The use of PrEP medicines during pregnancy is risky for the mother and baby		**Agree**	**Disagree**	**No idea**
Total		12 (9.0%)	40 (30.1)	**81 (60.9%)**
By hospital type	Secondary hospitals	15.6%	34.4%	**50.0%**
	Tertiary hospitals	6.9%	28.7%	**64.4%**
By years of experience	0-5 years	9.5%	21.6%	**68.9%**
	6-10 years	5.6%	33.3%	**61.1%**
	11-20 years	7.7%	42.3%	**50.0%**
	>20 years	13.3%	**46.7%**	40.0%
By types of professional degree	Residents	9.3%	21.3%	**69.4%**
	Specialists	11.4%	34.1%	**54.5%**
	Academics	0.0%	**64.3%**	35.7%
"If one of the partners is HIV-positive but on effective ART, unprotected sex can be allowed without any additional recommendation" does not seem sufficient and safe to me. In this case, PrEP seems to be an appropriate method as an additional protective measure for my patients		**Agree**	**Disagree**	**No idea**
Total		**59 (44.4%)**	20 (15.0%)	54 (40.6%)
By hospital type	Secondary hospitals	**50.0%**	21.9%	28.1%
	Tertiary hospitals	42.6%	12.9%	**44.5%**
By years of experience	0-5 years	36.5%	13.5%	**50.0%**
	6-10 years	**61.1%**	11.1%	27.8%
	11-20 years	**53.8%**	15.4%	30.8%
	>20 years	**46.6%**	26.7%	26.7%
By types of professional degree	Residents	40.0%	13.3%	**46.7%**
	Specialists	**43.2%**	20.4%	36.4%
	Academics	**71.5%**	7.1%	21.4%
If one of the partners is HIV-positive but on effective ART and the healthy partner is on PrEP, these partners can conceive through normal sexual intercourse without taking any additional protection		**Agree**	**Disagree**	**No idea**
Total		**49 (36.8%)**	41 (30.8%)	43 (32.4%)
By hospital type	Secondary hospitals	**40.6%**	28.1%	31.3%
	Tertiary hospitals	**35.6%**	31.7%	32.7%
By years of experience	0-5 years	**33.8%**	32.4%	**33.8%**
	6-10 years	**38.9%**	**38.9%**	22.2%
	11-20 years	**42.3%**	19.2%	38.5%
	>20 years	**40.0%**	33.3%	26.7%
By types of professional degree	Residents	33.3%	**36.0%**	30.7%
	Specialists	34.1%	25.0%	**40.9%**
	Academics	**64.3%**	21.4%	14.3%

U=U: Undetectable=untransmittable, B=B: Being safe=being sure, HIV: Human Immunodeficiency Virus, ART: Antiretroviral therapy, PrEP: Pre-exposure prophylaxis

Table 4. Questions to assess how obstetricians manage and treat HIV-positive pregnancies

If the female partner is HIV-positive and the male partner is negative, and provided she is on ART, the use of assisted reproductive techniques with semen from the male partner during the periovulatory period is a good option that I can recommend to my patients		**Agree**	**Disagree**	**No idea**
Total		**83 (62.4%)**	5 (3.8%)	45 (33.8%)
By hospital type	Secondary hospital	**78.1%**	3.1%	18.8%
	Tertiary hospital	**57.4%**	4.0%	38.6%
By years of experience	0-5 years	**50.0%**	4.1%	45.9%
	6-10 years	**83.3%**	5.6%	11.1%
	11-20 years	**73.1%**	0.0%	26.9%
	>20 years	**80.0%**	6.7%	13.3%
By types of professional degree	Residents	**50.7%**	4.0%	45.3%
	Specialists	**72.8%**	4.5%	22.7%
	Academics	**92.9%**	0.0%	7.1%
Even if the HIV-positive female partner is already on active ART and the male partner is on PrEP, I would definitely refer this couple to a clinic that offers assisted reproductive techniques		**Agree**	**Disagree**	**No idea**
Total		**64 (48.1%)**	23 (17.3%)	46 (34.6%)
By hospital type	Secondary hospital	**56.2%**	18.8%	25.0%
	Tertiary hospital	**45.5%**	16.9%	37.6%
By years of experience	0-5 years	36.5%	16.2%	**47.3%**
	6-10 years	**77.8%**	16.6%	5.6%
	11-20 years	**57.7%**	15.4%	26.9%
	>20 years	**53.3%**	26.7%	20.0%
By types of professional degree	Residents	40.0%	16.0%	**44.0%**
	Specialists	**52.3%**	20.4%	27.3%
	Academics	**78.6%**	14.3%	7.1%
The use of sperm preparation techniques (sperm washing followed by testing of the sample for HIV-RNA, intrauterine insemination, in vitro intracytoplasmic sperm injection) is no longer routinely recommended when the male partner is HIV-positive but on active ART and the woman has the opportunity to use PrEP		**Agree**	**Disagree**	**No idea**
Total		21 (15.8%)	31 (23.3%)	**81 (60.9%)**
By hospital type	Secondary hospitals	18.7%	25.0%	**56.3%**
	Tertiary hospitals	14.8%	22.8%	**62.4%**
By years of experience	0-5 years	12.2%	16.2%	**71.6%**
	6-10 years	27.8%	27.8%	**44.4%**
	11-20 years	3.8%	46.2%	**50.0%**
	>20 years	40.0%	13.3%	**46.7%**
By types of professional degree	Residents	12.0%	17.3%	**70.7%**
	Specialists	22.7%	20.5%	**56.8%**
	Academics	14.3%	**64.3%**	21.4%
Under no circumstances will I allow an HIV-positive pregnant woman for normal vaginal delivery		**Agree**	**Disagree**	**No idea**
Total		43 (32.3%)	**68 (51.1%)**	22 (16.6%)
By hospital type	Secondary hospitals	28.1%	**46.9%**	25.0%
	Tertiary hospitals	33.7%	**52.4%**	13.9%
By years of experience	0-5 years	33.8%	**45.9%**	20.3%
	6-10 years	27.8%	**66.7%**	5.5%
	11-20 years	34.6%	**50.0%**	15.4%
	>20 years	26.7%	**60.0%**	13.3%
By types of professional degree	Residents	34.7%	**48.0%**	17.3%
	Specialists	34.1%	**50.0%**	15.9%
	Academics	14.3%	**71.4%**	14.3%

Table 4. Continued

A pregnant woman who is newly diagnosed with HIV close to delivery should definitely be advised for a cesarean section		**Agree**	**Disagree**	**No idea**
Total		**78 (58.6%)**	36 (27.1%)	19 (14.3%)
By hospital type	Secondary hospitals	**65.6%**	18.8%	15.6%
	Tertiary hospitals	**56.4%**	29.7%	13.9%
By years of experience	0-5 years	**51.4%**	28.4%	20.2%
	6-10 years	**72.2%**	16.7%	11.1%
	11-20 years	**61.5%**	30.8%	7.7%
	>20 years	**73.3%**	26.7%	0.0%
By types of professional degree	Residents	**50.7%**	29.3%	20.0%
	Specialists	**72.7%**	18.2%	9.1%
	Academics	**57.1%**	42.9%	0.0%
There is no medical indication for cesarean delivery of an HIV-positive pregnant woman on active ART		**Agree**	**Disagree**	**No idea**
Total		**51 (38.3%)**	**51 (38.3%)**	31 (23.4%)
By hospital type	Secondary hospitals	37.5%	**40.6%**	21.9%
	Tertiary hospitals	**38.6%**	37.6%	23.8%
By years of experience	0-5 years	31.1%	**37.8%**	31.1%
	6-10 years	38.9%	**44.4%**	16.7%
	11-20 years	**46.2%**	38.5%	15.4%
	>20 years	**60.0%**	33.3%	6.7%
By types of professional degree	Residents	32.0%	**37.3%**	30.7%
	Specialists	**45.5%**	36.4%	18.1%
	Academics	**50.0%**	**50.0%**	0.0%

My main reason not to admit an HIV-positive pregnant woman to normal delivery even if she is on ART is.		**To prevent HIV transmission to the baby**	**The higher risk of HIV transmission to health personnel who deliver the baby**	**Both**	**No idea**
Total		42 (31.6%)	19 (14.3%)	**58 (43.6%)**	14 (10.5%)
By hospital type	Secondary hospitals	21.9%	21.9%	**53.1%**	3.1%
	Tertiary hospitals	34.6%	11.9%	**40.6%**	12.9%
By years of experience	0-5 years	25.7%	12.1%	**47.3%**	14.9%
	6-10 years	44.4%	5.6%	**50.0%**	0.0%
	11-20 years	30.8%	26.9%	**34.6%**	7.7%
	>20 years	**46.7%**	13.3%	33.3%	6.7%
By types of professional degree	Residents	26.7%	10.6%	**48.0%**	14.7%
	Specialists	36.4%	18.2%	**40.9%**	4.5%
	Academics	**42.9%**	21.4%	28.6%	7.1%

Zidovudine is a drug used to treat HIV and is used as a prophylaxis to prevent HIV transmission to the baby during labor		**Agree**	**Disagree**	**No idea**
Total		**97 (72.9%)**	7 (5.3%)	29 (21.8%)
By hospital type	Secondary hospitals	**71.9%**	12.5%	15.6%
	Tertiary hospitals	**73.2%**	3.0%	23.8%
By years of experience	0-5 years	**67.6%**	4.0%	28.4%
	6-10 years	**94.4%**	5.6%	0.0%
	11-20 years	**65.4%**	11.5%	23.1%
	>20 years	**86.7%**	0.0%	13.3%
By types of professional degree	Residents	**68.0%**	4.0%	28.0%
	Specialists	**75.0%**	9.1%	15.9%
	Academics	**92.9%**	0.0%	7.1%

Table 4. Continued

Zidovudine prophylaxis should be administered to an HIV-positive pregnant woman during labor under all circumstances		**Agree**	**Disagree**	**No idea**
Total		**82 (61.7%)**	18 (13.5%)	33 (24.8%)
By hospital type	Secondary hospitals	**59.4%**	25.0%	15.6%
	Tertiary hospitals	**62.4%**	9.9%	27.7%
By years of experience	0-5 years	**60.8%**	6.8%	32.4%
	6-10 years	**72.2%**	16.7%	11.1%
	11-20 years	**57.7%**	26.9%	15.4%
	>20 years	**60.0%**	20.0%	20.0%
By types of professional degree	Residents	**61.3%**	6.7%	32.0%
	Specialists	**59.1%**	20.5%	20.4%
	Academics	**71.4%**	28.6%	0.0%
There is no medical indication for IV zidovudine during labor in an HIV-positive pregnant woman who is on active ART		**Agree**	**Disagree**	**No idea**
Total		20 (15.0%)	**60 (45.1%)**	53 (39.9%)
By hospital type	Secondary hospitals	15.6%	**50.0%**	34.4%
	Tertiary hospitals	14.8%	**43.6%**	41.6%
By years of experience	0-5 years	10.8%	43.2%	**46.0%**
	6-10 years	22.2%	**61.1%**	16.7%
	11-20 years	15.4%	**53.8%**	30.8%
	>20 years	26.7%	20.0%	**53.3%**
By types of professional degree	Residents	12.0%	**44.0%**	**44.0%**
	Specialists	18.2%	**40.9%**	**40.9%**
	Academics	21.4%	**64.3%**	14.3%
In case of suspected HIV infection during labor or breastfeeding, breastfeeding should be stopped immediately and should not be resumed if the infection is confirmed		**Agree**	**Disagree**	**No idea**
Total		**92 (69.2%)**	21 (15.8%)	20 (15.0%)
By hospital type	Secondary hospitals	**65.6%**	18.8%	15.6%
	Tertiary hospitals	**70.2%**	14.9%	14.9%
By years of experience	0-5 years	**73.0%**	12.2%	14.8%
	6-10 years	**77.8%**	22.2%	0.0%
	11-20 years	**53.8%**	19.2%	27.0%
	>20 years	**66.7%**	20.0%	13.3%
By types of professional degree	Residents	**73.3%**	12.0%	14.7%
	Specialists	**63.6%**	20.5%	15.9%
	Academics	**64.3%**	21.4%	14.3%
Pregnant women with HIV-positive who are on active ART should not breastfeed their baby after delivery		**Agree**	**Disagree**	**No idea**
Total		35 (26.3%)	**64 (48.1%)**	34 (25.6%)
By hospital type	Secondary hospitals	34.4%	**37.5%**	28.1%
	Tertiary hospitals	23.8%	**51.5%**	24.7%
By years of experience	0-5 years	17.6%	**54.1%**	28.3%
	6-10 years	38.9%	**44.4%**	16.7%
	11-20 years	**34.6%**	**34.6%**	30.8%
	>20 years	40.0%	**46.7%**	13.3%
By types of professional degree	Residents	18.7%	**52.0%**	29.3%
	Specialists	29.6%	**47.7%**	22.7%
	Academics	**57.1%**	28.6%	14.3%

HIV: Human Immunodeficiency Virus, ART: Antiretroviral therapy, PrEP: Pre-exposure prophylaxis, IV: Intravenous

The p-value was presented in comparisons made in the research. It is not understood which variable or variables belong to the confidence intervals to be presented. The study did not aim to determine a risk coefficient or investigate factors affecting the level of information. In addition, the presentation of the effect size as a result of the chi-square test was not needed for these reasons.

Results

A total of 133 obstetricians and obstetric residents, comprising 90 (67%) females and 101 (75.9%) who worked in a tertiary care hospital, responded to our questionnaire. The respondents included 15 (11.3%) academic members, 43 (32.3%) specialists, and 75 (56.4%) residents.

Obstetricians reported that their level of knowledge about HIV and competence in HIV care was low or average that they had not recently been involved in scientific activities associated with HIV, and that they did not have a good command of the up-to-date literature. The survey results also reveal that obstetricians either do not follow up HIV-positive pregnancies at all or have limited experience of doing so (Table 1).

A significant proportion of those surveyed felt that they did not know (2.2%) or knew little (34.6%) about HIV/AIDS. Participants in their first 5 years (47.3%) and 6 to 10 years (38.9%) of practice and/or residency (46.7%) described their level of knowledge as lower, whereas those with more years of experience reported having more adequate knowledge (p=0.004). The proportion of those who felt competent to follow up with HIV-positive pregnant women was low (24.1%), and this did not differ by years of experience or other subgroups.

A significant proportion of obstetricians with <5 years of experience (40.5%, p=0.001) and/or residents (40%, p=0.001) reported they had never attended a scientific meeting on HIV and had never read a guideline or article, whereas 71.5% (p=0.001*)* of academic members stated they had read an article or guideline within a year.

A third to a quarter of the residents, specialist obstetricians, and those working in secondary care hospitals stated that they had never followed up an HIV-positive pregnant woman. The vast majority of obstetricians responded to the question "Compared to normal pregnancies, how would you approach the management of HIV-positive pregnant women?" with "I would definitely involve other specialties such as infectious diseases, internal medicine, and manage patients with a multidisciplinary team."

Although 34.6% of respondents had never followed up an HIV-positive pregnancy, 43.6% reported having followed up one to five HIV-positive pregnancies. All academic staff had followed up at least one HIV-positive pregnancy, 21.4% of whom had followed up >10 HIV-positive pregnancies.

Of the participants, 34.6% reported they felt very comfortable, as they do in HIV-negative pregnancies, whereas the rest stated they felt worried about contracting HIV or managing the pregnancy, and 30.1% of participants had no idea because they did not follow HIV-positive pregnant. Of those surveyed, 50.4% reported that they did not experience any problems with HIV-positive pregnancies, whereas 18.8% reported having experienced both medical and administrative difficulties.

Although 41.4% of the survey participants had never helped an HIV-positive woman give birth before, this rate was highest among residents at 61.3% (p=0.001), and 44.4% of participants reported having delivered only 1-5 deliveries (Table 1).

Although obstetricians' general knowledge on HIV is at an adequate level, it has been shown that they have incomplete or conflicting knowledge about HIV screening during pregnancy, the disease course, and how it is transmitted (Table 2).

Of the obstetricians surveyed, 97% agreed that HIV testing should be routinely included in antenatal screening. Among them, 33.1% agreed that an HIV test should be performed at the first antenatal visit and that the test need not be repeated later in the pregnancy. However, 75.2% reported performing an HIV test at the first antenatal visit and repeating it in the last trimester of the pregnancy. The proportion of participants who believed that HIV testing was unnecessary in the third trimester of pregnancy was highest among academics, and in parallel, the proportion of participants who reported that they performed HIV testing in the third trimester was lowest among academics.

The vast majority of respondents (94%) demonstrated a comprehensive understanding of the fact that HIV is a sexually transmitted infection. According to 96.2% of the participants, HIV can be asymptomatic for many years postinfection.

Of the participants, 96.2% agreed that HIV can be transmitted from an HIV-positive mother to her baby during pregnancy and childbirth, whereas 91.7% disagreed that HIV can be transmitted by hugging, eating in the same place, or sharing a swimming pool or a toilet. Of these, 82% agreed that HIV could be transmitted to a baby through breastfeeding.

The majority of respondents (96.2%) recognized that HIV treatment can stop the disease progression, although there is no cure for HIV. A substantial proportion of respondents expressed scepticism regarding the efficacy of the current treatment regimens in achieving a cure for HIV, with 85.7% of respondents believing that such a cure would not be attainable through the utilization of existing therapeutic interventions. Furthermore, a mere 51.9% of respondents attributed the phenomenon of opportunistic infections occurring within a timeframe of weeks

to months to the rapid destruction of the immune system by HIV. Of the participants, 84.2% agreed that with effective treatment, PLWH have almost the same life expectancy as the general population; conversely, 49.6% believed that HIV is an infection that will continue to progress and lead to death despite treatment.

Of the participants, 18.8% reported that HIV drugs should never be used during pregnancy as they can be toxic/teratogenic to the baby, and this rate was highest (26.7%) among residents (Table 2).

Obstetricians have low levels of knowledge on U=U and PrEP and low levels of knowledge on up-to-date antenatal counseling for couples planning to have a child in the U=U and PrEP era (Table 3).

Of the obstetricians, 74.4% reported they had never heard of the term U=U, and only 3.8% said they had an opinion about U=U. In PLWH who achieved viral suppression with effective ART, the rate of obstetricians who believed that HIV could not be transmitted even through unprotected sexual intercourse was 24.8%. If one of the partners planning to have a child is HIV-positive, 18% of respondents believe that unprotected sex can be allowed without the need for assisted reproductive technologies if the partner is on active HIV treatment. Of the respondents, 40.6% disagreed with the argument that further assisted reproduction techniques are not required, even if it is accepted that PLWH on effective treatment do not transmit HIV. In addition, 32.3% have no opinion on this argument. The proportion increases with professional experience and is highest among academics at 57.1%. In addition, 32.3% of respondents have no opinion on this argument.

Of those surveyed, only 18.8% said they had some knowledge of PrEP. Moreover, 63.9% agreed with the argument that PrEP is the use of certain HIV drugs to prevent the spread of HIV in high-risk groups, such as people who have an HIV-positive sex partner, who have multiple sex partners, or who inject drugs, whereas 18.8% agreed with the argument that it seems unnecessary/absurd that drugs used to treat HIV could be used by healthy people for prevention. About 45.9% of the respondents thought that PrEP could be used in pregnant women who are at risk of HIV transmission. Of the participants, 9% believed that using HIV drugs for PrEP in pregnant women would be risky for the mother or baby, and 60.9% had no opinion. Among respondents, 44.4% thought that PrEP could be an appropriate method of additional protection for people whose partner is HIV-positive but on effective ART, and this proportion was highest among academics at 71.5%. If one of the partners was HIV-positive but on effective ART and the healthy partner was on PrEP, 36.8% of participants thought that these partners could conceive through normal sexual intercourse without taking any additional protection; again, the highest rate was among academics at 64.3%. However, 30.8% disagreed and 32.4% had no opinion on this argument (Table 3).

Obstetricians have low levels of confidence in the protection of U=U and PrEP against HIV during pregnancy and childbirth (Table 4).

Of the obstetricians surveyed, 62.4% agreed with the statement: "If the female partner is HIV-positive and the male partner is negative, and provided she is on ART, the use of assisted reproductive techniques with sperm from the male partner during the periovulatory period is a good option that I can recommend to my patients"; the proportion was highest among academics at 92.9%. "Even if the HIV-positive female partner is already on active ART and the male partner is on PrEP, I would definitely refer this couple to a clinic offering assisted reproductive techniques." A mere 17.3% of the respondents expressed disagreement with the statement, whereas a significant majority of 48.1% agreed.

The proportion of respondents who agreed with the statement "The use of semen preparation techniques (semen washing followed by testing of the sample for HIV-RNA, intrauterine insemination, in vitro intracytoplasmic sperm injection) is no longer routinely recommended when the male partner is HIV-positive but on active ART and the woman has the option of using PrEP" was very low at 15.8%.

Approximately 32.3% of obstetricians said they would never allow an HIV-positive pregnant woman to have a normal delivery. Of the respondents, 58.6% agreed that a pregnant woman newly diagnosed with HIV close to delivery should definitely be referred for a cesarean section. The proportion of agreement and disagreement with the statement "There is no medical indication for cesarean section in an HIV-positive pregnant woman on effective ART" was equal at 38.3%. The proportion of main reasons for not allowing an HIV-positive pregnant woman to have a normal delivery, even if she is on ART, was to prevent HIV transmission to the baby for 31.6%, to prevent transmission to health professionals for 14.3%, and both for 43.6%. Of the participants, 72.9% knew that zidovudine (ZDV) is a drug used to treat HIV and is used as a prophylaxis to prevent HIV transmission to the baby during labor; this was highest among academics (92.9%) and those with 6-10 years of experience (94.4%). Of these, 61.7% agreed that ZDV prophylaxis should be administered to an HIV-positive pregnant woman during labor under all circumstances. If HIV infection was suspected during labor or breastfeeding, 69.2% of respondents agreed that breastfeeding should be stopped immediately. Furthermore, only 26.3% agreed that pregnant women with HIV who are on effective ART should not breastfeed their babies postdelivery, and this proportion was highest among academics (57.1%).

The results of the study indicated that 69.2% of participants advocated that if HIV infection was suspected during labor or breastfeeding, breastfeeding should be stopped immediately and should not continue if infection was confirmed (Table 4).

Discussion

In recent years, the advent of novel ART has transformed HIV from a fatal condition into a manageable chronic disease. This shift coincided with a remarkable increase in the life expectancy of PLWH, which now closely resembles that of the general population. Consequently, a discourse surrounding the desire of these individuals to conceive children has been emerging. The U=U paradigm, which has gained widespread acceptance, has further facilitated the discussion by emphasizing the safety of HIV serodiscordant couples in terms of the risk of HIV transmission through unprotected sexual intercourse.

The results of our study revealed that the vast majority of obstetricians have never heard of U=U, and almost all of them have no idea about it. Furthermore, the majority of obstetricians reported that even if they accepted the efficacy of U=U, they would not rely on it in their daily practice and would recommend advanced assisted reproductive techniques to HIV-serodiscordant couples.

PrEP is another prevention strategy that has been promoted in the last decade to fight the HIV epidemic. It is a new medical form of HIV prevention in which antiretroviral drugs are taken by people at high risk of acquiring HIV, and it is safe and effective in men who have sex with men (MSM) and serodiscordant couples to prevent HIV acquisition[9]. In 2014, the World Health Organization recommended that PrEP be made available to MSM, and in 2015, it extended the recommendation to anyone at substantial risk of HIV infection[10,11].

In HIV-serodiscordant couples, if the partner with HIV has not achieved viral suppression or the viral suppression status is unknown, PrEP is recommended for the partner without HIV to reduce the risk of sexual transmission. This recommendation also applies to HIV-serodiscordant couples who are trying to conceive through unprotected sex without using assisted reproductive techniques[5]. Only a few obstetricians who responded to our survey reported they had any idea about PrEP, and a significant number did not have enough knowledge regarding its indications, use in pregnancy, and risks. However, a significant proportion of participants stated they could recommend PrEP to their patients as an additional protection to U=U. This shows that adequate knowledge of PrEP among obstetricians can make a significant contribution to increasing the number of people who access PrEP within the indication.

When seeking pregnancy in serodiscordant couples where the male partner is HIV-positive, the use of sperm preparation techniques (e.g., "sperm washing" followed by HIV-RNA testing of the sample) and in vitro fertilization are no longer routinely recommended if the HIV-positive individual is adherent to ART and the HIV viral load is undetectable. These recognized indications for semen preparation techniques were largely developed in trials before the demonstration of the effectiveness of ART and PrEP in reducing the risk of HIV transmission[5]. However, few obstetricians surveyed believed these partners could conceive through normal intercourse without additional protection, and most reported they would still recommend sperm preparation techniques.

Although data on the use of PrEP in pregnant and postpartum women are less robust than in non-pregnant women, PrEP is highly effective in women, and the large amount of data from pregnant women using tenofovir disoproxil and emtricitabine for HIV and hepatitis B infection treatment indicates that these agents are safe for pregnant and breastfeeding women[5]. However, obstetricians are unaware of the potential effects of PrEP use in pregnant women and the fetus.

HIV infection should be diagnosed before or as early as possible during pregnancy. Early diagnosis offers the best chance of improving the health of the pregnant woman, the outcome of the pregnancy, and preventing HIV transmission to the baby. People who are at high risk of acquiring HIV, who have acute signs and symptoms of HIV, or who live in areas with high HIV incidence are advised to have a repeat HIV test in the third trimester before 36 weeks of pregnancy, even if the first HIV test during pregnancy was negative[5]. Analyzing the results of our survey, obstetricians in Türkiye agreed on HIV testing at the beginning of pregnancy; however, there was doubt or disagreement about the need for retesting in the later stages of pregnancy.

Planned cesarean section at 38 weeks of gestation is recommended to prevent perinatal HIV transmission in people with HIV-RNA levels of >50 copies/ml at the time of delivery and in those with unknown HIV-RNA levels[5,12]. No evidence planned cesarean section for the sole purpose of preventing perinatal HIV transmission in pregnant HIV-positive persons on active ART with an HIV-RNA level of ≤1000 copies/ml at the time of delivery provides any benefit and is not routinely recommended in these cases. Thus, there were no additional HIV-specific indications in addition to the normal obstetric indications[5]. Obstetricians are aware of the need to refer pregnant women who are not virologically suppressed or who are diagnosed with HIV close to term for cesarean section. However, only a few respondents had accurate information regarding the medical indication for cesarean section in an HIV-positive pregnant woman on active ART. When asked why they prescribed an HIV-positive pregnant woman with a cesarean section rather than a normal delivery, even if she is on ART, obstetricians say they do so to prevent

HIV transmission to the baby and the health workers during the delivery.

Intrapartum ZDV provides antiretroviral prophylaxis when infants are at increased risk of exposure to maternal blood and body fluids. The decision to use intrapartum ZDV is now based on maternal adherence to ART and HIV-RNA levels[5]. Regardless of ART use in HIV-positive pregnant women, IV ZDV is recommended if the HIV-RNA level is >1000 copies/ml in the 4 weeks before delivery; however, it was not required if the HIV-RNA level is ≤50 copies/ml in ART-adherent pregnant women[5]. In our study, obstetricians were aware that administering ZDV to the mother reduces HIV transmission to the baby, but they did not know under what conditions ZDV should be used and thought that ZDV could be given to any HIV-positive mother.

The majority of obstetricians who responded to our survey believe that breastfeeding should be stopped as soon as HIV positivity is detected; however, they are not sufficiently informed whether breastfeeding is permissible in HIV-positive pregnant women on ART. The available evidence cannot sufficient confirm whether breast milk is U=U in the context of vertical transmission[12]. With an undetectable viral load in the mother's blood, the risk of HIV transmission during breastfeeding is very low, but not zero; therefore, breastfeeding should be discouraged if a substitute for breast milk is available. The longer breastfeeding continues, the greater the risk of transmission; therefore, if breastfeeding is continued out of necessity, mothers should be encouraged to stop as soon as possible[12].

Globally, an estimated 1.3 million women and adolescents living with HIV become pregnant each year. Without proper intervention, the HIV transmission rate from a mother living with HIV to her child during pregnancy, childbirth, postpartum, or breastfeeding ranges from 15% to 45%[13]. Young and pregnant women are one of the most strategic groups in achieving global HIV elimination targets; therefore, obstetricians' knowledge and approach to women living with or at risk of acquiring HIV in line with antenatal counseling and during pregnancy in the era of modern HIV medicines, U=U, and PrEP is critical.

A review of the HIV/AIDS statistics in Türkiye reveals that between 1985 and November 7, 2024, a total of 45,835 individuals were reported to be HIV-positive. According to the most recent data, between January 1, 2024, and November 7, 2024, 1567 HIV-positive persons were identified. These cases occurred most frequently in the 25-29 age group and following heterosexual sexual contact. The number of HIV infections in Turkey is expected to increase by 27% annually until 2040, according to a modeling study, reaching 376,889 new HIV cases and 2,414,965 cases of HIV prevalence by 2040. Assuming that these new diagnoses are in young heterosexual people, gynecologists and obstetricians will encounter HIV-positive pregnant women much more frequently in the coming years[14,15].

Our study indicates a substantial knowledge deficit among obstetricians and gynecologists concerning general awareness of HIV, the concept of U=U, PrEP, and the clinical management of HIV-positive pregnancies, and the study addresses a significant public health issue, with a sample that includes different levels of expertise (residents, specialists, and academics), thus allowing for comparative analysis. To our knowledge, this is the first study to determine the level of HIV knowledge of obstetricians and gynecologists. We believe that this is the most important feature that makes our study valuable. A general consideration of the results of this study reveals that obstetricians and gynecologists do not feel the need to read guideline articles on this subject because of the low frequency with which they meet HIV-positive pregnant women. They also do not spend time attending meetings or symposia on this subject. Consequently, there are deficiencies in the general attitudes of obstetricians toward the follow-up of HIV-positive pregnancies, their general knowledge about HIV, their level of knowledge about U=U and PrEP, and their knowledge about the management of HIV-positive pregnancies.

Study limitations

The study's primary limitation is the relatively small sample size, which may not fully represent broader trends. A population of physicians may have refused to participate in the survey at the stage when the surveyors offered the physicians to participate. However, we think that this is due to time constraints and workload of the physicians rather than a situation that creates a volunteer bias. The fact that the population with a low level of knowledge is much more dominant in our survey results supports this view.

Conclusion

Considering the expected increase in the number of HIV-positive pregnant women in Türkiye in the future, this study found that the level of HIV knowledge, the disease course, the efficacy of antiretroviral drugs, and the use of these drugs in pregnancy among obstetricians are insufficient. Furthermore, their experience in managing HIV-positive pregnancies and deliveries is low, and young doctors particularly do not feel adequate and comfortable in managing HIV-positive pregnancies. The fact that obstetricians, especially residents, have not attended any meetings or read any literature on HIV in recent years suggests that HIV should be more integrated into the educational and training activities of obstetricians. Therefore, further research should be performed to draw general conclusions on this issue.

Ethics

Ethics Committee Approval: Ethics committee approval was graded by University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee (approval number: 27/33, dated: 30.12.2022).

Informed Consent: The consent form was filled out by all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Ç.E., E.Y., Concept: S.Ç.E., E.Y., T.Y., A.Ş., A.K., B.D., Design: S.Ç.E., E.Y., A.K., Data Collection or Processing: S.Ç.E., E.Y., T.Y., B.D., Analysis or Interpretation: S.Ç.E., E.Y., A.Ş., A.K., B.D., H.K., Literature Search: S.Ç.E., E.Y., T.Y., A.Ş., A.K., H.K., Writing: S.Ç.E., E.Y., T.Y., A.Ş., H.K.

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Current Status on the Epidemiology of Hepatitis B Virus Infection in İstanbul

İstanbul'daki Hepatit B Virüsü Enfeksiyonunun Epidemiyolojisine İlişkin Mevcut Durum

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Abstract

Introduction: Despite the availability of safe and effective vaccines against Hepatitis B virus (HBV), the infection remains a significant global health issue. This study examined all serological markers of HBV at the largest hospital in İstanbul to identify hepatitis B cases and assess current seroprevalence.

Materials and Methods: Data from cases analyzed between May 2020 and October 2023 included the following parameters: hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), antibody to hepatitis B surface antigen (anti-HBs), antibody to hepatitis B e antigen (anti-HBe), IgM antibody to hepatitis B core antigen (anti-HBc IgM), and total antibody to hepatitis B core antigen (anti-HBc total), all measured using the Roche cobas e 801 analyzer.

Results: HBsAg positivity was detected in 2.11% of 467,163 patients. Among 39,046 children, the HBsAg positivity rate was 0.47%. The highest HBsAg positivity was observed in the 51-60 age group. Acute hepatitis B, indicated by anti-HBc IgM positivity, was identified in 0.41% of 17,293 patients. Among those who tested positive for HBsAg, 1.90% were also positive for HBeAg. Anti-HBs was positive in 46.27% of 294,631 patients overall and in 67.35% of 44,293 children. The highest anti-HBs positivity was observed in the <1 year and 1-5 year age groups. The lowest positivity rates for both HBsAg and anti-HBs were recorded in 2023.

Conclusion: With an HBsAg positivity rate of 2.11%, the region can be classified as having intermediate endemicity. This study aims to support seroprevalence assessments by providing updated data, contributing to efforts toward hepatitis B control goals.

Keywords: Hepatitis B virus, acute hepatitis B, hepatitis B vaccine, seroprevalence, İstanbul

Öz

Giriş: Hepatit B virüsü (HBV) için güvenli ve etkili aşılar mevcut olmasına rağmen, enfeksiyon küresel bir sağlık sorunu olmaya devam etmektedir. Bu çalışmada, İstanbul'un en büyük hastanesinde hepatit B vakalarını ve güncel seroprevalansı belirlemek amacıyla hepatit B virüsüne ait tüm serolojik parametreler incelenmiştir.

Gereç ve Yöntem: Mayıs 2020 ile Ekim 2023 tarihleri arasında analiz edilen vakalarda, hepatit B yüzey antijeni (HBsAg), hepatit B e antijeni (HBeAg), hepatit B yüzey antijenine karşı antikor (anti-HBs), hepatit B e antijenine karşı antikor (anti-HBe), hepatit B çekirdek antijenine karşı IgM tipi antikor (anti-HBc IgM) ve toplam hepatit B çekirdek antijenine karşı antikor (anti-HBc total) parametreleri, Roche Cobas e 801 cihazı kullanılarak değerlendirilmiştir.

Bulgular: Çalışmada, 467.163 hastanın %2,11'inde HBsAg(+) saptanmıştır. Otuz dokuz bin kırk altı çocukta HBsAg pozitiflik oranı %0,47 olarak bulunmuştur. En yüksek HBsAg oranı 51-60 yaş grubunda görülmüştür. On yedi bin iki yüz doksan üç hastanın %0,41'i anti-HBc IgM pozitif bulunmuş ve akut hepatit B olarak değerlendirilmiştir. HBsAg(+) hastaların %1,90'ında HBeAg testi pozitif çıkmıştır. İki yüz doksan dört bin altı yüz otuz bir hastanın %46,27'si anti-HBs pozitifti. Kırk dört bin iki yüz doksan üç çocuğun %67,35'i anti-HBs pozitifti. En yüksek anti-HBs pozitifliği <1 ve 1-5 yaş gruplarında saptanmıştır. HBsAg ve anti-HBs pozitifliği 2023 yılında en düşük seviyede bulunmuştur.

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Öz

Sonuç: Bölgemiz %2,11 HBsAg pozitiflik oranı ile orta düzey endemisite göstermektedir. Bu çalışmanın, hepatit B'nin mevcut seroprevalansını ortaya koyarak hepatit B kontrol hedeflerine ulaşılmasında seroprevalans değerlendirmelerine katkı sağlayacağına inanıyoruz.
Anahtar Kelimeler: Hepatit B virüsü, akut Hepatit B, Hepatit B aşısı, seroprevalans, İstanbul

Introduction

Although effective and safe vaccines exist for the Hepatitis B virus (HBV), the infection continues to represent a global health burden[1]. HBV remains a major public health issue, with approximately 296 million individuals chronically infected worldwide and 820,000 deaths reported in 2019[2]. The highest burden of HBV infection is observed in the World Health Organization (WHO) Western Pacific and African Regions[3]. The prevalence of HBV is assessed based on the serological presence of hepatitis B surface antigen (HBsAg) in the general population of a given geographic area. A prevalence of HBsAg of ≥8% is categorized as high endemicity, 5-7% as high-intermediate, 2-4% as low-intermediate, and <2% as low endemicity[4]. Türkiye is considered a intermediate endemic region for HBV, with HBsAg prevalence reaching between 2-8%. The national average HBsAg positivity rate is approximately 3.9%, corresponding to an estimated three million HBV-infected individuals[5,6].

HBV is a DNA virus with an envelope, classified under the genus *Orthohepadnavirus* within the *Hepadnaviridae* family[7]. There are 10 recognized HBV genotypes, labeled A through J[8]. The distribution of these genotypes differs by geographic region[2]. In Türkiye, genotype D is the most prevalent[9]. HBV infection can be either acute or chronic, presenting with a spectrum that includes asymptomatic cases, mild illness, or severe and fulminant hepatitis. The age at which infection occurs plays a critical role in the likelihood of developing chronic infection. Chronic infection develops in approximately 90% of newborns and infants who contract the virus, compared to less than 5% of individuals infected in adulthood[10].

Vaccination is the most effective strategy for preventing HBV infection. The first HBV vaccine was approved by the US Food and Drug Administration in 1981. In 1986, the original plasma-derived vaccine was replaced with a recombinant version[11]. In Türkiye, the HBV vaccine was first introduced in 1998 as part of the national Extended Immunization Program. Since 2006, it has been administered at 0, 1, and 6 months of age[12]. The WHO recommends giving the first dose of HBV to all newborns within 24 hours of birth, followed by two or three doses spaced at least 4 weeks apart. For individuals who complete the three-dose schedule, booster doses are typically unnecessary. The vaccine confers protection for at least 20 years and likely provides lifelong immunity[3]. Although effective and safe vaccines are available, HBV infection remains a global health challenge. Understanding the epidemiology of HBV is important from a public health perspective. This study aimed to identify hepatitis B cases and assess current seroprevalence by evaluating all serological markers of HBV at the largest hospital in İstanbul.

Materials and Methods

This retrospective study included patients aged 0-99 years who were tested for any of the following parameters: HBsAg, HBeAg, anti-HBs, anti-HBe, anti-HBc IgM, and anti-HBc total-in the Medical Virology Laboratory of our hospital between May 2020 and October 2023. Demographic data of the participants were retrieved from the hospital's electronic medical records. Ethical approval for the study was granted by the Institutional Review Board of Başakşehir Çam and Sakura City Hospital (approval number: 2023/585, dated: 27.11.2023).

