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CONTENTS

Original Articles

Review

Original Article

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Investigation of brucellosis cases in and around Yozgat province

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ABSTRACT

Aims: Brucellosis causes a zoonotic infectious disease that is very common in our country as well as around the whole world. Infected individuals most frequently present with nonspecific symptoms such as fever, chills, malaise, and generalized body pain. Therefore, it is very difficult to diagnose. When diagnosis and treatment are delayed, it causes serious complications. It can cause pictures with high mortality due to endocarditis and morbidities such as epididymoorchitis, hepatitis, neurobrucellosis, and pancytopenia. The first approach to treatment is rest. Antibiotics with intracellular bactericidal action should be used in combination due to resistance development.

Methods: 136 individuals with serum titers who were diagnosed with brucellosis by serological tests and who applied to our hospital between 2017-2022 were included in the study. The patient files were analyzed to evaluate the complaints of these individuals, their *Brucella* ELISA titers, serum aspartate aminotransferase (AST), alanine aminotranspherase (ALT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH) values, if any, at the time of diagnosis, the treatments they received, and the response to the treatment.

Results: The first complaints of 136 patients who were diagnosed with brucellosis by serological tests were the most common; joint pain was present in 48 (35.29%), widespread body pain in 26 (19.11%), and fever in 18 (13.23%). Sacroiliitis in 5 (3.67%), gonarthrosis in 4 (2.94%), bursitis in 4 (2.94%), discitis in 3 (2.2), and psoriasis in 1 of the patients' abscess (0.73%) was detected, respectively. R=0.28 in the same direction between the first titers recognized by the patients and ALT; the same direction between titer and LDH R=0.30; the same ratio between titer and CRP is R=0.45; and there is a correlation coefficient of R=0.26 between titer and sediment in the same direction. It is important to take these correlation coefficients statistically ($p<0.05$). Accordingly, these values also change when it titrates. But it is weakened weights as a measure of relationship.

Conclusion: Although fever comes to mind first in brucellosis, it was observed that the first complaint of individuals in our study was complicated surgery, and fever ranked third. For this reason, Brucellosis should be approached with suspicion, since it is endemic in individuals presenting with non-specific complaints. It is widely present between serum titer and ESR, and C-reactive protein as markers of inflammation. In individuals with high vibration and inflammation markers, controlled caution should be exercised. Even treatment times can be changed.

Keywords: Brucellosis, symptoms, complications, diagnosis

INTRODUCTION

Brucella is a small, gram-negative coccobacillus. It causes a zoonotic infectious disease that is very common in our country as well as all over the world. The disease is transmitted by the consumption of body fluids, waste materials, poorly cooked meat, and milk from infected animals. Although rare, there are literature data on blood transfusion from infected donors, neonatal and sexual transmission. In studies conducted in 19-23 rural areas, infected unpasteurized milk was observed as the most common transmission. Individuals in close contact with animals, such as veterinarians, slaughterhouse workers, butchers, dairy operators, and laboratory workers, are at risk.[1-3] The incubation period of brucellosis is 7-21 days. The disease produces IgM and IgG positivity approximately 2-3 weeks after contact with infected material. IgG remains positive in the blood for a long time. The *Brucella* serum agglutination test (SAT) or Wright test is used in the diagnosis. However, the Rose Bengal screening test is also used to rapidly diagnose brucellosis.[4,5]

Infected individuals most commonly present with non-specific symptoms, such as fever, chills, malaise,

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generalized body pain, and headaches. Since it causes nonspecific symptoms, it is very difficult to diagnose. Brucellosis is characterized by a corrugated (fluctuating) fever, which has a specific definition of fever and continues for months with a fluctuating course.[6] While the success of treatment is high when diagnosed early, it can cause serious complications when diagnosis and treatment are delayed. It may progress with relapse and reinfection. Epididymoorchitis, endocarditis, hepatitis, neurobrucellosis, and pancytopenia may cause high mortality.[7,8]

The first approach to treatment is rest. Intracellular bactericidal antibiotics should be used. Tetracycline, streptomycin, rifampicin, and doxycycline are the most commonly used antibiotics. Doxycycline (200 mg/day) and rifampicin (600-900 mg/day) in combination for at least 6 weeks is the most commonly used treatment protocol. Treatment with single antibiotics leads to bacterial resistance and treatment failure.[9-14]

As the population is getting older and obesity is increasing, osteoarthrosis and muscle-joint problems are on the rise and may be confused with diseases involving the joints such as brucellosis, and sometimes the diagnosis of brucellosis may be delayed. In addition, almost every condition that causes fever can lead to muscle-joint pain, which makes it difficult to think of brucellosis at first.

Brucellosis was first diagnosed in our country in 1905 by Akalın et al.[11] in a military hospital. Subsequently, many studies have been conducted on brucellosis until today; however, in the new century, brucellosis cases have still not been prevented with both informative studies and measures taken.[12,13] Although brucellosis has been eradicated or controlled in many countries today, it is still common in some regions of our country and is included in the group of notifiable diseases. Our study shows that in the last five years, brucellosis cases have still been encountered in and around Yozgat province in the Central Anatolia Region, which is characterized as the endemic region of Turkey. Therefore, active screening and public awareness programs are needed.[14]

The most important point in the diagnosis of a disease is that the disease comes to mind. By examining the brucellosis cases in and around Yozgat Province, where livestock farming is common and brucellosis is therefore frequently seen, we aimed to bring the data from a region of our country to the literature, to remind people of the disease by sharing our data and experiences with our colleagues, and to contribute to their clinical practice.

METHODS

Ethics

Ethics committee approval was granted by Yozgat Bozok University Clinical Researches Ethics Committee (Date: 10.11.2022, Decision No: 2017-KAEK-189_2022.11.10_06. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Institutional approval was obtained.

Design

The study was planned as a retrospective cross-sectional study.

Patients

The data were collected after approval from the local ethics committee.

Inclusion Criteria

The files of 136 individuals who were admitted to our hospital between 2017 and 2022 and were serologically positive for brucella were reviewed.

Exclusion Criteria

Patients with missing data in their files were excluded.

Methods

Age, gender, presenting complaints and serum ALT, AST, lactate dehydrogenase (LDH), CRP, erythrocyte sedimentation rate, and brucella tube agglutination titer values were recorded. Treatment was received, and treatment response assessment markers were recorded. Treatment non-compliant and lost to follow-up patients were excluded from the study.

Statistical Analysis

The SPSS (Statistical Package for the Social Sciences) 22.0 program was used for statistical analysis of the data. Categorical measurements were summarized as number and percentage, and continuous measurements as mean and standard deviation (median and min-max where necessary). The Spearman rank correlation coefficient was used for analysis.

RESULTS

The minimum and maximum ages of the 138 individuals included in the study were 17 and 80 years, respectively, with a mean age of 43.99±14.63 and a median age of 45 years. Of these individuals, 92 (67.6%) were male and 44 (32.4%) were female. The initial presenting complaints were joint pain (40 knees, 8 hips) in 48 (35.29%), generalized body pain in 26 (19.11%), fever in 18 (13.23%), headache in 11, night sweats in 12 (5

Table 1. Data of biochemistry values of individuals with brucellosis						
	N	Minimum	Maximum	Mean	Medyan	Std. deviation
ALT (U/L)	134	6.00	253.00	44.9328	34.50	43.50615
AST (U/L)	129	11.00	210.00	39.2326	32.50	31.27337
LDH (U/L)	78	2.44	874.00	262.7086	234.50	136.10563
CRP (mg/L)	133	1.04	139.70	24.0995	15.55	27.25452
ESH (mm/hr)	128	1.00	84.00	28.8281	27.50	19.37411

Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

accompanied by weight loss), low back pain in 10, nausea in 5 (3.67%), testicular pain in 5 (3.67%), and palpitations in 1 (0.73%). Three individuals were asymptomatic, and their first-degree relatives were found positive during screening.

Complications included epididymoorchitis in 5 (3.67%), sacroiliitis in 5 (3.67%), gonarthrosis in 4 (2.94%), bursitis in 4 (2.94%), discitis in 3 (2.2%), and pseudo-abscess in 1 (0.73%). One of the patients with neurobrucellosis and one with endocarditis continued their treatment at the upper center. One individual was receiving standard tetracycline rifampicin treatment but did not comply with the treatment due to irregular drug use and treatment success could not be achieved, and streptomycin was added to the treatment.