The parameters HBsAg, HBeAg, anti-HBs, anti-HBe, anti-HBc IgM, and anti-HBc total were assessed using the commercial kits Elecsys HBsAg II, Elecsys anti-HBs II, Elecsys HBeAg, Elecsys anti-HBe, Elecsys anti-HBc IgM, and Elecsys anti-HBc II (Roche Diagnostics, Germany). These assays were performed using the electrochemiluminescence immunoassay method on the Roche cobas e 801 analyzer (Roche, Germany). Internal quality controls were implemented for each test.

Samples with a cutoff index ≥1.0 were interpreted as positive for HBsAg. Those with a cutoff index between ≥0.90 and <1.0 were classified as borderline, while samples with a cutoff index <0.90 were considered negative. For the anti-HBs test, a result was deemed positive if the cutoff index was ≥10 IU/L. A cutoff index ≥1.0 was used to define positivity for both anti-HBc IgM and HBeAg tests. For the anti-HBc total and anti-HBe tests, samples with a cutoff index ≤1.0 were considered positive. Based on Türkiye's national vaccination schedule, age groups for evaluating HBsAg and anti-HBs parameters were defined as <1, 1-5, 6-17, 18-30, 31-40, 41-50, 51-60, and ≥60 years.

Individuals with positive anti-HBc and anti-HBs but negative HBsAg results were classified as immune due to past infection. Patients positive for anti-HBs but negative for both anti-HBc and HBsAg were considered immune due to vaccination (serological evidence of immunization). Individuals negative for all serological markers were categorized as susceptible to HBV

infection. Cases with negative HBsAg and anti-HBs but positive anti-HBc total were identified as having isolated anti-HBc.

Statistical Analysis

Statistical analyses were conducted using SPSS version 22.0. The normality of variable distributions was assessed through visual methods (histograms and probability plots) and the Kolmogorov-Smirnov test. Comparisons of quantitative variables were performed using the Mann-Whitney U test, while qualitative variables were evaluated with the Pearson chi-squared test. The strength and significance of relationships between variables were determined using Spearman's rank correlation coefficient. A p-value of less than 0.05 was considered indicative of statistical significance.

Results

This study included a total of 480,620 individuals, of whom 6.54% were foreign nationals, and analyzed 675,503 samples for hepatitis B serology. The average age of participants was 37.93±19.18 years, with females comprising 49.99%. The mean age of foreign nationals (29.83±16.38) was significantly lower than that of Turkish citizens (38.50±19.23) (p<0.001).

HBsAg positivity was detected in 2.11% (n=9873) of the 467,163 patients tested (Table 1, Figure 1). Ninety-one cases (0.019%) were classified as borderline for HBsAg and excluded from further analysis. The mean age of HBsAg-positive patients was 47.41±16.04, with males having significantly higher values (p<0.001). Among 39,046 children (aged 0-18) tested for HBsAg, the positivity rate was 0.47%, which was significantly lower than in adults (p<0.001). The highest HBsAg positivity was found in the 51-60 age group (p<0.001) (Figure 2). There was no significant difference in HBsAg positivity between Turkish citizens and foreign nationals (p=0.190). The rate of HBsAg positivity in 2023 was lower compared to previous years (p<0.001). The yearly distribution of HBsAg positivity is detailed in Table 1.

Among 17,293 patients tested for anti-HBc IgM, 0.41% (n=70) were positive and diagnosed with acute hepatitis B. The mean age of these 70 patients was 45.09±12.91, and 64.29% (n=45) were male. All patients diagnosed with acute hepatitis B had positive HBsAg results. The HBeAg test was positive in 1.90% (n=188) of the HBsAg-positive patients. Anti-HBe positivity was found in 1.28% (n=5.964) of the 467,163 patients included in the study. Figure 1 shows the flowchart of the included cases and their serological results.

Out of 294,631 patients tested for anti-HBs, 46.27% were positive (Table 1, Figure 1). The mean age of anti-HBs-positive patients was 33.30±22.52 and the anti-HBs positivity rate was slightly but significantly higher in males (47.24%) than in females (45.47%, p<0.001). Among 44,293 children tested for anti-HBs, the positivity rate was 67.35%, which was significantly higher than in adults (p<0.001) (Table 1). The highest anti-HBs positivity was observed in the <1 and 1-5 age groups (p<0.001) (Figure 2). The anti-HBs positivity rate was higher in Turkish citizens compared to foreign nationals (p<0.001). Anti-HBs positivity was lower in 2023 than in previous years (p<0.001).

Table 1. HBsAg and Anti-HBs positivity rates by demographic factors and year

		HBsAg				Anti-HBs		
	Total, n	**Positive, n (%)**	**Negative, n (%)**	**p-value**	**Total, n**	**Positive, n (%)**	**Negative, n (%)**	**p[1]**
Number	467163	9873 (2.11)	457290 (97.87)		294631	136317 (46.27)	158314 (53.73)	
Age, mean		47.41±16.04	38.34±18.81			33.30±22.52	42.92±19.24	
Sex				<0.001				<0.001
Male	233156	5568 (2.39)	227588 (97.61)		132676	62674 (47.24)	70002 (52.76)	
Female	234007	4305 (1.84)	229702 (98.16)		161955	73643 (45.47)	88312 (54.53)	
Child	39046	185 (0.47)	38861 (99.53)	<0.001	44293	29832 (67.35)	14461 (32.65)	<0.001
Adult	428117	9688 (2.26)	418429 (97.74)		250338	106485 (42.54)	143853 (57.46)	
Nationality								
Turkish	436418	9231 (2.12)	427187 (97.88)	0.190	276519	129240 (46.74)	147279 (53.26)	<0.001
Foreigner	30745	642 (2.09)	30103 (97.91)		18112	7077 (39.07)	11035 (60.93)	
Years								
2020	35057	1111 (3.17)	33946 (96.83)	<0.001	22287	10421 (46.76)	11866 (53.24)	<0.001
2021	112341	2792 (2.49)	109549 (97.51)		75673	35758 (47.25)	39915 (52.75)	
2022	157566	3077 (1.95)	154489 (98.05)		95598	44692 (46.75)	50906 (53.25)	
2023	162199	2893 (1.78)	159306 (98.22)		101073	45446 (44.96)	55627 (55.04)	

[1]p-values <0.05 were considered statistically significant, HBsAg: Hepatitis B surface antigen

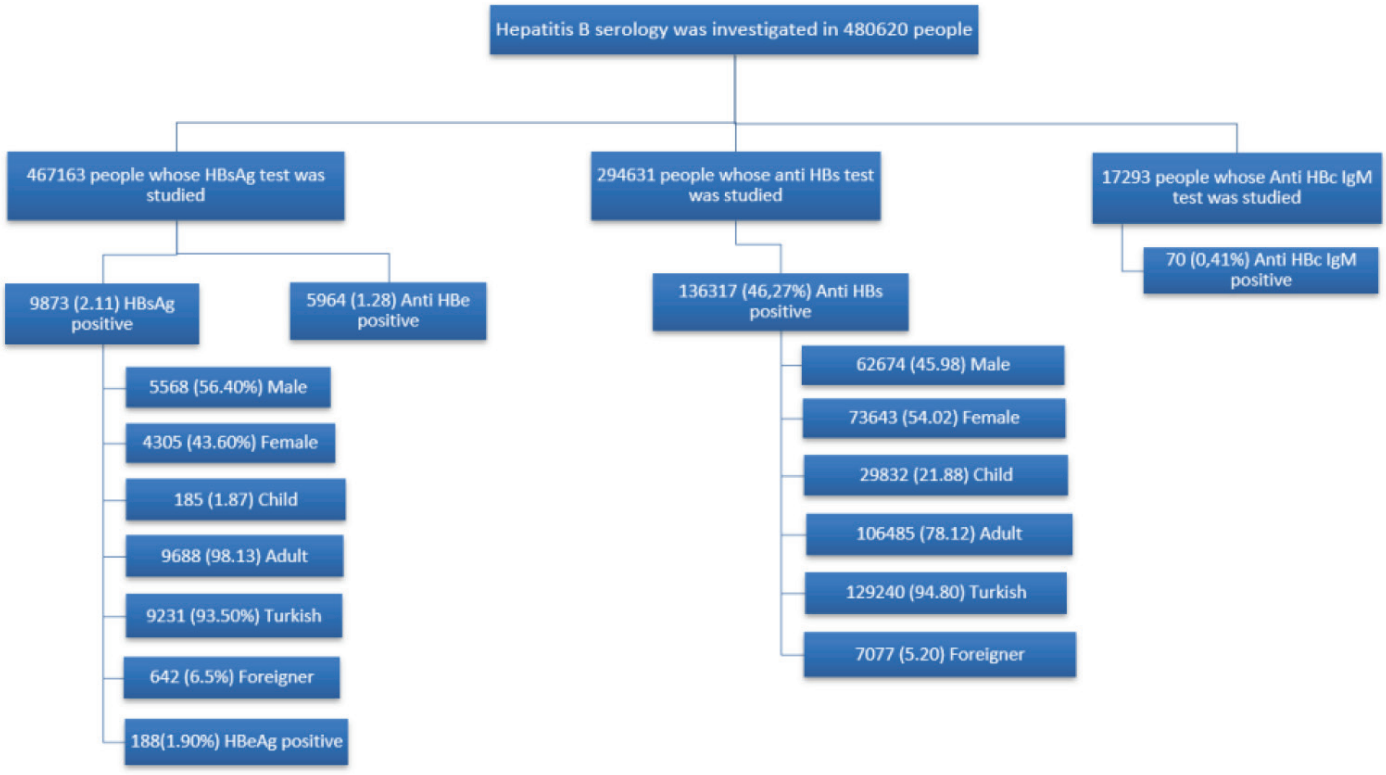

Figure 1. Flow chart and serological results of the people included in the study
HBsAg: Hepatitis B surface antigen, Anti-HBc IgM: IgM antibody to hepatitis B core antigen

The yearly distribution of anti-HBs positivity is presented in Table 1.

Immunity due to past infection was identified in 15.69% (4,688/29,874) of cases and was significantly higher among adults (p<0.001). The highest rate was seen in the >60 age group (p<0.001). Immunity from vaccination was observed in 25.10% (7,497/29,874) of cases. Isolated anti-HBc positivity was detected in 8.83% (2,639/29,874) of cases.

Discussion

Hepatitis B is among the most common infectious diseases worldwide. In our study, the prevalence of HBsAg positivity in the general population was 2.11%. A study from Northeast China reported an HBsAg positivity rate of 7.43%[13], while rates in Cameroon and South Africa were 5.08%[14] and 4.0%[15], respectively. Hepatitis B infection is endemic in many African countries, where HBsAg seroprevalence is higher compared to developed nations. This is linked to factors such as lower socioeconomic status, poor hygiene conditions, and limited education about infectious diseases in developing countries. Conversely, developed countries show lower prevalence rates. For instance, a study by Khetsuriani[16] found HBsAg prevalence rates of 0.3% in Germany and 0.2% in the Netherlands, which are significantly lower than those found in our study. This difference can be explained by established vaccination programs and better hygiene standards in developed countries. In Türkiye, a previous study reported an HBsAg positivity rate of 2.38%[17], aligning with our findings. The HBsAg prevalence of 2.11% found in our study indicates that Türkiye remains classified as a country with low to moderate endemicity (2-4%) according to WHO criteria. HBsAg positivity was 1.84% in females and 2.39% in males, with a significantly higher rate observed in males (p<0.001). In a study from Northeast China, HBsAg positivity was 5.80% in females and 8.94% in males[13]. In South Africa, the overall HBsAg positivity was 3.20%, with 4.80% in males. Both studies reported higher HBsAg positivity in males compared to females[15]. The prevalence of HBsAg was 0.47% in children and 2.09% among foreign nationals. HBsAg positivity was significantly higher in adults (p<0.001). There was no statistically significant difference between Turkish citizens and foreign nationals (p=0.190). The low prevalence of HBsAg in children (0.47%) is mainly attributed to the inclusion of HBV vaccine in the national childhood immunization program since 2006.

In our study, the mean age of HBsAg-positive patients was significantly higher (p<0.001). The highest HBsAg positivity was observed in the 51-60 age group (p<0.001). A study from

Northeast China reported the highest HBsAg prevalence in the 41-50 age group[13]. In Cameroon, the highest prevalence was found in the 17-31 age group, which differs from our findings[14]. In South Africa, the highest HBsAg prevalence was in the 40-44 age group[15]. A study conducted in Türkiye found the highest prevalence in the 25-44 age group[17]. The elevated HBsAg positivity in the older age group in Türkiye is thought to be related to the introduction of the hepatitis B vaccine in 2006. Therefore, individuals born before the vaccination program began may have been more susceptible to HBV infection and likely developed immunity through natural infection.

The anti-HBc IgM test was positive in 0.41% (n=70) of the 17,293 patients tested, indicating acute hepatitis B. The HBeAg test was positive in 1.90% (n=188) of the HBsAg-positive patients. All acute hepatitis cases were HBeAg positive. In a North American study involving 2,018 individuals, 60 were diagnosed with acute hepatitis B, with a mean age of 41.6 (33.7-51.1), and 28.33% (n=17) were female, consistent with our findings. However, unlike our study, only 43 of these acute hepatitis B cases were HBeAg positive[18]. In a Polish study, the number of acute

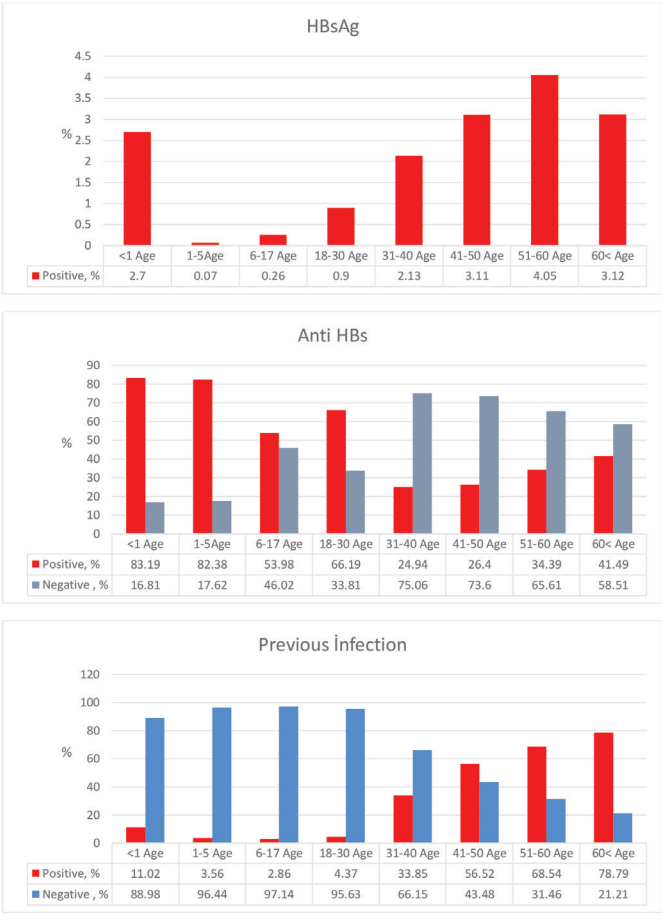

Figure 2. HBsAg, anti-HBs, and past infection positivity by age groups

HBsAg: Hepatitis B surface antigen

hepatitis B decreased from 649 in 2005 to 45 in 2019[19]. A study from Türkiye in 2013 reviewed acute hepatitis B notification rates between 1990 and 2012. The notification rate was 4.8 per 100,000 population in 1990, rising to 12.3 in 2005, then steadily declining to 3.9 and 3.6 per 100,000 in 2011 and 2012, respectively. In 1999, 64% of infants received three doses of the hepatitis B vaccine, and vaccination coverage increased to over 90% after 2006 following the implementation of the routine immunization program[20].

With the consistent implementation of vaccination programs in our country, along with improvements in socioeconomic conditions, better hygiene, and increased awareness about infectious diseases, we expect the number of cases to continue decreasing, eventually placing the country among those with low endemicity according to WHO classifications.

Among 294,631 patients tested for anti-HBs, 46.27% were positive. The mean age of anti-HBs-positive patients was 33.30±22.52 years. In a study from Northeast China involving 218,627 individuals, the prevalence of anti-HBs positivity was 46.88%, similar to our findings[13]. Another Chinese study reported an anti-HBs positivity rate of 44.75% among first-year university students between 2017 and 2019[21]. In a Turkish study of 309,037 individuals, the anti-HBs positivity rate was 55.38%[17]. Among 44,293 children tested for anti-HBs, 67.35% were positive, which was significantly higher than the rate observed in adults (p<0.001).

The highest anti-HBs positivity was found in the age group <1 to 5 years (p<0.001). In a study conducted in Italy among children aged 1-18 years, the prevalence of anti-HBs positivity was 59.4%, with the highest rate of 61.1% observed in the 16-18 age group[22]. The high rate of anti-HBs positivity among childhood in our country is likely due to the consistent implementation of childhood vaccination programs.

When total immunity was evaluated, vaccination-induced immunity accounted for 25.10% (7,497/29,874), while immunity from past infection accounted for 15.69% (4,688/29,874). Immunity from past infection was significantly higher in adults (p<0.001), with the highest rate seen in those >60 years of age (p<0.001). Although HBV infection is currently moderately endemic in our country, the rate of past infection remains considerable. However, we expect that the high prevalence of anti-HBs positivity will increase further in the coming years due to vaccination programs. The rate of anti-HBs positivity was lower among foreign nationals (39.07%) compared to Turkish citizens (p<0.001). This lower seroprevalence in foreigners may be related to the lack of or inadequate vaccination programs.

In our study, the prevalence of isolated anti-HBc positivity was found to be 8.83% (2,639/29,874). Isolated anti-HBc positivity

refers to the presence of anti-HBc alone without other hepatitis B serological markers. The frequency of isolated anti-HBc positivity varies from 0.1% to 20% across different populations. One study reported an average rate of 3-5% for isolated anti-HBc positivity in our country[23]. In the USA and Europe, this rate ranges between 1% and 4% of the population[24].

Isolated anti-HBc positivity can have multiple interpretations. It may represent a "false" positive caused by IgM-structured substances that disappear after treatment with reducing agents such as dithiothreitol, cysteine, or sodium metabisulfite, or it may result from diagnostic system errors (1-2%). It can also indicate acute infection during the window period when HBsAg has disappeared but anti-HBs has not yet developed; or chronic infection with HBsAg levels below the detection limit; or a humoral immune response defect to HBV antigens preventing the formation of other antibodies. Additionally, it may reflect the loss of anti-HBs over time or the inability to produce anti-HBs, especially in diabetic patients and those with kidney disease. Infections with viruses that share antigenic determinants with HBcAg (such as HCV) and, lastly, passive transfer of anti-HBc from mother to infant or through blood transfusion may occur[23].

Conclusion

Our region continues to show moderate endemicity for hepatitis B, with an HBsAg positivity rate of 2.11%. Therefore, the introduction of the anti-HBV vaccination program into the national immunization schedule in 2006 in our country is expected to prevent a worsening of the hepatitis B epidemiological situation in Türkiye from worsening, particularly by significantly reducing prevalence and incidence in the young population, which is the main target of vaccination efforts. Given the effectiveness of HBV vaccination in limiting the spread of the infection, it is expected that Türkiye will reach low endemicity for hepatitis B in the coming years. Measuring seroprevalence, preventing outbreaks, developing protective measures such as sanitation and hygiene, and especially implementing vaccination programs are important. By revealing the current status of hepatitis B in our region, we believe the results of this study will support efforts to improve vaccination coverage, implement regular population screening, and enhance HBV seroprevalence monitoring. These efforts will thereby aiding the achievement of hepatitis B control goals.

Study Limitations

This study has several limitations. First, because vaccination records were not available for the study population, it was not possible to assess vaccine failure or protection rates. Second, although the study was conducted in Istanbul, a cosmopolitan city, and at the largest city hospital, the findings may not be generalizable to the entire country.

Ethics

Ethics Committee Approval: Ethical approval for the study was granted by the Institutional Review Board of Başakşehir Çam and Sakura City Hospital (approval number: 2023/585, dated: 27.11.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: S.K., S.A., Design: M.K., S.K., S.A., Data Collection or Processing: M.K., Analysis or Interpretation: M.K., S.K., S.A., Literature Search: M.K., Writing: M.K.

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Evaluation of Cytomegalovirus Seroprevalence in Pregnant Women: A Multicenter Study

Gebe Kadınlardaki CMV Seroprevalansının Değerlendirilmesi: Çok Merkezli Bir Çalışma

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Abstract

Introduction: Cytomegalovirus (CMV) infection during pregnancy poses a significant risk of congenital infection, particularly in seronegative women. This study aimed to assess CMV seroprevalence among pregnant women and evaluate the incidence of primary CMV infections during pregnancy.

Materials and Methods: This retrospective multicenter study included pregnant women aged ≥18 year who were hospitalized between January 2018 and December 2022. Demographic data - including maternal age, gravidity, and educational and occupational status - along with CMV

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serological results, gestational age at CMV diagnosis, and fetal ultrasonographic (USG) findings were collected and analyzed. In cases with positive CMV immunoglobulin M (IgM) and IgG, CMV-IgG avidity values, amniotic fluid CMV-DNA polymerase chain reaction results, and fetal USG findings were recorded to assess the likelihood of primary infection.

Results: Among 16,761 pregnant women, 261 (1.6%) tested positive for CMV-IgM. Of these, 126 (48.3%) underwent CMV-IgG avidity testing, and three cases demonstrated low avidity, indicating recent primary infection. Ultrasonographic abnormalities in these three fetuses included hydrops fetalis, polyhydramnios, skin edema, and hyperechogenic bowel. Despite high CMV-IgG avidity, five cases showed abnormal findings on detailed fetal ultrasonography namely intrauterine growth restriction, oligohydramnios, and cranial anomalies.

Conclusion: Primary CMV infection during pregnancy is associated with adverse outcomes such as fetal anomalies, spontaneous abortion, and preterm birth. Preventive strategies, including educating CMV-seronegative women about transmission routes and routine assessment of CMV-IgG avidity and fetal USG findings, are essential for early diagnosis and improved perinatal outcomes.

Keywords: Abortion, congenital infection, cytomegalovirus, fetal abnormalities, pregnancy, seroprevalence

Öz

Giriş: Seronegatif kadınlarda sitomegalovirüs (CMV) enfeksiyonuna bağlı konjenital enfeksiyon riski çok yüksektir. Bu çalışmada gebelerde CMV seropozitivite prevalansı araştırılmıştır ve gebelikte primer CMV enfeksiyonu oranları değerlendirilmiştir.

Gereç ve Yöntem: Çalışma çok merkezli planlanmış olup; retrospektif dizayndadır. Ocak 2018 ile Aralık 2022 tarihleri arasında takip edilen 18 yaş ve üzeri kadınlar dahil edilmiştir. Hastaların CMV açısından tetkik edildiği yaş, gebelik sayısı, eğitim ve mesleki durumu, CMV seropozitifliği, gebelik yaşı ve fetal ultrasonografi (USG) sonuçları geriye dönük olarak incelendi. Sitomegalovirüs IgM ve IgG pozitifliği olan olgularda CMV-DNA polimeraz zincir reaksiyonu sonuçları ve fetal USG bulguları ile birlikte CMV-IgG avidite değerleri kaydedildi.

Bulgular: 16.761 gebenin CMV-IgM ve IgG tetkikleri birlikte mevcuttu. Toplam 261 (%1,6) gebenin CMV-IgM testi pozitifti. Yüz yirmi altısında (%48,3) CMV-IgG avidite test sonucu görüldü ve bunların üçü düşük avidite indeksine sahipti. Primer CMV enfeksiyonu saptanan üç fetüsün USG bulgularında hidropik değişiklikler, polihidramnios, deri ödemi ve hiperekojenik bağırsak saptandı. CMV-IgG avidite indeksleri yüksek olmasına rağmen, ayrıntılı fetal ultrasonografi yapılan beş olguda intrauterin büyüme kısıtlılığı, oligohidramnios ve kraniyal anomaliler saptandı.

Sonuç: Primer CMV enfeksiyonu fetal anomaliler, düşük, erken doğum gibi olumsuz gebelik sonuçlarına neden olabileceğinden, CMV seronegatif gebelerin CMV bulaşma yolları hakkında bilgilendirilmesi öncelikli olarak ele alınmalıdır. Sitomegalovirüs-IgG avidite ve fetal USG değerlendirmelerine dikkat edilmelidir.

Anahtar Kelimeler: Abortus, konjenital enfeksiyon, sitomegalovirüs, fetal anormallikler, gebelik, seroprevalans

Introduction

Cytomegalovirus (CMV) is a common viral pathogen that can cause congenital infection when transmitted during pregnancy. *In utero* transmission may result in intrauterine growth restriction, developmental delays, and long-term neurological sequelae in the fetus[1,2]. Although CMV can be transmitted at any stage of pregnancy, the risk of fetal infection is highest during the first half[2]. In addition to vertical transmission, CMV can also be acquired postnatally through exposure to infected oral secretions, urine, or other body fluids[3,4].

Globally, the estimated CMV seroprevalence in the general population is approximately 83%, with Europe reporting the lowest regional rate at 66%. Among women of reproductive age, seroprevalence rates are reported to be 86%, increasing to 97% in Türkiye. Cytomegalovirus is the most common congenital viral infection, with a prevalence during pregnancy ranging from 0.48% to 1.3%[5,6].

While the majority (about 90%) of infants with congenital CMV infection are asymptomatic at birth, approximately 10% present with clinical signs such as petechiae, jaundice, hepatosplenomegaly, intrauterine growth restriction, and microcephaly[7,8]. Recent advances in prenatal screening and imaging technologies have significantly enhanced the early detection of fetal anomalies, even in cases where serological markers may not yet be evident. Detailed fetal ultrasonography (USG) has become instrumental in identifying structural abnormalities associated with congenital infections.

Although several regional studies in Türkiye have assessed CMV seroprevalence in pregnant women, comprehensive nationwide data remain limited. This multicenter study aimed to evaluate CMV seropositivity among pregnant women and to determine the prevalence of primary CMV infections during pregnancy.

Materials and Methods

This nationwide, multicenter, retrospective, descriptive study included pregnant women aged ≥18 year who were admitted for routine obstetric follow-up between January 1, 2018, and December 31, 2022. Data were collected from multiple centers across various regions of Türkiye, including Bursa, İstanbul, Ankara, Çanakkale, Manisa, Kayseri, Konya, Kırıkkale, Trabzon, Van, and Şanlıurfa.

The following demographic and clinical variables were retrospectively reviewed from hospital records: maternal age,

number of pregnancies and living children, educational and occupational status, gestational week at CMV screening, hepatitis B and C serology, human immunodeficiency virus (HIV) serology, fetal USG findings, and CMV-IgM and IgG levels. Participants were categorized based on nationality, occupation, gestational age at testing, gravidity, and maternal age. Due to incomplete data, serological findings for hepatitis B, hepatitis C (HCV), and HIV were reported only for patients with available results.

Laboratory Testing for CMV Seropositivity and Diagnosis of Primary CMV Infection

Cytomegalovirus serological testing was performed using commercial platforms from Roche (Mannheim, Germany), Abbott (Ireland, USA), and bioMérieux (Marcy-l'Etoile, France), depending on the facility (Table 1). Given the variability in testing equipment across centers, a standardized sample-to-control index (S/C) cutoff value of 1.0 was used to define positivity for both CMV-IgM and IgG antibodies when the same assay technology was applied. For one center that used arbitrary units (AU/mL) rather than the S/C index, results were recorded as positive or negative according to the center's established cutoffs and included accordingly.

For patients with simultaneous CMV-IgM and IgG positivity - indicative of potential primary CMV infection - we further analyzed CMV-IgG avidity values, CMV-DNA polymerase chain reaction (PCR) results from biological fluids (e.g., urine or amniotic fluid), and fetal USG findings.

Study Population

Of the initial 17,059 pregnant women screened for CMV serology, 298 were excluded due to incomplete or inconclusive data: one had isolated CMV-IgM positivity, 175 had only CMV-IgG positivity, 121 had intermediate CMV-IgM levels without confirmatory IgM or IgG avidity testing, and one had an intermediate CMV-IgG level without control or avidity data (Figure 1). After exclusions, 16,761 women with complete CMV-IgM and IgG results were included in the final analysis of seroprevalence.

For subgroup analyses evaluating associations between CMV seropositivity and maternal characteristics (age, gravidity, gestational week at testing, and number of living children), only participants with complete datasets were considered. This subset comprised 4,022 women (Table 3).

Ethical approval for the study was granted by the University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital Local Institutional Ethics Committee (decision no: 2011-KAEK25 2023/01-04, decision date: 25.01.2023).

Statistical Analysis

Statistical analyses were conducted using IBM Statistical Package for the Social Sciences statistics for Windows, version 23.0

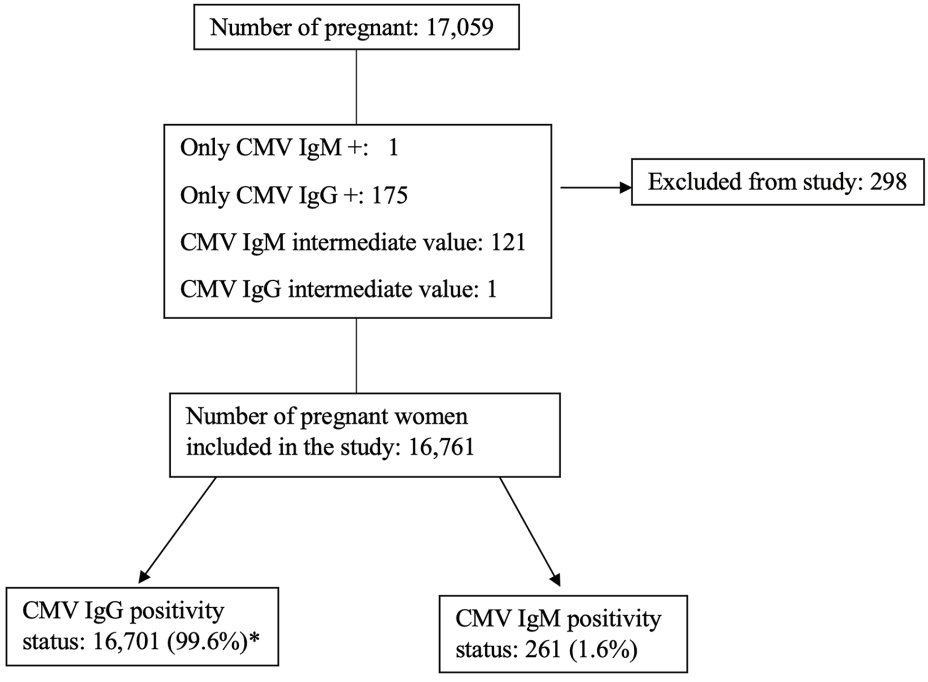

Figure 1. Number of pregnant evaluated in the study

*This group included in 201 patients with CMV-IgM and IgG co-positivity. CMV-IgM: Cytomegalovirus-immunoglobulin M, IgG: Immunoglobulin G

(IBM Corp., Armonk, New York). The distribution of continuous variables was assessed visually (histograms, probability plots) and analytically (Kolmogorov-Smirnov and Shapiro-Wilk tests). Normally distributed variables were reported as means with standard deviations, while non-normally distributed and discrete variables were presented as medians with interquartile ranges.

Comparisons between groups were performed using the Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed or categorical variables. A two-tailed p-value <0.05 was considered statistically significant.

Results

General Characteristics of the Study Population

A total of 16,761 pregnant women were included in the study, of whom 8% (n=1,342) were immigrants. The mean age of the participants was 28.08±6.5 year. Serological testing for CMV was performed at a mean gestational age of 11.22±7.58 weeks.

Occupational data were available for 539 participants. Among these, 41.3% (n=223) were housewives, 31.1% (n=168) were employed in the private sector, 24.8% (n=134) were employed in the public sector, and 2.5% (n=14) were blue-collar workers (Table 2).

Serological testing for hepatitis B surface antigen (HBsAg), anti-HCV, and anti-HIV antibodies was not available for all participants. Specifically, 4,598 women were tested for HBsAg, 4,601 for anti-HCV, and 4,234 for anti-HIV. The prevalence rates were as follows: HBsAg positivity, 1.69% (78/4,598); anti-HCV positivity, 0.15% (7/4,601); and anti-HIV positivity, 0% (0/4,234).

The prevalence of CMV-IgM positivity was 1.6% (n=261), while CMV-IgG positivity was observed in 99.6% of the participants.

Evaluation of Factors Associated with CMV-IgM Positivity

The association between CMV-IgM positivity and selected maternal factors was analyzed in a subgroup of 4,022 women for whom complete data were available on CMV-IgM/IgG levels, gestational age at testing, gravidity, and number of living children.

There was no statistically significant difference in the number of pregnancies between CMV-IgM-positive and CMV-IgM-negative women (p>0.05; Table 3). However, the gestational age at the time of CMV-IgM testing was significantly higher among IgM-positive women compared with the IgM-negative group (p=0.002). Additionally, the number of living children was significantly greater among CMV-IgM-positive women (p=0.029; Table 3).

Table 1. Commercial ELISA devices used and CMV-IgM and IgG cutoff values

Commercial ELISA device	CMV-IgM-positive cutoff value	CMV-IgG-positive cutoff value
Abbott (Irland, USA)[a]	1	1
Roche (Mannheim, Germany)[a]	1	1
Roche (Mannheim, Germany; AU/mL)	<15	0-5
Biomerux (Marcy-l'Etoile, France)[a]	1	6

[a]S/C: Sample control index ratio, CMV-IgM: Cytomegalovirus-immunoglobulin M, IgG: Immunoglobulin G

Table 2. Characteristics of pregnant women with CMV serology testing

Characteristic	Mean (±SD), n (%)
Total number of pregnant women	16,761 (100)
Nationality	
Turkish	15,419 (92)
Immigrant	1,342 (8)
Occupation (n=539)	
Housewife	223 (41.3)
Private sector employee	168 (31.1)
Public employee	134 (24.8)
General worker	14 (2.5)
Serological status of blood-borne infections	
HbsAg positivity (n=4,598)	78 (1.69)
Anti-HCV positivity (n=4,601)	7 (0.15)
Anti-HIV positivity (n=4,234)	0 (0)
CMV serological status	
CMV-IgM seropositivity	261 (1.6)
CMV-IgG seropositivity (including isolated IgG-positive and IgG/IgM co-positive cases)	16,701 (99.6)

CMV-IgM: Cytomegalovirus-immunoglobulin M, IgG: Immunoglobulin G, SD: Standard deviation, HbsAg: Hepatitis B surface antigen, HCV: Hepatitis C, HIV: Human immunodeficiency virus

Table 3. Factors associated with CMV-IgM positivity during pregnancy

Factor	CMV-IgM-positive (n=115)	CMV-IgM-negative (n=3,907)	p value
Age (mean±SD)	29.05±5.83	28.93±5.62	0.813[a]
Week of pregnancy at examination [median (IQR)]	10 (4)	8 (6)	0.002[b]
Number of pregnancies [median (IQR)]	2 (2)	2 (2)	0.964[b]
Number of living children [median (IQR)]	1 (2)	1 (2)	0.029[b]

[a]t-test. [b]Mann-Whitney U test. CMV-IgM: Cytomegalovirus-immunoglobulin M, SD: Standard deviation, IQR: Interquartile range

CMV-IgG Avidity, Fetal Ultrasonographic Findings, and Pregnancy Outcomes in CMV-IgM-positive Women

Of the 261 CMV-IgM-positive women, 126 (48.3%) underwent CMV-IgG avidity testing. Among them, three women (2.4%) had a low CMV-IgG avidity index, suggesting primary CMV infection. These women were evaluated via fetal USG at a mean gestational age of 18 weeks (range: 16-20 weeks).

Ultrasonographic findings varied among the three women: one exhibited no abnormalities, one had findings of hydrops fetalis, polyhydramnios, and skin edema, and the third showed a hyperechoic bowel. Amniotic fluid analysis using CMV-DNA PCR was conducted in the first case, revealing a viral load of 2,214 IU/mL. This woman subsequently underwent pregnancy termination at 20 weeks. The remaining two women experienced preterm delivery at 27 weeks (Table 4).

Of the 126 women who underwent CMV-IgG avidity testing, 43 (34.1%) also had detailed fetal USG evaluations. Among these women, despite five demonstrated high CMV IgG avidity indices; fetal ultrasonography showed intrauterine growth retardation, oligohydramnios, and cranial anomalies. Their mean gestational age at USG was 19.4 weeks (range: 10-23). These women underwent delivery or spontaneous abortion at an average gestational age of 32.4 weeks (range: 12-40).

Among 35 women with no evidence of CMV infection, fetal USG revealed no abnormalities (median gestational age at examination: 18.9 weeks; range: 6-32 weeks). No further serological data were available for the remaining CMV-IgM-positive women who did not undergo additional testing.

Discussion

This cross-sectional study investigated the prevalence of primary CMV infection among pregnant women in Türkiye and evaluated the diagnostic and clinical characteristics of CMV infection during pregnancy. Cytomegalovirus infection is frequently underdiagnosed in women of reproductive age, despite its potential to cause severe fetal complications when acquired during gestation.

Globally, CMV seroprevalence among women of reproductive age is estimated at 86%. While this rate is approximately 70% in Europe, it reaches 92% in the Eastern Mediterranean region. In Türkiye, reported CMV seroprevalence among this population is as high as 96%[5]. Regional studies have reported similar rates, including 98.7-94.2% in Izmir, 98.8% in Rize, 98.7% in Denizli, 100% in Konya, and 96.4% in Çorum[9-14]. In our study, the CMV-IgG seropositivity rate was 99.6%, consistent with the high prevalence observed in previous Turkish studies.

Due to this widespread seropositivity, routine CMV screening during pregnancy is not currently recommended in many clinical guidelines[15]. However, targeted screening may be warranted in high-risk populations, particularly among pregnant women with frequent contact with young children, especially those under three year of age[16]. Young children can shed CMV asymptomatically, posing a risk of transmission to susceptible pregnant individuals[17]. Primary maternal infection during pregnancy can result in congenital CMV, which may manifest as fetal anomalies, intrauterine growth restriction, or fetal loss[1,18]. The risk of fetal transmission varies by trimester, with estimated rates of 30% in the first trimester and 47% in the third trimester[19].