In the laboratory records, the mean ALT was 44.93±43.50 (ALT normal limits: 0-41 U/L) and the mean AST was 39.23±31.27 (AST normal limits: 0-41 U/L) at the time of the brucellosis diagnosis. In individuals with high ALT values, the mean ALT value was 99.5 U/L and the AST value was 84.92 U/L. The ALT value was more than three times the upper reference limit in 13 patients, while the AST value was more than three times the upper reference limit in 8 patients. C-reactive protein (CRP) was in the normal range at the time of diagnosis in 27 patients, between 50 and 100 mg/L in 9 patients, and 100 mg/L in 3 patients. ESR was in the normal range of 38 individuals, with a maximum value as high as 84. The mean CRP was 24.09±27.25 and the mean erythrocyte sedimentation rate (ESR) was 28.82±19.37 (Table 1).

The correlation coefficient between the initial agglutination titers and ALT was R=0.28 in the same direction; between the titer and LDH was R=0.30 in the same direction; between the titer and CRP was R=0.45 in the same direction; and between the titer and the ESR was R=0.26 in the same direction. This coefficient of association was statistically significant ($p<0.05$). Accordingly, when titer increases, these values also increase. However, they are weak correlations as a measure of association. No significant difference was found between titer and AST ($p>0.05$) (Table 2).

Table 2. Association of Brucella ELISA titers with biochemistry data					
Titer	ALT	AST	LDH	CRP	ESH
R	.141	.28	.30	.45	.26
P	.102	.001	.001*	.001*	.002*
n (individual)	136	136	136	136	136

Abbreviations: R: correlation coefficient, $p<0.05$ significant
ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, ESR; Erythrocyte sedimentation rate
(It is calculated as confidence interval R 95%, ALT 0.12-0.16, AST 0.22-0.30, LDH 0.27-0.33, CRP 0.39-0.51, ESH 0.24-0.28)

Distribution of *Brucell*a ELISA titer results among individuals in Table 3.

Table 3. Distribution of *Brucella* ELISA titer results among individuals		
Titer	n (Number of individuals)	Percentage (%)
40	2	1.5
80	8	5.9
160	17	12.5
320	27	19.9
640	22	16.2
1240	23	16.9
2560	11	8.1
5120	18	13.2
10240 and above	8	5.9
Total	136	100.0

DISCUSSION

The mean age of the 138 cases we reached within the scope of the study was 43.99 years, and 67.6% of the cases were male and 32.4% were female. In a study conducted by Köse et al.[15] in Western Anatolia, which is socioeconomically ahead of our region, 72 cases were retrospectively analyzed, and the mean age of the cases was found to be 44.8 years, similar to the figure we reached in this study. However, contrary to our findings, the majority of the patients in this study were women,

with a rate of 55.6%. We hypothesize that this difference is due to migration-based gender-based demographic segregation between regions and the relative lag of women in Central Anatolia in terms of participation in socioeconomic activities. Another hypothesis, which we hope is not true, is that women in our study region are behind in accessing health services for various reasons, and therefore cases are not detected and treated.

In the study conducted by Tohme et al.[16], the most common presenting complaints were fever, sweating, malaise, and pain. When we think of brucellosis, fever comes to mind first, but in the study conducted by Saçar et al.[17] the most common symptom was arthralgia, followed by fever. In our study, the most common presenting complaint was arthralgia, and fever was the third most common symptom. In a study by Sahin et al.[18] including 83 individuals, epididymoorchitis was the most common complication with 3.6%. In our study, epididymoorchitis was one of the most common complications with a rate of 3.67%, the same rate as in the study of Sahin et al.[19]. However, sacroiliitis was the other most common complication, with the same rate as epididymoorchitis.

CRP was within the normal range at the time of diagnosis in 27 patients (20.3%), between 50 and 100 in 9 patients (6.7%), and above 100 in 3 patients (2.25%). In 2018, a study conducted in Bosnia and Herzegovina examined brucellosis cases and analyzed CRP data from 19 of the cases. CRP values were below 5 mg/ml in 6 cases (31.6%), 50-100 mg/ml in 2 cases (10.5%), and above 100 mg/ml in 2 cases (10.5%). Although there is a significant difference between the groups when these figures are compared, it is seen in both studies that the CRP value was negative in the majority of the patients, and the number of cases decreased as CRP increased.[18] In terms of ESR, another acute phase reactant that is routinely used and attributed importance, 38 (29.68%) of the 128 patients in whom we had ESR values resulted in ESR within the normal range. In the Bosnia and Herzegovina study in which we compared CRP data above, ESR was found to be below 25 mm/hour in 12 of 19 patients (63.2%). Based on these data, it can be said that the importance of CRP and ESR in brucellosis should not be underestimated, but their negativity should be approached with caution, especially in the presence of clinical suspicion.

The relationship between brucella titer and disease has been studied.[19-22] In a study by Demir et al.[20] evaluating the relationship between agglutination and CRP as an acute phase reactant, 121 individuals with serum tube agglutination of 1/160 and above were included among 4041 patient sera sent with suspicion of brucellosis; the same directional relationship was found between titer and CRP. It was thought that CRP could be used in the diagnosis and follow-up of brucellosis. In our study, similar to many studies, a positive correlation was found between CRP and ESR values, which can be evaluated with disease severity and brucella titer.

The mean ALT in our patients was 44 (ALT: N: 0-41 U/L), and the number of patients with ALT values higher than three times the upper reference limit was 13 (9.7%). In a previous study conducted in Turkey, the mean ALT value was 32 IU/ and the number of cases with abnormally high ALT values was reported to be 34.8%. The aforementioned study and our data were considered consistent in the sense that patients with mean and abnormally high ALT measurements were in the minority.[23]

We had LDH measurements in 78 patients, and the mean LDH of these patients was 262.70 U/L. In a study conducted in China and including 109 cases, the mean LDH value of brucellosis cases was 288 U/L, close to our data. However, the maximum LDH value in their study was reported as 476.5 U/L, while the maximum value in our study was 874 U/L, which is quite high and confusing.[24]

In addition, the same directional relationship was observed between LDH and ALT elevation due to organ involvement and titer values. Therefore, patients diagnosed with Brucellosis with a high titer should be more careful in terms of complications. It is reported that combined and long-term antibiotic therapy affects the prognosis positively and prevents relapses. Although there is no definitive form of treatment, increasing the duration of treatment to more than six weeks is thought to reduce relapse.[25,26] Despite all studies, it is not clear what the optimal duration of treatment and regimen will be in cases of relapse, chronic brucellosis, complicated brucellosis, and further multicenter studies are needed in these cases. It is thought that regulating the duration of treatment will reduce the morbidity and mortality due to brucellosis.[27] Based on meta-analysis studies, the evaluation found that the risk of developing relapse was lower with six-week antimicrobial treatments compared to four-week regimens. It is recommended to use six-week therapy in patients diagnosed with acute brucellosis. However, the duration of treatment in complicated brucellosis varies.[28,29] In order to prevent the development of complications, studies can be conducted to give more aggressive and prolonged treatment to individuals with high titers and to give shorter treatment to individuals with low titers so that they are not exposed to the side effects of combined antibiotherapy for a long time.

Limitations

Retrospective and small number of cases. Lack of long-term follow-up results.

CONCLUSION

Although fever and then joint pain come to mind when we think of Brucellosis, in our study, joint pain was the first complaint and fever was the third most common complaint. Therefore, individuals presenting with nonspecific complaints should be suspected of having Brucellosis in endemic areas. There is a correlation between the Brucella serum tube agglutination titer and inflammation markers ESR and CRP. It may be necessary to be careful in terms of complications in individuals with high titers and inflammation markers. In fact, treatment duration may be changed in these patients before complications develop.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Yozgat Bozok University Medical Faculty Clinical Researches Ethics Committee (Date: 10.11.2022, Decision No: 2017-KAEK-189_2022.11.10_06).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

TRANSLATIONAL&PRACTICAL MEDICINE

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Is there a relationship between chronic low back pain and spinal sagittal balance? A prospective controlled study.