Table 4. CMV-IgG avidity, fetal ultrasonographic findings, and pregnancy outcomes in CMV-IgM-positive

Case	Week of CMV testing	CMV-IgM	CMV-IgG	CMV-IgG avidity	Week of fetal USG	Fetal USG findings	Week of birth	Pregnancy outcome
1	12	Positive	Positive	Low	16	No pathological findings	20	Abortion
2	9	Positive	Positive	Low	18	Hydrops, polyhydroamnios, skin edema	27	Preterm labor
3	11	Positive	Positive	Low	20	Hyperechogenic bowel	27	Preterm labor
4	22	Positive	Positive	High	22	Microcephaly, cerebral hypoplasia	40	Term birth
5	23	Positive	Positive	High	23	Microcephaly, cerebral hypoplasia	38	Term birth
6	8	Positive	Positive	High	10	Intrauterine growth retardation	12	Abortion
7	7	Positive	Positive	High	20	Oligohydroamnios	38	Term birth
8	14	Positive	Positive	High	22	Intrauterine growth retardation	34	Preterm labor

CMV-IgM: Cytomegalovirus-immunoglobulin M, IgG: Immunoglobulin G, USG: Ultrasonographic

In the present study, among 4,022 pregnant women with complete serologic data, CMV screening was more likely to be performed in later gestational weeks in those with CMV-IgM positivity. Additionally, CMV-IgM-positive women had significantly more children than CMV-IgM-negative women (Table 3). These findings highlight the importance of early CMV screening, particularly in multiparous women or those with regular exposure to young children.

Diagnosis of primary CMV infection relies on a combination of serological testing and detailed fetal USG[20]. Ultrasound findings such as periventricular echogenicity, ventriculomegaly, and intraparenchymal calcifications, as well as extracranial anomalies like echogenic bowel, cardiomegaly, hepatosplenomegaly, and pericardial effusion, can suggest congenital infection[21]. Feldman et al.[22] reported fetal echogenic bowel in nine of 17 cases, intrauterine growth restriction in four, and microcephaly in one. In our study, among 43 CMV-IgM-positive women who underwent fetal USG, 18.6% exhibited fetal anomalies, including cranial and extracranial abnormalities. The remaining 81.4% showed no abnormal findings on USG. Specific anomalies detected included hydrops fetalis, oligohydramnios, and intrauterine growth restriction. Although these women were diagnosed using serologic and USG findings, amniocentesis was not performed in most cases, limiting confirmation via CMV-DNA PCR.

In vitro studies have demonstrated that CMV can infect a variety of cell types, including epithelial cells, stromal cells, macrophages, and trophoblasts. Cytomegalovirus infection of trophoblasts induces inflammation and apoptosis, potentially impairing placental function and contributing to fetal complications[23]. Primary CMV infection during pregnancy has been associated with spontaneous abortion, preterm labor, and congenital anomalies[24]. Eletreby et al.[25] reported that among 201 pregnant women with CMV infection, 11% experienced preterm labor, and 3.77% had fetuses with congenital anomalies. In our study, of the eight women identified with primary CMV infection, one experienced pregnancy termination at 20 weeks, three had preterm deliveries, and the remaining three delivered at term. However, given the retrospective nature of the study and the inconsistent availability of advanced serologic and molecular testing across participating centers, it was not possible to evaluate all CMV-IgM-positive cases comprehensively. In particular, fetal USG and amniocentesis were not consistently performed, limiting our ability to accurately assess the incidence of primary CMV infection and its outcomes.

Study Limitations

This study had several limitations due to its retrospective and multicenter design. We were unable to obtain complete data from all participating centers, including information on participants' occupations, hepatitis B and C status, HIV serology, number of pregnancies, and gestational age. These data gaps hindered comprehensive statistical analysis. The use of different equipment across centers for serological testing introduced variability and may have affected the consistency of results. Additionally, some centers did not perform advanced serologic testing in CMV-IgM-positive cases. The number of patients who underwent fetal USG and amniocentesis was also limited in centers where advanced testing was available. These limitations reduced the study's ability to accurately determine the rate of primary CMV infection.

Conclusion

Our findings indicate that CMV seropositivity among pregnant women in Türkiye remains high, at 99.6%. Eight cases of congenital CMV infection were identified. Cytomegalovirus-IgM positivity was more common in women with more advanced gestational age and a higher number of children. Despite the high seroprevalence, early CMV screening during prenatal care, particularly in the first trimester, should be considered, especially for women at increased risk of exposure. Pregnant women with regular contact with infants should receive targeted screening and counseling to minimize transmission risk. Additionally, comprehensive diagnostic evaluation, including CMV-IgG avidity testing, fetal USG, and amniocentesis when appropriate, is critical for confirming congenital CMV infection and guiding clinical management.

Ethics

Ethics Committee Approval: Ethical approval for the study was granted by the University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital Local Institutional Ethics Committee (approval number: 2011-KAEK25 2023/01-04, dated: 25.01.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.S.S., Concept: M.S.S., Y.Ç., N.Y., Design: All authors, Data Collection or Processing: All authors, Analysis or Interpretation: All authors, Literature Search: All authors, Writing: M.S.S., Y.Ç., N.Y.

Conflict of Interest: Yasemin Çağ, the author of this article, is a member of the editorial board of the Mediterranean Journal of Infection, Microbes and Antimicrobials. However, she was not involved in any stage of the editorial review or decision-making process for this manuscript.

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Efficacy and Safety of Glecaprevir/Pibrentasvir in Chronic Hepatitis C Patients: Real-World Data

Kronik Hepatit C Hastalarında Glekaprevir/Pibrentasvir'in Etkinliği ve Güvenliği: Gerçek Yaşam Verileri

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Abstract

Introduction: Glecaprevir/pibrentasvir (G/P) is a pan-genotypic direct-acting antiviral therapy approved for use in adults with chronic hepatitis C virus (HCV) infection. This study aimed to assess the real-world efficacy and safety profile of G/P in individuals with chronic HCV.
Materials and Methods: The analysis included patients over 18 years with detectable HCV-RNA who began G/P treatment for chronic HCV between January 1, 2021, and March 1, 2024. The primary outcome measure was sustained virologic response (SVR), defined as undetectable HCV-RNA 12 weeks after therapy completion. Safety and tolerability of the regimen were also evaluated.
Results: G/P was administered to 191 patients, of whom 85.5% were male. Among them, 124 patients (64.9%) reported intravenous drug use. The most frequently identified genotype was GT 3 (57.1%). At 12 weeks post-treatment, 105 patients returned for follow-up, and all achieved SVR12. Adverse events occurred in 12 patients (6.3%). One patient discontinued treatment at week 4 due to pruritus and rash.
Conclusion: G/P demonstrates high effectiveness, good tolerability, and a favorable safety profile as a pan-genotypic therapeutic option for chronic HCV infection.
Keywords: HCV, chronic hepatitis C, glecaprevir/pibrentasvir, direct-acting antivirals, real-world efficacy

Öz

Giriş: Glekaprevir/pibrentasvir (G/P), kronik hepatit C virüsü (HCV) enfeksiyonu olan yetişkinlerin tedavisi için onaylanmış, pan-genotipik, doğrudan etkili bir antiviral rejimdir. Bu çalışmanın amacı, kronik HCV hastalarında G/P'in gerçek yaşam etkinliğini ve güvenliğini araştırmaktır.
Gereç ve Yöntem: 1 Ocak 2021 ile 1 Mart 2024 tarihleri arasında, kronik HCV enfeksiyonu için G/P tedavisi başlanan, tespit edilebilir HCV-RNA'sı olan, 18 yaş üstü hastalar analiz edildi. Birincil sonlanım noktası olan sürekli virolojik yanıt (SVR), tedavinin tamamlanmasından 12 hafta sonra tespit edilemeyen HCV-RNA olarak tanımlandı. Ayrıca G/P'nin güvenliği ve tolere edilebilirliği de değerlendirildi.
Bulgular: Toplam 191 hasta (%85,5 erkek) G/P ile tedavi edildi. Bunlardan 124'ü (%64,9) intravenöz uyuşturucu kullanıcısıydı. En yaygın genotip (GT) GT 3'tü (%57,1). Tedavinin tamamlanmasından on iki hafta sonra, 105 hasta takibe katıldı ve hepsi SVR12'ye ulaştı. Yan etki 12 hastada (%6,3) gözlendi. Bir hastada tedavi, 4. Haftada, kaşıntı ve döküntü nedeniyle kesildi.
Sonuç: G/P, kronik HCV enfeksiyonu olan hastalar için oldukça etkili, iyi tolere edilen ve güvenli bir pan-genotipik tedavi seçeneğidir.
Anahtar Kelimeler: Hepatit C virüsü, tedavi, glecaprevir, pibrentasvir

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Introduction

Hepatitis C virus (HCV) infection represents a major global public health concern. Among those infected, 75%-85% develop chronic infection, which can progress to severe conditions such as cirrhosis and hepatocellular carcinoma[1]. An estimated 50 million individuals globally are affected by chronic HCV infection, with approximately 1 million new cases reported each year[2]. In Türkiye, studies have shown that HCV prevalence ranges from 0.5% to 1%, with genotype 1b being the most prevalent[3-5].

The introduction of direct-acting antivirals (DAAs) in recent years has led to improved sustained virologic response (SVR) rates and reduced incidence of adverse events. Among these therapies is glecaprevir/pibrentasvir (G/P), which combines an NS3/4A protease inhibitor with an NS5A inhibitor. This regimen has a high barrier to resistance and is effective against all HCV genotypes. It is approved for use in patients without cirrhosis or with compensated cirrhosis. Previous research has shown that G/P treatment achieves SVR rates of 95%-100%, with most commonly reported adverse events being fatigue and headache[6-8].

The objective of this study was to evaluate the efficacy and safety of G/P in HCV-infected individuals using real-world data.

Materials and Methods

This retrospective study included patients over the age of 18 with chronic HCV infection and detectable HCV-RNA, regardless of prior HCV treatment status, who were seen at the Infectious Diseases and Clinical Microbiology outpatient clinic of Konya City Hospital between January 1, 2021, and March 1, 2024, and initiated on combination therapy with G/P. Patients were excluded if they were under 18 years of age, had hepatocellular carcinoma, had a history of liver transplantation, or were pregnant or breastfeeding. In Türkiye, G/P therapy is covered by the national health insurance for treatment-naive, non-cirrhotic patients regardless of HCV genotype, and liver biopsy is not required for reimbursement.

Baseline and end-of-treatment data were collected, including demographic characteristics, risk factors for HCV infection, history of previous HCV treatments, HCV genotype, and laboratory parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alpha-fetoprotein (AFP), and platelet count (PLT). HCV-RNA levels were assessed at baseline, weeks 4 and 8 of therapy, and 12 weeks after completing treatment. Since no patients underwent liver biopsy and elastography was unavailable at the study site, liver fibrosis status was evaluated using the AST-to-platelet ratio index (APRI) and fibrosis-4 (Fib-4) scores. The Fib-4 score was calculated based on Sterling's formula[9]: Age (years) × AST (IU/L)/PLT (10^9/L)x√ALT (IU/L). The APRI score was determined using Wai's formula[10]: (AST/upper limit of normal)/PLT (10^9/L)x100. Both scores were assessed at the initiation and completion of G/P therapy.

HCV-RNA levels were assessed using the AltoStar HCV RT-PCR kit, which has a detection range of 25 IU/ml to 1x10^7 IU/ml. An SVR at 12 weeks (SVR12) was defined as undetectable HCV-RNA at 12 weeks following the completion of G/P therapy.

The primary endpoint of the study was the SVR12 rate associated with the G/P regimen. Secondary endpoints included changes in liver fibrosis indicators (APRI, Fib-4) and selected biochemical markers (AST, ALT, AFP) in patients receiving G/P, virologic response rates at weeks 4 and 8 (defined as undetectable HCV-RNA level at 4 and 8 weeks after treatment initiation), the profile of drug-related adverse events, and the frequency of adverse events.

This study received approval from the KTO Karatay University Clinical Research Ethics Committee (approval number: 2024/012, dated: 06.06.2024) and was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Categorical variables were reported as frequencies and percentages. Continuous variables were presented as mean ± standard deviation or as median (minimum-maximum). As the continuous variables did not follow a normal distribution based on the Kolmogorov-Smirnov test, non-parametric methods were applied. The Wilcoxon signed-rank test was used to compare continuous variables before and after treatment. Statistical analyses were conducted using IBM SPSS version 26.0 (IBM SPSS, Chicago, IL), and a p-value of <0.05 was considered statistically significant.

Results

A total of 191 patients were included in the study. Of these, 169 (85.5%) were male, with a median age of 30 years (range 18-83). Intravenous drug use (IVDU) was reported in 124 patients (64.9%). None of the patients had cirrhosis. HCV genotype analysis was performed in 112 patients (59%): GT 3 in 57.1%, GT 1b in 15.2%, GT 1a in 12.5%, GT 2 in 8.9%, and GT 4 in 6.4%. Among patients who reported IVDU, GT 3 was found in 66.2% and GT 1a in 19.1% (Table 1). The mean baseline HCV-RNA level was 2,475,512 IU/ml. Median ALT and AST levels were 55 U/L and 35 U/L, respectively. The median APRI and Fib-4 scores at baseline were 0.4 and 0.6, respectively. Five patients had a history of prior treatment for

chronic HCV infection (two received sofosbuvir plus ribavirin, and three received interferon plus ribavirin). Among these, three had GT 3 and two had GT 1b.

All patients were prescribed an 8-week course of G/P therapy. Among those who completed follow-up at weeks 4 and 8, virologic response rates were 91.4% (32/35) and 100% (131/131), respectively. The three patients who did not achieve a virologic response at week 4 were all treatment-naive and infected with GT 3. Each of these patients subsequently achieved virologic response and SVR12 by week 8 post-treatment. At 12 weeks after treatment completion, 105 patients returned for follow-up, and all achieved SVR12 (per-protocol efficacy, 105/105 [100%]; intention-to-treat 105/191 [55%]) (Table 1). A statistically significant reduction was observed in ALT (p<0.001), AST (p<0.001), and APRI scores (p <0.001) at week 8 compared to baseline. No significant change was noted in AFP levels or Fib-4 scores (Table 2).

Table 1. Baseline characteristics of patients and treatment efficacy of G/P and G/P-related adverse events

	n=191
Male n (%)	169 (88.5%)
Age	
Mean ± SD	33.9±14
Median (minimum-maximum)	30 (18-83)
IV drug user n (%)	124 (64.9%)
Treatment experience, n(%)	
HCV treatment-naïve	186 (97.4%)
HCV treatment-experienced	5 (2.6%)
HCV genotype, n(%)	
Genotype 1a	14 (12.5)
Genotype 1b	17(15.2)
Genotype 2	10 (8.9)
Genotype 3	64 (57.1)
Genotype 4	7 (6.3)
Unknown	79 (41.4%)
HCV-RNA (mean) (IU/ml)	2.475.512
G/P efficacy n(%)	
Virologic response at week 4*	31 (91.4%)
Virologic response at week 8**	131 (100%)
SVR12***	105 (100%)
AE's n (%)	
Patients with any AEs	12 (6.3)
AEs leading to G/P discontinuation****	1 (<1)[a]
AEs profile	
Headache	6 (3.1)
Fatigue	4 (2.1)
Itching	3 (1.6)
Rash	3 (1.6)
Nausea	3 (1.6)

*4th week evaluation available in 35 patients, ** 8th week evaluation available in 131 patients, ***SVR12 evaluation available in 105 patients, ****for itching and rash. G/P: Glecaprevir/pibrentasvir, SVR12: Sustained virologic response at 12 weeks, AE: Advers event, SD: Standard deviation, HCV: Hepatitis C virus

A total of 19 adverse events were reported in 12 patients (12/191, 6.3%): headache in 6 patients, fatigue in 4, pruritus in 3, rash in 3, and nausea in 3. Four patients experienced both headache and fatigue, while three patients had concurrent pruritus and rash. One patient with pruritus and rash discontinued G/P therapy at week 4 due to persistent symptoms despite antihistamine use. This patient achieved a virologic response at week 4 and SVR12 (Table 1).

Discussion

This real-world study demonstrated a 100% SVR rate among non-cirrhotic HCV patients treated with the G/P regimen. Real-world multicenter studies have similarly reported SVR rates with G/P ranging from 95% to 100%[5-8,11].

According to international guidelines, an 8-week G/P regimen is recommended for treatment-naive HCV patients without cirrhosis. However, baseline NS5A polymorphisms such as A30K and Y93H are known to confer high resistance to NS5A inhibitors, potentially reducing SVR12 rates in treatment-experienced patients with GT 3. For this reason, a 12-week G/P treatment course is advised for GT 3-infected patients with prior treatment experience and no cirrhosis[12-14]. In this study, all patients were non-cirrhotic and the majority were treatment-naive. All patients received an 8-week course of G/P therapy. Contrary to guideline recommendations, three treatment-experienced patients with GT 3 also received 8 weeks of therapy, and all achieved SVR12.

Shorter treatment durations with G/P may enhance access to therapy by lowering healthcare costs and improving patient

Table 2. Laboratory values and fibrosis scores of patients before and after G/P treatmen

	Pre-treatment Median (minimum-maximum)	Post-treatment Median (minimum-maximum)	p-value
AST (U/l)	35 (11-842)	17 (7-70)	<0.001
ALT (U/l)	55 (9-986)	14 (5-68)	<0.001
AFP (µ/l)	2.5 (0.9-14.9)	2.5 (0.9-16)	0.08
PLT (10^3/µl)	243 (36-690)	246 (53-431)	0.878
APRI score	0.4 (0.1-10.6)	0.2 (0.1-2)	<0.001
Fib-4 score	0.6 (0.1-11.2)	0.6 (0.3-7.8)	0.138

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, AFP: Alpha-fetoprotein, G/P: Glecaprevir/pibrentasvir PLT: Platelet count, APRI: Aspartate aminotransferase-to-platelet ratio index, Fib-4: Fibrosis-4

adherence. A multinational study assessing the efficacy of a 4-week G/P regimen in individuals with HCV infection found that although 87% achieved HCV-RNA negativity at week 4, the SVR12 rate was only 78%, indicating reduced effectiveness compared to longer treatment durations[15]. In the present study, the virologic response rate at week 4 was 91.4%. However, since all patients were treated with an 8-week regimen, the efficacy of shorter treatment durations was not assessed.

In contrast to earlier studies identifying GT 1b as the most prevalent in Türkiye[3-5,16], over half of the patients in this study had HCV GT 3. This discrepancy in genotype distribution may be due to differences in the demographic characteristics of the study population compared to the general population in Türkiye. The high proportion of IVDU among the study participants supports this explanation. Although previous research suggests that the efficacy of G/P may be reduced in patients with GT 3[13,17], all patients with this genotype in our study achieved SVR12 following 8 weeks of treatment.

Earlier studies have shown that treatment of chronic HCV with DAAs is associated with improvements in noninvasive markers of liver fibrosis[18-20]. In our study, APRI scores significantly decreased after G/P therapy, while Fib-4 scores did not show a similar regression.

Overall, G/P was well tolerated in this study, with adverse event rates considerably lower than those reported in registration trials. Headache and fatigue were the most frequently reported adverse events. None of the adverse events were fatal. Only one patient discontinued treatment due to pruritus and rash. The observed safety and tolerability were consistent with those reported in registration studies[21].

Study Limitations

This study has several limitations due to its retrospective, real-world design. First, some clinical information may be incomplete or inaccurately documented. Additionally, adverse events might have been underreported, which could affect the interpretation of drug safety. Furthermore, since the study was conducted at a single center, the generalizability of the results is limited. Therefore, further research involving multiple centers from different regions of Türkiye is needed.

Conclusion

G/P is a highly effective, well-tolerated, and safe pan-genotypic treatment for patients with chronic HCV infection. Broadening access to this therapy could play an important role in efforts to eliminate HCV.

Ethics

Ethics Committee Approval: This study received approval from the KTO Karatay University Clinical Research Ethics Committee (approval number: 2024/012, dated: 06.06.2024) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.R.T., Y.G., Concept: M.R.T., Y.G., Design: M.R.T., Y.G., Data Collection or Processing: M.R.T., Y.G., Analysis or Interpretation: M.R.T., Y.G., Literature Search: M.R.T., Writing: M.R.T.

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Hepatitis A Screening and Vaccination Among People Living with HIV: When is the Ideal Time?

HIV ile Yaşayan Bireylerde Hepatit A Taraması ve Aşılama: İdeal Zaman Ne Zaman?

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Abstract

Introduction: This study aimed to determine the hepatitis A seroprevalence and vaccination status among [people living with Human Immunodeficiency Virus (HIV) (PLWH)], assess serologic responses to vaccination, and identify age groups for which hepatitis A vaccination is recommended.
Materials and Methods: This research was conducted between January 2019 and 2024, comparing groups with positive and negative anti-hepatitis A virus (HAV) immünoglobulin G (IgG) antibodies based on age and sex. A receiver operating characteristic (ROC) analysis was performed to identify the optimal age cutoff for predicting anti-HAV IgG positivity. Anti-HAV IgG serology was screened at least 1 month after the second vaccine dose to evaluate antibody formation.
Results: Of the 1,140 participants, 61.5% tested positive for anti-HAV IgG at baseline. Those with positive results exhibited significantly higher mean age (44.6±11.6 years) than those with negative results (33.7±8.6 years; p<0.001). Seropositivity was significantly higher among women (75.0%, n=87/702; p=0.002) and individuals >40 years of age (83.3%, p<0.001). The ROC analysis identified 40 years as the optimal age cutoff, with an area under the curve of 0.78 (95% confidence interval, 0.75-0.81), a sensitivity of 61.6%, and a specificity of 80.1%. Of the seronegative individuals, 86.1% received two vaccine doses; of the 268 with follow-up anti-HAV IgG serology, 86.1% had seroconverted and the results of 109 patients are still awaited.
Conclusion: Examining individuals living with HIV for hepatitis A antibodies at their initial hospital admission is critical so that those with seronegativity can be vaccinated with two doses of hepatitis A. Vaccination can be administered to those <40 years of age without prior serological testing. These findings provide valuable insights for developing hepatitis A vaccination policies and monitoring strategies for PLWH.
Keywords: HIV, HAV, vaccination, prophylaxis

Öz

Giriş: Bu çalışmanın amacı, İnsan Bağışıklık Yetmezliği Virüsü (HIV) ile yaşayan bireylerde (PLWH) hepatit A seroprevalansını ve aşılanma durumunu belirlemek, aşılara karşı serolojik yanıtı değerlendirmek ve hepatit A aşısının önerileceği yaş gruplarını saptamaktır.

Gereç ve Yöntem: Çalışma, Ocak 2019-2024 yılları arasında yürütülmüş ve anti-hepatit A virüsü (HAV) immünoglobulin G (IgG) antikoru pozitif olan bireyler ile negatif olan bireyler, yaş ve cinsiyet açısından karşılaştırılmıştır. Anti-HAV IgG pozitifliğini öngörmede en uygun yaş sınırını belirlemek

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Öz

amacıyla alıcı işletim özelliği (ROC) analizi uygulanmıştır. Antikor yanıtını değerlendirmek için ikinci aşı dozundan en az bir ay sonra anti-HAV IgG serolojisi taranmıştır.

Bulgular: Toplam 1.140 katılımcının %61,5'inde başlangıçta anti-HAV IgG pozitifti. Anti-HAV IgG pozitif saptanan bireylerin yaş ortalaması (44,6±11,6 yıl), negatif saptanan bireylerin yaş ortalamasına (33,7±8,6 yıl) kıyasla anlamlı derecede daha yüksekti (p<0,001). Seropozitivite oranı kadınlarda (%75,0; n=87/702; p=0,002) ve 40 yaş üzerindeki bireylerde (%83,3; p<0,001) belirgin olarak daha fazlaydı. ROC analizine göre anti-HAV IgG pozitifliğini öngörmek için en uygun yaş sınırı 40 olarak belirlendi (eğri altı alan: 0,78; %95 güven aralığı: 0,75-0,81; duyarlılık: %61,6; özgüllük: %80,1). Seronegatif bireylerin %86,1'ine iki doz aşı yapıldı ve aşılama sonrası 268 kişinin %86,1'inde serokonversiyon saptandı. Ancak 109 olgunun seroloji sonuçları henüz beklenmektedir.

Sonuç: HIV ile yaşayan bireylerin ilk sağlık kuruluşu başvurusunda hepatit A antikorları yönünden taranması ve seronegatif olanlara iki doz hepatit A aşısı uygulanması önem arz etmektedir. Serolojik test yapılmaksızın doğrudan aşılama, 40 yaş altı bireyler için uygun bir strateji olabilir. Bu çalışma, HIV ile yaşayan bireylere yönelik hepatit A aşı politikalarının geliştirilmesine ve izlem stratejilerinin oluşturulmasına katkı sağlamaktadır.

Anahtar Kelimeler: HIV, HAV, aşı, profilaksi

Introduction

Hepatitis A infection is a global public health threat and is common in underdeveloped and developing countries because of poor hygiene conditions. The virus mainly spreads through the fecal-oral route via contaminated food, water, or close physical contact such as oral-anal sex. In regions with high endemicity, most hepatitis A infections occur in early childhood[1]. In contrast, in developed and resource-rich regions, hepatitis A outbreaks are generally restricted to vulnerable populations, such as homeless people, drug users, and men who have sex with men (MSM), transmitted via direct person-to-person contact[2]. The seroprevalence of hepatitis A infection in [people living with human immunodeficiency virus (HIV) (PLWH)] is higher than that in HIV-negative individuals[1], which could be attributed to the higher prevalence of oral-anal sex, the higher number of sexual partners, and on rare occasions, intravenous drug use, a common risk factor for both conditions[1,3]. Screening for hepatitis A and vaccinating seronegative individuals is crucial for PLWH. Although the guidelines for hepatitis A screening and vaccination are clear, several factors, including test kit and vaccine shortages, antivaccine attitudes, and non-compliance with follow-up visits, may hinder effective screening and vaccination practices[4].

Hepatitis A remains endemic in our country, and the age of exposure to the virus has shifted toward adolescence and young adulthood. The introduction of the hepatitis A vaccine in our country in 2012, along with improved hygiene, increased socioeconomic status, and enhanced vaccination coverage, has led to a decrease in the incidence of hepatitis A virus (HAV). However, this scenario has escalated the population susceptible to the virus among unvaccinated groups[5]. This study aimed to assess the seroprevalence of hepatitis A, the vaccination status of individuals susceptible to it, and the serologic response to vaccination among PLWH in our cohort. The secondary aim was to determine the specific age groups for which the hepatitis A vaccine could be recommended without serology screening owing to recent changes in hepatitis A epidemiology in our country.

Materials and Methods

This study included PLWH registered in our cohort who attended follow-up visits between January 2019 and January 2024. Screening for anti-HAV immünoglobulin G (IgG) antibodies at baseline is routinely performed for PLWH presenting to our clinic using the Alinity i anti-HAV IgG (Abbott, USA) antibody kit. Those who test negative are scheduled to receive two subcutaneous shots of hepatitis A vaccination, administered 6 months apart. Anti-HAV IgG antibodies are rescreened at least 1 month after completing the vaccination schedule.

The baseline screening results were retrospectively derived from the medical records and outpatient clinic notes. Groups with positive and negative anti-HAV IgG antibody results were compared in terms of sex and age. Data regarding hepatitis A vaccination of individuals susceptible to hepatitis A were derived from the National Vaccine Tracking System and hospital records. In contrast, postvaccination rescreening data were obtained from medical records.

Statistical Analyses

Statistical analyses and visualizations were performed using R version 4.3.1, a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/). Categorical variables were compared using the Pearson chi-square test, and continuous variables were compared using Student's t-test. A p-value of <0.005 was considered statistically significant. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cutoff point for age in predicting anti-HAV IgG positivity.

Ethical Approval

This study was approved by the Ege University Medical Research Ethics Committee (approval number: 2023-1702, dated: 31.10.2023).

Results

This study included 1,140 PLWH [average age 40.4±11.8 years, 1,024 (89.8%) men]. Anti-HAV IgG antibodies were positive at baseline in 61.5% (n=702/1140). None of the patients presented with acute hepatitis A. Patients with anti-HAV IgG positivity at baseline exhibited a higher mean age than those who were negative (44.6±11.6 and 33.7±8.6, respectively; p<0.001). Anti-HAV IgG positivity was significantly higher among women (n=87/702; 75.0%) than men (n=615/702; 59.6%) (p=0.002). The seropositivity rate was 83.3% in individuals >40 years of age and 42.9% in the ≤40 age group (p<0.001). According to the ROC analysis, the optimal cutoff point was 40 years (area under the curve, 0.78; 95% confidence interval, 0.75-0.81; sensitivity, 61.6%; specificity, 80.1%) (Figure 1). Of the 438 seronegative individuals, 377 (86.1%) received two doses of the hepatitis A vaccine. Analysis of 61 individuals who did not receive the vaccine revealed that 21 were lost to follow-up, 2 had died, and 38 were referred to their family doctor owing to a temporary stockout of the hepatitis A vaccine in our hospital; however, they did not receive the vaccination (Figure 2). Of the 377 individuals who received two doses of hepatitis A vaccine, follow-up anti-HAV IgG serology was available for 268 (71.1%) and 86.1% had seroconverted; the results are still awaited for 109 patients.

Discussion

The World Health Organization has provided guidelines for achieving the goal of eradicating viral hepatitis infections by 2030 via improved sanitation, food safety, and vaccination practices[6]. The introduction of the hepatitis A vaccine in our country in 2012, along with improvements in living conditions, socioeconomic status, and vaccination coverage, has led to a decrease in HAV incidence[5,7]. In middle-to-high-income societies, the lack of exposure to HAV during childhood may result in a young adult population susceptible to hepatitis A outbreaks. A study involving 22 European countries reported that most hepatitis A patients were MSM, including those coinfected with HIV[8]. HAV and HIV coinfection may lead to a higher hepatitis A viral load and a longer duration of viremia than monoinfection, extending the transmission period and resulting in more severe liver damage[9]. In addition, the presence of HAV infection can increase the HIV viral load and the probability of HIV transmission[9]. Thus, screening for hepatitis A antibodies in PLWH at presentation and vaccinating those who test negative is critical from both individual and public health perspectives. The prevalence of hepatitis A exposure in Europe has been reported to vary between 0.00055‰ and 0.0001%[10]. However, screening rates show significant variations throughout the continent, with very low rates in Central and Eastern European countries (54.5% in 2019 and 47.4% in 2022)[11].

Our study revealed that most PLWH were already seropositive for hepatitis A at baseline. Other studies from Türkiye have obtained similar results[12-14]. The introduction of the hepatitis A vaccine into the national vaccination program in Türkiye was delayed until 2011. Therefore, the high positivity rate in our study was due to past infection rather than childhood vaccination. However, because of the retrospective design of the research, distinguishing between the two is challenging.

Recent reports have highlighted the changing epidemiological profile of hepatitis A, with outbreaks appearing more among homeless individuals, drug users, and MSM than other segments of the society, resulting in severe adverse outcomes[2,15]. During

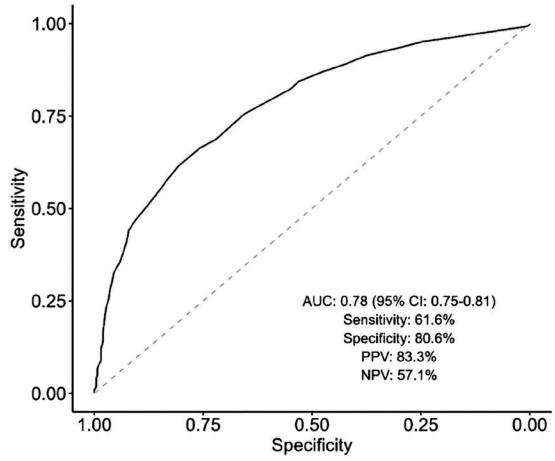

Figure 1. Receiver operating characteristic curve to find best cutoff of age for anti-hepatitis A virus IgG positivity

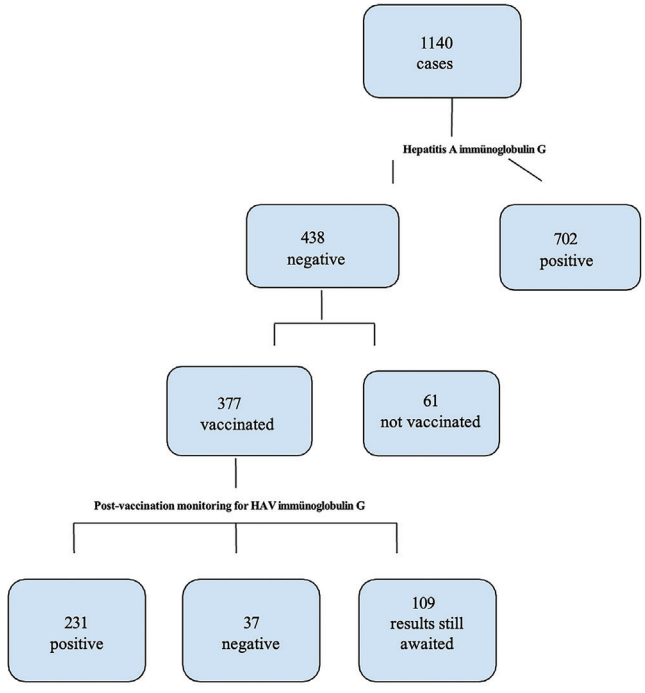

Figure 2. Schematic summary of the cases included in the study

2017, 1,521 outbreak-associated HAV cases were reported from California, Kentucky, Michigan, and Utah, with 1,073 (71%) hospitalizations and 41 (3%) deaths. Overall, 866 (57%) patients stated drug use, homelessness, or both. Of all cases, 818 (54%) had an indication for hepatitis A vaccination before becoming infected (i.e., using drugs or being MSM), as recommended by the Advisory Committee on Immunization Practices (ACIP)[16]. Similarly, between 2016 and 2017, a large outbreak of >4000 acute hepatitis A cases were reported from the European Union and European Economic Area countries, of which 84% were MSM[17]. In an outbreak in Canada between 2017 and 2018, 52 acute hepatitis A cases were reported; 64% were MSM, and 36% of the possible or confirmed cases were coinfected with HIV[18]. These reports suggest that even in developed countries, vaccination rates among vulnerable populations remain low and the disease is overlooked.

Vaccines coupled with safe sexual behaviors are known to be highly effective in preventing acute hepatitis A infection. The Centers for Disease Control and Prevention (CDC) and the ACIP recommend vaccinating individuals at risk of HAV infection, such as those aged ≥1 year, homeless individuals, and MSM, or those at high risk of severe HAV infection (e.g., individuals with chronic liver disease or those living with HIV) with the hepatitis A vaccine[19]. Furthermore, their prioritization for vaccination during outbreaks is recommended[19]. The vaccination acceptance rate was exceptionally high in our study, with 86% of the nonimmune individuals receiving the full dose hepatitis A vaccine. Referrals to other healthcare facilities owing to vaccine stockouts in the clinic appeared to be a major obstacle to vaccination, highlighting the importance of integrating healthcare services in a single setting. Questioning the reason for not being vaccinated was not possible because of the retrospective design of the study.

The antibody response to vaccination may be lower in PLWH than in HIV-negative individuals. Vaccine response rates may be low after the first dose but usually increase significantly after the second dose[1,3,19]. The response rates to the two doses of hepatitis A vaccine were considerably high in our cohort. Reports suggest that 85% of PLWH remain seropositive 6-10 years after the two-dose vaccine series[20]. A higher CD4 T cell count at the time of vaccination has been shown to enhance the vaccine response[21]. Our local guidelines recommend testing for anti-HAV IgG in PLWH at baseline and vaccinating seronegative individuals with two doses if the CD4 T lymphocyte count is >350 cells/mm^3 and with three doses if it is <350 cells/mm^3[22]. A third dose of the vaccine is planned for our patients who did not develop an antibody response after receiving a full dose of vaccination. According to CDC recommendations, immunoglobulin (IG) administration may be necessary for PLWH who do not seroconvert after two doses of vaccine in high risk contact situations (e.g., sexual or household contact); however, this issue is controversial[23]. Indications for IG use are based on ACIP recommendations published in 2007 for the prevention of hepatitis A infection after exposure to HAV and in international travelers. Information about the relative efficacy of the vaccine compared with IG postexposure is limited, and no data are available for individuals aged >40 years and those with underlying medical conditions[24].

Interruptions in the availability of antibody screening tests for hepatitis A may hamper vaccination practices. Screening rates are considerably low in several countries in our region[11]. The findings of our study suggest that individuals <40 years of age and who do not have a history of receiving the hepatitis A vaccine can be vaccinated even if antibody testing is not available. The hepatitis A vaccine does not increase the HIV viral load, influence the CD4 T lymphocyte count, or accelerate the progression to acquired immunodeficiency syndrome (AIDS); thus, vaccination is a safe practice for PLWH[19].

Although there seems to be a consensus on vaccinating individuals with negative hepatitis A serology, guidelines on serological follow-up and booster vaccination differ[1,2]. The British HIV Association recommends HAV vaccination every 10 years for PLWH with an ongoing exposure risk, whereas the European AIDS Clinical Society advises periodic monitoring of hepatitis A serologies[2].

Study Limitations

The primary limitation of our study is the inability to reach all patients, preventing the evaluation of postvaccination control serologies. Moreover, the retrospective, single-center design may limit the generalizability of the findings. Further multicenter, prospective studies are needed to validate our results.

Conclusion

Although most of our cohort seems to have been exposed to hepatitis A, either via vaccination or via infection, there remains a susceptible group who would benefit from late vaccination. As recommended by international and national guidelines, screening PLWH for hepatitis A antibodies at baseline and administering two doses of hepatitis A vaccine to those who are seronegative is critical for preventing adverse outcomes due to acute hepatitis A infection. The inability to perform hepatitis A serology is not a barrier to vaccination. Our study suggests that individuals <40 years of age can be vaccinated without serological testing as the seropositivity rates are extremely low in this group. We believe that the findings from this research will inform the development of policies on hepatitis A vaccination and the monitoring of serologic responses in PLWH.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Medical Research Ethics Committee (approval number: 2023-1702, dated 31.10.2023).

Informed Consent:

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.P., M.T., D.G., Concept: A.N.E., H.P., M.T., D.G., Design: .N.E., H.P., M.T., Data Collection or Processing: C.T., D.G., Analysis or Interpretation: M.C., A.K., Literature Search: M.C., C.T., Writing: M.C., A.K.