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ABSTRACT

Aims: Evaluation of whether there is a significant relationship between chronic low back pain and spinal sagittal alignment

Methods: This prospective, controlled study was conducted between April 2023 and September 2023, among patients aged 18-50, who complained of chronic low back pain and a healthy control (HC) group. In addition to the participant's demographic information, sagittal vertical axis (SVA), thoracic kyphosis (TK), and lumbar lordosis (LL) values on the lateral whole-spine radiograph and degenerations on the lumbar vertebra MRI were compared. Visual analogue scale (VAS) and ODI scores of the patients were also included in the statistical evaluation.

Results: A total of 64 participants (44 patients, 20 controls) were included in the study. There was no significant difference in age, gender, body mass index (BMI). SVA significantly increased in the patient group ($p<0.001$), but not LL and TK. In a linear discriminant analysis (LDA), SVA discriminates 100% of the two groups. No significant correlation was observed between VAS and ODI scores and the patients' age, gender, BMI, and spinal parameters.

Conclusion: SVA is a crucial parameter of spinal balance, and as shown in this study, deviations from normal SVA appear to be a significant contributor to low back pain. We recommend an easy-to-implement and cost-effective method for assessing SVA in evaluating and treating patients with chronic low back pain.

Keywords: Low back pain, lumbar lordosis, oswestry disability index, spinal sagittal balance, sagittal vertical axis, thoracic kyphosis

INTRODUCTION

Low back pain (LBP) is one of the most common reasons for seeking medical treatment.[1] While 95% of patients experience relief from their pain within the first three months,[2] LBP is a leading symptom that accounts for workday losses and disability.[3,4] The most common etiologies of LBP include myofascial pain, facet-mediated pain, discogenic pain, spinal stenosis, trauma, and neoplasms. However, only 10-20% of patients can be diagnosed with a precise pathoanatomical condition, and most cases are non-specific.[5] These etiologies vary from patient to patient, and management of LBP also varies; not every patient responds the same to similar treatment.[6] Despite the various guidelines for managing LBP, some patients' pain does not entirely subside, or even if there is relief, the complaints may recur after a while. This situation has prompted further studies in the field of low back pain.

In recent years, numerous studies have explored the biomechanics of the spine, uncovering that spinal curves collectively maintain a state of equilibrium. Normal sagittal spinal alignment plays a critical role in maintaining an upright posture while minimizing muscle energy expenditure. Disruption of this alignment increases the load on the muscles, leading to muscle fatigue and is believed to be a contributing factor in the development of chronic pain.

The fact that we do not fully understand the etiology of chronic low back pain, which significantly impacts people's functionality, emphasizes the need for further research in this field. When there is pain in the lower back, it is possible to focus solely on the lumbar region and forget the fact that the entire spine functions as a whole. The patient's pathology can be overlooked in this process. We believe that if the connection between lower back pain and spinal sagittal balance is clearly understood,

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the concept of nonspecific lower back pain will largely disappear. With this understanding, we can offer patients diagnoses and treatment options to correct spinal sagittal balance. Many studies have compared radiological data, but the number of publications evaluating the patient's pain and disability simultaneously is low. According to this objective, in this study, we aimed to assess whether a significant relationship exists between sagittal spinal alignment parameters in patients with chronic low back pain and age, sex, body mass index (BMI), the severity of their pain, functionality, and lumbar MRI findings.

METHODS

This prospective, controlled study was conducted between May 2023 and September 2023 in the Department of Neurosurgery at University of Health Sciences, Van Training and Research Hospital. This study was performed after approval by the Ethics Committee of University of Health Sciences Van Training and Research Hospital (Date: 26.04.2023, Decision No: 2023/09-03). All subjects signed detailed informed consent before their inclusion in the study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Specific selection criteria were applied to minimize study bias and ensure consistent results. Male and female patients aged from 18 to 50 who had experienced LBP for more than three months (chronic LBP) were included. The following exclusion criteria were applied: (1) Patients with a history of spinal surgery; (2) chronic diseases that may affect spinal alignment like rheumatoid arthritis or ankylosing spondylitis; (3) complaints of leg pain (4) history of lower extremity pathologies like osteoarthritis (5) findings such as disc protrusion or extrusion, spondylolisthesis, spinal stenosis, congenital defect, tumor, infection, fracture or any finding that need for surgical intervention in radiological imaging. We also excluded patients who had been receiving painkillers or spasmolytic agents at the time of application to the hospital, which may affect the reliability of the study. Additionally, we also included normal subjects free from LBP and leg pain for the healthy control (HC) group.

The collected data for each subject included age, sex, height, weight, and BMI. For the patient's group, the duration of LBP was recorded. Pain intensity was assessed using the visual analogue scale (VAS), which ranged from 0 to 10 points (0 point=no pain, 10 points= worst pain possible). To evaluate patients' disability, we utilized the oswestry disability index (ODI), a self-administered questionnaire[10,11] on a scale ranging from 0 to 100%. The obtained scores were associated with varying degrees of disability, ranging from minimal to bedbound.

All subjects underwent non-contrast lumbar vertebrae magnetic resonance imaging (MRI) and lateral long cassette radiographs of the entire spine. Lateral radiography was performed with subjects standing in their most relaxed position, shoulders flexed, and forearm extended. All radiographs were taken using the same technique, the same radiography device, with a constant distance between the subject and the radiographic source. On the lateral radiographs, the following measurements were performed: distance between C7 plumb line and the posterior superior corner of the sacrum endplate -Sagittal vertical axis (SVA), Cobb's angle between superior endplate of T4 and inferior endplate of T12- thoracic kyphosis (TK), Cobb's angle between superior endplate of L1 and superior endplate of S1- lumbar lordosis (LL)[12] (Figure 1). In the case of SVA, values are considered positive when the plumb line is located anteriorly, whereas they are considered negative when the plumb line is positioned posteriorly. These measurements were independently performed by two neurosurgeons, and the average values were recorded.

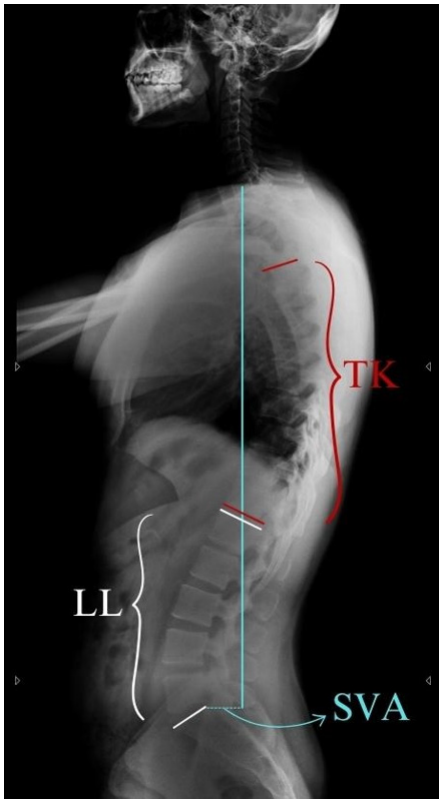

Figure 1. The figure shows how SVA, TK and LL measurements are made.
Note: TK: Thoracic kyphosis, LL: Lumbar lordosis, SVA: Sagittal vertical axis

Lumbar vertebra MRIs, which include T1 and T2 weighted sagittal images and T2 weighted axial images, were interpreted similarly by two neurosurgeons. Lumbar disc degenerations were evaluated using the

Priffman degeneration grading scale.[13] For patients with more than one level of degeneration on lumbar MRI, the number of degenerated levels was noted, and the Priffman degeneration grade (PDG) of the most degenerated level was used.

Statistical analysis was conducted using IBM Statistical Package for Social Sciences (SPSS) version 20.0 (IBM, NY, USA). Following each variable's assessment for normality of data distribution, skewness, kurtosis, and histogram plots were examined. Continuous variables were presented as mean and standard deviation (SD), while categorical variables were expressed as percentages or frequencies. Parametric tests, including two-tailed Student's t-tests and partial correlations, were employed for variables with a normal distribution. The chi-square test was used to compare categorical variables. For SVA, TK, and LL (dependent variables), an analysis of covariance (ANCOVA) was performed, with diagnostic groups as a fixed factor and age, BMI, and PDG as covariates. Linear discriminant analysis (LDA) was employed to assess the angles' ability to discriminate among groups, with standardized canonical discriminant function coefficients used to determine the variables contributing to a more accurate classification of the two groups. Significance was set at $p \leq 0.025$ for Bonferroni-corrected ANCOVA to reduce type I errors and $p \leq 0.05$ for other comparisons, with all tests being two-tailed. Effect sizes were measured using Cohen's d, partial Eta-squared, and Pearson's r.