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Evaluation of Factors Associated with Fatality in Hospitalized Patients with *Clostridioides difficile* Infection

Hastanede Yatan *Clostridioides difficile* Enfeksiyonu Olan Hastalarda Fatalite ile İlişkili Faktörlerin Değerlendirilmesi

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Abstract

Introduction: *Clostridioides difficile* typically arises from changes in the microbiota following antibiotic use and can be fatal, especially in hospitalized patients. In this study, we investigated fatality and the associated factors following *C. difficile* infection (CDI) in hospitalized patients.
Materials and Methods: This case-control study included death cases within 30 days, with a corresponding control group comprising survivors. Demographic and clinical data were compared between the two groups. The risk factors for 30 day fatality were analyzed through logistic regression and Kaplan-Meier (KM) survival analysis.
Results: A total of 67 adult patients were enrolled. All-cause mortality occurred in 14 (20.9%) patients within 30 days of diagnosis. Procalcitonin level >0.5 ng/ml at the onset of the episode [odds ratio (OR): 7.407, confidence interval (CI) 1.487-39.906], ongoing antibiotic therapy for infections other than CDI after the onset of a CDI episode (OR: 5.927, CI 1.053-33.357), and the occurrence of CDI in the intensive care unit (ICU) (OR: 4.800, CI 1.066-21.609) were identified as independent risk factors for all-cause 30 day fatality. The impact of these three variables on 30 day fatality was demonstrated through KM survival analysis (log-rank test, p<0.05).
Conclusion: The occurrence of CDI in hospitalized patients warrants special attention owing to its potential to cause mortality. The onset of CDI during an ICU stay and elevated procalcitonin levels at the onset of the related episode may predict poor outcomes. The management of antibiotic use cases leading to CDI following its development may improve survival chances.
Keywords: *Clostridioides difficile*, fatality, procalcitonin

Öz

Giriş: *Clostridioides difficile* sıklıkla antibiyotik kullanımı sonrası mikrobiyotadaki değişiklikler sonucu gelişmektedir ve özellikle hastanede yatan hastalarda fatal olabilir. Çalışmamızda hastanede yatarak takip edilen hastalarda *C. difficile* enfeksiyonu sonrası gelişen ölüm oranı ve ilişkili faktörler araştırılmıştır.
Gereç ve Yöntem: Bu vaka-kontrol çalışmasında vaka grubunu 30 gün içinde ölenler, kontrol grubunu ise hayatta kalanlar oluşturmaktaydı. İki grup arasında, demografik ve klinik veriler karşılaştırıldı. Otuz günlük fatalite için risk faktörleri lojistik regresyon analizi ve Kaplan-Meier (KM) sağkalım analizi ile araştırıldı.
Bulgular: Toplam 67 erişkin hasta çalışmaya dahil edildi. Tanıdan sonraki 30 gün içinde 14 (%20.9) hastada tüm nedenlere bağlı ölüm meydana geldi. Atak başlangıcında prokalsitonin >0,5 ng/ml olması [olasılık oranı (OR): 7,407 (1,487-39,906)], *C.difficile* enfeksiyonu tanısı sonrası *C. difficile* enfeksiyonu dışındaki enfeksiyonlar için devam eden antibiyotik tedavisi [OR: 5,927 (1,053-33,357)] ve *C. difficile* enfeksiyonu atağının yoğun bakım ünitesinde gelişmesi [OR: 4,800 (1,066-21,609)] tüm sebeplere bağlı 30 günlük fatalite için bağımsız risk faktörleri olarak saptandı. Bu üç değişkenin 30 günlük fatalite üzerine etkisi KM sağkalım analizi ile de gösterildi (log-rank testi, p<0,05).
Sonuç: Sonuç olarak hastanede yatan hastalarda gelişen *C. difficile* enfeksiyonu ölüme sebep olabilmesi nedeniyle önemlidir. *C. difficile* enfeksiyonu atağının yoğun bakım ünitesinde yatarken gelişmesi ve atak başlangıcındaki prokalsitonin yüksekliği, kötü sonuçlar için öngördürücü olabilir. *C. difficile* enfeksiyonu atağına sebep olan antibiyotik kullanımının, *C. difficile* enfeksiyonu gelişimi sonrası uygun yönetimi sağkalıma fayda sağlayabilir.
Anahtar Kelimeler: *Clostridioides difficile*, fatalite, prokalsitonin

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Introduction

Clostridioides difficile is a Gram-positive anaerobic bacterium causing antibiotic-associated diarrhea. *C. difficile* infection (CDI) is characterized by colitis that frequently develops due to disruptions in the gut flora following antibiotic use. Antibiotics impair the barrier function of a normal colonic microbiota, thereby providing an environment for *C. difficile* proliferation and toxin production[1]. The other reported risk factors for CDI include advanced age, history of hospitalization, cancer chemotherapy, gastrointestinal surgery, inflammatory bowel diseases, and gastric acid suppression[2-5].

Studies on diarrhea causes across regions have implicated *C. difficile* among the most common agents[6-9]. *C. difficile* is also a significant cause of hospital-acquired diarrhea. Extensive antibiotic use, gastrointestinal procedures, and medications that suppress gastric acid increase the frequency of this disease among hospitalized patients. The development of CDI in hospitalized patients can lead to prolonged hospital stay, increased cost, morbidity, and, most importantly, mortality. Previous studies have reported 30 day all-cause mortality rates following CDI, ranging from 8% to 20%[10-12]. Clinical variables such as advanced age, immunosuppression, and presence of comorbid conditions, as well as laboratory parameters including high white blood cell count, elevated creatinine level, low albumin level, and ribotype 027 infection, have been associated with CDI-related mortality[13-16].

In this study, we aimed to determine the fatality rates and associated risk factors for 30-day fatality in hospitalized CDI patients so as to contribute to the design of approaches toward reducing CDI-related mortality.

Materials and Methods

Study Design and Population

This study was conducted at Giresun Training and Research Hospital, a tertiary care hospital (approval number: 19.02.2025/06, date: 20.02.2025), between September 2021 and December 2024. The hospital has a total of 450 beds [85 intensive care unit (ICU) beds], providing care to a wide range of patients, including those with various comorbidities such as cancer. Adult patients who developed acute diarrhea (characterized by three or more loose stools within 24 h) during hospitalization and with positive *C. difficile* detection in stool samples through gastrointestinal polymerase chain reaction (PCR) were included. Patients aged <18 years, those who were unable to provide stool samples for *C. difficile* testing, and those with incomplete medical records or who were transferred to other hospitals during the study period were excluded from the analysis. Patient data were retrospectively collected from the hospital's electronic records. Age, gender, hospitalization unit (ward or ICU), Charlson Comorbidity Index, use history of proton pump inhibitor, statin, and corticosteroid, hospitalization in the last 3 months, gastrointestinal procedures (such as esophagogastroscopy or colonoscopy) in the last 2 months, prior antibiotic use in the past 2 months (if any, the specific class), severity of CDI, ongoing antibiotic therapy for infections other than CDI after the onset of a CDI episode, antibiotic treatment for CDI, laboratory values at CDI onset (white blood cell count, creatinine, procalcitonin), and 30 day all-cause mortality were recorded. The patients were categorized into two groups based on the occurrence of 30 day fatality, and their demographic and clinical data were compared to identify the independent risk factors for 30 day fatality in a case-control study. The case group included patients who died within 30 days following CDI diagnosis, whereas the control group included patients who survived beyond this period.

Definitions

Severe CDI was characterized by a white blood cell count of >15,000 cells/µl, serum creatinine level >1.5 mg/dl, or serum albumin level <3 g/dl at the onset of a CDI episode. Immunosuppression was defined as undergoing chemotherapy for malignancy, the use of an immunosuppressive biological agent for systemic autoimmune disease, or receiving corticosteroids at a dose equivalent to ≥20 mg/day of prednisone for at least 14 days. In a patient who developed diarrhea due to *C. difficile* during hospitalization, the continued antibiotic therapy initiated for an infection other than those induced by CDI (such as pneumonia, urinary tract infection, bacteremia, and surgical site infection) in the pre-diarrhea period after diarrhea was defined as ongoing antibiotic therapy for infections other than CDI.

Microbiology

Stool samples from hospitalized patients with acute diarrhea were analyzed using the QIAstat-Dx Analyzer 1.0 (Qiagen N.V., Hilden, Germany) and QIAstat-Dx Gastrointestinal Panel 2 (Qiagen N.V.) with multiplex real-time PCR. Patients who tested positive for *C. difficile* toxin A and B genes via this method were classified as having CDI.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics included the mean, standard deviation, percentage, and median (minimum-maximum). The Kolmogorov-Smirnov test was performed to assess the normality of numerical variables. Independent sample t-test was applied for variables showing a normal distribution, and the Mann-Whitney U-test was performed for variables without normal distribution to

compare the numerical variables. The chi-square or Fisher's exact test was performed to compare categorical variables. Variables with p<0.05 in univariable analysis were included in a multivariable logistic regression model (backward:LR) to determine independent risk factors for 30 day fatality. Kaplan-Meier (KM) survival analysis was performed to evaluate the impact of these risk factors on survival, and the differences were compared using the log-rank test. The sample size was not calculated, and all patients diagnosed with CDI who met the inclusion criteria were enrolled. p<0.05 was considered to indicate statistical significance.

Results

During the study period, 67 adult patients who developed acute diarrhea during hospitalization and tested positive for *C. difficile* in gastrointestinal PCR testing were enrolled in the study. The mean age of the study population was 75.5±15.8 (range: 22-100) years. Of the total, 37 (55.2%) were male. The most frequently observed comorbidities included hypertension, coronary artery disease, and chronic kidney disease. A total of 62 (92.5%) patients had used antibiotics within the last 2 months before the occurrence of the CDI episode, with cephalosporins and beta-lactam/beta-lactamase inhibitors being the most frequently used antibiotic groups. The rate of CDI episodes occurring in the ICU was 26.9%, whereas that of severe CDI was 62.7%. The medications used for CDI treatment were metronidazole (61.2%), oral vancomycin (28.4%), and their combination (10.4%). leukocyte count and the levels of creatinine and procalcitonin were higher in the fatality group; however, statistical significance was detected only for procalcitonin. A comparison of patients' demographic, clinical, and laboratory values is shown in Table 1.

Among all patients, 14 (20.9%) died within 30 days after the CDI episode. In the 30-day fatality group, ICU-onset CDI, severe CDI, ongoing antibiotic therapy for infections other than CDI after the onset of a CDI episode, and elevated procalcitonin levels were more common (p-values were 0.004, 0.009, 0.002, and 0.004, respectively).

In the logistic regression model that included cases of ICU-onset CDI, severe CDI, continued antibiotic treatment for infections other than CDI after the onset of a CDI episode, and procalcitonin level >0.5 ng/ml, the following were identified as independent risk factors for 30 day fatality: procalcitonin level >0.5 ng/ml [odds ratio (OR): 7.407, confidence interval (CI) 1.487-39.906], continued antibiotic treatment for infections other than CDI after the onset of a CDI episode (OR: 5.927, CI 1.053-33.357), ICU-onset CDI (OR: 4.800, CI 1.066-21.609) (Table 2). KM survival analysis revealed that ICU-onset CDI, continued antibiotic treatment for infections other than CDI after the onset of a CDI episode, and procalcitonin level ≥0.5 ng/ml had a significant impact on the survival time (log-rank test, p<0.05). The KM survival analysis curves for these three risk factors are depicted in Figure 1.

Table 1. Comparison of the demographic data and clinical characteristics of patients with fatality and survivors

	Died within 30 days (n=14)	Survived (n=53)	p-value
Age, median (min.-max.)	86 (22-100)	78 (29-96)	0.177
Female gender, n (%)	9 (64.3)	21 (39.6)	0.099
CDI episode in ICU, n (%)	8 (57.1)	10 (18.9)	**0.004**
CCI, median (min.-max.)	5.5 (0-9)	5 (0-10)	0.666
Hypertension, n (%)	11 (78.6)	35 (66.0)	0.369
Diabetes mellitus, n (%)	6 (42.9)	12 (22.6)	0.129
Coronary artery disease, n (%)	5 (35.7)	24 (45.3)	0.520
Congestive heart failure, n (%)	0 (0.0)	7 (13.2)	0.151
Chronic pulmonary disease, n (%)	2 (14.3)	12 (22.6)	0.494
Malignancy, n (%)	1 (7.1)	13 (24.5)	0.155
Immunosupression, n (%)	2 (14.3)	13 (24.5)	0.414
Chronic kidney disease, n (%)	5 (35.7)	16 (30.2)	0.692
Hemodialysis, n (%)	1 (7.1)	3 (5.7)	0.835
Cerebrovascular disease, n (%)	6 (42.9)	11 (20.8)	0.091
Dementia, n (%)	3 (21.4)	5 (9.4)	0.218
PPI use, n (%)	9 (64.3)	27 (50.9)	0.373
Hospitalization in the last 3 months, n (%)	11 (78.6)	38 (71.7)	0.606

Table 1. Continued

	Died within 30 days (n=14)	Survived (n=53)	p-value
GI procedure in the last 2 months, n (%)	1 (7.1)	13 (24.5)	0.155
Statin use, n (%)	3 (21.4)	14 (26.4)	0.703
Corticosteroid use, n (%)	2 (14.3)	4 (7.5)	0.432
Antibiotic use in the last 2 months, n (%)	13 (92.9)	49 (92.5)	0.959
Cephalosporin use, n (%)	10 (71.4)	28 (52.8)	0.212
Beta-lactam/beta-lactamase inhibitor use, n (%)	4 (28.6)	20 (37.7)	0.525
Fluoroquinolone use, n (%)	0 (0.0)	6 (11.3)	0.187
Carbapenem use, n (%)	1 (7.1)	12 (22.6)	0.192
Severe infection, n (%)	13 (92.9)	29 (54.7)	**0.009**
Continued antibiotic use for infections other than CDI after CDI diagnosis, n (%)	12 (85.7)	21 (39.6)	**0.002**
Metronidazole treatment, n (%)	9 (64.3)	32 (60.4)	0.790
Oral vancomycin treatment, n (%)	3 (21.4)	16 (30.2)	0.518
Metronidazole and oral vancomycin combined treatment, n (%)	2 (14.3)	5 (9.4)	0.598
WBC, median (min.-max.)	13.44 (2.77-23.28)	8.59 (0.44-27.56)	0.060
Creatinine, median (min.-max.)	1.84 (0.19-4.25)	0.98 (0.34-7.72)	0.367
Procalcitonin, median (min.-max.)	1.58 (0.17-49.80)	0.35 (0.08-17.66)	**0.002**
Procalcitonin >0.5 ng/ml, n (%)	11 (78.6)	19 (35.8)	**0.004**

CCI: Charlson Comorbidity Index, CDI: Clostridioides difficile infection, GI: Gastrointestinal, ICU: Intensive care unit, min.-max.: Minimum-maximum, PPI: Proton pump inhibitor, SD: Standard deviation, WBC: White blood cell

Table 2. Univariable and multivariable logistic regression analyses of risk factors associated with 30 day fatality

	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
CDI episode in the ICU	5.733 (1.622-20.263)	0.007	4.800 (1.066-21.609)	0.041
Severe infection	10.759 (1.311-88.265)	0.027	-	-
Continued antibiotic use for infections other than CDI after CDI diagnosis	9.143 (1.855-44.056)	0.007	5.927 (1.053-33.357)	0.044
Procalcitonin >0.5 ng/ml	6.561 (1.627-26.464)	0.008	7.407 (1.487-39.906)	0.015

CDI: *Clostridioides difficile* infection, CI: Confidence interval, ICU: Intensive care unit, OR: Odds ratio

Discussion

CDI is a significant nosocomial infection occurring in hospitalized patients that can lead to mortality. In this study, the 30 day fatality rates and the fatality-associated risk factors were analyzed in 67 hospitalized patients diagnosed with CDI. The 30 day fatality rate was 20.9%, which is similar to the rates reported in studies involving hospitalized CDI cases[12,17,18]. In our study, the onset of CDI during an ICU stay, severe CDI episode, ongoing antibiotic therapy for infections other than CDI after the onset of a CDI episode, and elevated procalcitonin level were more frequently observed in patients having fatal outcomes. In logistic regression analysis, ICU-acquired CDI, continuation of antibiotic therapy for infections other than CDI, and elevated procalcitonin level were recognized as independent risk factors for 30 day fatality. The impact of these variables on 30 day survival was also evaluated through KM survival analysis. The examination of survival curves revealed a significant survival disadvantage among patients with these risk factors.

Although the current guidelines recommend oral vancomycin or fidaxomicin as first-line therapies for CDI, the majority of patients in our cohort received metronidazole, considering the limited availability of these drugs and the suboptimal adherence to guidelines. Oral vancomycin was available, but used in only 38.8% of the cases, whereas fidaxomicin was not accessible at our center during the study period. These points reflect real-world challenges in resource-limited settings that could influence decision-making during a treatment.

Past studies have also reported the association of CDI with increased all-cause mortality and the higher mortality rate in hospital-acquired CDI[19,20]. These findings highlight CDI as a critical cause of mortality and a significant healthcare concern, especially among hospitalized patients. Previous studies have

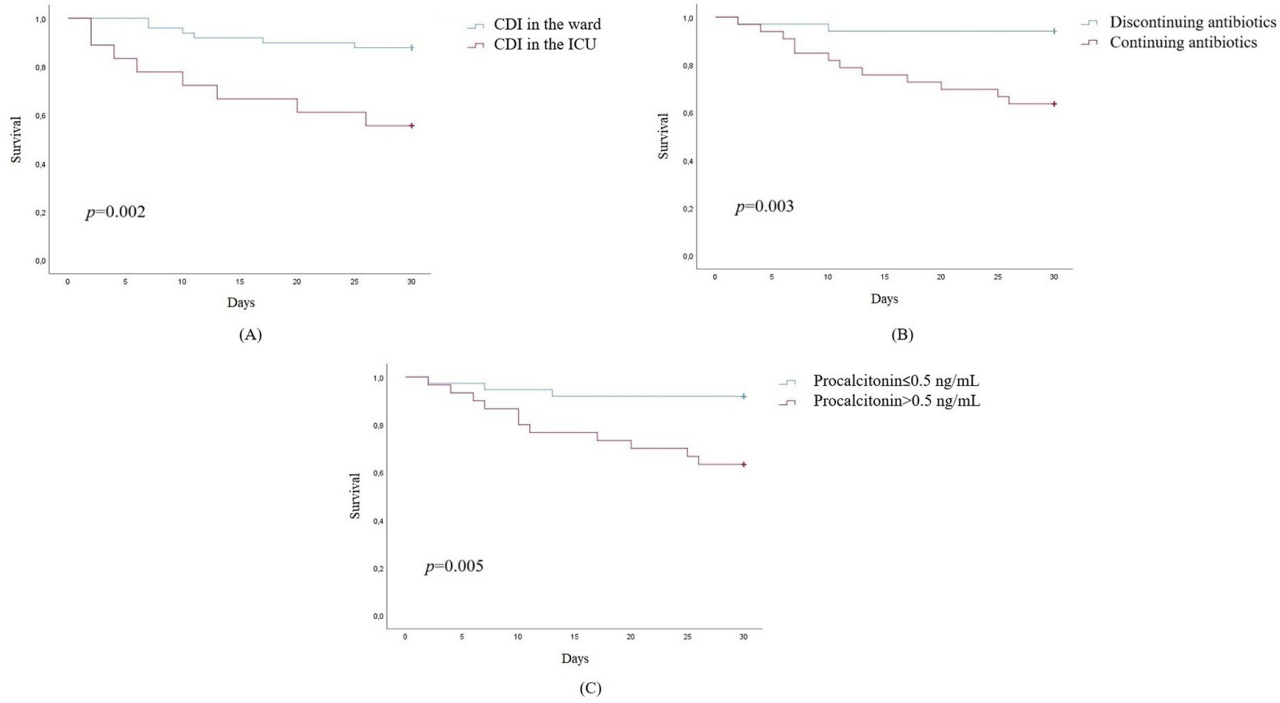

Figure 1. Kaplan-Meier survival curves demonstrating the effect of (A) *Clostridioides difficile* infection onset in the intensive care unit, (B) continued antibiotic use for infections other than *C. difficile*, and (C) elevated procalcitonin levels on 30 day fatality

identified risk factors for 30 day mortality in these patients, including advanced age, malignancy, Charlson Comorbidity Index, elevated serum creatinine levels, ICU admission, high leukocyte count, and low albumin levels[18,21,22]. The mean age of our patient population was relatively high, with only 8 patients aged <60 years. Consequently, although the median age was higher in the fatality group, no statistical significance was observed in our already older cohort. Laboratory findings such as the leukocyte count and creatinine level were also higher in the fatality group, albeit without any statistical significance. No differences were observed between the two groups in terms of comorbid conditions or the Charlson Comorbidity Index. In our study, ICU-acquired CDI was identified as an independent risk factor that increased 30 day fatality by 4.8 times, which may be explained by the fact that ICU patients typically have more comorbidities, undergo invasive procedures, and receive broad-spectrum antibiotics more frequently. Similar findings in the literature have indicated that ICU-acquired CDI cases have higher mortality rates[23,24]. In addition, factors such as immunosuppression, gastrointestinal stress, and a higher incidence of sepsis in critically ill patients may contribute to worse prognoses in ICU-acquired CDI cases. Furthermore, nutritional deficiencies are common among ICU patients may be additional factors that increase the mortality rate. Another identified risk factor for fatality was an ongoing antibiotic therapy for infections other than CDI after the onset of a CDI episode, which increased the fatality risk by approximately 5.9 times. Previously, it was demonstrated that antibiotics disrupt the gut microbiota, promoting *C. difficile* proliferation, increasing toxin production, and weakening the intestinal barrier function[1]. Continuing the use of antibiotics that trigger CDI after its onset may create a vicious cycle, resulting in a more severe and persistent disease and worse clinical outcomes. The application of broad-spectrum antibiotics, particularly, is a significant factor contributing to CDI recurrence and mortality. Therefore, when considering the continuation of causative antibiotics in CDI-diagnosed patients, the necessity of such treatment should be carefully evaluated, with a preference for narrow-spectrum agents.

Procalcitonin can indicate systemic inflammation and the severity of bacterial infections. In the past, it has been shown that elevated procalcitonin levels can serve as a biomarker for disease severity and complications in different bacterial and viral infections[25-30]. The prognostic value of procalcitonin investigated by Rao et al.[31] revealed that the procalcitonin levels in CDI patients were associated with infection severity and were significantly elevated in severe cases. Similarly, Dazley et al.[32] reported that procalcitonin could indicate CDI severity, with levels >0.5 ng/ml indicating high sensitivity, specificity, and positive predictive value for severe disease. In more recently published studies investigating the relationship between procalcitonin level and mortality, procalcitonin was found useful in predicting mortality during CDI[33,34]. In our

study, a procalcitonin level >0.5 ng/ml emerged as the strongest risk factor for 30 day fatality, increasing the overall risk by 7.4 times. Furthermore, KM survival analysis revealed a significantly reduced survival time among patients with procalcitonin level >0.5 ng/ml (p=0.005). These findings suggest that procalcitonin is not only an inflammatory marker in CDI patients but may also serve as a prognostic parameter in clinical management. In addition, patients with high procalcitonin levels may require more aggressive treatment and closer monitoring.

Study Limitations

Our study has some limitations, including its retrospective design, single-center nature, and limited sample size. As a single-center study, its generalizability may be restricted. Moreover, the comparison between the two groups could not be performed in a matched or one-to-one manner concerning risk factors, comorbidities, and other baseline characteristics. In addition, the study did not adjust for certain potential confounding factors, such as the time interval between hospital admission and the initiation of antibiotic therapy, due to the inconsistent availability of related data in the medical records. Furthermore, as the overall sample size was limited, our study could have been susceptible to a type II error; therefore, the lack of statistical significance for variables associated with mortality in larger cohorts should be interpreted with caution, as it may reflect insufficient power rather than a true absence of association.

Conclusion

Thus, ICU-acquired CDI, continuation of antibiotic therapy that triggers CDI after a CDI episode, and high procalcitonin levels act as independent risk factors for fatality. The strengths of our study include the use of multivariable regression analysis to identify factors associated with 30 day fatality and the reassessment of these variables using KM survival analysis. These findings highlight the importance of managing antibiotic therapy following CDI onset. In addition, the initial and follow-up measurement of procalcitonin levels may help in assessing the disease progression. Close monitoring and aggressive treatment strategies for ICU-acquired CDI episodes may thus contribute to improved survival. Larger, multicenter studies are expected to provide valuable contributions to the deeper understanding of this subject.

Ethics

Ethics Committee Approval: This study was conducted at Giresun Training and Research Hospital, a tertiary care hospital (approval number: 19.02.2025/06, date: 20.02.2025), between September 2021 and December 2024.

Informed Consent: Retrospective study.

Footnotes

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Mandibular Osteomyelitis Caused by *Candida glabrata*: A Case Report

Candida glabrata'nın Neden Olduğu Mandibular Osteomiyelit: Bir Olgu Sunumu

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Abstract

Osteomyelitis is an infection involving the bone and bone marrow, most commonly caused by bacterial pathogens, though it can rarely occur due to fungal organisms. *Candida glabrata* is a *Candida* species that is challenging to treat because of its inherent resistance to azoles. Fungal osteomyelitis of the mandible is exceedingly uncommon, and infection with *C. glabrata* at this site has not been previously reported.

This report describes an unusual case of mandibular osteomyelitis that developed following a dental procedure, with *C. glabrata* identified as the pathogen. A 36-year-old man with diabetes mellitus presented with painful swelling extending to the face and neck after undergoing root canal treatment on his right lower molar. Despite receiving antibiotics, his symptoms persisted, and contrast-enhanced magnetic resonance imaging confirmed mandibular osteomyelitis with abscess formation. *C. glabrata* was isolated from tissue obtained during surgical debridement, and antifungal susceptibility testing was performed. The patient received intravenous caspofungin for 6 weeks, followed by oral fluconazole to complete a 6-month total treatment course once clinical improvement was noted.

The patient demonstrated clear clinical and radiological improvement. This case highlights that fungal pathogens should be included in the differential diagnosis of infections occurring after dental procedures that do not respond to antibiotics. Selecting an appropriate antifungal agent and performing timely surgical management are essential for successful treatment.

Keywords: Antifungal agents, *Candida glabrata*, mandible, osteomyelitis

Öz

Osteomiyelit, genellikle bakteriyel patojenlerle ilişkili olmakla birlikte, nadiren mantar enfeksiyonlarına bağlı olarak gelişebilen bir kemik ve kemik iliği enfeksiyonudur. *Candida glabrata*, intrinsik azol direnci nedeniyle tedavi yönetimi zor olan *Candida* türlerinden biridir. Mandibula yerleşimli fungal osteomiyelit oldukça nadirdir ve bu lokalizasyonda *C. glabrata* enfeksiyonu daha önce hiç bildirilmemiştir.

Bu vaka raporunda, dental müdahale sonrası mandibular osteomiyelit gelişen ve etken olarak *C. glabrata* izole edilen nadir bir olgu sunulmaktadır. Diyabet mellitus tanılı 36 yaşındaki erkek hasta, sağ alt molar dişine uygulanan kanal tedavisi sonrası yüz ve boyun bölgesine yayılan ağrılı şişlik ile başvurmuştur. Antibiyotik tedavisine rağmen semptomlarda gerileme olmamış, kontrastlı manyetik rezonans görüntüleme ile mandibular osteomiyelit ve apse saptanmıştır. Cerrahi debridmanla elde edilen örnekte *C. glabrata* üremesi saptanmış ve antifungal duyarlılık testleri yapılmıştır. Hastaya 6 hafta boyunca intravenöz kaspofungin tedavisi uygulanmış; klinik stabilite sağlanmasının ardından tedaviye, toplamda 6 aya tamamlanacak şekilde oral flukonazol ile devam edilmiştir.

Hastada, uygulanan tedaviye belirgin klinik ve radyolojik yanıt alınmıştır. Bu olgu, dental girişim sonrasında gelişen ve antibiyotik tedavisine yanıtsız seyreden enfeksiyonlarda fungal etkenlerin ayırıcı tanıda mutlaka göz önünde bulundurulması gerektiğini ortaya koymaktadır. Uygun antifungal ajan seçimi ve zamanında gerçekleştirilen cerrahi müdahale, tedavi başarısının sağlanmasında kritik öneme sahiptir.

Anahtar Kelimeler: Antifungal ajanlar, *Candida glabrata*, mandibula, osteomiyelit

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Introduction

Osteomyelitis is an inflammatory disease that arises in the bone and bone marrow due to a persistent infection[1]. Although it most commonly occurs as a result of bacterial pathogens, fungal, parasitic, and viral infections can also cause osteomyelitis[1]. The primary route of spread for *Candida* osteomyelitis is hematogenous dissemination, and in adults, the vertebrae, ribs, and sternum are the sites most frequently involved[2]. Osteomyelitis of the mandible due to *Candida* is very rare, and there are no established guidelines for diagnosis, treatment, or prognosis at this site. *Candida* species normally exist as commensals in the oral cavity; however, under certain local or systemic conditions, they may occasionally lead to invasive infections such as osteomyelitis[3].

Candida osteomyelitis typically has a chronic course, may persist for months from symptom onset, and can cause significant morbidity if not recognized early or managed properly[4]. These infections often show a mild or moderate inflammatory response, and inflammatory markers may not rise noticeably[4]. In this report, we describe a rare case of mandibular osteomyelitis due to *Candida glabrata* following a dental procedure. The patient was successfully managed with surgical debridement and prolonged antifungal therapy.

Case Report

A 36-year-old man with a known history of diabetes mellitus visited a dentist about 1 month earlier with a complaint of tooth pain. He underwent root canal treatment on his right lower molar. However, he developed swelling and pain on the right side of his face after the procedure, leading to extraction of the tooth. The patient was prescribed oral amoxicillin–clavulanate and clindamycin, but his symptoms did not improve, and the resulting dental abscess required surgical drainage.

He was then referred to our infectious diseases clinic due to persistent swelling on the right side of the face, which had extended to the neck. At the time of admission, he was afebrile and his vital signs were stable. Physical examination revealed swelling and warmth on the right side of the face. A fistula was observed extending from the right mandibular area to the skin surface. Laboratory tests showed a leukocyte count of 7400/mm^3, neutrophil count of 3800/mm^3, C-reactive protein of 4 mg/L and erythrocyte sedimentation rate of 18 mm/h. Contrast-enhanced neck magnetic resonance imaging (MRI) demonstrated a focal diffusion restriction indicating an abscess near the tooth root in the posterior right mandible, along with infectious-inflammatory T1A hypointense signal changes (focal osteomyelitis) within the bone marrow. There was also evidence of increased inflammatory signal in the adjacent masseter and pterygoid muscles and soft tissue enhancement. Additionally, a collection consistent with an abscess was identified within the superficial fascia, measuring 4 cm anteroposteriorly, with a maximum thickness of 4 mm and peripheral enhancement following IV contrast administration (Figure 1).

Based on these findings, the patient was empirically started on ampicillin-sulbactam. Abscess drainage and surgical debridement were carried out by the Ear, Nose, Throat and Maxillofacial Surgery teams. *C. glabrata* was identified in the abscess specimen collected during the procedure. Susceptibility testing showed that micafungin [minimum inhibitory concentration MIC <0.06 mg/L caspofungin MIC < 0.12 mg/L and amphotericin B (MIC<0.25) were effective. Given these results, the patient was treated with piperacillin-tazobactam, teicoplanin, and caspofungin. The antibiotic course was planned for a total of 6 weeks (piperacillin-tazobactam and teicoplanin for 2 weeks, followed by oral amoxicillin-clavulanate and ciprofloxacin for an additional 4 weeks). Caspofungin was administered intravenously for 6 weeks, and therapy was then continued with oral fluconazole (400 mg daily) to complete a 6-month total treatment duration.

A contrast-enhanced neck Magnetic resonance imaging (MRI) obtained at the sixth month of treatment showed complete resolution of the osteomyelitis and abscesses previously seen in the right mandibular ramus (Figure 2). In addition, the swelling in the patient's right facial and neck region had fully subsided.

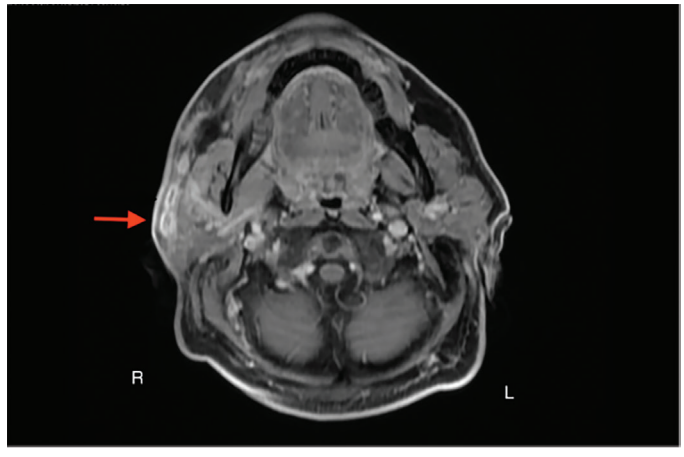

Figure 1. Peripheral enhancing abscess formation in the posterior region of the right mandible shown on a fat-suppressed contrast-enhanced T1-weighted axial MRI image

MRI: Magnetic resonance imaging

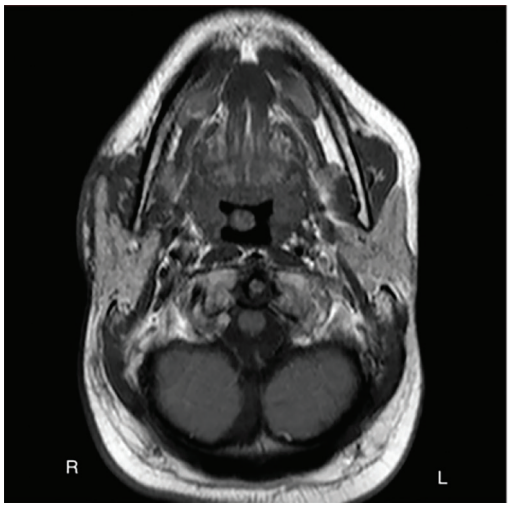

Figure 2. Contrast-enhanced T1-weighted MRI (T1W TSE) image demonstrating resolution of infectious and inflammatory findings

MRI: Magnetic resonance imaging

Discussion

The pathways of infection in *Candida* osteomyelitis are categorized as hematogenous spread (67%), direct inoculation (25%), and contiguous spread from nearby tissues (9%)[2]. The most frequent causative species are *Candida albicans* (65%), *Candida tropicalis* (16%), and *C. glabrata* (8%), while the vertebrae, sternum, and ribs are the bone sites most commonly affected in adults[2,4]. Mandibular osteomyelitis caused by *Candida* is very uncommon.

Most patients who develop *Candida* osteomyelitis are not receiving immunosuppressive medications. Reported risk factors include surgical procedures, intravenous drug use, orthopedic implants, trauma, and open wounds. In addition, factors related to candidemia, such as the presence of a central venous catheter and total parenteral nutrition, are also important predisposing conditions. However, *Candida* osteomyelitis can also occur in conditions that suppress the immune system, such as leukemia, lymphoma, or kidney and liver transplants[5].

Attie et al.[6] described two cases of mandibular osteomyelitis due to *C. albicans* following tooth extraction. These patients had a history of substance abuse and recovered after surgical debridement and fluconazole therapy. Choi et al.[3] reported a case of maxillary and mandibular osteomyelitis caused by *C. albicans* in an individual without any immune deficiency; complete resolution was achieved with debridement and antifungal therapy (micafungin followed by fluconazole). This shows that *Candida* osteomyelitis can also develop in immunocompetent individuals. To date, there has been no report in the literature of mandibular osteomyelitis due to *C. glabrata*. In this sense, our case adds to the existing literature.

Gagliano et al.[7] described a case of *C. glabrata* spondylodiscitis in a diabetic patient, diagnosed through surgical sampling after antibiotics failed, with successful treatment using antifungal agents. This highlights the importance of considering fungal pathogens and obtaining surgical samples for diagnosis in cases unresponsive to antibiotics. Similarly, in our patient, the diagnosis was made through culture obtained after surgical drainage.

Managing antifungal therapy in *Candida* osteomyelitis can be difficult, particularly with species like *C. glabrata* that have inherent resistance to azoles. The 2016 Infectious Diseases Society of America clinical practice guidelines for treating *Candida* osteomyelitis recommend oral fluconazole 400 mg daily for 6-12 months, or an echinocandin (e.g., caspofungin, micafungin, or anidulafungin) for at least 2 weeks, followed by a step-down to oral fluconazole 400 mg daily for 6-12 months, along with surgical debridement when appropriate[8]. In our patient, a treatment regimen aligned with these guidelines was implemented, resulting in clinical success.

Chesdachai et al.[9] analyzed 1,046 *C. glabrata* isolates collected at the Mayo Clinic from 2012 to 2022 and found that 17.9% were resistant to fluconazole based on CLSI standards and 24.5% according to European Committee on Antimicrobial Susceptibility Testing criteria. This study highlighted the limited effectiveness of fluconazole for *C. glabrata* and the need for antifungal susceptibility testing to guide therapy.

In a retrospective study by Eschenauer et al.[10] involving 224 patients with *C. glabrata* bloodstream infections, it was demonstrated that fluconazole MIC values play a key role in predicting treatment success. Outcomes were significantly better in patients with a fluconazole dose/MIC ratio above 12.5. These results suggest that fluconazole should be used only for isolates confirmed as susceptible and at appropriate doses. In our case, although fluconazole susceptibility was not specifically tested, the patient could not continue intravenous therapy, but after achieving clinical stability, treatment was successfully maintained with oral fluconazole.

The capacity of *Candida* species to form biofilms is another key factor that complicates treatment. Biofilm presence limits antifungal penetration and contributes to treatment resistance. Godart et al.[11] reported that prolonged antifungal therapy and surgical intervention were needed due to biofilm formation in a *C. albicans* infection that developed on the basis of mandibular osteoradionecrosis. Gamaletsou et al.[5] described biofilm formation in *Candida* species as involving adhesion, proliferation, maturation and dissemination stages and noted that echinocandins are more effective against these biofilms than triazoles.

In a meta-analysis including 1,072 patients, long-term antifungal therapy was found to improve survival, whereas short-term treatment was linked to higher mortality. Although not statistically significant, surgical intervention is also thought to potentially reduce mortality[12]. In our patient, caspofungin was started as antifungal therapy, and a favorable response was achieved with extended treatment, supporting the role of echinocandins in overcoming biofilm-related resistance. Additionally, timely surgical drainage was important in controlling the infection.

This case adds to the literature as a rare example of *C. glabrata* osteomyelitis that arose after dental treatment, was initially presumed bacterial, but was identified by abscess culture due to its persistent course. Fungal pathogens should be considered, especially when immunosuppressive conditions like diabetes are present and when dental infections do not respond to standard antibiotics.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Concept: E.Z., F.P., Design: B.Ç., E.Z., F.P., Data Collection or Processing: B.Ç., İ.N.B., Analysis or Interpretation: B.Ç., E.Z., İ.N.B., F.P., Literature Search: B.Ç., Writing: B.Ç.

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Chronic *Coxiella burnetii* Infection in a Patient with a Left Ventricular Assist Device: A Case Report

Sol Ventrikül Destek Cihazı Olan Bir Hastada Kronik *Coxiella burnetii* Enfeksiyonu: Olgu Sunumu

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Abstract

Chronic infection with *Coxiella burnetii*, the pathogen responsible for Q fever, presents considerable diagnostic and treatment difficulties, especially in individuals with implanted devices like left ventricular assist devices (LVADs). We describe the case of a 28-year-old man with an LVAD who experienced persistent fever, weight loss, night sweats, and a productive cough. Blood and sputum cultures returned negative, and transthoracic echocardiography did not indicate endocarditis. Nevertheless, serological tests showed elevated levels of *C. burnetii* immunoglobulin G Phase I antibodies, and positron emission tomography-computed tomography revealed increased metabolic uptake at the aortic insertion site of the LVAD. Initial therapy with doxycycline and hydroxychloroquine was switched to doxycycline and moxifloxacin due to recurrent fever. After more than 18 months of monitoring, the patient remained symptom-free with reduced inflammatory markers. This case highlights the need to consider Q fever in LVAD patients with prolonged fever, particularly those with animal-related occupational exposure, and emphasizes the diagnostic and therapeutic challenges of chronic *C. burnetii* infection in this group.

Keywords: *Coxiella burnetii*, Q fever, left ventricular assist device, device-associated infection

Öz

Q hummasının etkeni *Coxiella burnetii*, özellikle sol ventrikül destek cihazı (LVAD) gibi implante tıbbi cihaz taşıyan hastalarda tanı ve tedavi açısından önemli güçlüklere neden olur. Bu yazıda, LVAD'si olan ve uzamış ateş, kilo kaybı, gece terlemesi ve balgamlı öksürük şikayetleriyle başvuran 28 yaşında erkek bir hastayı sunuyoruz. Kan ve balgam kültürleri negatif bulunmuş ve transtorasik ekokardiyografide endokardit bulgusu saptanmamıştır. Ancak, serolojik incelemede *C. burnetii* immünoglobulin G Faz I antikorlarında yüksek titreler saptanmış; pozitron emisyon tomografi-bilgisayarlı tomografi ise LVAD'ın aort giriş noktasında artmış metabolik aktivite göstermiştir. Başlangıç tedavisinde tercih edilen doksisiklin ve hidroksiklorokin ile ateş yüksekliklerinin tekrarlaması üzerine hastanın tedavisi doksisiklin ve moksifloksasin kombinasyonu ile değiştirilmiştir. On sekiz aydan uzun takip süresinde hasta semptomsuz kalmış ve inflamatuar belirteçlerinde azalma gözlenmiştir. Bu olgu, özellikle mesleki hayvan temas öyküsü olan ve uzamış ateşi bulunan LVAD hastalarında Q hummasının mutlaka akılda tutulması gerektiğini ve kronik *C. burnetii* enfeksiyonlarının tanı ve tedavi zorluklarını vurgulamaktadır.

Anahtar Kelimeler: *Coxiella burnetii*, Q humması, sol ventrikül destek cihazı, endokardit

Introduction

Coxiella burnetii, the organism responsible for Q fever, can manifest with both acute and chronic forms. It poses a notable occupational risk for those employed in animal-related work and is linked to contact with both domestic and wild animals[1]. In humans, acute Q fever commonly appears as atypical pneumonia or acute febrile hepatitis. About 1-5% of patients with an acute infection may develop the chronic form, which can lead to endocarditis or vascular involvement and has an estimated mortality rate of 15%[2]. Infections related to LVADs are generally categorized as driveline infections, bloodstream

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infections, pocket infections, and localized infections not directly involving the device, including cases with negative cultures, which create substantial diagnostic difficulties[3,4]. This case report outlines the clinical course, diagnostic workup, and treatment of chronic *C. burnetii* infection in a patient with an LVAD. Written informed consent was obtained from the patient for this publication.

Case Report

A 28-year-old man presented with fever, chills, night sweats, marked weight loss (6-7 kg over 2 weeks), and a productive cough persisting for 2 months. His symptoms had started 2 months before admission, with episodes of high-grade fever and chills that had worsened during the preceding 10 days. Although he had visited several outpatient clinics and had been prescribed empirical antibiotics including moxifloxacin, amoxicillin–clavulanate, and cefixime, his symptoms did not resolve. He was therefore admitted for further evaluation of his prolonged fever.

His medical history included LVAD implantation and aortic valve replacement in 2021 due to advanced heart failure. There was no notable family medical history. He resided in a rural area, worked in livestock farming, and regularly consumed raw milk and dairy products.

On physical examination, his vital signs were as follows: body temperature 38.4 °C, pulse rate 115 beats per minute, blood pressure 85/50 mmHg, respiratory rate 20 breaths per minute, and peripheral oxygen saturation of 94% on room air. He appeared pale and diaphoretic. Cardiovascular examination was limited due to the mechanical sound from the LVAD. Petechial rashes were noted on both lower limbs. Examination of other systems revealed no abnormalities.

Initial laboratory investigations showed a white blood cell count of 5,120/mm^3, with neutrophils at 3,340/mm^3 and lymphocytes at 1,420/mm^3. The hemoglobin level was 10.2 g/dl, and the platelet count was 164,000/mm^3. Liver enzymes were slightly elevated, with aspartate aminotransferase at 63 U/l and alanine aminotransferase at 52 U/l. Renal function was normal, with a creatinine level of 0.78 mg/dl. Inflammatory markers were raised, with a C-reactive protein (CRP) of 80 mg/l and a procalcitonin level of 1.37 ng/ml. The international normalized ratio was 2.22.

Chest X-ray and high-resolution computed tomography scans did not identify any abnormalities that could explain the patient's symptoms. Blood and sputum cultures were negative for bacterial growth. Further serological tests, including *Brucella* tube agglutination and Human Immunodeficiency Virus 1/2 antibody-p24 antigen tests, were negative. The purified protein derivative test was anergic.

Transthoracic echocardiography (TTE) performed twice over a 2-week period showed no vegetations on intracardiac structures. However, transesophageal echocardiography could not be done due to the presence of the LVAD. Serological testing revealed a positive *C. burnetii* immunoglobulin G (IgG) Phase I immunofluorescence assay (IFA) with a titer of 1:2048. Real-time polymerase chain reaction (PCR) for *C. burnetii* was negative. Positron emission tomography-computed tomography (PET-CT) indicated increased metabolic uptake at the LVAD's aortic entry point (SUV_{max}, 3), suggestive of infection.

Doxycycline (100 mg twice daily) and hydroxychloroquine (200 mg three times daily) were started. A consultation with cardiovascular surgery determined that replacing the LVAD was not an option. After a 26-day hospital stay, the patient was discharged with ongoing doxycycline and hydroxychloroquine treatment.

One month after discharge, the patient was re-admitted due to recurrent fever and elevated CRP levels. Moxifloxacin was started at another facility, and he was then referred back to our clinic for further care. With the addition of moxifloxacin (400 mg daily), both his symptoms and inflammatory markers improved. Hydroxychloroquine was subsequently stopped because of possible drug interactions, and therapy was continued with doxycycline and moxifloxacin.

At the third month of follow-up, the patient remained symptom-free, with a positive *C. burnetii* IgG Phase I IFA titer of 1:8192. Moxifloxacin was completed at that point, and treatment continued with doxycycline and hydroxychloroquine.

During follow-up visits every 3 months, the patient stayed clinically stable. At the 1-year follow-up, the *C. burnetii* IgG Phase I IFA titer was 1:16,384, and the Phase II titer was 1:32,768. A repeat PET-CT showed minimal residual metabolic activity at the LVAD entry site, with decreased intensity and area compared to earlier imaging.

By the 18-month follow-up, serology showed a further drop in the *C. burnetii* IgG Phase I IFA titer to 1:8192, while the Phase II titer remained at 1:32,768. The patient stayed asymptomatic and continues treatment with doxycycline and hydroxychloroquine. Another PET-CT is planned at the 2-year follow-up to reassess disease activity.

Discussion

Q fever is a zoonotic infection caused by *C. burnetii*, most commonly spread through inhalation of contaminated aerosols or consumption of unpasteurized animal products[5]. Infection with *C. burnetii* presents notable diagnostic and treatment difficulties, especially when it progresses to a chronic form. Chronic Q fever is uncommon, occurring in less than 5% of

people following an acute infection, and can appear months or even decades after the initial exposure. Those with underlying valvular heart disease, vascular grafts, or arterial aneurysms are at the highest risk. Endocarditis is the predominant presentation of chronic Q fever, accounting for 60-78% of cases, followed by vascular infections[6,7]. In this patient's case, classic signs of chronic Q fever were observed, including prolonged fever, marked weight loss, and night sweats, further complicated by a history of LVAD implantation and aortic valve replacement.

The patient's work involving livestock and regular intake of unpasteurized dairy products were significant risk factors for *C. burnetii* infection[8]. Diagnosis of chronic Q fever depends on identifying an elevated or rising Phase I IgG titer, generally ≥1:1024, along with clinical evidence of an ongoing infection focus such as endocarditis, a vascular infection, or osteomyelitis[7]. For this patient, diagnosis was challenging because of persistent symptoms despite several outpatient antibiotic treatments. Blood and sputum cultures stayed negative, and TTE showed no vegetations. However, serology revealed markedly elevated *C. burnetii* IgG Phase I titers, and PET-CT showed increased metabolic uptake at the LVAD's aortic entry site, indicating localized infection.

Infection is the most frequent complication among LVAD recipients, and a considerable number of these infections are culture-negative, creating specific diagnostic and treatment difficulties. In the MOMENTUM 3 trial, out of 1,213 major infection events reported in 585 patients, bacterial pathogens were found in 66% of cases, fungal in 2%, viral in 3%, and polymicrobial in 2%, while in 26% of cases, no causative organism was identified. When broken down by infection type, culture negativity was highest in localized non-device-related infections (33%), followed by driveline infections (20%), and was lowest in bloodstream infections (14%). In LVAD patients, culture-negative infections often require empiric antimicrobial treatment based on clinical suspicion and known risk factors, including the patient's immune status and any prior use of antibiotics. Having an implanted device and heart failure-related immune system dysfunction may further increase susceptibility to atypical pathogens and subtle clinical presentations. Therefore, clinicians should keep a high level of suspicion for culture-negative infections in LVAD patients and apply multiple diagnostic approaches, including advanced imaging and serologic tests, as illustrated in this case[3].

The standard treatment for chronic Q fever generally involves doxycycline (100 mg twice daily) together with hydroxychloroquine (200 mg three times daily), with treatment duration adjusted depending on the infection's location and severity[7]. Alternative options, such as moxifloxacin, clarithromycin, trimethoprim-sulfamethoxazole, and rifampin, may be used for patients unable to tolerate doxycycline[8]. In this case, treatment was begun with doxycycline and hydroxychloroquine according to current recommendations[7]. Within the first month of therapy, the patient developed recurrent fever, and moxifloxacin was started at another facility. After being referred back to our clinic, moxifloxacin was continued alongside doxycycline, while hydroxychloroquine was stopped due to possible drug interactions[9]. Treatment continued with doxycycline and moxifloxacin[10] for 3 months. Afterward, since the patient had no active symptoms, the regimen was switched back to doxycycline and hydroxychloroquine.

The main treatment goal in chronic Q fever is to achieve at least a fourfold drop in Phase I IgG antibody titers or reach a titer of ≤1:1024 before stopping antibiotic therapy[11]. However, the prognostic significance of serologic follow-up remains debated. Some studies have shown higher mortality rates in patients who do not reach a fourfold reduction in Phase I IgG titers after 1 year of treatment. Furthermore, persistent Phase II IgM antibodies at 1 year have also been linked to increased mortality, as shown by Million et al.[12].

Conversely, although elevated Phase I IgG titers during and after treatment have been associated with treatment failure in certain reports[13], other studies, including one involving 337 patients, did not find a significant link between serologic titers and negative clinical outcomes[14]. These results indicate that serological testing alone may not reliably predict treatment success in chronic Q fever. Therefore, management decisions should be based on clinical evaluation, PCR results, and imaging, while research continues to identify better prognostic indicators[14]. In this case, despite persistently high Phase I and Phase II IgG titers at the 1-year follow-up, the patient remained clinically stable, and repeat PET-CT at that time showed reduced metabolic activity at the device insertion site. By the 18-month follow-up, the Phase I IgG titer had declined further, which supported the overall favorable clinical progress.

Conclusion

To the best of our knowledge, this is the first reported case of *C. burnetii* infection in a patient with an LVAD, illustrating the distinctive diagnostic and treatment challenges involved. Although IgG titers remained elevated during early follow-up, successful management was achieved through careful clinical assessment, serologic testing, and advanced imaging. This case highlights the need to consider Q fever in LVAD patients with prolonged fever and occupational exposure to animal products and points to the necessity for further research to improve diagnostic and treatment approaches for this specific patient group.

Ethics

Informed Consent: Written informed consent was obtained from the patient for this publication.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.K., S.F.Ö., E.D.K., Concept: H.K., S.F.Ö., E.D.K., Design: H.K., S.F.Ö., Data Collection or Processing: H.K., S.F.Ö., Analysis or Interpretation: H.K., E.D.K., Literature Search: H.K., Writing: H.K., S.F.Ö., E.D.K.,

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Visceral Leishmaniasis in the Republic of North Macedonia: A Retrospective Cohort Study

Kuzey Makedonya Cumhuriyeti'nde Visseral Leishmaniasis: Retrospektif Bir Kohort Çalışması

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Abstract

Introduction: Visceral leishmaniasis (VL) is a systemic protozoan vector-borne disease and represents the most severe clinical form of leishmaniasis, with fatal outcomes if left untreated. This study aimed to evaluate the key epidemiological, clinical, and laboratory findings, treatment options, and outcomes in patients with VL.

Materials and Methods: A retrospective analysis was conducted on the epidemiological and clinical characteristics of 84 patients diagnosed and treated for VL at the University Hospital for Infectious Diseases in Skopje, Republic of North Macedonia (RNM), between 2001 and 2023.

Results: The median age of patients was 47 years (range 1-74), with 77.4% being male. Contact with dogs was reported in 41.7% of cases. Seven percent of patients were immunosuppressed, and all were Human Immunodeficiency Virus-negative. The median time from symptom onset to diagnosis was 30 days (range 4-330 days). The predominant clinical manifestations were splenomegaly (97.6%), fever (96.4%), hepatomegaly (90.5%), and weight loss (54.8%). On admission, anemia, leukopenia, thrombocytopenia, and hypergammaglobulinemia were detected in 75%, 73.8%, 70.2%, and 63.1% of patients, respectively. A favorable outcome was achieved in 91.7% of cases; therapeutic failure occurred in 1.2%, and 7.1% of patients died.

Conclusion: VL should be considered a crucial differential diagnosis in patients from the RNM presenting with prolonged unexplained fever, splenomegaly, cytopenia, and hypergammaglobulinemia.

Keywords: Visceral leishmaniasis, fever, splenomegaly, cytopenia, treatment

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Öz

Giriş: Visseral leishmaniasis (VL), sistemik bir protozoan vektör kaynaklı hastalıktır ve tedavi edilmediği takdirde ölümcül sonuçlara yol açan en ciddi leishmaniasis klinik formunu temsil eder. Bu çalışma, VL hastalarında temel epidemiyolojik, klinik ve laboratuvar bulgularını, tedavi seçeneklerini ve sonuçları değerlendirmeyi amaçlamaktadır.
Gereç ve Yöntem: 2001-2023 yılları arasında Kuzey Makedonya Cumhuriyeti, Üsküp Üniversitesi Enfeksiyon Hastalıkları Hastanesi'nde (RNM) VL tanısı konulan ve tedavi edilen 84 hastanın epidemiyolojik ve klinik özellikleri retrospektif olarak analiz edilmiştir.
Bulgular: Hastaların ortanca yaşı 47 yıl (1-74) olup, %77,4'ü erkektir. Vakaların %41,7'sinde köpeklerle temas bildirilmiştir. Hastaların %7'sinde bağışıklık sistemi baskılanmıştı ve tamamı Insan Immün Yetmezlik Virüsü negatifti. Semptom başlangıcından tanıya kadar geçen ortanca süre 30 gündü (aralığı 4-330 gün). Baskın klinik bulgular; splenomegali (%97,6), ateş (%96,4), hepatomegali (%90,5) ve kilo kaybı (%54,8) idi. Başvuru sırasında hastaların sırasıyla %75'inde anemi, %73,8'inde lökopeni, %70,2'sinde trombositopeni ve %63,1'inde hipergamaglobulinemi tespit edildi. Vakaların %91,7'sinde olumlu sonuç elde edildi; %1,2'sinde tedavi başarısızlığı meydana geldi ve hastaların %7,1'i hayatını kaybetti.
Sonuç: Uzun süreli açıklanamayan ateş, splenomegali, sitopeni ve hipergamaglobulinemi ile başvuran ve RNM'den gelen hastalarda VL önemli bir ayırıcı tanı olarak düşünülmelidir.
Anahtar Kelimeler: Visseral leishmaniasis, ateş, splenomegali, sitopeni, tedavi

Introduction

Visceral leishmaniasis (VL), also known as Kala-Azar, is the most severe clinical form of leishmaniasis, with a fatality rate exceeding 95% if left untreated[1,2]. It is a chronic systemic disease caused by flagellated protozoan parasites of the genus *Leishmania* (Trypanosomatida, Trypanosomatidae), most commonly *L. donovani* and *L. infantum* (syn. *L. chagasi*)[3,4]. The latter is almost the only autochthonous species in Europe[5,6].

Transmission occurs through the bite of infected female sandflies (Diptera, Psychodidae) during blood feeding, with vectors belonging to the genus *Lutzomyia* in the New World and *Phlebotomus* in the Old World[1,7]. In rare cases, transmission may occur via needle sharing, blood transfusion, or vertically from mother to child during pregnancy[8]. Dogs represent the major domestic reservoir of *L. infantum* and the most susceptible host species, while humans act as accidental hosts[5].

Globally, VL acts as the second deadliest parasitic disease[9]. Most cases occur in tropical and subtropical regions, particularly in India, Brazil, and East Africa[2]. Only 25-45% of VL cases are officially reported to the World Health Organization, yet statistics estimate 50,000-90,000 new cases annually[10]. Moreover, more than 350 million individuals across 98 countries remain at risk of infection[11].

Environmental and climatic changes affecting vector and reservoir distribution[12,13], inadequate control of competent reservoirs and vectors, population migration[14,15], and the rising number of immunocompromised individuals[16] present increasing challenges in the understanding and management of VL. In addition, disease characteristics such as the long incubation period, the potential for relapses, high mortality rate, long life pathogen persistence in infected humans, limited drug availability, and drug toxicity[2], as well as the lack of a commercially available vaccine, together contribute to VL being a serious global concern[2,12,17].

The southern countries of Europe, particularly those in the Mediterranean basin, are home to most of the VL vectors[18]. In this region, the high incidence of canine leishmaniasis, with an increase in the stray dog population, expansion of *Phlebotomus* sandfly populations, insufficient control measures, and an increasing number of immunocompromised patients, has made VL a growing public health concern[5,14,19]. The reported cumulative annual incidence in this region during 2005-2020 ranged from 0.02 to 2.1 per 100,000 population[5], equating to 700-875 reported[20] and 1,200-2,000 estimated new cases annually[21].

The Balkans represent a hotspot region for leishmaniasis. The challenging conditions of recent decades have resulted in a limited understanding of the epidemiology of this disease and other zoonoses[18]. The Republic of North Macedonia (RNM), as a part of the broader Mediterranean region, is no exception when it comes to favorable environmental conditions for local disease transmission. *L. infantum* is the causative agent, with *P. tobbi, P. neglectus*, and *P. perfiliewi* serving as vectors[22], and domestic dogs act as proven or suspected reservoirs[5]. Over the past two decades, the annual incidence has ranged from 0.1 to 1.0 per 100,000 inhabitants, with a median annual incidence of 0.371 per 100,000 population[23]. Despite its low incidence in the country, VL possesses a considerable public health burden due to diagnostic difficulties, the requirement for targeted therapy, and the risk of lethality. Additionally, RNM has been identified as a source of infection for travelers[22,24,25].

In this study, we aimed to evaluate the demographic, epidemiological, clinical, and laboratory findings, diagnostic tools, treatment options, and the outcome of VL among patients treated in a tertiary care hospital in Skopje, RNM, during 2001-2023.

Materials and Methods

Study Design and Patients

The RNM is a country in the Balkan Peninsula with an area of 25,700 km^2 and a total population of approximately 2 million. This single-center, descriptive, retrospective analysis was conducted on hospital records from 84 consecutive patients with confirmed VL, who were diagnosed and treated at the university hospital for infectious diseases and febrile conditions in Skopje during 2001-2023. This tertiary hospital serves as the sole referral center for diagnosing and treating VL in adults and some pediatric patients nationwide. The study analyzed the patients' demographic, epidemiological, clinical, and laboratory characteristics as well as the diagnostic methods, treatment regimens, and outcomes. Patients who withdrew from treatment or had incomplete medical records were excluded from the study.

Diagnosis

VL diagnosis was based on the clinical and laboratory characteristics (such as prolonged fever, fatigue affecting daily functions, splenomegaly, hepatomegaly, significant weight loss, cytopenia, and hypergammaglobulinemia) alongside laboratory confirmation. Laboratory confirmation involved detection of serum antibody titers by using the indirect immunofluorescence antibody test [(IFAT), *Leishmania* Spot-IF; bioMérieux, Marcy l'Etoile, France] at a threshold of 1:80 or higher and/or identifying *Leishmania* amastigotes through microscopic examination of Giemsa-stained smears from sternal punctures or iliac crest biopsies by experienced laboratory personnel. Although the parasite species was not definitively identified, clinical and epidemiological data strongly indicated *L. infantum* as the infection agent.

Data Collection

Data on the demographic, epidemiological, clinical, and baseline laboratory parameters, as well as the treatment regimens and patient outcomes, were collected retrospectively from medical records by using a standardized protocol chart. The extracted data included information on age, sex, exposure history, such as the presence of dogs near the patients' residence, family history of VL, travel to endemic areas within the year before the symptom onset, Human Immunodeficiency Virus (HIV) status, other immunodeficiencies, and previous VL episodes. Clinical data included duration of illness before diagnosis, fever, weight loss, cough, vomiting, diarrhea, abdominal pain, hepatomegaly, splenomegaly, bleeding, jaundice, peripheral edema, and ascites. Laboratory investigations comprised kidney and liver function tests, complete blood count, erythrocyte sedimentation rate (ESR), and protein electrophoresis. Diagnostic confirmation was established through parasitological and serological methods. Treatment regimen, time to defervescence, and outcomes, including cure, relapse, therapeutic failure, or death, were also recorded. Notably, the study did not investigate the vector and the disease reservoir.

Definitions

Fever was defined as an axillary temperature ≥37.5 °C on different occasions. Hematological abnormalities were defined as the presence of anemia (hemoglobin <11 g/L), leukopenia (leukocyte count <4.0 × 10^9/L), and thrombocytopenia (platelet count <150,000 × 10^9/L). Elevated ESR, hypoalbuminemia, and hypergammaglobulinemia were considered with values >20 mm Hg, <35 g/L, and >35 g/L, respectively. The illness duration (or diagnostic delay) was defined as the number of days between the onset of symptoms and the establishment of a VL diagnosis. Defervescence was defined as the period from the initiation of specific treatment to the normalization of temperature. Patients who exhibited an improvement in their general condition, weight gain, resolution of fever, regression of splenomegaly, and restoration of laboratory parameters by the end of treatment, with no recurrence of symptoms during the follow-up, were considered to have been cured. Therapeutic failure was defined as the lack of initial improvement, with the persistence or worsening of laboratory and clinical findings at the end of treatment. Relapse was defined as the recurrence of symptoms and signs after an initial successful treatment course.

Treatment

The therapeutic regimen was selected based on the year in which VL was diagnosed and drug availability. Meglumine antimonate was administered intramuscularly at a dosage of 20 mg/kg of pentavalent antimony per day, starting with a gradually increasing daily dose during the first 3 days of therapy. It was administered for 14 days, stopped for 14 days, and resumed for another 14 days. Conventional amphotericin B deoxycholate was administered at a dosage of 0.75-1 mg/kg/day, either daily or every alternate day, for 15-20 doses. Liposomal amphotericin B (L-AmB) was administered at 3 mg/kg daily on days 1-5, 14, and 21. Amphotericin B lipid complex was administered at a 3 mg/kg daily dose for 7-10 consecutive days. In addition, antipyretics, blood transfusions for severe anemia, antimicrobials for coinfection, and appropriate hydration and electrolyte replacement were provided, along with therapy for chronic diseases.

Follow-Up

The patients were hospitalized for the entire duration of antileishmanial therapy. During this period, physical examination was conducted daily, and their temperature was monitored at least four times a day. Standard laboratory tests were repeated every 3-5 days. Electrocardiograms and checks of diastases

were routinely performed every 7 days during the treatment with meglumine antimonate and additionally, as clinically indicated. After discharge, clinical evaluations and laboratory analyses were repeated monthly for the first 3 months and then at 3-6-month intervals. Abdominal ultrasonography was performed upon hospital admission and on days 15, 30, 90, and 180 after the initiation of therapy. The IFAT titers were recorded at 3-6 months during the follow-up period.

Statistical Analysis

Data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics included frequencies and percentages for categorical variables and medians with ranges for continuous variables.

Ethics Statement

Clinical samples were collected during the routine diagnosis, treatment, and follow-up. Patients' identities were anonymized before conducting the analysis. The study was approved by the Ss. Cyril and Methodius University Faculty of Medicine Ethics Committee in Skopje (approval number: N.03-96/9, dated: 17.01.2025). Further, all participants provided their informed consent.

Results

Out of 171 reported cases of VL in the RNM between 2001 and 2023, 96 patients were treated at the University Hospital for Infectious Diseases and Febrile Conditions in Skopje. Twelve cases were excluded due to incomplete data or inadequate follow-up, leaving 84 patients eligible for analysis. Of these, 65 (77.4%) were male. The median age was 47 years (range: 1-74 years), with 5 patients (6.0%) younger than 14 years and 11 (13.1%) older than 64 years (Table 1). Symptom onset occurred most frequently in winter (30 patients, 35.7%), followed by spring (24, 28.6%), summer (18, 21.4%), and autumn (12, 14.3%). A history of close contact with dogs, mostly stray, was reported in 35 patients (41.7%), while 7 (8.3%) had traveled to neighboring countries within the past year. None reported a family history or prior VL infection. Six patients (7.1%) were immunosuppressed, although all were HIV-negative.

Table 1. Demographic and epidemiological data in 84 patients with VL

Parameter		Patients data
Age in years - median (range)		47 (1-74)
Male gender		65 (77.4%)
Symptom onset	Spring	24 (28.6%)
	Summer	18 (21.4%)
	Autumn	12 (14.3%)
	Winter	30 (35.7%)
Contact with dogs		35 (41.7%)
Travel abroad		7 (8.3%)
Immunosuppression		6 (7.1%)
HIV positive		0
Diagnostic delay in days - median (range)		30 (4-330)

VL: Visceral leishmaniasis, HIV: Human Immunodeficiency Virus

The median time from symptom onset to diagnosis was 30 days (range: 4-330 days). Forty-six patients (54.8%) were diagnosed within the first month, and an additional 14 (16.7%) by the end of the second month.

As shown in Figure 1, the most common clinical manifestations included splenomegaly in 82 patients (97.6%), fever in 81 (96.4%), hepatomegaly in 76 (90.5%), malaise in 55 (66.0%), and weight loss in 46 (54.8%). Less frequent symptoms were respiratory involvement in 17 patients (20.2%), gastrointestinal symptoms in 14 (16.7%), peripheral edema in 6 (7.1%), and jaundice, petechiae, or ascites in 2 (2.4%) each. Epistaxis was observed in 4 patients (4.8%).

Laboratory findings at admission revealed elevated ESR in 76 patients (90.5%), anemia in 63 (75.0%), leukopenia in 62 (73.8%), thrombocytopenia in 59 (70.2%), pancytopenia in 45 (53.6%), hypergammaglobulinemia in 53 (63.1%), and hypoalbuminemia in 59 (70.2%) (Figure 2). Positive serology for VL by Indirect immunofluorescence was obtained in 72 of 79 patients (91.1%), while amastigotes were identified in 25 of 39 patients (64.1%) who underwent sternal puncture or iliac crest biopsy. Both serology and myelogram were positive in 13 patients. In 14 cases, serology was positive but the myelogram was negative, while in 7 cases serology was negative despite a positive myelogram. Diagnosis was also confirmed in 45 patients based on serology alone and in 5 patients based solely on myelogram findings.

Therapeutic regimens are summarized in Table 2. The median defervescence period was 4 days (range: 1-21 days), and 77 patients (91.7%) achieved full recovery.

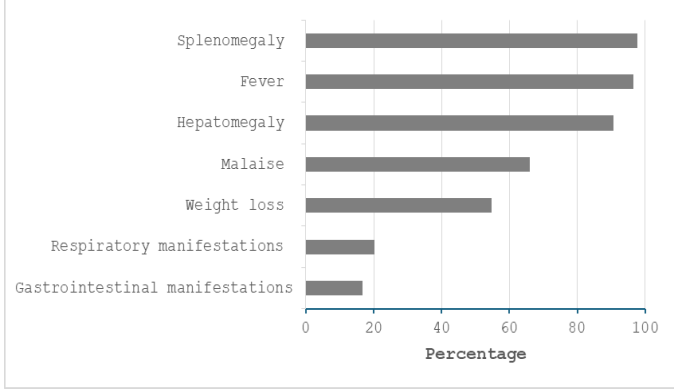

Figure 1. Frequency of clinical findings in patients with VL
VL: Visceral leishmaniasis

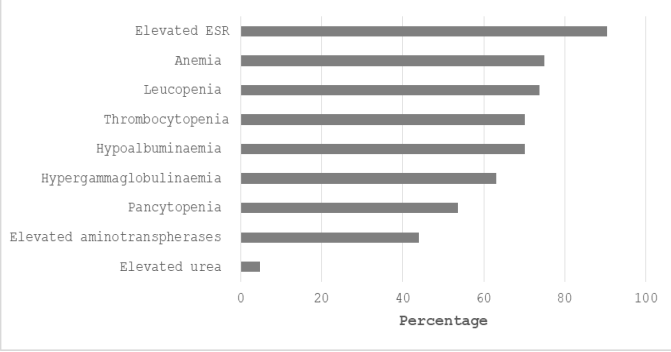

Figure 2. Frequency of initial hematological and biochemical features in patients with VL

VL: Visceral leishmaniasis

Table 2. Therapeutical regimens employed in patients with VL

Therapeutical regimen	n (%) of the patients
Meglumine antimonite	64 (76.2)
Conventional amphotericin B deoxycholate	8 (9.5)
Liposomal amphotericin B (L-AmB)	7 (8.3)
Amphotericin B lipid complex	4 (4.8)
No treatment	1 (1.2)

No relapses were observed. One patient (1.2%) experienced therapeutic failure, while 6 patients (7.1%) died. Fatal outcomes were linked to advanced disease in 4 cases (due to severe bacterial superinfections and hemorrhagic diathesis) and to meglumine antimonate cardiotoxicity in 2 cases. Survivors were followed for a median of 4 months (range: 3-63 months).

Discussion

This study represents the first report on a cohort of patients with VL from the RNM. In this country, VL is a sporadic, endemic, and primarily autochthonous disease. However, the possibility of a small number of imported cases cannot be excluded, as many Macedonian citizens frequently travel to and reside in neighboring countries for business and holidays. Some of these countries also report a proportion of imported VL cases[20,22,26]. Distinguishing between autochthonous and imported cases remains challenging, as molecular techniques such as multilocus enzyme electrophoresis or species-specific identification[26] are not widely available.

Two-thirds of patients experienced the onset of illness during the winter or spring season, which may support the theory of the seasonal activity of sandflies and the long incubation period reaching up to 1 year[8]. A report from Greece found that 67% of cases had a symptom onset in the seasons of spring and summer[27], although an Italian study showed that 81% of symptoms occurred in the seasons of autumn and winter[28]. However, two other studies from Greece reported no seasonal difference in the disease onset[3,29].

Our cohort was primarily composed of immunocompetent male adults. In addition to the nature of activities practiced by males (such as work in agriculture, herding, etc.), this group tended to reside in open areas and was more frequently exposed to phlebotomine bites. According to some religious and societal traditions, females tend to cover most of their body area, which reduces the possibility of phlebotomine bites compared to males[13,30]. The dominance of male sex among VL patients ranges from 45%[31] to 100%[11], with several studies showing similar findings to ours[15,28,32,33]. The age distribution in our study was comparable to that reported from neighboring countries[3,20,22,34,35]. Only five patients were aged <14 years, and not all were malnourished. The remaining children with VL in the country were treated at the University Hospital for Pediatric Diseases. Pediatric VL is typically associated with malnutrition, and the incidence of VL in children in European countries has decreased with the improvement in living standards[5].

The high prevalence of canine leishmaniasis and the absence of an effective prevention strategy contribute significantly to the persistence of human disease in RNM. As highlighted by Khezzani et al.[36], the negligence of some dog owners in providing appropriate health care for their dogs represents an important risk factor for various zoonoses, including VL. The reported seroprevalence rate of canine leishmaniasis in endemic regions ranges from 2% to 86%[3,19,20,29,35,37]. In RNM, a study documented a 28% canine seroprevalence, with only 6% of infected dogs displaying clinical symptoms[38]. Interestingly, we did not identify HIV-positive patients with VL, and the incidence among immunosuppressed individuals was low, which contrasts with the well-established knowledge that *L. infantum* causes diseases in such populations. A similarly low or absent frequency of HIV co-infection has been reported in neighboring Balkan countries[17,20,22,34,35]. Nevertheless, other studies describe higher VL incidence among immunosuppressed patients due to non-HIV-related causes[3,7,16,17,29,39]. The prolonged diagnostic delay observed in our cohort may be attributed to the long incubation period, the non-specific nature of the initial clinical presentation, the broad differential diagnosis (including hematological malignancies and infectious and autoimmune diseases), as well as the lack of familiarity with VL among healthcare providers in the region. Similar diagnostic delays to ours have been reported in other studies[16,33,40].

The clinical manifestations of VL depend on the *Leishmania* species and the host's immune response[4]. Our findings regarding clinical features and laboratory parameters are consistent with those reported across the world. For example, fever was reported in 64% of cases[17] to 100%[1,11,41-43], malaise in 49%[32] to 93%[43], weight loss in 18%[27] to 100%[41], gastrointestinal

and respiratory manifestations in 12%[17] to 81%[42], and 6%[44] to 76%[42], respectively. In addition, splenomegaly was reported in 58%[17] to 100% of cases[1,11,16,41,43], and hepatomegaly in 36%[1] to 100%[11,16,45]. Jaundice prevalence ranged from 3%[16,44] to 78%[11], peripheral edema from 3%[17,42] to 24%[46], and bleeding and ascites ranged from 2%[44] to 51% and 2%[42] to 32%[15], respectively. Our present laboratory findings were comparable to those reported elsewhere: elevated ESR in 78%[41] to 100%[45], anemia in 69%[7] to 100%[11,41,45], leucopenia in 33%[11] to 100%[45,47], thrombocytopenia in 33%[41] to 100%[11], pancytopenia in 33%[11,17] to 85%[47], hypergammaglobulinemia in 60%[7,17] to 100%[27], and hypoalbuminemia in 14%[48] to 100%[39]. These discrepancies in the frequency of clinical and laboratory manifestations reported by different studies may be attributed to factors such as population characteristics (e.g., socio-demographics, comorbidities, nutritional status, HIV, and other immune status), the nature of the causative agent, geographic variations, illness duration, diagnostic and therapeutic procedures, the country's economic conditions, and even the study design[9,40].

Serological testing and direct microscopic identification of *Leishmania* amastigotes in bone marrow aspirates are the most commonly employed diagnostic methods for VL[2,28,49]. The reported utility of serology in diagnosis ranges from 41%[17,45] to 100%[16,33], whereas that of direct microscopy ranges from 27%[28,33] to 97%[16]. On the other hand, VL misdiagnosis is common, which leads to dangerous delays in proper treatment and causes death in some cases[18].

Treatment depends on the *Leishmania* species, geographic region, and host immune status[32]. Between 2001 and 2017, our patients were mainly treated with meglumine antimonate, guided by drug availability, clinical experience, and literature recommendations[5,12,46,50]. Our protocol, involving gradual dose escalation and two treatment intervals, differed from standard regimens. Although rarely used elsewhere[27,51], this approach was acceptable in our setting, particularly as relapses in immunocompetent patients were infrequent (as confirmed in our results). The 14-day break also allowed resolution of injection site complications from high-volume intramuscular therapy. After 2017, amphotericin B derivatives became the treatment of choice, with formulation determined by availability. While antimonials and amphotericin formulations are similarly effective in[50] immunocompetent patients, liposomal amphotericin B (L-AmB) should be preferred for Mediterranean VL due to shorter treatment duration and reduced toxicity[16,17,52]. The complete recovery rate in our series aligns with previous studies, which reported recovery rates ranging from 61%[53] to 100%[35,45]. Similar to other reports[35,45], we did not observe any relapses, although the relapse rate could range from 6-7%[7,16,27,53] to 17-19%[28,31,40]. The occurrence of fatal outcomes in our study was similar to that reported from previous studies[17,28,34], with mortality rates ranging from 0%[35,45] to 22%[40,41]. VL-related mortality can often be attributed to bacterial superinfections, acute bleeding, severe anemia, heart or liver failure, or drug toxicity[15,48].

Several challenges have been reported in association with the VL outbreak in the Balkans and Mediterranean areas. In the context of the host, a recent study by Alcover et al.[54] suggested expanding the list of *L. infantum* potential hosts to include new species of small wild mammals, such as *Mus spretus*, *Erinaceus europaeus*, and *Sciurus vulgaris*. In addition to *L. infantum*, the only autochthonous species in Europe, some studies report new species, such as *L. donovani* sensu stricto in Cyprus and *L. tropica* in Greece[5]. On the other hand, most recent studies and reports agree that climate change has exacerbated the problem related to mosquito-borne diseases[13].

The migration and refugee crisis is another dilemma surrounding Eastern European countries. Because conflict and terror can contribute to leishmaniasis incidence or coincide with it through processes of population displacement and health system deterioration[55], the situation in the Balkan countries is believed to worsen as they are a transit area for migrants and refugees. In this regard, *Phlebotomus* spp. sandflies collected in Greece from refugee camps have displayed significant infection rates of *L. tropica* and *L. donovani*[56]. Cumulatively, all these factors complicate the situation and add to the challenges against VL control.

Currently, there are no registered vaccines against human leishmaniasis[4]. Although preventive measures to combat leishmaniasis may vary from one region to another[57], most studies agree that animal and human reservoir control, vector population control, and personal protection are the main axes that can reduce the rate of human leishmaniasis incidence[22], with a high emphasis on the development of a human vaccine.

Study Limitations

The main limitations of this study are its retrospective design and the exclusion of pediatric cases managed at the University Hospital for Pediatric Diseases, which limits the generalizability of our findings to children.

Conclusion

VL is a sporadic endemic disease in RNM, primarily attributable to insufficient surveillance and control of the competent reservoir and vectors. Despite its low incidence, the severe course and potential for fatal outcomes make VL a significant public health concern. As such, VL should be considered in the diagnostic workup for patients presenting with prolonged fever, splenomegaly, hepatomegaly, hypergammaglobulinemia, and/or

persistent pancytopenia. Early diagnosis and treatment are thus considered crucial for improving patient outcomes.