RESULTS

A total of 80 participants were initially invited to participate in the study; however, 11 of them were subsequently excluded based on the exclusion criteria. Four participants were excluded due to extruded lumbar disc herniation observed on lumbar MRI scans, one participant's lateral whole spine radiogram did not meet the scanning criteria, eight participants had chronic diseases, and three were taking spasmolytic medication during the examination. This study enrolled 44 patients and 20 HCs for the final analysis. In the patient group, there were 15 males (34%) and 29 females (66%), while the HC group consisted of nine males (45%) and 11 females (55%). No significant differences were observed in gender, age, body weight, and BMI between the two groups. The mean VAS score was 6.41±SD, and the mean ODI was 41.05%±SD. The median number (IQR) of degenerated levels was 1 (0-1) for both groups, and the median PDG for the most degenerated level was 2 (0-3) for both groups. There were no significant differences in these parameters. Demographic and clinical data are summarized in Table 1.

We found significant differences between the groups using two-tailed t-tests with SVA, but not with TK and LL. Figure 2 shows these analyses. Specifically, SVA values were significantly higher in patients with LBP compared to HCs ($p<0.001$, Cohen's $d=1.03$). Furthermore, after adjusting for age, BMI, and PDG, ANCOVA analysis confirmed that SVA remained significantly higher in patients with LBP ($F=10.125$, $p=0.002$, $\eta p^2=0.15$). In contrast, no significant differences were observed in TK and LL. Additionally, SVA was significantly higher among female patients ($p=0.036$). Table 2 presents the Bonferroni-corrected results among the groups.

Table 1. Demographic and clinical characteristics of the participants

Characteristics	Patient with low back pain (n=44)	Controls (n=20)	P-value
Age (years)	30.86±8.4	33.95±7.77	0.186
Gender (female)	29 (66%)	11 (55%)	0.403
Body Weight (kg)	69.64±13.21	68.5±11.25	0.74
BMI (kg/m²)	25.32±4.99	24.78±3.54	0.666
Duration of the pain [months, median (IQR)] *	12 (4-24)		
VAS score	6.41±1.9 (Min: 2, Max: 10)		
ODI (%)	41.05±12.9 (Min: 14, Max: 78)		
PDG*, **	2 (0-3)	2 (0-3)	0.604
Number of degenerated level on lumbar MRI *	1 (0-1)	1(0-1)	0.695
SVA (mm)	-32.11±34.45 (-102 to 55)	0.62±29.09 (-62 to 90)	<0.001
TK (°)	36.58±8.48 (Min: 17, Max: 51)	39.63±10.3 (Min: 22, Max: 56.8)	0.218
LL (°)	57.93±12.04 (Min: 35.4, Max: 88.1)	56.12±11.83 (Min: 38.7, Max: 75.7)	0.578

Note: Plus–minus values are given as mean ± standard deviation, non-normally distributed data were given as median (interquartile). BMI: Body mass index, TK: Thoracic kyphosis, LL: Lumbar lordosis, Min: Minimum, Max: Maximum, ODI: Oswestry Disability Index, PDG: Priffman degeneration grade, SVA: Sagittal vertical axis, VAS: Visual analogue score, *: Median values, ** Priffman degeneration grade of the most degenerated level

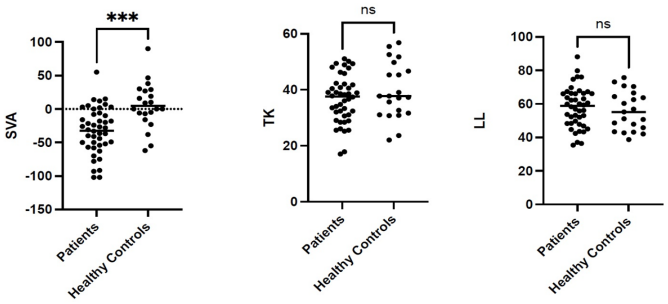

Figure 2. Figure shows results in two groups.
Note: *** p<0.001, TK: Thoracic kyphosis, LL: Lumbar lordosis, ns: non-significant, SVA: Sagittal vertical axis.

Table 2. Bonferroni-corrected ANCOVA results of parameters

	Patients (n=44)	HC (n=20)			
Parameters	**Estimated marginal means ± standard error[a]**		**F**	**p**	**ηp^2**
SVA (mm)	-31.072±5.05	-1.65±7.59	10.13	**0.002[b]**	0.15
TK (°)	36.804±1.31	39.142±1.97	0.949	0.334	0.02
LL (°)	58.076±1.796	55.792±2.7	0.483	0.49	0.008

Note:
[a] adjusted for age, body mass index and Priffman degeneration grade of the most degenerated level
b Significantly different: p≤0.025
TK: Thoracic kyphosis, LL: Lumbar lordosis, SVA: Sagittal vertical axis.

TK values and the number of degenerated levels had weak and very weak correlations between age, respectively (r=0.329 p=0.031, r=0.352 p=0.020). After controlling for age and BMI, we conducted partial correlations between SVA, TK, and LL and clinical variables. Table 3 presents the partial correlation matrix. We found a significant relationship between SVA and LL (r=-0.501, p<0.001). TK scores were associated with LL scores (r=0.377, p=0.015) but not with SVA (p=0.71). VAS scores significantly correlated with the ODI scores (r=0,521, p<0.001). However, SVA, TK, and LL did not correlate significantly with the VAS and ODI scores (all p>0.05). Furthermore, there were no significant relationships between SVA and the duration of pain symptoms or body weight of the patients, even after controlling for age and BMI (all p>0.05).

Table 3. Correlation analysis results (r-values) after controlling for age and BMI

Variables	SVA	TK	LL
Duration of pain	0.072	0.023	-0.048
Body Weight	0.222	-0.042	0.062
VAS	-0.205	-0.135	0.108
ODI	-0.037	-0.131	0.019
PDG on MRI	-0.054	0.033	-0.023
Number of Degenerated Level on MRI	-0.09	-0.008	0.099
SVA	-	-0.60	**-0.501****
TK	-0.60	-	**0.377***

Note: *<0.05, **<0.001. TK: Thoracic kyphosis, LL: Lumbar lordosis, ODI: Oswestry Disability Index, PDG: Priffman degeneration grade, SVA: Sagittal vertical axis, VAS: Visual analogue score.

As a final step, a linear discriminant analysis was employed to assess the discriminative ability of the SVA between patients with LBP and HCs. The overall model yielded statistical significance, with Wilk's λ at 0.82, $\chi 2$=12.21, p<0.001, and explained 100% of the variance in predicting the difference between the two groups (patients vs. HCs). The overall effect size of the model, as indicated by the canonical correlation value, was 0.42.

DISCUSSION

The "Cone of Economy" theory, as described by Dubousset[9], has shed light on our understanding of spinal balance. The axial skeleton aligns itself within a compact cone shape, minimizing muscle activity and serving as the key to energy conservation. When spinal balance is disrupted, this cone, whose base is on the cranial side, grows and results in increased energy expenditure required for maintaining an upright posture. This, in turn, triggers muscle fatigue and initiates the pain process. While several authors have explored spinal alignment concerning low back pain[14-21], the precise connection between sagittal alignment and low back pain remains incompletely understood. Many of these studies have overlooked evaluating patients' pain and disability. In this study, we assessed spinal alignment and considered both the pain and disability of the patients, seeking to identify any statistically significant differences.

While women showed higher VAS and ODI scores, as well as a longer symptom duration, we did not observe any statistically significant differences between patients and healthy controls (HCs) regarding age, gender, BMI, symptom duration, VAS and ODI scores, PDG, and the number of degenerate levels.