Ethics

Ethics Committee Approval: The study was approved by the Ss. Cyril and Methodius University Faculty of Medicine Ethics Committee in Skopje (approval number: N.03-96/9, dated: 17.01.2025).

Informed Consent: Further, all participants provided their informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.B., F.C., K.P., D.J., D.G., M.D., Concept: M.B., B.K., J.N., D.G., M.D., Design: M.B., B.K., F.C., K.P., D.J., J.N., D.G., M.D., Data Collection or Processing: M.B., F.C., K.P., J.N., D.G., Analysis or Interpretation: M.B., B.K., F.C., K.P., D.J., J.N., D.G., M.D., Literature Search: M.B., B.K., D.J., M.D., Writing: M.B., B.K., D.J., M.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Salmonella-induced Psoas Abscess in a Patient with Multiple Myeloma: A Case Report and Systematic Literature Review

Multipl Miyeloma Tanılı *Salmonella* Kaynaklı Psoas Absesi: Olgu Sunumu ve Sistematik Literatür Taraması

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Abstract

Salmonella is a gram-negative enteric bacillus primarily responsible for gastrointestinal infections. Psoas abscess due to *Salmonella* is an exceptionally rare clinical entity. Here, we have presented the case of a 65-year-old woman with multiple myeloma who developed a *Salmonella*-induced psoas abscess. She was admitted to the emergency department with persistent nausea and vomiting for the past 1 month. Blood cultures grew *Salmonella* spp., and abdominal computed tomography (CT) revealed a 43-mm abscess in the right psoas muscle. On the 10th day of hospitalization, CT-guided percutaneous drainage was performed, and *Salmonella* spp. was isolated from the abscess culture. Despite administering 6 weeks of antibiotic therapy, the patient's clinical course was fatal. We also reviewed 29 previously published cases of *Salmonella*-associated psoas abscesses, among which two (6.8%) had fatal outcomes. This case adds to the limited literature by highlighting a rare clinical presentation and providing a review of the clinical features, therapeutic strategies, and outcomes of *Salmonella*-related psoas abscesses.
Keywords: *Salmonella*, psoas abscess, immunosuppression, multiple myeloma, antibiotic resistance

Öz

Salmonella, esas olarak gastrointestinal enfeksiyonlardan sorumlu gram negatif enterik bir basildir. *Salmonella* kaynaklı psoas apsesi, son derece nadir görülen bir klinik durumdur. Burada, multipl miyelom tanılı 65 yaşında bir kadın hastada *Salmonella* kaynaklı psoas apsesi sunulmaktadır. Hasta son 1 aydır devam eden bulantı ve kusma şikayetiyle acil servise başvurdu. Kan kültürlerinde *Salmonella* spp. üredi ve abdominal bilgisayarlı tomografi (BT) ile sağ psoas kasında 43 mm çapında bir apse görüldü. Yatışının 10. gününde BT eşliğinde perkütan drenaj uygulandı ve apse kültüründen *Salmonella* spp. izole edildi. 6 hafta antibiyotik tedavisine rağmen hasta kaybedildi. Ayrıca, daha önce yayınlanmış 29 *Salmonella* ilişkili psoas apsesi vakasını inceledik; bunlardan ikisinin (%6,8) öldüğünü saptadık. Bu vaka, hem nadir görülen bir klinik tabloyu vurgulamakta, hem de *Salmonella* ile ilişkili psoas apselerinin klinik özellikleri, tedavi stratejileri ve sonuçları hakkında bir inceleme sunarak sınırlı literatüre katkıda bulunmaktadır.
Anahtar Kelimeler: *Salmonella*, psoas apsesi, immünosupresyon, multipl miyelom, antibiyotik direnci

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Introduction

Salmonellosis, caused by the gram-negative bacillus *Salmonella*, remains a significant infectious disease burden, particularly in low-income countries[1]. Its clinical spectrum most commonly includes acute gastroenteritis, bacteremia, enteric fever, and asymptomatic carriage. Although focal infections are more typical in immunocompromised individuals, extraintestinal manifestations such as musculoskeletal involvement have also been reported in immunocompetent patients[2].

A psoas abscess, which is defined as a purulent collection within the iliopsoas muscle of the retroperitoneal space, is most often caused by *Staphylococcus aureus*[3]. In contrast, *Salmonella*-induced psoas abscess is exceptionally rare, with fewer than 40 cases described in the literature[4-31]. Here, we have presented a unique case of *Salmonella* psoas abscess in a patient with multiple myeloma in light of a systematic review of published cases.

Case Presentation

A 65-year-old woman with a history of multiple myeloma presented to the emergency department with persistent nausea and vomiting for the past month. On admission, she was in moderate general condition, conscious, oriented, and cooperative. Her vital signs were as follows: temperature 38 °C, blood pressure 110/70 mmHg, pulse 73 bpm, respiratory rate 20 breaths/min, and oxygen saturation 99% on room air. Respiratory examination revealed normal breath sounds, and the abdomen showed no guarding, rebound, or tenderness. Other systemic findings were unremarkable.

Laboratory evaluation demonstrated a white blood cell count of 3.28 × 10^3/μL, hemoglobin 7.4 g/dL, platelet count 6 × 10^9/L, C-reactive protein 216 mg/L, and creatinine 3.5 mg/dL (baseline 2.0 mg/dL). Thoracic computed tomography (CT) revealed a left-sided pleural effusion measuring up to 8 cm in thickness with associated passive atelectasis (Figure 1). Accordingly, she was admitted to the hematology department and transfused with two units of erythrocyte suspension and one unit of platelet concentrate. Blood cultures yielded nontyphoidal *Salmonella* spp. (identified by MALDI-TOF MS; Bruker Daltonics, Germany; score 2.132), susceptible to fluoroquinolones and cephalosporins (Table 1). For this, intravenous ciprofloxacin (400 mg/day) was initiated.

To investigate the source of infection, abdominal CT was performed, which revealed a 43-mm fluid collection with gas formation in the right psoas muscle (Figure 2). Magnetic resonance (MR) cholangiography further suggested bilateral psoas collections, extending up to 9 cm on coronal T2-weighted images (Figure 3). CT-guided percutaneous drainage of the abscess was accordingly performed, and the culture of the aspirate again grew *Salmonella* spp. (serovar not identified; MALDI-TOF MS score 2.070). Following the emergence of ciprofloxacin resistance, therapy was switched to ceftriaxone 2 g IV every 12 h (Table 2).

The patient's history included hospitalization 3 months ago for *Salmonella* bacteremia after an episode of gastroenteritis, which was treated with a 14-day course of ceftriaxone. At that time, stool cultures were negative, and abdominal imaging

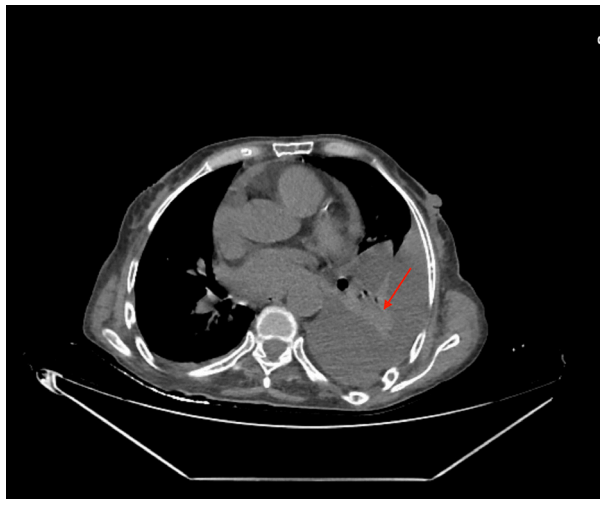

Figure 1. Thoracic exhibiting a pleural effusion in the left hemithorax with a thickness of up to 2 cm and passive atelectasis
CT: Computed tomography

Table 1. Antibacterial minimum inhibitory concentration results for *Salmonella* spp. in the blood culture

Antimicrobial agent	Minimum inhibitory concentration (mg/mL)	Sensitivity
Amikacin	≤8	Resistant
Ampicillin	≤4	Sensitive, standard dose
Ampicillin/sulbactam	≤1/8	Sensitive, standard dose
Cefepime	≤1	Sensitive, standard dose
Ceftazidime	≤1	Sensitive, standard dose
Ceftriaxone	≤1	Sensitive, standard dose
Ciprofloxacin	<0.0625	Sensitive, standard dose
Ertapenem	≤0.25	Sensitive, standard dose
Gentamicin	≤2	Resistant
Imipenem	≤0.25	Sensitive, standard dose
Levofloxacin	≤0.5	Sensitive, standard dose
Meropenem	≤0.125	Sensitive, standard dose
Piperacillin/tazobactam	≤4/4	Sensitive, standard dose
Trimethoprim/sulfamethoxazole	≤2/38	Sensitive, standard dose

showed no abscess formation. During the current admission, her condition progressively deteriorated, requiring transfer to the intensive care unit. Follow-up thoracic CT revealed recurrent pleural effusion (8 cm) and multiple mediastinal lymph nodes. Pleural drainage was performed, though cultures were negative. Ceftriaxone therapy was continued.

Further evaluation for possible spondylodiscitis was planned, but MR imaging (MRI) with contrast could not be performed due to worsening renal function. Positron emission tomography imaging was scheduled; however, the patient's condition declined further, and she ultimately succumbed to her illness.

Literature Review

A comprehensive literature review was conducted with reference to the PubMed, Scopus, and Web of Science databases, covering studies published from database inception through May 2025. The search strategy employed the keywords "*Salmonella*" and "psoas abscess" and was restricted to adult patients (age ≥18 years). Only English-language case reports were considered, whereas pediatric cases were excluded.

From the retrieved literature, cases were screened for eligibility based on the availability of summary or full-text data. Extracted variables included demographic characteristics, clinical presentation, underlying risk factors, immune status, culture results, antimicrobial therapy, and clinical outcomes. A total of 33 cases were identified as such, of which 29 adult cases met the inclusion criteria for detailed analysis. An overview of the study selection process and the summarized case characteristics is illustrated in Figure 4.

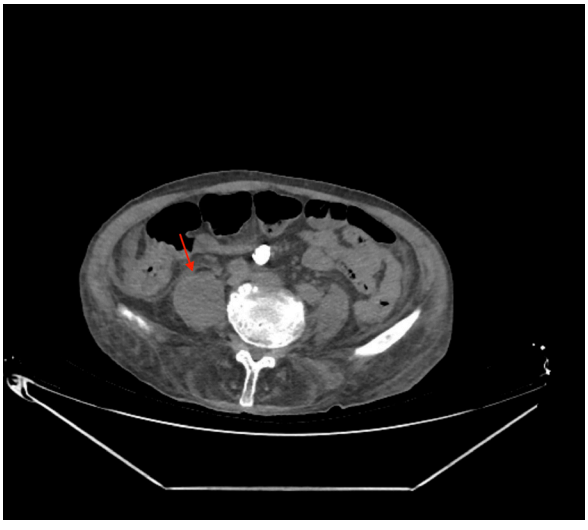

Figure 2. Abdominal CT showing a 43-mm fluid collection with gas formation in the right psoas muscle

CT: Computed tomography

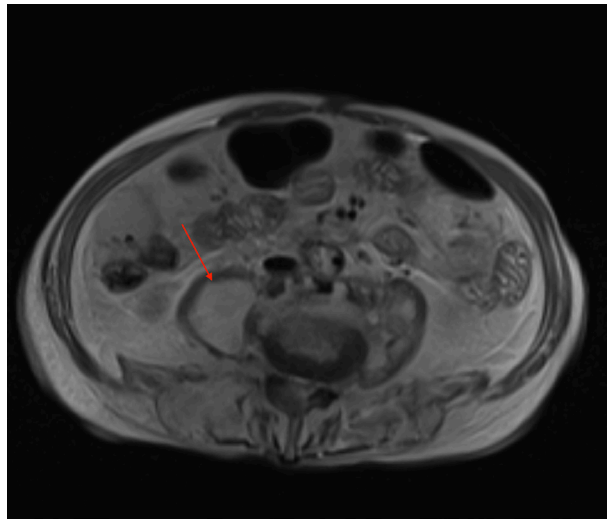

Figure 3. MRI cholangiography displays suspected collection areas suggestive of psoas abscess in both psoas muscles, reaching up to 9 cm

MRI: Magnetic resonance imaging

Table 2. Antibacterial minimum inhibitory concentration results for *Salmonella* spp. in the abscess culture

Antimicrobial agent	Minimum inhibitory concentration (mg/mL)	Sensitivity
Amikacin	≤8	Resistant
Ampicillin	≤4	Sensitive, standard dose
Ampicillin/sulbactam	≤1/8	Sensitive, standard dose
Cefepime	≤1	Sensitive, standard dose
Ceftazidime	≤1	Sensitive, standard dose
Ceftriaxone	≤1	Sensitive, standard dose
Ciprofloxacin	>1	Resistant
Ertapenem	≤0.25	Sensitive, standard dose
Gentamicin	≤2	Resistant
Imipenem	≤0.25	Sensitive, standard dose
Levofloxacin	>2	Resistant
Meropenem	≤0.125	Sensitive, standard dose
Piperacillin/tazobactam	≤4/4	Sensitive, standard dose
Trimethoprim/sulfamethoxazole	≤2/38	Sensitive, standard dose

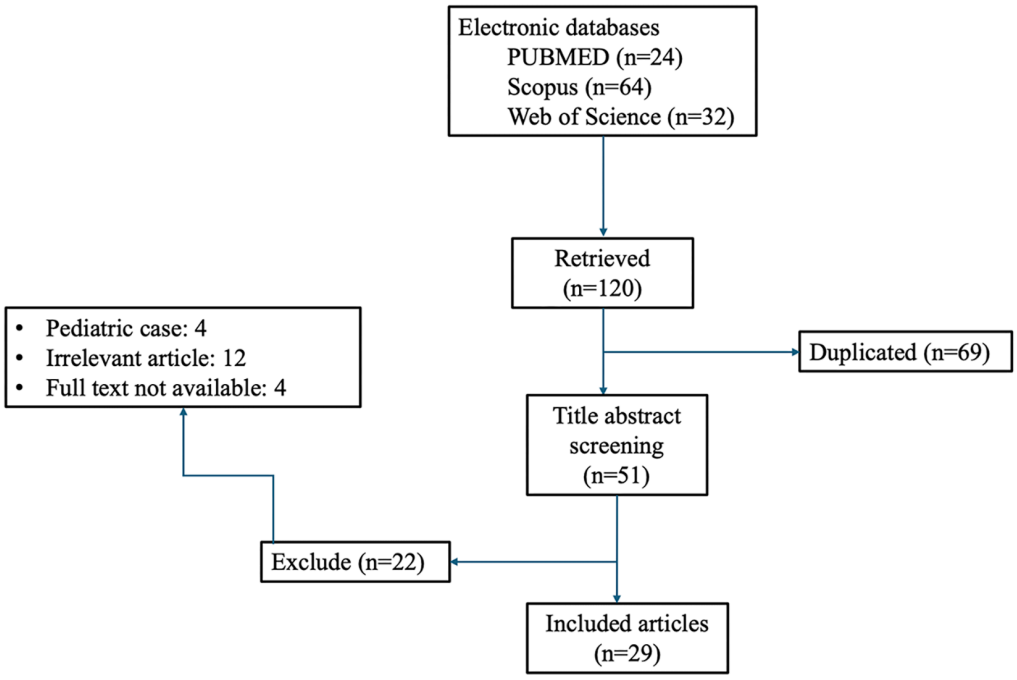

Figure 4. MRI cholangiography displays suspected collection areas suggestive of psoas abscess in both psoas muscles, reaching up to 9 cm
MRI: Magnetic resonance imaging

Discussion

Salmonella-induced psoas abscess is an exceptionally rare clinical entity. Our review of the English-language literature identified 33 reported cases, of which 29 adult cases with accessible summary or full-text data were analyzed. The mean patient age was 55.4 years, and 72% (n=21) of them were male. The most frequently reported symptoms were fever (65%, n=19), back pain (41%, n=12), and hip pain (38%, n=11). Commonly identified risk factors included diabetes mellitus (17%, n=5), steroid use (7%, n=2), and malignancy (7%, n=2), although 45% (n=13) of patients had no known underlying conditions (Table 3). In our case, the main risk factor was multiple myeloma, which is a hematologic malignancy associated with profound immunosuppression.

Psoas abscesses are typically classified as primary, arising from hematogenous or lymphatic spread, or secondary, resulting from contiguous spread of nearby infections[32]. In several cases, the distinction is challenging. In our review, concurrent infections such as vertebral osteomyelitis/spondylodiscitis (24%, n=7) and sacroiliitis/septic arthritis (21%, n=6) were identified, whereas 34% (n=10) had no additional infectious focus. Our patient had a prior episode of *Salmonella* bacteremia following gastroenteritis 3 months earlier, with no evidence of abscess formation at that time. This clinical course suggested hematogenous seeding as the likely mechanism of a primary abscess.

Imaging plays a central role in diagnosis. CT remains the gold standard owing to its high sensitivity and specificity, although MRI and ultrasound may be valuable, especially for early detection or in patients where radiation exposure is a concern[32]. Microbiological confirmation through blood and abscess cultures is critical for guiding targeted therapy[33]. In the reviewed cases, abscess cultures were positive in 59% (n=17), blood cultures in 55% (n=16), and both in 21% (n=6) of the patients. In our patient, both blood and abscess cultures grew *Salmonella* spp., although serotyping was not performed.

Optimal management generally requires a combination of antibiotics and drainage, either percutaneous or surgical. Reported antibiotic regimens include fluoroquinolones, ampicillin, trimethoprim/sulfamethoxazole, and third-generation cephalosporins[12,23]. In our review, drainage was performed in 79% (n=23) of the cases. Treatment duration varied between 5 weeks and 10 months, with most patients achieving full recovery. In the present case, intravenous ciprofloxacin was initiated based on blood culture results, but resistance was later detected in the abscess culture, necessitating a switch to ceftriaxone. Despite applying appropriate therapy and drainage, the patient's condition deteriorated, and she ultimately died.

Although most cases in the literature showed favorable outcomes, two fatalities were reported. One involved a previously healthy 56-year-old male with a perinephric abscess and aortic wall involvement, likely complicated by vascular compromise[6].

Table 3. Characteristics of patients with psoas abscess induced by *Salmonella*

Reference	Age/ gender	Symptoms	Risk factor(s)	Source of the positive culture	*Salmonella spp.*	Other infection focus	Drainage	Treatment	Outcome
Reichle et al.[5]	51/M	Fever and back pain	None	Blood, abscess, urine, aneurysm, and stool	*S. typhimurium*	Aortic wall aneurysm	Yes	Chloramphenicol*	Cured
Kanwar et al.[6]	56/M	Fever	None	Blood, abscesses, and urine	*S. enteritidis*	Perinephric abscess, aortic wall	Yes	Chloramphenicol*	Death
Yu[7]	63/F	Prolonged fever for two weeks	None	Abscess	*S.* group B	None	Yes	Ciprofloxacin*	Cured
Lortholary et al.[8]	40/F	Fever, back, and joint pain	History of typhoid fever and psoas abscess	Abscess	*S. typhi*	None	Yes	Following ceftriaxone and amikacin, and ciprofloxacin for 8 weeks	Cured
Inufusa et al.[9]	56/M	Fever, chills, and low-back pain	None	Abscess	*S. dublin*	Rupture of the infected abdominal aortic aneurysm	Yes	8 weeks*	Cured
Heyd et al.[10]	75/F	Left hip pain and fever	Steroid treatment for ITP	Blood and urine	*S. enteritidis*	None	Yes	Ciprofloxacin*	Cured
	74/F	Fever, right groin, hip, and upper thigh pain	Chronic steroid treatment for MG	Blood	*S. enteritidis*	None	Yes	Ciprofloxacin*	Cured
Carnevalini et al.[11]	63/M	Fever, abdominal pain	DM, abdominal aortic aneurysm rupture surgery	Abscess	*S. typhimurium*	Aorto-bisiliac graft infection, Abdominal aortic mycotic aneurysm	Yes	Ciprofloxacin 10 weeks	Cured
Shakespeare et al.[12]	32/M	Left lower back and left inguinal pain	None	Abscess	*S. typhi*	None	Yes	Cefotaxime 5 weeks	Cured
Jean et al.[13]	50/FM	Abdominal pain	Hemodylasis	Blood and abscess	*S. choleraesuis*	None	Yes	Imipenem 6 weeks	Cured
Altay et al.[14]	56/M	Abdominal and back pain, fever, cough, and sputum	DM hemodialysis, S. infection history	Blood, abscesses, and urine	*S. choleraesuis*	Lumbar osteomyelitis	Yes	Ciprofloxacin 6 weeks	Cured
Navin et al.[15]	21/F	Painful restriction of movement of the left hip	None	Abscess	*S. paratyphi A*	Sacroiliitis and iliac bone osteomyelitis	Yes	Following ciprofloxacin, TMP/SMX for 6 weeks	Cured
Reddix et al.[16]	36/F	Fever, left hip, thigh, and buttock pain	None	Abscess	*S. enterica*	Sacroiliac joint involvement	Yes	Ceftriaxone (4 weeks) and TMP/SMX (6 months)	Cured
Compain et al.[17]	64/M	Fever and right hip pain	Total left hip arthroplasty for osteoarthritis	Synovial fluid	Non-typhi *S.*	Septic arthritis of the hip	Yes	Ceftriaxone and ciprofloxacin*	Cured

Learch et al.[18]	75/M	Abdominal and back pain	DM	Blood and abscess	*S. enterica*	Aortic aneurysm, paravertebral abscess	Yes	No information	Cured
Zheng et al.[19]	42/M	Fever and back pain	None	Abscess	*S.* group B	Thoracal osteomyelitis	Yes	Following iv levofloxacin and TMP/SMX, moxifloxacin (oral) 6 weeks	Cured
Hirai et al.[20]	52/M	Fever and back pain	DM	Blood, epidural fluid, and stool	*S. altona*	Epidural abscess and spondylodiscitis	Yes	Following ceftriaxone and ciprofloxacin for 12 weeks	Cured
Kuo et al.[21]	52/M	Left hip pain	Aplastic anemia	Blood and abscess	*S.* O9 (Group D)	Osteomyelitis	Yes	Ciprofloxacin 10 months	Cured
Abu Bakar et al.[22]	66/F	Fever, epigastric pain that radiated to the back	None	Blood	*S. paratyphi* B.	Paraaortic abscess	No (It was denied by the patient)	Following Ceftriaxone (4 weeks), oral ciprofloxacin	Cured
Yanagisawa et al.[23]	53/M	Fever and right groin pain	HIV positivity	Abscess	*S. enterica* subsp. enterica serovar *Enteritidis*	None	Yes	Ciprofloxacin*	Cured
Aoyama et al.[24]	71/M	Fever and stupor	Gastric cancer	Blood	*S. choleraesuis* ssp.	None	No (Because of thrombocytopenia)	Ceftriaxone 2 weeks	Death
Farrar et al.[25]	65/M	Polyuria, polydipsia, back pain, and dysuria	DM	Blood and bone byopsia	*S. enterica*	Spondilodiscitis and an epidural abscess	Yes	Following meropenem, Fuscidic acid, and ertapenem for 8 weeks	Cured
Bhosale and Sanjay[26]	59/M	Abdominal pain	HT	Abscess	*S. parathyphi* A	None	Yes	No information	Cured
Peker et al.[27]	55/M	Hip pain, restriction of movements	Chronic renal failure	Abscess	*S.* spp.	Septic arthritis of the hip	Yes	Ciprofloxacin 6 weeks	Cured
Lucia et al.[4]	77/M	Hip pain	Prostate cancer	Blood	*S. enterica*	Lumbar osteomyelitis	No (It was denied by the patient)	Ceftriaxone (10 days), levofloxacin (8 weeks)	Cured
Ghazanfar et al.[28]	22/F	Back pain	None	Urine	*S. enterica*	Urine, septic arthritis	No	Ceftriaxone and levofloxacin 6 weeks	Cured
Ng and Heng[29]	80/M	Fever	History of intra-abdominal surgery (cholecystectomy)	Blood	*S. enteritidis*	None	Yes	No information	Cured
Mousselli et al.[30]	50/M	Fever, back pain, and hip pain	None	Blood	*S. enterica*	Epidural phlegmon	No	Ceftriaxone and levofloxacin (6 weeks)	Cured
Kumar et al.[31]	18/M	Fever and right hip pain	None	Blood	*S. typhi*	Sacroiliitis	No	Following ceftriaxone, ciprofloxacin*	Cured
Present case	65/F	Fever, nausea, and vomiting	Multiple myeloma	Blood and abscess	*S.* spp.	None	Yes	Ciprofloxacine (2 weeks), ceftriaxone (4 weeks)	Death

*Clear information is not given about the duration of treatment. **Antibiotic type not specified. M: Male, F: Female, DM: Diabetes mellitus, HT: Hypertension, HIV: Human Immunodeficiency Virus, TMP/SMX: Trimethoprim sulfamethoxazole, ITP: Immune thrombocytopenic purpura, MG: Myasthenia graves

The second occurred in a 71-year-old male with gastric cancer; treatment failure was likely influenced by inadequate drainage, a short antibiotic course, and immunosuppression[24]. In our patient, multiple myeloma-related immunosuppression, the emergence of ciprofloxacin resistance, and progressive clinical decline despite appropriate interventions likely contributed to the fatal outcome. Collectively, these cases emphasize the importance of timely diagnosis, effective drainage, and careful consideration of host factors and antimicrobial resistance in determining prognosis.

This report has certain limitations. First, the *Salmonella* strain was not serotyped, which restricted comparisons with previously published cases. Second, ciprofloxacin resistance could not be assessed at the molecular level, which limited our understanding of underlying resistance mechanisms in this context.

Conclusion

Salmonella-induced psoas abscess is an uncommon but clinically significant condition, and it has been reported in both immunocompetent and immunocompromised individuals. Although most patients achieve favorable outcomes with timely antibiotics and drainage, prognosis worsens with delayed diagnosis, antimicrobial resistance, or underlying immunosuppression. Clinicians should therefore maintain a high index of suspicion in cases of *Salmonella* bacteremia presenting with musculoskeletal symptoms to facilitate early recognition and optimal management.

Ethics

Informed Consent: In this case report, informed consent has been taken from the patient, and there is not any specific data in the manuscript identifying the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.Ö.K., H.T., Concept: Y.Ç.K., Design: Y.Ç.K., Data Collection or Processing: İ.Ö.K., H.T., Analysis or Interpretation: İ.Ö.K., H.T., Literature Search: Y.Ç.K., Writing: Y.Ç.K., İ.Ö.K., H.T.

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Enhancing Microbiological Testing Rates Prior to Antimicrobial Therapy in Hospitalized Patients Using the FOCUS-PDCA Cycle Model

FOCUS-PDCA Döngüsü Modeli Kullanılarak Hastanede Yatan Hastalarda Antimikrobiyal Tedavi Öncesi Mikrobiyolojik Test Oranlarının Artırılması

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Abstract

Introduction: Enhancing compliance with microbiological testing prior to antimicrobial therapy is fundamental to diagnostic stewardship, precision antimicrobial prescribing, and the containment of antimicrobial resistance—a key objective of national healthcare quality and safety initiatives. This study evaluated the effectiveness of the Find, Organize, Clarify, Understand, Select, Plan, Do, Check, Act (FOCUS-PDCA) cycle model as a quality improvement framework to improve adherence to microbiological testing protocols in hospitalized patients.

Materials and Methods: Baseline data were collected from hospitalized patients receiving antimicrobial therapy between January and December 2022 to evaluate three diagnostic stewardship indicators: (1) overall microbiological testing rate before antimicrobial therapy, (2) microbiological testing rate for hospital-acquired infection (HAI) diagnoses, and (3) submission rate before the concomitant use of key antimicrobials. From January to June 2023, the FOCUS-PDCA model was implemented, incorporating systematic problem identification, root cause analysis, targeted interventions, and subsequent evaluation of performance metrics to assess improvements in testing compliance.

Results: Implementation of the FOCUS-PDCA model led to statistically significant improvements across all indicators. The overall pre-antimicrobial testing rate increased from 44.29% to 69.94% post-intervention [odds ratio (OR): 0.64; 95% confidence interval (CI), 0.63–0.65; p<0.001). The HAI-related testing rate rose from 72.63% to 90.0% (OR: 0.81; 95% CI, 0.74–0.88; p<0.001), achieving the national target. The submission rate before concomitant use of key antimicrobials increased from 89.76% to 96.47% (OR: 0.91; 95% CI, 0.88–0.95; p<0.001), although it remained slightly below the national threshold of 100%. All observed differences were statistically significant (p<0.05).

Conclusion: The FOCUS-PDCA model effectively enhanced diagnostic stewardship by significantly increasing compliance with microbiological testing protocols prior to antimicrobial therapy in hospitalized patients. These findings underscore the value of structured quality improvement frameworks in antimicrobial stewardship programs to promote rational, evidence-based antimicrobial use.

Keywords: FOCUS-PDCA, diagnostic stewardship, microbiological testing, antimicrobial therapy, hospital-acquired infection

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Öz

Giriş: Antimikrobiyal tedavi öncesi mikrobiyolojik testlere uyumun artması, tanı yönetimi, hassas antimikrobiyal reçeteleme ve antimikrobiyal direnç kontrolü için temel öneme sahiptir. Bu, ulusal sağlık hizmetleri kalite ve güvenlik girişimlerinin temel amaçlarından biridir. Bu çalışmada, hastanede yatan hastalarda antimikrobiyal tedavi öncesi mikrobiyolojik test protokollerine uyumu artırmak için bir kalite iyileştirme çerçevesi olarak Bul, Organize Et, Açıkla, Anla, Seç, Planla, Uygula, Kontrol Et, Önlem Al (FOCUS-PDCA) döngü modelinin etkinliği değerlendirilmiştir.
Gereç ve Yöntem: Ocak ve Aralık 2022 arasında antimikrobiyal tedavi gören hastanede yatan hastalardan temel veriler toplanarak üç temel tanı yönetimi göstergesi değerlendirilmiştir: 1) antimikrobiyal tedavi öncesi mikrobiyolojik test oranı, 2) hastane kaynaklı enfeksiyon tanılarıyla ilişkili mikrobiyolojik test oranı ve 3) temel antimikrobiyallerin eş zamanlı kullanımından önceki başvuru oranı. Ocak-Haziran 2023 arasında, sistematik sorun tanımlama, kök neden analizi, hedefli müdahalelerin geliştirilmesi ve uygulanması ve mikrobiyolojik test uyumluluğundaki iyileştirmeleri değerlendirmek için performans ölçütlerinin daha sonraki değerlendirmesini içeren FOCUS-PDCA modeli uygulanmıştır.
Bulgular: FOCUS-PDCA modelinin uygulanması sonrasında, ölçülen tüm göstergelerde istatistiksel olarak anlamlı iyileştirmeler sağlanmıştır. Antimikrobiyal tedavi öncesi genel mikrobiyolojik test oranı, başlangıçta %44,29 iken müdahaleden sonra %69,94'e yükselmiştir [odds ratio (OR): 0,64, %95 güven aralığı (GA): 0,63–0,65, p<0,001). Hastane kaynaklı enfeksiyonla ilişkili tanı testleri için başvuru oranı, %72,63'ten %90,0'a yükselmiştir (OR: 0,81, %95 GA: 0,74–0,88, p<0,001) ve ulusal hedefe ulaşmıştır. Ek olarak, temel antimikrobiyallerin eş zamanlı kullanımından önceki başvuru oranı, %89,76'dan %96,47'ye yükselmiştir (OR: 0,91, %95 GA: 0,88–0,95, p<0,001), ancak %100'lük ulusal eşik değerinin altında kalmıştır. Başlangıç ve müdahale sonrası oranlar arasında gözlemlenen tüm farklılıklar istatistiksel olarak anlamlı saptanmıştır (p<0,05).
Sonuç: FOCUS-PDCA modelinin uygulanması, hastanede yatan hastalarda antimikrobiyal tedaviden önce mikrobiyolojik test protokollerine uyumu önemli ölçüde artırarak tanı yönetimi uygulamalarını etkili bir şekilde iyileştirmiştir. Çalışma, FOCUS-PDCA modelinin akılcı ve kanıta dayalı antimikrobiyal kullanımını teşvik etmedeki klinik önemini vurgulamıştır. Bu bulgular, tanı uygulamalarını optimize etmek için yapılandırılmış kalite iyileştirme çerçevelerinin antimikrobiyal yönetim programlarına entegre edilmesini desteklemektedir.
Anahtar Kelimeler: FOCUS-PDCA, mikrobiyolojik test, antimikrobiyal tedavi, hastane kaynaklı enfeksiyon

Introduction

The National Institute of Hospital Administration launched (HAI) a special action initiative (2021–2023) aimed at increasing microbiological testing rates prior to antimicrobial therapy in hospitalized patients—a central objective of national healthcare quality and safety efforts[1]. This initiative established tiered benchmarks: a minimum submission rate of 50% for all hospitalized patients receiving therapeutic antibiotics, at least 90% for those diagnosed with hospital-acquired infections (HAIs), and 100% for cases involving the empirical use of two or more key antibiotics. Key antibiotics include carbapenems, glycopeptides, new tetracyclines, polymyxins, β-lactams, and systemic antifungals. The Find, Organize, Clarify, Understand, Select, Plan, Do, Check, Act (FOCUS-PDCA) cycle model, an extension of the traditional PDCA framework, has demonstrated efficacy in identifying workflow deficiencies and improving microbiological testing rates among inpatients receiving antimicrobial therapy. The model involves sequential steps—FOCUS—followed by PDCA—providing a systematic and iterative method for process optimization. This study applied the FOCUS-PDCA cycle model to evaluate microbiological testing rates among hospitalized patients, providing evidence-based guidance for optimizing specimen submission and promoting rational antimicrobial use in clinical practice.

Materials and Methods

Study Design and Participants

This retrospective study analyzed microbiological testing rates prior to the initiation of systemic antimicrobial therapy in hospitalized patients. Baseline (pre-intervention) data were collected from January 1 to December 31, 2022. Post-intervention data, following implementation of the FOCUS-PDCA cycle model, were collected from January 2023 to June 2023. Thus, microbiological testing data from the full year of 2022 were used for pre-intervention analysis, while data from the first half of 2023 were used for post-intervention evaluation. The study included patients who received systemic antimicrobial therapy during hospitalization. Patients receiving prophylactic antibiotics or localized antimicrobial treatments—such as eye drops, irrigation solutions, enemas, or topical formulations—were excluded.

Problem Identification

Current Status Assessment: A retrospective analysis of inpatient data from January 1 to December 31, 2022, was conducted using the hospital's infection monitoring system to evaluate microbiological testing practices. The results revealed that the pretreatment specimen submission rate was substantially below the national benchmark of 50%, as specified in the national special action plan for antimicrobial stewardship.

Establishment of Quality Improvement Team: A multidisciplinary quality improvement team was formed under the leadership of the Department of Hospital Infection Control. The team comprised 10 members representing key departments, including Hospital Infection Control, Medical Affairs, Clinical Laboratory, Information Technology, Nursing, and major clinical units. In addition, representatives from the hospital's infection surveillance software provider and personnel from affiliated group hospitals were included. The team's primary responsibilities were to develop, implement, and monitor targeted interventions aimed at improving microbiological testing rates across the institution.

Clarification of Microbiological Testing Process and Operational Standards: The standard submission workflow began with physicians ordering microbiological tests based on clinical indications. Orders were verified by nursing staff prior to specimen collection—such as blood, urine, or respiratory samples—to ensure accurate labeling and timely transport to the laboratory under prescribed conditions. Upon receipt, the Clinical Laboratory Department processed the specimens according to standardized microbiological protocols, and results were recorded in the hospital's data system for statistical analysis. The system automatically calculated the microbiological submission rate prior to antimicrobial therapy using timestamps for antibiotic administration and specimen collection/orders. These results were subsequently distributed to relevant clinical departments as part of performance assessments within the quality improvement initiative.

Root Cause Analysis: To identify factors contributing to the low baseline pretreatment specimen submission rate, the quality improvement team conducted structured brainstorming sessions and comprehensive root cause analyses. The following categories of contributing factors were identified:

(1) Personnel-related factors: Limited awareness among medical staff regarding the importance of pretreatment specimen collection for guiding empirical therapy, lack of initiative in performing essential clinical duties, insufficient emphasis and clear guidance from department heads on timely specimen submission, and inadequate or infrequent training on diagnostic stewardship principles and practical specimen collection procedures

(2) System-related factors: Limitations of the information system, including inaccuracies in capturing indications for antimicrobial use, absence of time-stamped records for specimen collection in inpatient units, and inadequate data validation processes for quality control

(3) Management-related factors: Structural weaknesses in management, such as underdeveloped accountability frameworks, absence of performance-based incentives, delayed feedback on submission compliance, and insufficient oversight from functional departments

(4) Documentation-related factors: Incomplete documentation of antimicrobial stewardship protocols, limited feasibility of existing work plans, non-standardized workflows, and poorly defined responsibilities (Figure 1).

Quality Improvement Plan

Target: Based on the standards outlined in the National Special Action Guide, a continuous quality improvement (CQI) target was set to achieve a microbiological testing rate of ≥50% among hospitalized patients receiving systemic antimicrobial therapy.

Timeline and Strategy: In early January 2023, personnel from the Department of Hospital Infection Control conducted a comprehensive baseline assessment and formally established the CQI Team. By late January, the team collaborated with relevant departments to identify operational challenges, perform a root cause analysis, and develop targeted intervention strategies. The intervention plan was fully implemented from February to June 2023. Outcomes were evaluated in June 2023, and the results were analyzed to determine areas of success and identify remaining gaps.

Implementation

Based on the findings of the root cause analysis, a multifaceted intervention strategy was developed and implemented (Table 1). Key components of the strategy included enhancements to institutional management structures and the promotion of cross-disciplinary collaboration. A quality control team was established to monitor improvements in microbiological testing prior to antimicrobial initiation. The team was led by the hospital Vice President and included representatives from the Departments of Hospital Infection Control, Pharmacy, Medical Affairs, and the Microbiology Laboratory. Regular multi-departmental meetings were convened to monitor progress, coordinate efforts, and refine operational procedures (Figure 2). Structured, tiered training programs were introduced to strengthen the clinical knowledge of medical staff and improve compliance with microbiological testing protocols. Training modules were tailored to specific clinical roles and delivered through multiple channels, including director briefings, head nurse meetings, and part-time staff seminars. Training sessions focused on updating knowledge of hospital infection epidemiology and relevant clinical guidelines, as well as providing case-based analyses of non-compliant practices, particularly in departments with suboptimal performance. Multidisciplinary collaboration was promoted to enhance clinical specimen submission and testing. The Pharmacy and Laboratory Departments jointly educated physicians on diagnostic antimicrobial stewardship, rational antimicrobial use, and standardized specimen submission

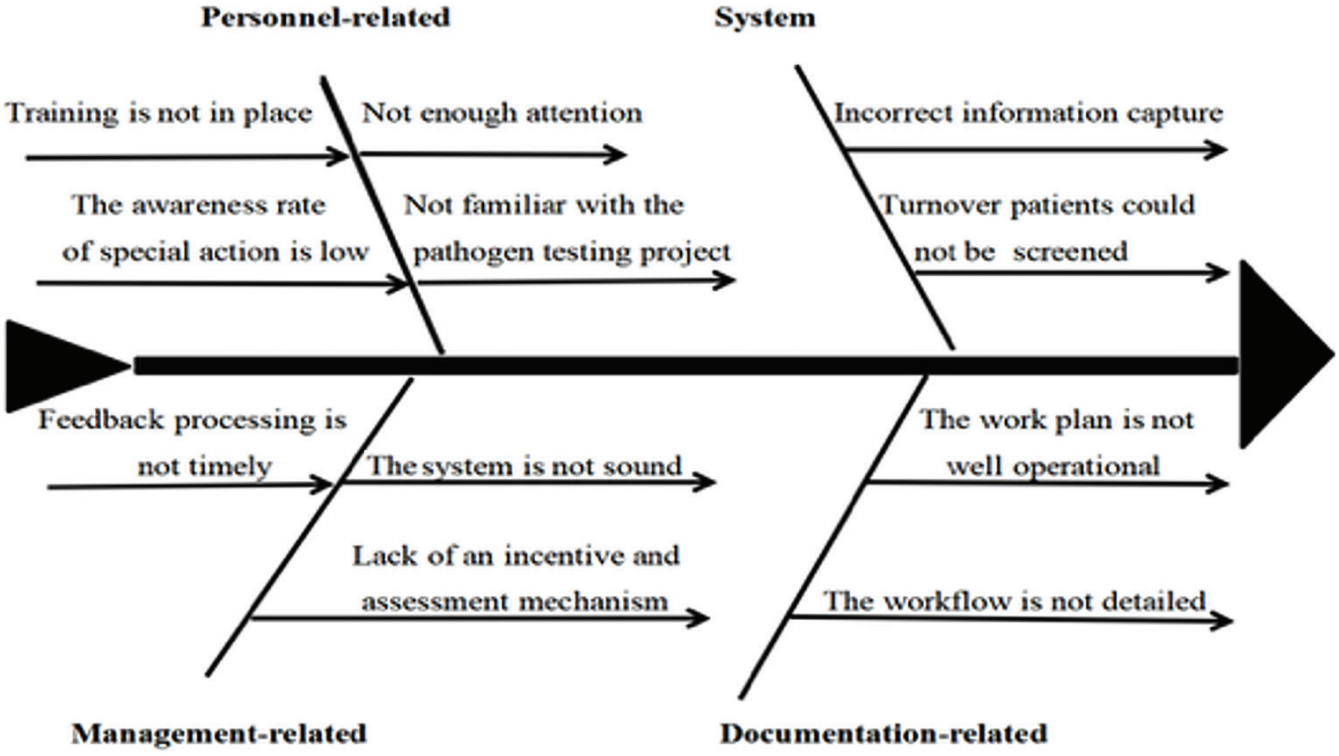

Figure 1. Root cause analysis of quality management factors affecting microbiological testing rates prior to antimicrobial therapy

procedures. The Hospital Infection Control Department revised the accountability framework to incorporate stricter performance evaluations and feedback mechanisms. Incentive and penalty structures were introduced to encourage compliance and sustain adherence to quality standards (Supplementary File 1). In addition, the hospital's information management systems were integrated and optimized to enhance operational efficiency. System functionality was upgraded to automatically intercept microbiological testing requests submitted prior to the concomitant administration of critical antimicrobials. Relevant microbiological test items were also incorporated into the appendix of the special action guide, supporting improved clinical decision-making.

Performance Indicators

The effectiveness of the FOCUS-PDCA model was assessed by comparing pre- and post-intervention performance across three key indicators: (1) overall microbiological testing rate prior to antimicrobial therapy, (2) microbiological testing rate for HAI diagnoses, and (3) microbiological testing rate prior to the concomitant use of key antimicrobials.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0. Continuous variables were expressed as mean ± standard deviation, and differences between independent groups were assessed using the two-sample t-test. Categorical variables were presented as counts and percentages, with group comparisons conducted using the chi-squared (χ^2) test. A two-tailed p-value of <0.05 was considered statistically significant.

Results

Baseline Pre-Antimicrobial Therapy Microbiological Testing Rates

A baseline analysis was conducted to evaluate microbiological testing rates among inpatients receiving systemic antimicrobial therapy prior to the implementation of the FOCUS-PDCA quality improvement model. The results indicated suboptimal compliance with diagnostic stewardship standards, with all evaluated indicators falling below the thresholds set by the National Special Action Guide. Specifically, the overall microbiological testing rate prior to antimicrobial therapy was 44.49% (below the national target of ≥50%), the submission rate for HAI diagnoses was 72.63% (below the recommended threshold of ≥90%), and the submission rate prior to concomitant use of key antimicrobials was 89.76% (below the threshold of 100%) (Table 2).

Impact of Intervention on Overall Pre-Antimicrobial Therapy Microbiological Testing Rates

Following implementation of the FOCUS-PDCA-guided quality improvement intervention, the overall pretreatment

Table 1. Improvement plan and implementation scheme

Problem	Causation	Countermeasure scheme	The person in charge	Execute time	Place of execution
What	**Why**	**How**	**Who**	**When**	**Where**
The rate of etiological examination for antimicrobial drugs in hospitalized patients is not up to standard	Insufficient training efforts	Develop a specialized training program, conduct hierarchical training, and ensure that all staff are informed	The Hospital Infection Control Department	February–May	Conference room
		Online training and assessment of all clinical departments	The Hospital Infection Control Department	February–June	Clinical departments
		Monitoring doctors and nurses in the clinical departments of the hospital	The Hospital Infection Control Department	June	Clinical departments
		Internal training of the department	Director of each section and part-time duty personnel	January–June	Clinical departments
	Insufficient attention to medical staff	Multidisciplinary combination to strengthen the awareness of clinical inspection	Hospital infection department, Pharmacy Department, microbiology room	January–June	Clinical departments
		Establish an effective reward and punishment mechanism	Hospital infection department	Mar	Hospital infection department
	Information support	Information exchange meeting	Hospital infection department, Information section	April	Hospital infection department
		Add the function of pathogen inspection and reminder before issuing antibiotics	Hospital infection department, Information section	April–May	Information section
		Supplement and improve the information system etiology project	Hospital infection department, Information section	April	Information section
		Internal verification of the information ensures the accuracy of the data	Hospital infection department	June	Information section

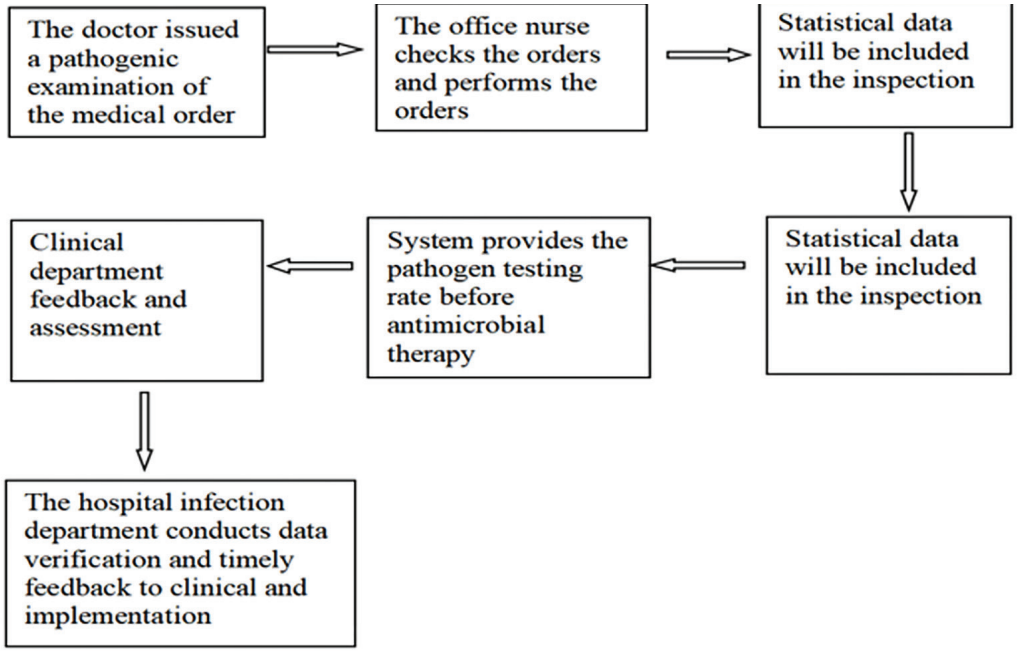

Figure 2. Optimized workflow for microbiological testing prior to antimicrobial therapy following implementation of the FOCUS-PDCA quality improvement model

FOCUS-PDCA: Find, Organize, Clarify, Understand, Select, Plan, Do, Check, Act

microbiological testing rate among inpatients receiving systemic antimicrobial therapy increased significantly. The post-intervention submission rate reached 69.94%, compared with a baseline rate of 44.29% (OR: 0.64; 95% CI, 0.63–0.65; p<0.001), demonstrating enhanced compliance with diagnostic stewardship protocols (Table 3).

Impact of Intervention on Microbiological Testing Rates for HAI Diagnoses

Post-intervention, the microbiological testing rate for etiological specimens associated with suspected or confirmed HAI increased to 90%, compared with 72.63% at baseline. This improvement was statistically significant (OR: 0.81; 95% CI, 0.74–0.88; p<0.001), meeting the national target of ≥90% for infection-related diagnostic testing (Table 4).

Impact of Intervention on Microbiological Testing Rates Prior to Concomitant Use of Key Antimicrobials

The microbiological testing rate prior to the concomitant use of key antimicrobials increased from 89.76% at baseline to 96.47% post-intervention. This difference was statistically significant (OR: 0.91; 95% CI, 0.88–0.95; p<0.001), indicating improved compliance with antimicrobial stewardship protocols in high-risk antibiotic regimens (Table 5).

Discussion

Global antimicrobial consumption has been steadily increasing, with a reported 90.9% rise in per capita use between 2000 and 2015[2]. This upward trend contributes to widespread antimicrobial misuse and the escalating problem of antimicrobial resistance (AMR). Antimicrobial-resistant organisms have been associated with approximately 4.95 million deaths globally[3], highlighting the urgent need for effective antimicrobial stewardship strategies. Consequently, antimicrobial stewardship has become a global health priority, emphasizing the importance of timely and appropriate microbiological testing prior to initiating antimicrobial therapy. Submitting clinical specimens prior to antibiotic administration is a cornerstone of diagnostic stewardship, as it guides targeted therapy, reduces unnecessary empirical antimicrobial use, and helps mitigate the development of resistance. International guidelines, including those from

Table 2. Pathological testing of hospitalized patients before intervention before antimicrobial use

Project	Number of cases investigated	Number of test cases before use	The inspection rate is (%)
Antimicrobial use before treatment	22299	9875	44.29
Diagnosis of nosocomial infection was related	296	215	72.63
Combined use of key drugs	469	412	89.76

The total amount amounted to 23064 units, with 10502 units being utilized effectively, representing a utilization rate of 45.53%

Table 3. Pre-intervention and post-intervention microbiological testing situation before antibiotic use in hospitalized patients

Time	Number of survey cases	Number of cases sent for inspection beforehand	Inspection rate (%)	χ2 value	OR (95% CI)	p value
Pre-intervention	22299	9875	44.29	1987.49	1	<0.001
After intervention	12822	8839	69.94		0.64 (0.63-0.65)	

OR: Odds ratio, CI: Confidence interval

Table 4. Intervention-related changes in the etiological examination of hospital-acquired infections among inpatients before and after the intervention

Time	Number of survey cases	Number of cases sent for inspection beforehand	Inspection rate (%)	χ2 value	OR (95% CI)	p value
Pre-intervention	296	215	72.63	15.84	1	<0.001
After intervention	130	117	90		0.81 (0.74-0.88)	

OR: Odds ratio, CI: Confidence interval

Table 5. Microbiological testing before and after intervention for combined use of key antibiotics

Time	Number of survey cases	Number of cases sent for inspection beforehand	Inspection rate (%)	χ2 value	OR (95% CI)	p value
Pre-intervention	469	412	89.76	22.39	1	<0.001
After intervention	425	410	96.47		0.91 (0.88-0.95)	

OR: Odds ratio, CI: Confidence interval

the Centers for Disease Control and Prevention in the United States and Nigeria, recommend that antimicrobial prescriptions be guided by microbiological test results[4]. Despite this, improving microbiological testing rates prior to antimicrobial therapy remains a significant challenge. Most existing studies in this area are descriptive and provide limited evaluations of structured, evidence-based interventions[5]. To address this gap, the present study employed the FOCUS-PDCA cycle model, a structured framework for CQI first introduced in the United States in the 1990s, to enhance microbiological testing rates prior to antimicrobial therapy. This comprehensive framework facilitates root cause analysis, targeted intervention design, and systematic performance evaluation, thereby optimizing healthcare process[6,7]. The FOCUS-PDCA model extends the traditional PDCA cycle by incorporating five additional preparatory steps.

In this study, the FOCUS-PDCA cycle model was systematically applied to improve the submission rate of microbiological specimens prior to antimicrobial therapy. Key interventions included identifying factors influencing testing rates, revising submission workflows, developing and implementing tailored interventions, providing specialized training for healthcare professionals, optimizing information systems, and introducing performance-based accountability mechanisms. These multifaceted initiatives significantly increased the overall microbiological testing rate from 44.29% to 69.94%, surpassing the national special action improvement target of 50%. The post-intervention rate of 69.94% was also substantially higher than the 43.23% average reported by tertiary general hospitals in the National Sentinel Hospital Information Monitoring System in 2022[8]. However, these rates remained lower than those reported in international settings[9]. Additionally, the microbiological testing rate for HAI-associated diagnoses reached 90%, meeting the national standard of ≥90.00%.

Similarly, the submission rate prior to the concomitant use of key antibiotics increased to 96.47% post-intervention. While this represents a notable improvement, it remains below the 100% target set by the National Health Commission. This shortfall may be attributed to persistent reliance on empirical antibacterial therapy—particularly in urgent or severe cases—a lack of clinician awareness regarding the timing and clinical importance of pathogen collection before treatment, and prevailing misconceptions that diminish the perceived value of routine microbiological testing. In some instances, specimens are submitted without clear diagnostic rationale or with poor coordination between sampling and antimicrobial administration, leading to delays, reduced diagnostic utility, and non-compliance with submission standards. Effective management of bacterial infections depends on the timely collection and processing of microbiological specimens, including pathogen isolation, cultivation, and identification, and antimicrobial susceptibility testing. Results from susceptibility testing provide the basis for precise antimicrobial selection and individualized patient management. Furthermore, routine microbiological specimen submission plays a critical role in the early detection of multidrug-resistant bacteria and other clinically significant pathogens, enabling timely infection prevention and control measures and improving outcomes for both individual patients and the healthcare system.

While significant improvements were achieved in pre-antibiotic and HAI-related microbiological testing rates—meeting national standards—the submission rate prior to the concomitant use of key antibiotics remained below the 100% benchmark, highlighting the need for continued efforts to achieve full compliance. Future interventions should focus on optimizing the timing of specimen collection, standardizing diagnostic and therapeutic protocols, and strengthening multidisciplinary oversight. Cultivating a culture of evidence-based, rational antibiotic prescribing is essential for combating AMR and improving healthcare quality.

Study Limitations

This study has some limitations. The post-intervention observation period was shorter than the pre-intervention period, which may have introduced bias in outcome comparisons. Therefore, the effectiveness of the proposed management model requires further investigation and validation through long-term, multicenter studies to provide more robust and generalizable evidence for clinical practice.

Conclusion

The systematic implementation of the FOCUS-PDCA quality improvement model—supported by coordinated interdepartmental collaboration and enhanced integration of information technology into clinical workflows—significantly improved microbiological testing rates prior to the initiation of antimicrobial therapy in hospitalized patients. These improvements in diagnostic antimicrobial stewardship are critical for promoting evidence-based antimicrobial prescribing, which helps combat AMR and ultimately enhances patient outcomes and overall healthcare quality. Ongoing refinement and expansion of these strategies are essential to ensure sustained compliance with national and international standards for diagnostic and antimicrobial stewardship.

Ethics

Ethics Committee Approval: Not required.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.C., H.G., Concept: L.Z., Design: M.W., Data Collection or Processing: Y.H., Y.L., Analysis or Interpretation: T.C., H.G., Literature Search: T.J., Writing: T.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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During the preparation of this work, the authors used ChatGPT in order to improve language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Risk Factors and Treatment Determinants of Mortality in Carbapenem-Resistant Gram-Negative Bloodstream Infections in the Intensive Care Unit

Yoğun Bakım Ünitesinde Karbapeneme Dirençli Gram-Negatif Bakteriyemilerde Mortaliteyi Etkileyen Risk Faktörleri ve Tedavinin Değerlendirilmesi

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Abstract

Introduction: Carbapenem-resistant Gram-negative bacteria (CR-GNB) represent a major global health challenge, associated with limited therapeutic alternatives and elevated mortality rates. This study aimed to evaluate factors linked to mortality in bloodstream infections (BSI) caused by CR-GNB and to compare the effectiveness of various treatment modalities.

Materials and Methods: We conducted a single-center, retrospective cohort study of all consecutive patients with hospital-acquired CR-GNB BSI treated in the intensive care unit (ICU) of a 1010-bed tertiary university hospital between 2019 and 2022. Demographic characteristics, severity scores, invasive procedures, antibiotic regimens, and 28-day mortality outcomes were collected.

Results: A total of 156 patients met the inclusion criteria. The mean age was 68.6±15.8 years, and 91 (58.3%) were male. The overall 28-day mortality rate was 52.5%. Mortality was significantly higher among patients who underwent mechanical ventilation (p<0.001) or central venous catheterization (p=0.005) and among those with solid organ malignancy (p<0.001), hematologic malignancy (p<0.001), or immunosuppressive therapy (p=0.024). Independent predictors of mortality included Charlson Comorbidity Index [odds ratio (OR), 1.55; 95% confidence interval (CI), 1.22-1.97; p<0.001], septic shock (OR, 6; 95% CI, 1.74-21.18; p=0.05), total parenteral nutrition (TPN) (OR, 202.7; 95% CI, 13.5-3036.9; p<0.001), length of ICU stay prior to bacteremia diagnosis (OR, 0.95; 95% CI, 0.91-0.99; p=0.04), and receipt of effective treatment based on antibiogram results (OR, 0.06; 95% CI, 0.01-0.34; p=0.002). Mortality did not differ remarkably between patients receiving combination therapy and those receiving monotherapy, nor between those who received appropriate empiric therapy and those who did not.

Conclusion: Where feasible, invasive procedures such as central venous catheterization and mechanical ventilation should be minimized. TPN should be reserved for cases where alternative nutritional support is not possible. Mortality was reduced by the administration of effective therapy guided by antibiogram results. Given the scarcity of effective agents, the development of new antibiotics remains an urgent priority.

Keywords: Carbapenem-resistant Gram-negative bacteria, bloodstream infections, mortality, intensive care unit, antibiogram-guided therapy

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Öz

Giriş: Karbapenem dirençli Gram-negatif bakteriler (KD-GNB), sınırlı tedavi alternatifleri ve yüksek ölüm oranları ile önemli bir küresel zorluk teşkil etmektedir. Bu çalışma, KD-GNB'lerin neden olduğu kan dolaşımı enfeksiyonlarında (KDİ) ölüme bağlı faktörleri değerlendirmeyi ve çeşitli tedavi yöntemlerinin etkinliğini karşılaştırmayı amaçlamıştır.
Gereç ve Yöntem: Bu çalışma, 2019'dan 2022'ye kadar 1010 yataklı bir üçüncül düzey üniversite hastanesinin yoğun bakım ünitesinde tedavi edilen hastane kaynaklı KD-GNB KDİ olan ardışık tüm hastaları içeren tek merkezli, retrospektif bir kohort analizidir. Demografik veriler, şiddet skorları, invaziv işlemler, antibiyotik tedavisi ve hastanın 28 günlük mortalite sonuçları kaydedilmiştir.
Bulgular: Toplamda 156 hasta dahil etme kriterlerini karşıladı. Hastaların ortalama yaşı 68,6±15,8 yıl idi. Yirmi sekiz günlük kümülatif mortalite oranı %52,5'ti. Mekanik ventilasyon (p<0,001), santral venöz kateterizasyon (p=0,005), solid organ malignitesi (p<0,001), hematolojik malignite (p<0,001) ve immünsüpresif ilaç kullanımı (p=0,024) mortalite gelişen grupta anlamlı derecede daha yüksekti. Charlson Komorbidite İndeksi [olasılık oranı (OR): 1,55, %95 güven aralığı (GA): 1,22-1,97, p<0,001], septik şok (OR: 6, %95 GA: 1,74-21,18, p=0,05), total parenteral nutrisyon (TPN) (OR: 202,7, %95 GA: 13,5-3036,9, p<0,001), bakteriyemi öncesi yoğun bakım ünitesinde kalış günü (OR: 0,95, %95 CI: 0,91-0,99, p=0,04) ve antibiyogram sonuçlarına göre etkili tedavi alma (OR: 0,06, %95 GA: 0,01-0,34, p=0,002) mortalite ile ilişkili bağımsız faktörler olarak belirlenmiştir. Kombinasyon tedavisi ile monoterapi arasında mortalitede önemli bir fark kaydedilmedi. Ampirik tedavinin uygun bir şekilde başlanması, ölüm oranlarında belirgin bir fark yaratmamıştır.
Sonuç: İnvaziv yöntemler, santral venöz kateterizasyon ve mekanik ventilasyon dahil, mümkün olan en büyük ölçüde minimize edilmelidir. Alternatif beslenme yöntemleri mevcut olmadığı durumda TPN düşünülmelidir. Antibiyogram sonuçlarına göre yönlendirilen etkili tedavi uygulaması, ölüm oranlarını azaltmıştır.
Anahtar Kelimeler: Gram-negatif bakteriler, mortalite, yoğun bakım enfeksiyonları, karbapenem dirençli enterobacterales

Introduction

Infections are a common problem among patients in intensive care units (ICUs), contributing substantially to morbidity, mortality, and healthcare costs. In Türkiye and worldwide, the incidence of healthcare-associated infections caused by carbapenem-resistant enteric bacteria has been increasing[1]. According to the US Centers for Disease Control and Prevention's (CDC) Antibiotic Resistance Threats Report, more than 2.8 million antibiotic-resistant infections occur annually in the United States, leading to over 35,000 deaths. A considerable portion of this burden is attributable to multidrug-resistant (MDR) Gram-negative pathogens[2].

In 2024, the World Health Organization (WHO) updated its bacterial priority pathogen list, highlighting microorganisms that necessitate the research and development of novel antibiotics. These include carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant Enterobacterales, and third-generation cephalosporin-resistant Enterobacterales[3]. Infections caused by these pathogens are associated with high mortality rates. Prolonged hospitalization, the use of broad-spectrum antibiotics, central venous catheterization, intubation, immunosuppression, and severe comorbidities are recognized risk factors for mortality[4].

The current recommendation for managing carbapenem-resistant Enterobacterales bloodstream infections (CRE-BSI) is the use of next-generation β-lactam/β-lactamase inhibitors. In cases involving metallo-β-lactamase production, either the combination of ceftazidime–avibactam with aztreonam or cefiderocol monotherapy is advised. For CRAB, high-dose ampicillin–sulbactam in combination therapy is suggested as an alternative option[5]. In Türkiye, however, ceftazidime–avibactam is the only available agent in this novel beta-lactam/beta-lactamase inhibitor (BLBLI) class, and its use is restricted to select patients under specific reimbursement criteria.

This study aimed to evaluate mortality rates and risk factors associated with death in hospital-acquired BSI caused by carbapenem-resistant Gram-negative bacteria (CR-GNB) in the ICU and compare the effectiveness of different treatment regimens.

Materials and Methods

Study Design

This was a single-center, retrospective cohort study conducted at a 1010-bed tertiary care academic hospital. We included patients admitted to the ICU between January 2019 and January 2022 with CR-GNB bacteremia.

Patient Inclusion

Eligible participants were adult patients (≥18 years) admitted to the ICU during the study period. Only the initial episodes of monomicrobial bacteremia associated with clinical signs and symptoms of infection were analyzed. Additional inclusion criteria were (1) hospitalization in the ICU for at least 48 hours; (2) detection of CR-GNB in blood cultures; (3) fulfillment of healthcare-associated infection criteria; (4) a minimum of 48 hours of follow-up after initiation of treatment.

Exclusion of Patients

Patients were excluded if they were aged less than 18 years, if blood cultures were obtained within 48 hours of hospitalization, or if positive culture results were not accompanied by clinical manifestations of bacteremia.

Data Collection

The following data were extracted from medical records: demographic characteristics, Charlson Comorbidity Index (CCI), Acute Physiology and Chronic Health Evaluation II (APACHE II) score on the first day of ICU admission, and Pittsburgh Bacteremia Score (PBS) at the time of blood culture collection. Information was also collected on invasive procedures, primary cause of ICU admission, nutritional status, pathogens isolated from blood cultures, sources of bacteremia, antibiotic treatment details (monotherapy vs. combination therapy), delay in initiation of optimal therapy, presence of septic shock, ICU length of stay before bacteremia onset, and 28-day mortality.

Definition of Terms

BSI, carbapenem resistance, and nosocomial infection were defined according to the CDC criteria[6]. BSI is characterized by a positive blood culture for specified pathogens obtained ≥48 hours after hospital admission. The PBS was used to evaluate the immediate severity of illness and predicts mortality in patients with BSI. All parameters were assessed on the day of the initial positive blood culture or within the preceding 48 hours, and the highest score during this period was recorded. Scoring was given as follows:

- **Temperature:** 35.1-36 °C or 39-39.9 °C =1 point; ≤35 °C or ≥40 °C =2 points
- **Blood pressure:** A rapid decline in systolic pressure >30 mmHg or diastolic pressure >20 mmHg, systolic pressure <90 mmHg, or the need for intravenous vasopressors =2 points.
- **Mechanical ventilation:** 2 points
- **Cardiac arrest:** 4 points
- **Mental Status:** Alert, 0; disoriented, 1; stuporous, 2; comatose, 4[7].

Monotherapy was defined as the administration of a single *in vitro*-active antibiotic, whereas combination therapy was defined as the concurrent administration of at least one *in vitro*-active antibiotic. The onset of bacteremia was defined as the date of blood culture collection. Antibiotic therapy was considered appropriate if it included at least one active agent at an adequate dosage. Empirical treatment was defined as antimicrobial therapy initiated before antibiotic susceptibility results were available, whereas definitive treatment was therapy initiated after susceptibility testing. Delay in optimal treatment was defined as the interval between blood culture collection and the initiation of appropriate therapy according to antibiogram results. Septic shock was defined as a serum lactate level > 2 mmol/L despite adequate fluid resuscitation, together with the need for vasopressors to maintain a mean arterial pressure < 65 mmHg[8].

Identification and Antimicrobial Susceptibility Testing of Strains

Blood cultures were processed in the clinical microbiology laboratory using the BACTEC FX automated blood culture system (Becton Dickinson, USA). From 2019 to 2021, bacterial identification and antimicrobial susceptibility testing were performed with the BD Phoenix M50 system (Becton Dickinson, USA). From 2021 onward, identification was conducted using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; Bruker, Germany), whereas susceptibility testing was continued with the BD Phoenix M50 system. Colistin susceptibility was assessed using automated methods. Antimicrobial susceptibility results for isolates were interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria, using either the Kirby-Bauer disk diffusion method or the BD Phoenix automated system.

Statistical Analysis

The Shapiro-Wilk test was used to evaluate the normality of continuous variables. Continuous variables were compared between groups using the Mann-Whitney U test when the data are not normally distributed, whereas categorical variables were compared using the chi-squared test, for which Pearson, Yates' continuity correction, Fisher's exact, and Monte Carlo exact tests were applied as appropriate. The two-proportion z-test was used to compare chi-squared subcategories. Backward stepwise logistic regression analysis was performed to calculate odds ratios (ORs) with 95% confidence intervals (CIs). A two-tailed p-value <0.05 was considered statistically significant. Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Ethics Approval

The study protocol was reviewed and approved by the Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (approval number: 29, dated: 26.04.2022).

Results

Description of the Cohort

A total of 871 cases of Gram-negative bacteremia were identified. The majority (n=715, 82.1%) were excluded for multiple reasons. A total of 156 patients (17.9%) were included in the final analysis (Figure 1).

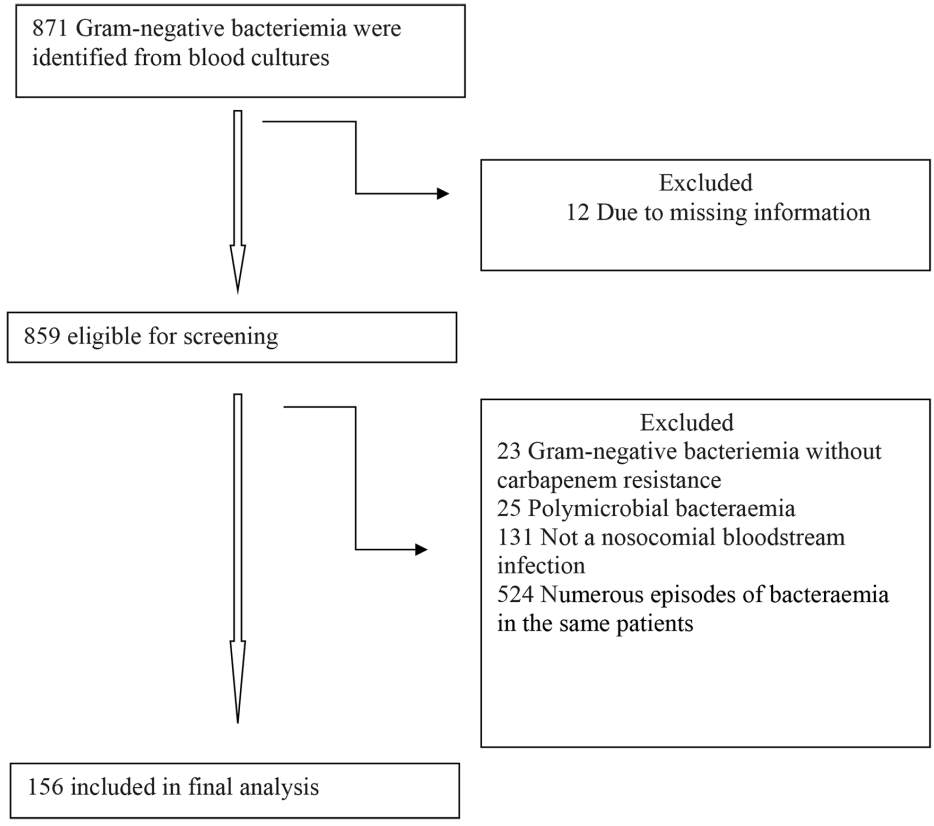

Figure 1. Flow diagram for enrollment in the study cohort

Clinical Characteristics and Mortality Risk Factors

The study cohort comprised 156 patients who met the inclusion criteria, with a mean age of 68.6±15.8 years; 91 (58.3%) were male. By day 28, 82 patients (52.5%) had died.

Compared with the survivors, nonsurvivors were considerably older (p=0.03) and had higher CCI scores (p=0.001) and PBS (p<0.001). No significant difference was observed in the APACHE II score at admission. The prevalence of Coronavirus Disease 2019 (COVID-19) was remarkably higher among nonsurvivors (p=0.012) (Table 1).

Statistically significant differences were also noted in the distribution of solid versus hematologic malignancies (p<0.001) and in the use of immunosuppressive drugs (p=0.024) (Table 2).

The incidence of mechanical ventilation (p<0.001), central venous catheterization (p=0.005), admission with respiratory distress (p<0.05), and receipt of total parenteral nutrition (TPN) (p<0.05) was remarkably higher among nonsurvivors (Tables 2 and 3). In contrast, survivors were more likely to have undergone tracheostomy (p=0.03), surgical intervention within the previous 3 months (p=0.02), trauma (p=0.03), or were receiving oral nutrition (p<0.05) (Tables 2 and 3). At the time of blood culture collection, the proportion of patients in septic shock was significantly higher in the nonsurvivor group (p<0.001) (Table 1). No marked difference in mortality was observed across the microorganisms isolated from blood cultures (p=0.57) (Table 4).

Mortality Rates Based on Antimicrobial Therapy

The effect of antibiotic regimens on mortality was evaluated. Patients received meropenem, imipenem, piperacillin–tazobactam, third-generation cephalosporins, or combinations with colistin, aminoglycoside, or fosfomycin. Five patients received ceftazidime–avibactam monotherapy. After 28 days, no statistically significant differences were observed in the antibiotics administered between survivors and nonsurvivors (Table 5).

Similarly, no statistically significant differences were noted between monotherapy and combination therapy. Neither the postponement of optimal treatment nor the initiation of appropriate empiric therapy influenced mortality rates. However, the proportion of patients who received effective treatment according to antibiogram results was markedly higher in the survivor group (p<0.001) (Table 5).

Table 1. Demographic and clinical characteristics of the study cohort

	Nonsurvivors (n=82)	Survivors (n=74)	Total	p-value
Sex, male	47 (57.3%)	44 (59.5%)	91 (58.3%)	0.786
Age Mean ± SD	70.9±15.4	66.1 ± 16	68.6±15.8	**0.03**
CCI Mean ± SD	6±2.7	4.4 ± 2.7	5.2±2.8	**0.001**
APACHE II Median (IQR)	17 (11-25)	15 (9-21)		**0.17**
PBS Mean ± SD	6.6±2.8	4.3 ± 2.8	5.5±3	**<0.001**
COVID-19 (+)	33 (40.2%)	16 (21.6%)	49 (31.4%)	**0.012**
Septic shock	45 (54.9%)	10 (%13.5)	55 (35.2%)	**<0.001**
Day of ICU stay before onset of bacteremia Mean ± SD	14.9±12.56	21.66 ± 19.2	18.1±16.3	**0.01**
Day of hospitalization before onset of bacteremia Mean ± SD	19.82±14.78	25.72 ± 20.97	22.6±18.17	0.102

SD: Standard deviation, CCI: Charlson Comorbidity Index, PBS: Pittsburgh Bacteremia Score, APACHE II: Acute Physiology and Chronic Health Evaluation II, Coronavirus Disease 2019, ICU: Intensive care unit

Table 2. Comorbidities and use of invasive procedures or devices

	Nonsurvivors (n=82)	Survivors (n=74)	Total	p-value
Comorbidities				
Chronic renal failure	5 (6.1%)	5 (6.8%)	10 (6.4%)	1
Renal replacement therapy	3 (3.7%)	3 (4.1%)	6 (3.8%)	1
Diabetes mellitus	29 (35.4%)	25 (33.8%)	54 (34.6%)	0.83
Hypertension	41 (50%)	36 (48.6%)	77 (49.4%)	0.86
COPD	13 (15.9%)	12 (16.2%)	25 (%16)	1
Chronic liver disease	1 (1.2%)	2 (2.7%)	3 (1.9%)	0.6
Cardiovascular disease	24 (29.3%)	21 (28.4%)	45 (28.8%)	1
Cerebrovascular disease	14 (17.1%)	17 (23%)	31 (19.9%)	0.47
Dementia	13 (15.9%)	9 (12.2%)	22 (14.1%)	0.66
Solid organ tumor	25 (30.5%)	7 (9.5%)	32 (20.5%)	<0.001
Hematologic malignancy	6 (7.3%)	0 (0%)	6 (3.8%)	<0.001
Immunosuppressive drug use**	23 (28%)	9 (12.2%)	32 (20.5%)	0.024
Invasive procedures or devices				
Mechanical ventilation	63 (76.8%)	41 (55.4%)	104 (66.7%)	< 0.001
Tracheostomy	13 (15.9%)	23 (31.1%)	36 (23.1%)	0.03
Chest tube	4 (4.9%)	7 (9.5%)	11 (7.1%)	0.42
Central venous catheterization	57 (69.5%)	35 (47.3%)	92 (59%)	0.005
Urinary catheterization	81 (98.8%)	73 (98.6%)	154 (98.7%)	0.72
Nasogastric tube	48 (58.5%)	35 (47.3%)	83 (53.2%)	0.16
Percutaneous endoscopic gastrostomy	8 (9.8%)	11 (14.9%)	19 (12.2%)	0.46
Surgical intervention in the last 3 months	23 (28%)	34 (45.9%)	57 (36.5%)	0.02
Trauma	6 (7.3%)	15 (20.3%)	21 (13.5%)	0.03

**: Use of corticosteroids (prednisone equivalent >20 mg/day for ≥14 days) or other recognized immunosuppressive therapy. COPD: Chronic obstructive pulmonary disease

Table 3. Primary cause of ICU admission, nutritional status, and prior location before ICU admission

	Nonsurvivors (n=82)	Survivors (n=74)	Total	Comparison of ratios**	p-value*
Primary cause of ICU admission					
Respiratory distress	53 (64.6%)	33 (44.6%)	86 (55.1%)	**<0.05**	**0.028**
Trauma	4 (4.9%)	16 (21.7%)	20 (12.9%)	**<0.05**	
GCD	14 (17.1%)	10 (13.5%)	24 (15.4%)	>0.05	
Post-res.	5 (6.1%)	8 (10.8%)	13 (8.3%)	>0.05	
Surgery	4 (4.9%)	4 (5.4%)	8 (5.1%)	>0.05	
Sepsis	2 (2.4%)	3 (4.1%)	5 (3.2%)	>0.05	
Nutritional status					
NG	44 (53.7%)	35 (47.3%)	79 (50.6%)	>0.05	**<0.001**
PEG	5 (6.1%)	11 (14.9%)	16 (10.3%)	>0.05	
TPN	20 (24.4%)	2 (2.7%)	22 (14.1%)	**<0.05**	
Oral	10 (12.2%)	26 (35.1%)	36 (23.1%)	**<0.05**	
Enteral + TPN	3 (3.7%)	0	3 (1.9%)	>0.05	
Place of stay before the ICU					
Community	33 (40.2%)	50 (67.6%)	83 (%53.2)	**<0.05**	**<0.001**
Nursing home	1 (1.4%)	0	1 (0.6%)	>0.05	
Hospital service	49 (59.9%)	23 (31.2%)	72 (46.3%)	**<0.05**	

*: Monte Carlo chi-square exact test, **: Two-proportion z-test, GCD: General condition disorder, Post-res.: Post-cardiopulmonary resuscitation, ICU admission, NG: Nasogastric catheter, PEG: Percutaneous endoscopic gastrostomy, TPN: Total parenteral nutrition, ICU: Intensive care unit

Table 4. Microorganisms isolated and source of bacteremia

Microorganisms isolated	Nonsurvivors (n=82)	Survivors (n=74)	Total	p-value
Acinetobacter spp.	49 (59.7%)	42 (56.7%)	91 (58.3%)	0.57
Klebsiella spp.	19 (23.1%)	18 (24.3%)	37 (23.7%)	
Pseudomonas spp.	7 (8.5%)	5 (6.7%)	12 (7.6%)	
Proteus mirabilis	2 (2.4%)	5 (6.7%)	7 (4.4%)	
Escherichia coli	1 (1.2%)	2 (2.7%)	3 (1.9%)	
Others	4 (4.8%)	2 (2.7%)	6 (3.8%)	
Bacteremia source				
Primary	19 (23.2%)	15 (20.3%)	34 (21.8%)	0.7
Respiratory system	51 (62.2%)	46 (62.2%)	97 (62.2%)	
Urinary system	4 (4.9%)	1 (1.4%)	5 (3.2%)	
Central venous catheter	5 (6.1%)	6 (8.1%)	11 (7.1%)	
Intra-abdominal infection	2 (2.4%)	2 (2.7%)	4 (2.6%)	
Others	1 (1.2%)	4 (5.4%)	5 (3.2%)	

Backward stepwise logistic regression was used to identify independent risk factors for mortality. Collinearity testing revealed a correlation between the PBS and septic shock; therefore, PBS was excluded from the model. Variables that were statistically significant in the univariate analysis (Table 6) were included in the initial model and subsequently analyzed by backward stepwise regression. The multivariate analysis demonstrated that higher CCI scores (OR, 1.55; 95% CI, 1.22-1.97; p<0.001), the presence of septic shock (OR, 6.00; 95% CI, 1.74-21.18; p=0.05), and TPN feeding (OR, 202.7; 95% CI, 13.5-3036.9; p<0.001) were associated with increased mortality. In contrast, a longer duration of ICU stays before the onset of bacteremia (OR, 0.95; 95% CI, 0.91-0.99; p=0.04) and receipt of effective treatment based on antibiogram results (OR, 0.06; 95% CI, 0.01-0.34; p=0.002) were protective factors.