In the general population, no established norm for sagittal balance exists.[22] Therefore, we conducted this study with a HC group. The main difference between patients and HCs was observed in terms of SVA. The mean SVA for patients was -32.11, while for HCs, it was 0.62. SVA exhibited a statistically significant posterior shift relative to the S1 endplate in patients. Even after excluding age, sex, BMI, and PDG as confounding factors, SVA remained significantly higher in the patient group. Several publications have previously identified a relationship between SVA and low back pain[14,16,20,21], and our study contributes to the existing literature by further supporting these findings. Also, with linear discriminant analysis, we saw that SVA discriminates between the two groups powerfully (explaining 100% of the variance). This strongly indicates that SVA may be essential for evaluating patients with chronic low back pain.

While TK was slightly lower and LL was slightly higher in patients, we did not observe any significant differences between the two groups. Following partial correlation analysis, we identified a moderate correlation between LL and SVA and a weak correlation between TK and LL in patients. We thought an increase in LL results in a significant posterior displacement of SVA and a decrease in TK. Similar to present study, some prior studies[17,23]

did not find a significant difference in LL between patient and control groups. However, in studies where disc herniation and degeneration played a prominent role[18,19,24], a significant decrease in LL was observed; this decrease in LL leads to an anterior shift of SVA.[14,20] These structural changes are primarily attributed to the loss of intervertebral disc height, the reduction of lordosis, and the compensatory anterior displacement of the C7 plumb line. In our study, since most patients had standard lumbar disc heights (only three patients had grade four PDG, while the rest had grade three or lower PDG), we postulated that patients tend to perform lumbar extension to alleviate lumbar muscle tension, increasing lumbar lordosis. This increase in lumbar lordosis manifests as a posterior shift in SVA and leads to decrease in TK. Following the 'cone of economy' theory, expanding the cone due to increased SVA places a more significant workload on the lower back muscles, leading to muscle fatigue and chronic pain.

Hira et al.[21] and Sardar et al.[24] demonstrated a correlation between TK and age. Consistent with these findings, our present study revealed that TK increases with age. Myatani et al.[25] also identified a significant loss in truncal muscle volume with age, which may explain the observed increase in TK with age.

In this prospective study, our focus was on patients with chronic low back pain who did not have radicular pain. To enhance data reliability, we established a control group. In contrast to many studies in the literature, we assessed not only the radiological images of the patients but also their subjective assessments, including VAS and ODI scores.

Limitations

We are aware that this study has some strengths as well as some weaknesses (1) a cross-sectional assessment, (2) a relatively small number of subjects. We know that a multicenter study with a more prominent participant must provide more comprehensive results.

CONCLUSION

SVA is a critical parameter for assessing spinal balance, and as demonstrated in the present study, deviations from the normal SVA appear to play a significant role in the development of low back pain. We acknowledge the importance of further research into the factors influencing SVA. Therefore, we recommend an easy-to-implement and cost-effective method to assess SVA in evaluating and treating patients experiencing chronic low back pain.

Abbreviations

BMI: Body mass index

HC: Healthy control

LBP: Low back pain

LDA: Linear discriminant analysis

LL: Lumbar lordosis

MRI: Magnetic resonance imaging

ODI: Oswestry disability index

PDG: Priffman degeneration grade

SVA: Sagittal vertical axis

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was performed after approval by the Ethics Committee of University of Health Sciences Van Training and Research Hospital (Date: 26/04/2023, Decision No: 2023/09-03).

Informed consent: All subjects signed detailed informed consent before their inclusion in the study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Hand hygiene beliefs and practices and five indications-oriented hand hygiene observation results among healthcare professionals: a retrospective study

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ABSTRACT

Aims: The present study attempted to retrospectively depict hand hygiene beliefs and practices and five indications-oriented hand hygiene observation results among physicians and nurses employed in the internal, surgical, emergency, and intensive care units of a district state hospital.

Methods: While the target population consists of healthcare professionals deployed in the internal, surgical, emergency, and intensive care units of a district hospital (n=426), we carried out this study with 122 nurses and 53 physicians (n=175). We collected the data using a demographic information form, the hand hygiene beliefs scale (HHBS), and hand hygiene practices inventory (HHPI).

Results: The findings revealed the participants' mean scores to be 93.05±13.08 on the HHBS (61.90±9.16 on the hand hygiene importance subscale and 27.22±5.33 on the hand hygiene beliefs subscale) and 67.96±5.07 on the HHPI. We also considered a total of 1.228 notes from hand hygiene observations. While 78.25% of these observations were found to comply with hand hygiene standards, 59.55% (n=159) of 267 observations regarding non-compliance with hygiene rules were realized to be linked with improper gloves use.

Conclusion: Overall, the participating healthcare professionals adopted firmer hand hygiene beliefs and practices, which may be thanks to the achievement of relevant in-service training and the effective planning of the infection control committee. Yet, most of the hygiene non-compliance could be attributed to improper gloves use.

Keywords: Hand hygiene, healthcare professionals, belief, observation, compliance

INTRODUCTION

Despite improvements in hospital healthcare services and health technologies, healthcare-associated infections continue to be among significant health problems worldwide. Indeed, they may engender functional disorders, emotional distress, reduced quality of life, morbidity, and mortality. Besides, they can be considered an alerting social problem since leading to prolonged hospitalization, job losses, increased drug use, and elevated healthcare expenditures due to extra diagnostic techniques used.[1] One may comply with hand hygiene practices and isolation measures as the most apparent practices to eliminate or reduce the risk of infection in healthcare settings.[2,3] The level of compliance with both isolation measures and hand hygiene among healthcare professionals also emerges as a critical factor in the prevention of healthcare-associated infections since it was previously reported that while pathogenic microorganisms are hosted on the hand surfaces of only 6% of healthy individuals, this rate rises up to 68% of healthcare professionals.[4] Hand hygiene is, therefore, the initial and essential step in infection control and hygiene practices.

Despite being a cheap and efficient method of infection control, previous research often reported poorer hand

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hygiene compliance among healthcare workers.[5,6] Yet, monitoring and feedback may contribute to healthcare professionals' compliance with hand hygiene. The World Health Organization (WHO) offers the observation technique as the most efficient way to directly measure healthcare professionals' compliance with hand hygiene rules. Moreover, it recommends that findings of compliance with hand hygiene indications (moments) will help provide feedback, inform the target audience about the indications, and improve the relevant personnel's hand hygiene knowledge.[7] Thus, the present study aimed to reveal selected healthcare professionals' hand hygiene compliance in different indications and to interpret the compliance findings by profession.

Healthcare services are provided through the collaborative efforts of professionals from diverse educational and medical backgrounds working within an organisation. The key feature of this multidisciplinary work is their joint efforts to enhance patient outcomes. In healthcare institutions, where patient improvement is the top priority, teamwork and cooperation are of paramount importance. Therefore, an analysis of hand hygiene practices across different professions would be informative.

METHODS

The present study attempted to retrospectively depict hand hygiene beliefs and practices and five indications-oriented hand hygiene observation results among healthcare professionals. While the target population consists of healthcare professionals (n=426) deployed in the internal, surgical, emergency, and intensive care units of a district hospital in Ankara, we carried out this study with 122 nurses and 53 physicians (n=175) between January 1 - December 31, 2022. We collected the data using a demographic information form, the hand hygiene beliefs scale (HHBS), and hand hygiene practices inventory (HHPI). The data collection tools were consolidated on one-to-one committee observation reports and Google Forms. The Scientific Researches and Publication Ethics Committee of Doğu Akdeniz University granted ethical approval to our study (Date: 27.01.2023, Decision No: ETK00-2023-0029), and we obtained institutional permission (E-69051143-774.01.01) from the Chief Physician Office of Kahramankazan State Hospital. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Demographic Information Form

We designed this form to cover seven questions about the demographic characteristics of the participating healthcare professionals (i.e., age, gender, educational attainment, profession, the unit deployed, seniority in the profession, and seniority in the institution).