Table 5. Antimicrobial treatments administered

	Nonsurvivors (n=82)	Survivors (n=74)	Total	p-value
Antibiotics				
Meropenem	9 (11%)	3 (4.1%)	12 (7.7%)	0.235
İmipenem	2 (2.4%)	0 (0%)	2 (1.3%)	
Piperacillin-tazobactam	3 (3.7%)	4 (5.4%)	7 (4.5%)	
Third-generation cephalosporin	4 (4.9%)	6 (8.1%)	10 (6.4%)	
Quinolone/TMP-SMX	0 (0%)	1 (1.4%)	1 (0.6%)	
Carbapenem + colistin	35 (42.7%)	37 (50%)	72 (46.2%)	
Carbapenem + AG	11 (13.4%)	15 (20.3%)	26 (16.7%)	
Carbapenem + tigesiklin	5 (6.1%)	3 (4.1%)	8 (5.1%)	
Carbapenem + quinolone/TMP-SMX	5 (6.1%)	0 (0%)	5 (3.2%)	
Ceftazidime - avibactam	2 (2.4%)	3 (4.1%)	5 (3.2%)	
Ceftazidime + AG	2 (2.4%)	1 (1.4%)	3 (1.9%)	
Ceftazidime + colistin	2 (2.4%)	0 (0%)	2 (1.3%)	
Carbapenem + fosfomycin	1 (1.2%)	1 (1.4%)	2 (1.3%)	
Carbapenem + polymyxin B	1 (1.2%)	0	1 (0.6%)	
Total	82 (100%)	74 (100%)	156 (100%)	
Treatment				
Monotherapy	20 (24%)	17 (23%)	37 (23.7%)	0.835
Combination therapy	62 (75.6%)	57 (77%)	119 (76.3%)	
Delay in optimal treatment (day) Mean ± SD	3.64±3.25	4.22±3.55	3.96±3.42	0.312
Empirical treatment initiated appropriately	16 (19.5%)	20 (27%)	36 (23.1%)	0.35
Receiving effective treatment	55 (67.1%)	68 (91.9%)	123 (78.8%)	**<0.001**

AG: Aminoglycoside, TMP-SMX: Trimethoprim-sulfamethoxazole, SD: Standard deviation

Discussion

CR-GNB infections are associated with high treatment failure rates and elevated mortality, largely owing to limited antibiotic options and restricted global access to novel agents. Patients with CR-GNB BSIs in the ICU face particularly poor prognoses[9]. In the present study, the 28-day mortality rate was 52.5%, which is higher than the 32% and 45% rates reported in previous studies[10,11]. Age was an important determinant of the outcome, as the mean age was markedly higher among nonsurvivors. Prior research has also identified advanced age—specifically >55 years—as an independent risk factor for mortality in CR-GNB BSI[11]. Consistent with earlier findings, our multivariate analysis demonstrated that higher CCI scores were independently associated with increased risk of death, with each unit increase in CCI conferring a 1.55-fold rise in mortality risk. A comparable study also reported that a CCI score ≥2 was an independent predictor of 28-day mortality[12]. Additionally, the PBS was markedly higher in the nonsurvivor group, further supporting its prognostic relevance. In a study investigating mortality predictors in patients with CRE-BSI, the PBS was also found to be markedly higher among nonsurvivors[13], consistent with our findings. Although prior research has demonstrated an association between APACHE II scores and mortality risk[14], our analysis did not identify APACHE II as an independent predictor.

Furthermore, the proportion of patients with solid organ and hematologic malignancies receiving immunosuppressive therapy was remarkably higher in the nonsurvivor group. This observation aligns with the findings by Shi et al.[15], who reported that solid organ tumors were independent risk factors for mortality in CRE-BSI.

The use of central venous catheters and mechanical ventilation has consistently been associated with higher mortality rates in patients with CR-GNB BSI[15-17]. In contrast, a history of surgery within 3 months preceding bacteremia, tracheostomy, and trauma has been reported as a protective factor[18-20]. In our study, mechanical ventilation and central venous catheterization were notably more common among nonsurvivors, whereas

Table 6. Univariate and multivariate analyses of factors associated with mortality

	Univariate analysis		Multivariate analysis	
	p-value	**OR (95% CI)**	**p-value**	**OR (95% CI)**
CCI	<0.001	1.24 (1.10-1.41)	**<0.001**	1.55 (1.22-1.97)
COVID-19 (+)	0.01	2.44 (1.2-4.99)		
Septic shock	<0.001	7.78 (3.51-17.2)	**0.05**	6 (1.74-21.18)
Day of ICU stay before bacteremia	0.015	0.97 (0.94-0.99)	**0.04**	0.95 (0.91-0.99)
Solid organ tumor	0.01	4.69 (1.88-11.7)		
Hematologic malignancy	0.99			
Immunosuppressive drug use**	0.017	2.81 (1.20-6.57)		
Central venous catheterization	0.005	2.54 (1.31-4.89)		
Mechanical ventilation	0.001	4.05 (1.82-8.99)		
Surgical intervention in the last 3 months	0.02	0.45 (0.23-0.89)		
Trauma	0.02	0.31 (0.11-0.84)		
Tracheostomy	0.02	0.41 (0.19-0.9)		
Respiratory distress	0.004	0.1 (0.02-0.49)		
TPN feeding	0.007	7.95 (1.74-36.36)	**<0.001**	202.72 (13.5-3036.9)
Oral feeding	0.007	0.3 (0.13-0.71)		
Place of stay before the ICU, hospital service	0.003	2.82 (1.43-5.57)		
Place of stay before the ICU, community	0.06			
Receiving effective treatment	<0.001	0.18 (0.06-0.46)	**0.002**	0.06 (0.01-0.34)

: Use of corticosteroids (prednisone equivalent >20 mg/day for ≥14 days) or other recognized immunosuppressive therapy, CCI: Charlson Comorbidity Index, COVID-19:** Coronavirus Disease 2019, ICU: Intensive care unit, TPN: Total parenteral nutrition, OR: Odds ratio, CI: Confidence interval

tracheostomy, recent surgical intervention, and trauma history were more frequently observed in survivors. TPN emerged as an independent risk factor for mortality, whereas oral feeding was associated with improved survival[21]. The protective effects of trauma and surgery may be attributable to the younger age and lower comorbidity burden in these patients.

Tracheostomy may reduce mortality by lowering the risk of aspiration of secretions, thereby decreasing pulmonary complications.

The multivariate analysis revealed that septic shock increased mortality risk nearly sixfold, consistent with previous reports identifying septic shock as a major contributor to adverse outcomes[16,22].

In contrast, the timely initiation of empiric therapy did not considerably affect mortality rates. Although the empiric treatment group showed a lower mortality rate (19.5% vs. 27%), the difference was not statistically significant. This result may have been influenced by the subsequent administration of appropriate therapy as patients who received effective empirical treatment were often more severely ill. A similar observation has been reported in a previous study[23].

A delay in optimal treatment was not found to affect mortality, though this result warrants careful interpretation. In survivor and nonsurvivor cohorts, the time to initiation of appropriate therapy was relatively prolonged (3.6 days vs. 4.2 days), and the high proportion of patients (78.8%) who ultimately received effective antibiotics may have influenced outcomes. Moreover, the early administration of broad-spectrum antimicrobials in high-risk patients, such as those with sepsis, may not have improved survival outcomes as some patients could have died before antibiogram-guided therapy could take effect, thereby limiting the observable benefit. In contrast, lower-risk patients may have received treatment at a later stage without much impact on outcomes. Our findings align with those of a prospective cohort study that also reported no statistically significant association between delays in optimal therapy and 28-day mortality[24]. However, other studies have shown that timely and appropriate antibiotic administration is associated with reduced mortality[10,25]. While the indiscriminate use of broad-spectrum antibiotics carries substantial risks, prompt and targeted antimicrobial therapy remains essential for managing hospital-acquired BSI (HA-BSI).

No difference in mortality was observed between patients receiving monotherapy and those receiving combination therapy. However, the proportion of patients receiving effective treatment based on antibiogram results was remarkably higher among survivors, and this was identified as an independent

predictor of survival. A study evaluating 28-day mortality in CR-GNB BSI similarly reported no marked difference between monotherapy and combination therapy, while demonstrating that inappropriate therapy was associated with increased mortality[9]. Likewise, Zhou et al.[13] found that appropriate treatment reduced mortality, although no survival benefit was observed with combination therapy compared to monotherapy, consistent with our findings.

For CRAB infections, however, current recommendations support the use of combination therapy, incorporating at least two agents with confirmed *in vitro* activity, regardless of the susceptibility profile of a single agent. This approach reflects the limited treatment options and the need to maximize therapeutic efficacy against this highly resistant pathogen. Combination therapies incorporating sulbactam-ampicillin, polymyxin B, colistin, and tigecycline are commonly recommended for CRAB infections[26,27]. In our cohort, *Acinetobacter* spp. was the predominant pathogen, which led to the frequent use of carbapenem-colistin combinations. However, recent guidelines favor use of novel BLBIs as the preferred agents, given the increased mortality and nephrotoxicity associated with use of polymyxin- or aminoglycoside-based regimens when combined with meropenem for the treatment of CRE[28]. In Türkiye, reimbursement for ceftazidime-avibactam was only approved 8 months before the end of our study period and was restricted by stringent criteria. Consequently, this agent was administered to only five patients with CR-GNB BSI.

Patients with severe infections caused by CRE that demonstrate *in vitro* susceptibility only to polymyxins, aminoglycosides, tigecycline, or fosfomycin—and in the absence of newer BLBI combinations—should be managed according to the European Society of Clinical Microbiology and Infectious Diseases guidelines with a regimen comprising multiple *in vitro*–active agents. However, no specific recommendations for or against particular drug combinations can be made[26].

In our cohort, comparison of different antibiotic regimens revealed no statistically significant differences in mortality. Receiving effective treatment guided by antibiogram results emerged as an independent factor influencing survival. Combination therapy was administered with at least one agent demonstrating *in vitro* activity. Owing to high resistance rates, many isolates were susceptible to only a single antibiotic, necessitating monotherapy in such cases. Previous studies on the management of CR-GNB infections have likewise reported no marked differences among treatment protocols[17,25].

Study Limitations

This study has several limitations. First, carbapenem resistance genes were not analyzed, and colistin resistance was assessed only with automated systems. Second, restricting the cohort to initial monomicrobial BSIs improved statistical independence but limited the evaluation of recurrent infections, cumulative risk, and treatment failure.

Conclusion

This study identified key mortality risk factors in patients with BSIs caused by WHO-designated priority pathogens. CCI, septic shock, TPN, duration of ICU stays prior to bacteremia, and receipt of effective treatment based on antibiogram results were independent predictors of mortality. No specific antibiotic regimen demonstrated superiority, and no difference in mortality was observed between monotherapy and combination therapy. Our findings emphasize the importance of minimizing invasive procedures and ensuring timely access to antibiogram-guided therapy to reduce mortality. TPN was associated with increased mortality and should be used with caution. The growing prevalence of antibiotic resistance and the need for alternative therapies highlight the critical importance of access to novel antimicrobial agents.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (approval number: 29, dated: 26.04.2022).

Informed Consent: Because of the retrospective design, informed consent was not obtained from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.A.Ö., N.E., B.Y., Concept: B.A.Ö., N.E., H.K., Design: B.A.Ö., N.E., E.D.K., S.N.A., H.K., B.Y., Data Collection or Processing: B.A.Ö., H.K., Analysis or Interpretation: B.A.Ö., N.E., E.D.K., S.N.A., H.K., B.Y., Literature Search: B.A.Ö., N.E., H.K., Writing: B.A.Ö., N.E., E.D.K., S.N.A., H.K., B.Y.

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Unexpected Threat: Cutaneous *Mycobacterium marinum* from a Chestnut Thorn

Beklenmedik Tehdit: Kestane Dikeninden Bulaşan Kutanöz *Mycobacterium marinum*

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Abstract

Nontuberculous mycobacterial infections are typically seen in immunocompromised individuals; however, *Mycobacterium marinum* is a rare pathogen that can also affect immunocompetent hosts. It generally presents as a non-disseminated cutaneous infection limited to the skin and soft tissues, showing manifestations like papules, plaques, or single/multiple lesions. Water and fish exposures are well-known risk factors. However, our case shows no history of aquatic exposure; instead, the patient reports a chestnut thorn injury at the affected site. The differential diagnosis should include other granulomatous infections and autoimmune diseases. Species-level identification is essential for the disease diagnosis, but it is not feasible in every center. *M. marinum* is generally susceptible to ethambutol, rifampicin, sulfonamides, and macrolides. By contrast, our case reveals an unexpected resistance pattern. The species-level identification and the antibiotic susceptibility testing are of paramount importance for establishing accurate diagnosis and ensuring effective treatment.
Keywords: *Mycobacterium marinum*, chestnut thorn, soft tissue infections, nontuberculous mycobacteria, resistance

Öz

Tüberküloz dışı mikobakteriyel enfeksiyonlar genellikle immün sistemi baskılanmış bireylerde görülmektedir. Ancak, Mycobacterium marinum immünkompetan konakları da etkileyebilen ve nadir görülen bir patojendir. Genellikle sadece deri ve yumuşak doku ile sınırlı, sistemik yayılım göstermeyen kutanöz bir enfeksiyon şeklinde ortaya çıkar; papül, plak veya tekil/çoklu lezyonlar gibi belirtilerle kendini gösterebilir. Su ve balıkla temas, iyi bilinen risk faktörleri arasında yer almaktadır. Ancak, sunduğumuz olguda bu tarz bir riskli teması öyküsü bulunmamasına karşın lezyonların olduğu bölgeden kestane ağacı dikeniyle yaralanma hikayesi mevcuttu. Ayırıcı tanıda diğer granülomatöz enfeksiyonlar ve otoimmün hastalıklar göz önünde bulundurulmalıdır. Hastalığın tanısı için tür düzeyinde tanımlama şarttır ancak her merkezde bunu yapabilmek mümkün değildir. M. marinum genellikle etambutol, rifampisin, sülfonamid ve makrolidlere duyarlıdır. Oysa olgumuzda beklenmedik bir direnç profiliyle karşılaşılmıştır. Doğru tanı ve etkili tedavi için tür düzeyinde tanımlama ve antibiyotik duyarlılık testleri büyük önem taşımaktadır.
Anahtar Kelimeler: Mycobacterium marinum, kestane dikeni, yumuşak doku enfeksiyonları, tüberküloz dışı mikobakteri, direnç

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Introduction

Mycobacterium marinum is an aerobic and Gram-positive, acid-fast bacterium that is classified as nontuberculous mycobacteria (NTM). In nature, *M. marinum* is found in soil, water sources, aquatic organisms (e.g., fish), and various plants. It appears as pink-colored bacilli on Ziehl–Neelsen staining. It is photochromogenic, producing a lemon-yellow pigment during light exposure, and is categorized in the first group of the Runyon classification. Phylogenetically, it is closely related to *M. tuberculosis*. *M. marinum* grows slowly on the Löwenstein–Jensen medium, depicting an optimal growth temperature of 32 °C, which is lower than that of *M. tuberculosis*[1]. It is an intracellular pathogen that may result in a positive tuberculin skin test similar to *M. tuberculosis*[2].

M. marinum was first isolated from tubercles in 1926 during the autopsy of a dead saltwater fish inside an aquarium[3]. It primarily causes a tuberculosis-like systemic infection in fish and other aquatic animals. In humans, however, it typically presents as a non-disseminated cutaneous infection limited to the skin and soft tissues. Rare cases of disseminated *M. marinum* infection had been reported, particularly in patients with human immunodeficiency virus/acquired immunodeficiency syndrome[4].

This report presents a rare case of *M. marinum* infection in an immunocompetent patient without a typical exposure history. This work also documents an unexpected antibiotic resistance pattern.

Case Report

A 57-year-old woman presented with a 3-month history of swelling, erythematous raised lesions, and pain on the dorsal aspect of her right hand and forearm. She showed no known immunocompromised conditions. Her physical examination results revealed a painful nodule on the dorsum of the right hand, multiple impetigo-like plaques on the back of the right hand, and an erythematous plaque in the antecubital area, as displayed in Figure 1. An ultrasound of the superficial tissue over the dorsal aspect of the second metacarpal of the right hand showed a 2 × 1 cm irregular, hypoechoic, mostly solid mass. A purified protein derivative test resulted in a 16 mm induration. The skin punch biopsy of the erythematous plaque revealed a chronic granulomatous inflammation that was rich in neutrophils (Figure 2). The Ziehl–Neelsen staining of the biopsy sample exhibited pink bacilli (Figure 3). The cultures in the Lowenstein–Jensen and blood agar media grew NTM identified by a mycobacteria growth indicator tube and using rapid kit tests. Samples were sent to the National Tuberculosis Reference Laboratory because our center cannot perform species-level typing and antibiotic susceptibility testing. Pending results, the patient was empirically treated with oral ciprofloxacin at a dose of 500 mg twice daily and oral clarithromycin at a dose of 500 mg twice daily. A partial clinical response was observed by the fourth week of the empiric therapy, with reduced nodules becoming evident from the sixth week onward. *M. marinum* was identified after 13 weeks of treatment. The susceptibility testing results showed resistance to ethambutol, trimethoprim-

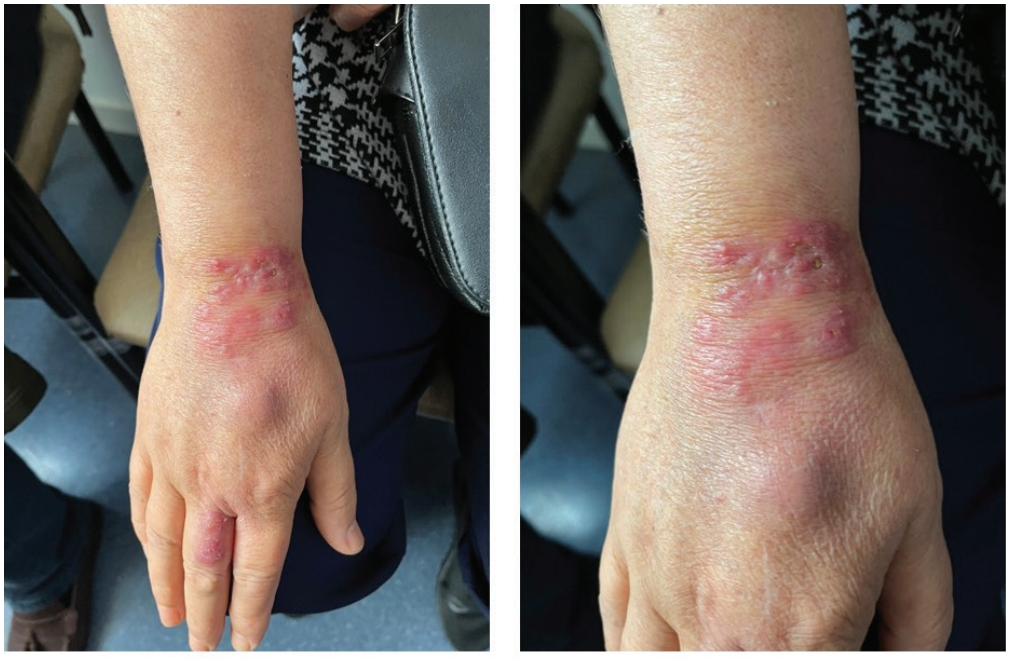

Figure 1. Nodules and multiple impetiginous plaques on the dorsum of the right hand, with the erythematous plaque extending to the antecubital area

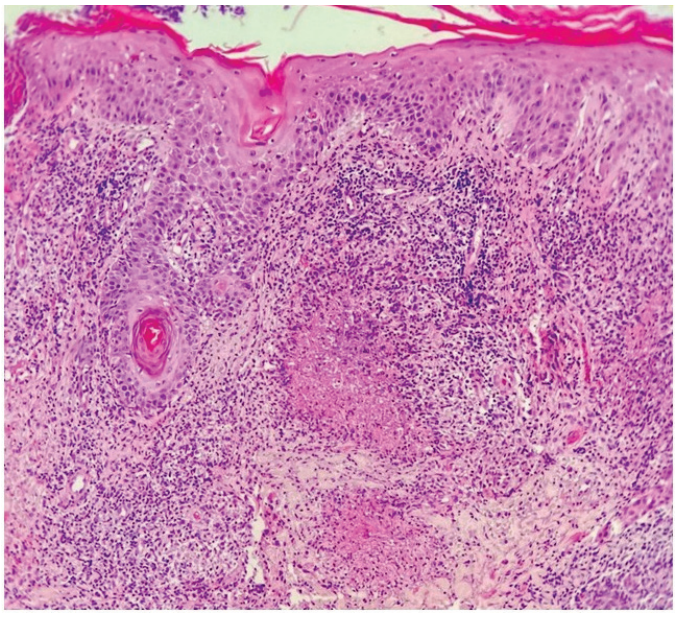

Figure 2. Skin punch biopsy of the erythematous plaque revealing a neutrophil-rich chronic granulomatous inflammation

sulfamethoxazole, and rifampicin. Meanwhile, the strain was sensitive to linezolid, moxifloxacin, and clarithromycin (Table 1). Considering the insufficient response, as depicted in Figure 4, linezolid at a dose of 600 mg twice daily was added on the 14th week, consequently leading to a significant improvement by the third week of its addition. The total duration of the antibiotic therapy was 24 weeks, including 6 weeks following clinical regression (Figure 5). No drug-related adverse effects were observed, except for mild gastrointestinal symptoms.

Discussion

M. marinum infections are classically associated with aquatic environments and occur in both immunocompetent and immunocompromised individuals; however, our case underscores that this pathogen can also affect immunocompetent hosts and may arise in the absence of a typical exposure history, consequently posing diagnostic challenges. It was first identified in humans in 1951 as the "swimming pool granuloma," a skin infection observed in swimmers exposed to polluted pools[5]. The infection can be transmitted through inoculation following skin trauma, which can range from minor abrasions to more significant injuries. The infection can spread along the lymphatics, leading to the formation of granulomatous nodules that may have a crusted or verrucous surface and contain pus. Lesions may appear as single or multiple papules, plaques, abscesses, or ulcers typically on the distal extremities[6].

The diagnosis can be established through the histopathologic and microbiologic examinations of a biopsy specimen taken from a suspicious nodule or plaque. The presence of granulomatous inflammation on histopathology supports the diagnosis, but it is not specific and may be confused with noninfectious granulomatous conditions, most commonly sarcoidosis[7]. The Ziehl–Neelsen staining or detection of the photochromogenic pigment is often challenging because of the typically low bacterial load. Cultures must be incubated at lower temperatures for at least 6 weeks. Polymerase chain reaction plays a critical role in species differentiation. A significantly positive tuberculin skin test was reported in more than two-thirds of the documented cases[8].

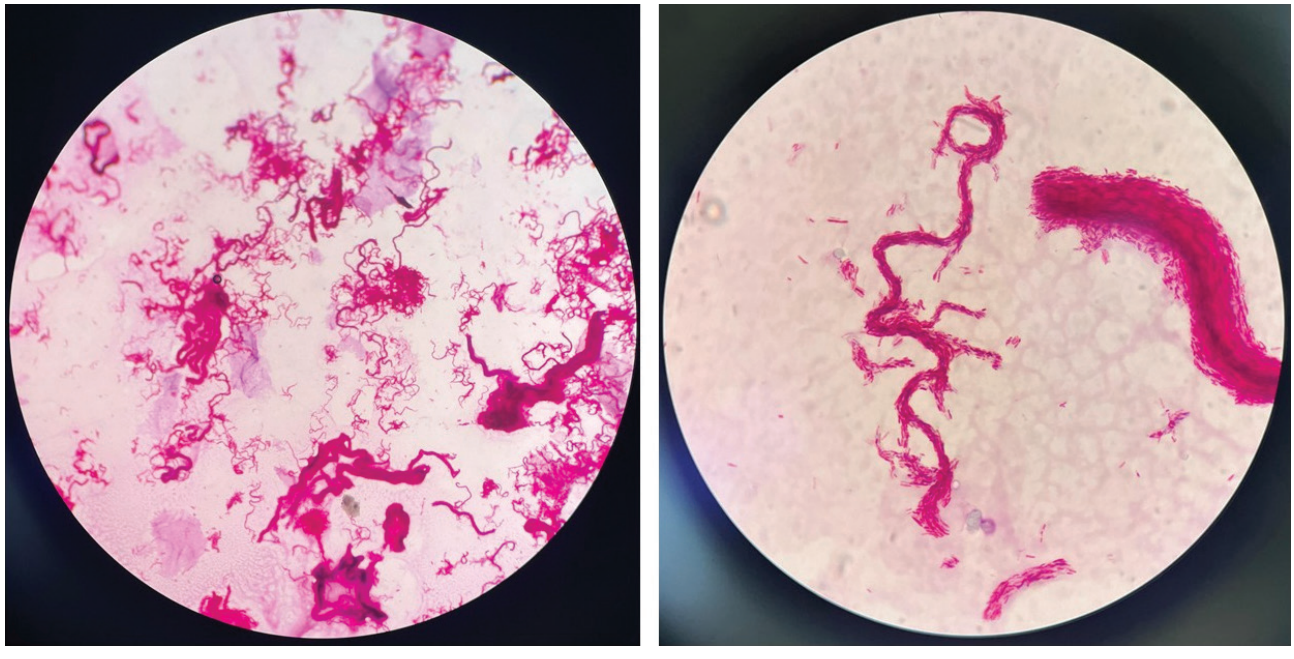

Figure 3. Ziehl–Neelsen staining of the biopsy sample showing pink bacilli: (a) image at a 10× objective; (b) image at a 100× objective

Table 1. Typing and antibiotic susceptibility results at the species level of the National Tuberculosis Reference Laboratory of the General Directorate of Public Health of the Ministry of Health

Microscopy and culture confirmation	**Positive**
Mycobacterium tuberculosis – other mycobacteria Differentiation test	*M. tuberculosis*-negative
Nontuberculous mycobacteria species identification	*M. marinum*
Antibiotic susceptibility results (minimum inhibitory concentration)	
Amikacin	Susceptible (2 µg/ml)
Clarithromycin	Susceptible (0.25 µg/ml)
Doxycycline	Resistant (16 µg/ml)
Ethambutol	Resistant (16 µg/ml)
Linezolid	Susceptible (4 µg/ml)
Moxifloxacin	Susceptible (0.25 µg/ml)
Rifabutin	Susceptible (0.5 µg/ml)
Rifampin	Resistant (4 µg/ml)
Trimethoprim-sulfamethoxazole	Resistant (8 µg/ml)

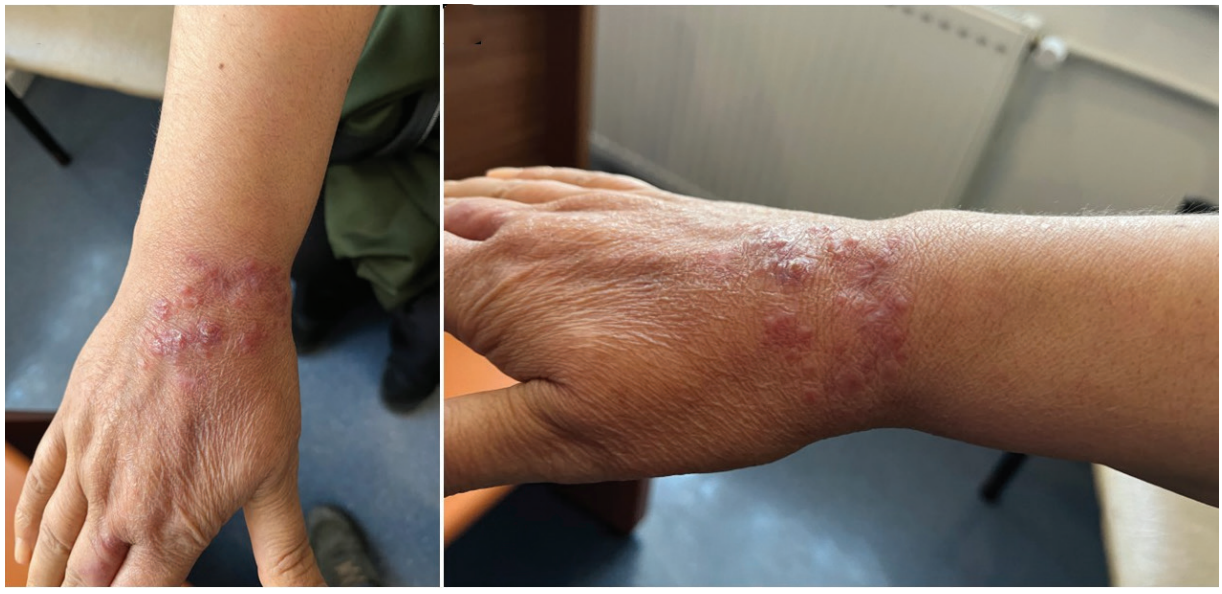

Figure 4. Nodule and plaque regression after empiric treatment prior to linezolid addition

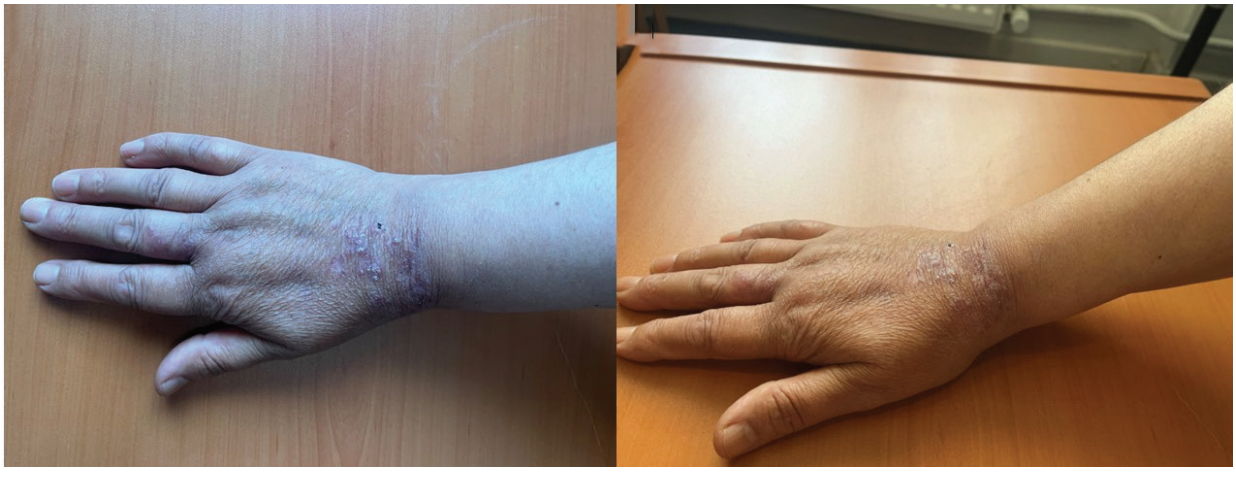

Figure 5. Final examination after 24 weeks of antibiotic treatment showing marked lesion improvement

The limited accessibility of the species-level identification and the antimicrobial susceptibility testing for NTM represents a major diagnosis and treatment selection challenge. Although matrix-assisted laser desorption/ionization time-of-flight mass spectrometry is routinely employed in our center, a reliable species-level identification cannot be achieved in our case. The isolates were referred to the national reference laboratory because a precise identification cannot be established. However, the process of transferring samples and obtaining results from the reference laboratory may take weeks or even months due to the workload and shortages of diagnostic test kits. At this stage, empirical therapy may be initiated, considering that patients frequently request prompt treatment without waiting for the test results.

Rifampicin, rifabutin, ethambutol, clarithromycin, sulfonamides, and trimethoprim sulfamethoxazole are effective against *M. marinum*. However, the organism is intrinsically resistant to isoniazid and pyrazinamide, which are critically important anti-tuberculosis agents[9]. Streptomycin, amikacin, linezolid, tetracyclines, and fluoroquinolones are also preferable alternative agents. Another limitation of empirical therapy is our country's restricted access to anti-tuberculosis agents, such as ethambutol and rifabutin, which are expected to be active against *M. marinum*, outside of a confirmed tuberculosis diagnosis. In our case, considering the most likely NTM species based on clinical presentation and the availability of effective agents, an empirical regimen comprising ciprofloxacin and clarithromycin was initiated.

Combination regimens containing clarithromycin, ethambutol, and rifampicin are the most commonly utilized and recommended therapeutic options[9,10]. However, alternative therapeutic strategies may be required because of atypical resistance profiles, treatment failures, limited drug accessibility, and adverse effects. Previous studies demonstrated the *in vitro* activity of linezolid and fluoroquinolones against *M. marinum*[11]. Among the fluoroquinolones, moxifloxacin shows higher susceptibility rates compared to ciprofloxacin[11,12]. In some reported cases, successful treatments were realized with linezolid-containing combination regimens[13,14]. In our case, linezolid may represent a suitable alternative when an adequate response cannot be achieved with a quinolone and clarithromycin combination or when drug substitution is required considering the adverse effects. Clarithromycin-based combination regimens are generally associated with the highest clinical success and antibiotic susceptibility rates[15-17]. In some reported cases as well, adjunctive thermotherapy in combination with antibiotic therapy was proven to be beneficial[18, 19]. The treatment duration may vary according to the depth and extent of infection. The involvement of the joints, tendons, or bone and the presence of an abscess formation particularly necessitates prolonged therapy courses. Surgical excision may be considered as an adjunct to medical therapy in certain cases. Although no consensus has yet been reached on the optimal treatment duration, therapy is generally recommended to continue for 4–8 weeks after the clinical resolution of symptoms[20].

Although routine antibiotic susceptibility testing is not recommended in managing *M. marinum* infections, susceptibility testing is advised in cases failing to respond to therapy[9,10]. In our case, the isolation of *M. marinum* that is resistant to doxycycline, ethambutol, rifampicin, and trimethoprim-sulfamethoxazole is unexpected and noteworthy. Several studies and case reports documented resistance to doxycycline, trimethoprim-sulfamethoxazole, rifampicin, and ethambutol[11,12,20-22], but our case is particularly rare and valuable because of the concomitant *in vitro* resistance to both rifampicin and ethambutol. Ideally, treatment must be guided by a species-level identification and an antibiotic susceptibility testing. Nevertheless, logistical limitations and the urgency of therapy initiation often render this approach difficult. In these circumstances, empiric treatment with clarithromycin-based combination regimens appears to be a safe and reasonable strategy.

The patient was carefully questioned about the possible risk factors for *M. marinum* infection, including contact with aquariums, fish, and other aquatic animals, swimming pools, or seawater; however, no such exposure was reported. Note that she sustained a chestnut thorn injury to the affected arm a few months before the lesions appeared. A literature review did not reveal any previous cases of the *M. marinum* infection linked to chestnut thorns or similar plants. In the reported case series, the majority of cases showed a history of exposure to an aquarium, a pool, or fish, although cases linked to procedures (e.g., trauma or injections) were also presented[14,20,23]. By contrast, our case showed no history of prior injection or similar interventions before the lesions. *M. marinum* was isolated from both aquatic environments and animals and from soil and plants in natural settings. These reservoirs were theoretically proposed as the potential transmission sources between organisms[24]. A risky exposure history cannot be found in some patients within the reported case series, and "source unknown" classifications were used, suggesting that there may be as yet unidentified sources and relationships underlying the *M. marinum* transmission. In this context, a recently published case report on *M. marinum* found no aquatic or water-associated exposure, as in our case. The proposed source was transmission from a pet reptile[25].

The literature has not yet identified cases of *M. marinum* arising after injuries from chestnut-tree thorns or other plant-related grazes. Conversely, given that the patient had a history of chestnut harvesting with injury from a chestnut thorn to the affected limb, and the bacterium was isolated from the soil and

plants, the most plausible hypothesis is transmission via this injury.

In summary, our case represents the first instance of *M. marinum* arising from a chestnut-tree or plant-related injury.

Conclusion

M. marinum must be considered in patients with chronic skin lesions resistant to treatment, even without typical aquatic exposure. In the case presented herein, a chestnut thorn injury was identified as a potential infection source, highlighting the importance of considering environmental trauma. Clarithromycin-based combination therapy is a reliable empirical treatment in the absence of definitive data. This case underscores the need to consider NTM infections in unusual clinical presentations.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Ö., Ş.B.A., C.Ö., U.Ö., Concept: E.Ö., U.Ö., Design: E.Ö., U.Ö., Data Collection or Processing: E.Ö., Ş.B.A., C.Ö., Analysis or Interpretation: E.Ö., U.Ö., Literature Search: E.Ö., U.Ö., Writing: E.Ö.

Conflict of Interest: Uğur Önal, one of the authors of this article, is a member of the editorial board of the Mediterranean Journal of Infection, Microbes and Antimicrobials; however, he did not participate in any stage of the editorial evaluation process of this manuscript. The other authors declare no conflict of interest.

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