Hand Hygiene Beliefs Scale (HHBS)

The HHBS was developed by Thea van de Mortel and adapted into Turkish by Karadağ.[8,9] It consists of 22 items within two subscales: hand hygiene importance (items 1, 2, 3, 4, 6, 7, 9, 11, 12, 13, 14, 15, 21and 22) and hand hygiene beliefs (items 20, 19, 8, 5, 18, 10, 16, and 17). The items are scored on a five-point Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree). One may obtain 22-110 points on the HHBS, and the scale offers no cut-off point. While the adaptation study calculated its internal consistency coefficient to be 0.80, we discovered it to be 0.75 in this study.

Hand Hygiene Practices Inventory (HHPI)

Karadağ also adapted the 15-item HHPI, designed by Thea van de Mortel, into Turkish. The items are scored on a five-point Likert-type scale ranging from 1 (Never) to 5 (Always). One may obtain 15-75 points on the HHPI, and the tool offers no cut-off point. Higher scores on the scale indicate one's higher compliance with hygiene practices. While Karadağ found Cronbach's alpha coefficient for the scale to be 0.85, we calculated it to be 0.77 in this study.

Hand Hygiene Observations

The infection control committee of our hospital performs observations every three months pertinent to healthcare professionals' hand hygiene practices in the working environment every three months. We categorized the mentioned observational data into five hand hygiene indications (moments) recommended by the WHO and, accordingly, explored hand hygiene attitudes and behaviors of the participating healthcare professionals.

Statistical Analysis

Initially, we calculated the internal consistency coefficients (Cronbach's alpha) of the measurement tools above. While continuous variables are expressed as means (*M*) ± standard deviations (*SD*) and minimum-maximum values, categorical variables are presented as numbers (n) and percentages (%). We display the participants' demographic characteristics as frequencies and descriptive statistics of their HHBS and HHPI scores. Then, we ran a Pearson correlation analysis to investigate the relationships between the participants' hand hygiene beliefs and practices. All analyses were performed on Statistical Package for Social Sciences (SPSS) 26.0, and a p-value of <0.05 was considered statistically significant.

RESULTS

Participants' Demographic Characteristics

The findings revealed that 72% of the participants were females, 69.7% were nurses, 44% had undergraduate education, and 27.4% held a doctorate degree. The mean age of the participants was calculated to be 37.8±9.6 years. While they had a mean professional seniority of 13.3±9.08 years, the mean seniority in the institution was found to be 7.8±7.06 years. About one-third (35.43%) of the participants were employed in the internal medicine department of the hospital (Table 1).

Table 1. Participants' demographic characteristics

		n	%
Gender	Female	126	72
	Male	49	28
Educational attainment	Associate degree and below	32	18.3
	Undergraduate	77	44
	Master's degree	18	10.3
	Doctorate degree	48	27.4
Profession	Nurse	122	69.7
	Physician	53	30.3
Unit deployed	Emergency	41	23.43
	Surgical medicine	59	33.71
	Internal medicine	62	35.43
	Intensive care	13	7.43
Seniority in profession (M±SD=13.3±9.08)	1-10 years	66	37.7
	11-20 years	74	42.3
	21 years and above	35	20
Seniority in the institution (M±SD=7.8±7.06)	1 year and below	57	32.56
	2-10 years	69	39.4
	10-20 years	47	26.89
	21 years and above	2	1.1
Mean age (years)	**M±SD**=37.8±9.6	**min.=22 - max.=63**	

Findings of the HHBS and the HHPI

The findings revealed the participants' mean scores as 93.05±13.08 on the HHBS (61.90±9.16 on the hand hygiene importance subscale and 27.22±5.33 on the hand hygiene beliefs subscale) and 67.96±5.07 on the HHPI. The participating physicians got a mean score of 85.43±11.55 on the HHBS (58.37±10.1 on the hand hygiene importance subscale and 24.58±3.98 on the hand hygiene beliefs subscale) and 66.71±6.92 on the HHPI. On the other hand, we found the nurses obtained a mean score of 96.36±12.3 on the HHBS (63.44±8.2 on the hand hygiene importance subscale and 28.37±5.45 on the hand hygiene beliefs subscale) and 68.5±3.92 on the HHPI (Table 2).

Correlations Between Hand Hygiene Beliefs and Practices

The findings revealed significant relationships between the participants' HHPI scores and their HHBS total and hand hygiene importance scores (p=0.000). Nevertheless, it was not the case for their HHBS hand hygiene beliefs scores (p=0.450) (Table 3).

Table 3. Correlations between hand hygiene beliefs and practices

		HHBS	HHBS Hand hygiene beliefs	HHBS Hand hygiene importance
HHPI	**r**	0.268	0.057	0.264
	p	0.000*	0.450*	0.000*

p<0.05

Analysis of Observations Pertinent to Hand Hygiene Compliance and Non-compliance

The infection control committee gathered the data regarding the observations of the healthcare professionals' compliance and non-compliance with hand hygiene rules (n=1228). Accordingly, 78.25% of the observations revealed the participants' compliance with hand hygiene standards. This rate was 79.3% among the nurses and 75.82% among the physicians. On the other hand, 59.55% (n=159) of 267 observations regarding hand hygiene non-compliance were attributed to improper gloves use. We found this rate to be 71.35% among the nurses and 35.96% among the physicians (Table 4).

Table 2. Participants' scores on the HHBS and the HHPI by profession

	HHBS		HHBS Hand Hygiene Beliefs		HHBS Hand Hygiene Importance		HHPI	
	M±SD	**min.- max.**	**M±SD**	**min.- max.**	**M±SD**	**min.- max.**	**M±SD**	**min.- max.**
Nurses	96.36 ±12.3	52-110	28.37±5.45	17-35	63.44±8.20	61.86±9.01	68.50±3.92	34-70
Physicians	85.43±11.55		24.58±3.98		58.37±10.1		66.71±6.92	
Total	93.05±13.08		27.22±5.33		61.90±9.16		67.96±5.07	
Cronbach's alpha	0.75						0.77	

Table 4. Analysis of observations hand hygiene compliance and Non-compliance

Profession	Number of observations pertinent to hand hygiene compliance and Non-compliance	Total observations	Hand hygiene compliance rate	Number of observations pertinent to hand hygiene Non-compliance	Number of gloves in hand hygiene Non-compliance	Attribution of hand hygiene Non-compliance to improper gloves use
Nurse	682	860	79.3	178	127	71.35
Physician	279	368	75.82	89	32	35.96
Total	**961**	**1228**	**78.25**	**267**	**159**	**59.55**

Hand Hygiene Compliance Rates by Five Indications (Moments)

We also analyzed the participants' hand hygiene observation results by five indications (moments) for hand hygiene (Table 5). Accordingly, the rates of positive observations related to hand hygiene compliance by the mentioned indications were found to be as follows (nurses and physicians, respectively): 69.44% (n=324) vs. 69.33% (n=163) before touching a patient; 79.52% (n=83) vs. 81.82% (n=55) before an aseptic procedure; 100% (n=182) vs. 93.94% (n=66) after a procedure or body fluid exposure risk; 87.97% (n=424) vs. 87.11% (n=225) after touching a patient; 83.64% (n=110) vs. 61.11% (n=18) after touching a patient's surroundings.

Table 5. Hand hygiene compliance rates by five indications

Indication		Nurse	Physician
Before touching a patient	**Compliant**	225	113
	Total	324	163
	Rate (%)	69.44	69.33
Before an aseptic procedure	**Compliant**	66	45
	Total	83	55
	Rate (%)	79.52	81.82
After a procedure or body fluid exposure risk	**Compliant**	182	62
	Total	182	66
	Rate (%)	100	93.94
After touching a patient	**Compliant**	373	196
	Total	424	225
	Rate (%)	87.97	87.11
After touching a patient's surroundings	**Compliant**	92	11
	Total	110	18
	Rate (%)	83.64	61.11

DISCUSSION

It is often emphasized that healthcare personnel exhibits insufficient hand hygiene compliance, although it was previously shown that it helps reduce nosocomial infections by about 50%. In this respect, the WHO recommends designating multifaceted strategies and national campaigns to promote hand hygiene compliance.[10] Our findings showed that the nurses had higher HHBS and HHPI scores than the physicians, albeit the difference was not statistically significant. In their study, Ataei et al.[11] discovered nurses had higher adaptation to hand hygiene compliance (8.4%) than physicians (3.8%), students (7.3%), and auxiliary staff (0.9%). Rosenthal et al.[12] investigated 62.626 patient contacts between 1998-2005 in Argentina, Brazil, Colombia, India, Mexico, Morocco, Peru, and Türkiye and concluded that nurses had the highest hand hygiene compliance among other healthcare professionals. Moreover, Azim et al.[13] found that nurses are likely to show 1.5 times more hand hygiene compliance than physicians despite having three times more contact with patients. Overlapping these findings, considering the hand hygiene compliance by five indications, the nurses achieved more hand hygiene compliance in 4 indications than the physicians.

Erasmus et al.[14] systematically reviewed 96 studies on hand hygiene compliance guidelines in patient care and discovered that healthcare professionals' hand hygiene compliance remained at 40%. Thus, they uttered a need for research and training to boost hand hygiene compliance among healthcare staff. In another study, Karabey et al.[15] reported the rate of handwashing among healthcare staff to be 12.9%. Our findings demonstrated the participating healthcare personnel's hand hygiene compliance rate to be 78.25%. The higher hand hygiene compliance rate in this study compared to other studies may be a positive consequence of periodic hand hygiene training by the hospital's infection control committee, practical training at the bedside, and visual materials on five hand hygiene indications in all units.

Toraman et al.[16] found hand hygiene compliance among the participating healthcare personnel was higher (81%) in the case of body fluid exposure risk. Similarly, we found hand hygiene compliance rates were high among the participating physicians (93.94%) and nurses (100%) in the case of body fluid exposure risk. There may be a greater tendency among healthcare professionals to wash hands in the case of an apparent or tangible risk of contamination since contact with body fluids may be considered a critical situation for

catching infections. On the other side, the low rate (61.1%) of hand hygiene compliance after touching a patient's surroundings may support the view that healthcare personnel may not perceive a need for washing hands in the case of an implicit or intangible risk of contamination. In the same vein, Demir et al.[17] reported that hand hygiene is ensured at least (0%) "after touching a patient's surroundings". Therefore, poor hand hygiene compliance in this indication may be considered an alarming issue in controlling nosocomial infections.

Given the hand hygiene observation results by the WHO-recommending five hand washing indications, we found hand hygiene compliance to be the most frequent in the case of body fluid exposure risk among both nurses and physicians. In their study, Koşucu et al.[18] discovered that the participants engaged in handwashing before aseptic procedures the most (80%), followed by body fluid exposure risk (71%). Artan and Türeyen asked their participants to rank the frequency of their hand hygiene compliance by the five handwashing indications. Accordingly, while the participants ranked washing hands before aseptic procedures first (68.8%), followed by body fluid exposure risk (33.1%), washing hands before touching a patient remained in the last place (65%).[19] Since we designed this study based on hygiene observations, it seems rather usual that self-report and practical behaviors differ in the order of importance of these indications. Thus, different from what has been reported in the literature so far, the observations showed that the participants had higher hygiene compliance rates in the case of body fluid exposure risk in daily practice than other handwashing indications. Our findings overlap with the idea that healthcare professionals are often more inclined to wash their hands and intuitively engage in self-protection in case of perceived contamination.

We also considered observations regarding non-compliance with hygiene rules. Accordingly, 59.55% (n=159) of 267 observations regarding non-compliance with hygiene rules were attributed to improper gloves use. We found this rate to be 71.35% among the nurses and 35.96% among the physicians. These findings may imply that gloves use may potentially distract healthcare professionals from applying routine hygiene procedures, which may highlight the importance of in-service training regarding hygiene procedures before and after gloves use.

Limitations

We could not reach the targeted sample size because carrying out this research in a single center with an insufficient number of healthcare professionals deployed in the units with a high workload. Hence, further research may be designed as a multicenter with a larger sample size to achieve more robust findings.

CONCLUSION

Undertaking a primary role in every step of healthcare, healthcare professionals also have responsibilities in preventing healthcare-associated infections. In our study, the participating nurses and physicians scored higher on the HHBS and HHPI, which may document greater adoption of hand hygiene beliefs and practices among healthcare staff. Yet, it should be noted that self-report and observational data may exhibit relative differences regarding the actual picture of hand hygiene behaviors, highlighting the significance of observational data. Overall, prospective researchers may consider scrutinizing the subjects on a larger sample with the help of observational data.

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ETHICAL DECLARATIONS

Ethics Committee Approval: The Scientific Research and Publication Ethics Committee of Doğu Akdeniz University granted ethical approval to our study (Date: 27.01.2023, Decision No: ETK00-2023-0029), and we obtained institutional permission (E-69051143-774.01.01) from the Chief Physician Office of Kahramankazan State Hospital.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Association of chronic disease self-management with health locus of control study on diabetic patients

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ABSTRACT

Aims: It was aimed at determining the relationship between chronic disease self-management and health locus of control in diabetic patients.

Methods: Data were collected by the face-to-face survey method from diabetic patients over the age of 18 who were receiving inpatient treatment in a public hospital.

Results: According to the research results; the total score average of the participants from the chronic disease self-management scale was moderate (mean: 64.11 Min: 21-Max: 105), w but treatment compliance (mean:15.81 Min:5-Max:25)) was found to be at a medium level. The participants' internal locus of control score (mean: 25.08, Min: 9-Max: 36) was found to be higher than other sub-dimensions. As a result of the correlation analyses carried out; statistically significant relationships were obtained between chronic disease self-management total and sub-dimensions and health locus of control sub-dimensions.

Conclusion: Statistically significant relationships were obtained between the chronic disease self-management total and sub-dimensions and the health locus of control sub-dimensions. It can be said that the participants have more internal locus of control beliefs.

Keywords: Diabetes, health care focus, chronic disease self-management

INTRODUCTION

The World Health Organization defines chronic diseases as conditions that cannot be treated medically, progress over time, require support and follow-up to control the disease and maximize the patient's responsibilities, and affect daily life.[2,5] The most common chronic diseases in the world include diabetes, cancer, chronic obstructive pulmonary disease (COPD), and cardiovascular diseases.[7]

In order to improve health outcomes, health behaviors, and quality of life in chronic diseases, it is important that the individual's self-management be developed. Chronic disease self-management is an approach that aims to enable the individual to manage the care and treatment of his/her disease, to regulate his/her lifestyle socially, physically, and psychologically, to develop activities that center the patient, to prevent or reduce the health risks that may occur, and to improve his/her health and quality of life.[20,14] When self-management increases, positive results in treatment increase, quality of life and health outcomes improve, and health service utilization and social cost burden decrease.[27,9,3]

The individual with chronic disease sees himself/herself as responsible for the situation he/she is experiencing in relation to his/her health and places himself/herself in the center or looks for other factors outside. The concept of health locus of control was developed to explain these behaviors of the individual in the face of the disease.[25]

The Julian Rotter-developed social learning theory, which explains the beliefs that guide individual and long-term behaviors related to health, is where the health locus of control originated.[4] The health locus of control includes a personality factor that the individual develops over time and includes social learning experiences. It focuses on explaining to whom the person attributes control in the disease process, the source of their expectations about their health status, the positive or negative situation they face, the factors that affect behavior or outcomes, and the belief that control belongs to whom. While some individuals think that they themselves are effective in their well-being or illness, some individuals think that other external factors influence and manage the disease.[8,13,26] Individuals with a developed health locus of control are more successful in

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showing health-protective and health-promoting behaviors, approving and complying with treatment, and avoiding and adapting to health-damaging behaviors.[13,15]

With the aging population, sedentary lifestyle, and increasing obesity, diabetes has become a global epidemic and a major health crisis.[11,12] Diabetes is a rapidly growing socio-economic problem that creates a huge economic burden.[10] It is estimated that the number of patients with diabetes in the world will be 536.6 million in 2021, and this number will be 783.2 million in 2045.[28] Diabetes rates are also rising rapidly in Turkey. According to data from the International Diabetes Federation, there are 7 million diabetic patients between the ages of 20-79 in Turkey. Especially 80% of Type 2 diabetes cases are preventable. It is possible for countries to minimize the negative consequences of patients with diabetes individually and socially, to increase the quality of life of patients, to develop human resources, which are important for sustainable economic development, and to minimize the negative impact on economic development.[29]

METHODS

This study is a cross-sectional exploratory study conducted with primary data. The aim of the study is to determine the relationship between socio-demographic characteristics, chronic disease self-management levels, health locus of control, health locus of control and chronic disease self-management of diabetes patients. In order to carry out this research, Ethics Committee Approval was received from Kırıkkale University Non-invasive Researches (Date: 21.12.2022, Decision No: 2022.12.01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The research covers diabetes patients over the age of 18 who were treated in Kırıkkale High Specialization Hospital Internal Medicine Department inpatient services between December 15, 2022, and March 30, 2023, and who voluntarily agreed to participate in the research. Data were collected by the face-to-face questionnaire method. The questionnaire consists of three parts: a personal information form, a chronic disease self-management scale, and a health locus of control scale. The Chronic Disease Self-Management Scale was developed by Ngai et al. (2020). The Turkish validity and reliability of the scale were conducted by Öztürk et al.[19] in 2021. The Health Locus of Control Scale was developed by Wallston et al.[6] in 1978, and its Turkish validity and reliability were performed by Güzel.

Statistical Analysis

In order to evaluate the normal distribution of the data in the study, kurtosis and skewness values were calculated for the sub-dimensions and total scores of each scale. The values of the chronic disease self-management scale were calculated as 0.209–1.878, and the values of the multidimensional health locus of control scale were calculated as -0.697–0.797. According to these results, the data show a normal distribution. Cronbach's alpha values were calculated to determine the reliability of the scales and found to be between 0.76-0.923.

RESULTS

The socio-demographic data of the participants are given in Table 1.

Table 1. Socio-demographic characteristics of participants

	N	%	Total
Gender			
Male	140	48.8	**287**
Female	147	51.2	
Age			
35 years and below	39	13.6	**287**
36-50 years old	85	29.6	
51-65 years old	104	36.2	
66-81 years old	59	20.6	
Marital Status			
Married	193	67.2	**287**
Single	94	32.8	
Education Status			
High school and below	211	73.5	**287**
Associate degree	46	16.0	
Bachelor's degree	30	10.5	
Income Groups			
Under 7500 ₺	64	22.3	**287**
7500-14999 ₺	158	55.1	
15000 ₺ and above	65	22.6	
Social Security			
SSI	267	93.0	**287**
Private insurance	6	2.1	
No	14	4.9	
Diabetes type			
Type 1	10	3.5	**287**
Type 2	277	96.5	
Concomitant Disease			
Yes.	118	41.1	**287**
No	169	58.9	
Place of residence			
Province	180	62.7	**287**
District	95	33.1	
Neighborhood (village)	12	4.2	

51.2% of the participants were women, 36% were between the ages of 51-65 with a mean age of 52.31, 67.2% were married, 73.5% had high school education or less, 55.1% had an income between 7.500-14.999 TL, 93.0% were covered by SSI, 96.5% had type II diabetes, 41.1% had comorbidities, and 62.7% resided in the city center. When the occupations of the participants are analyzed, it is seen that 39% of the participants are housewives, 29.0% are retired, and 2% are teachers, students, tradesmen, guards, and hairdressers. The distribution of occupations is given in Figure 1.

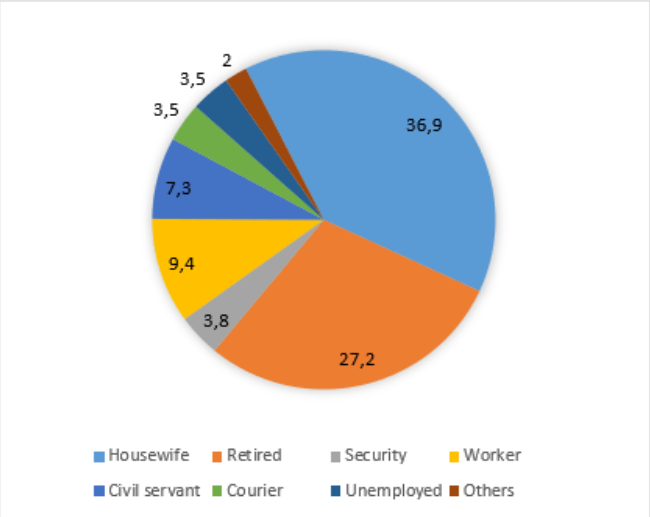

Figure 1. The distribution of occupations

When the comorbidities of diabetes patients were analyzed, it was seen that 77% of 287 diabetes patients had hypertension, 87.1% had heart failure, 94.8% had asthma, and 91.6% had chronic renal failure. Comorbidities are given in Figure 2.

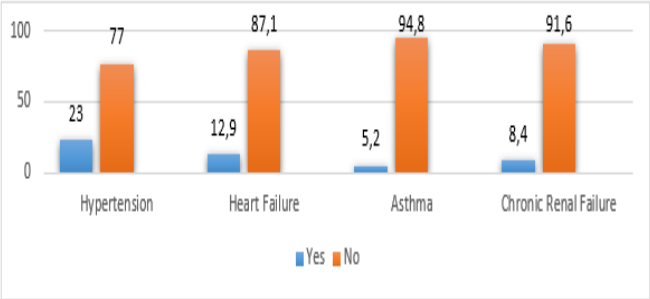

Figure 2. Comorbidities

Findings regarding participants' chronic disease self-management and health locus of control are given in Table 2.

The mean total score obtained by the participants from the chronic disease self-management scale was moderate (mean: 64.11±5.4 min: 21 max: 105). Among the sub-dimensions, self-stigmatization (mean: 20.80±4.2 min: 9 max: 33), coping with stigmatization (mean: 16.39±3.4 min: 9 max: 25), and health care effectiveness (mean: 12.73±2.7 min: 8 max: 20) were at a low level, but compliance with treatment (mean: 15.81±4.0 min: 5 max: 25) was at a moderate level. The participants' internal locus of control sub-dimension score (mean: 25.08±5.2 min: 9 max: 36) was found to be higher than the other sub-dimensions. According to these results, it can be said that the participants have more internal locus of control beliefs.

Table 2. Participants' chronic disease self-management and health locus of control levels

	N	Min.	Max.	Mean	SD
Chronic disease self-management scale	287	21	105	64.11	5.4
Self-stigmatization	287	9.0	33.0	20.80	4.2
Dealing with stigmatization	287	9.0	25.0	16.39	3.4
Health care effectiveness	287	8.0	20.0	12.73	2.7
	N	**Min.**	**Max.**	**Mean**	**SD**
Treatment compliance	287	5.0	25.0	15.81	4.0
Internal locus of control	287	9.0	36.0	25.08	5.2
Luck locus of control	287	11.0	35.0	23.45	4.8
Locus of control of significant others	287	8.0	25.0	19.29	2.1

The relationship between chronic disease self-management and health locus of control sub-dimensions was evaluated by Pearson correlation analysis, and the results are given in Table3.

According to the results of the Pearson correlation analysis in Table 3 (**. p<0.01), there is a moderately significant positive relationship between the total chronic disease self-management and self-stigmatization sub-dimensions (r=0.504; p=0.000). As patients' self-stigmatization behaviors related to their diseases increase, chronic disease self-management increases moderately.

There is a positive, low-level, significant relationship between the total chronic disease self-management and the coping with stigmatization sub-dimension (r=0.337; p=0.000). As the patients' ability to cope with stigmatization increases, chronic disease self-management power also increases, albeit slightly.

There is a positive, low-level, significant relationship between the total chronic disease self-management and the health care effectiveness sub-dimension (r=0.193; p=0.001). As the health care activities of the patients increase, their chronic disease self-management power also increases, albeit slightly.

Table 3. The relationship between chronic disease self-management and health locus of control sub-dimensions

		1	2	3	4	5	6	7	8	
Chronic disease self-management total (1)	**r**	1								
	p									
	n	287								
Self-stigmatization (2)	**r**	**.504****	1							
	p	.000								
	n	287	287							
Dealing with stigmatization (3)	**r**	**.337****	**-425****	1						
	p	.000	.000							
	n	287	287	287						
Health care effectiveness (4)	**r**	**.193****	**-423****	**.675****	1					
	p	.001	.000	.000						
	n	287	287	287	287					
Treatment compliance (5)	**r**	**-.402****	**-.281****	**.418****	**.562****	1				
	p	.000	.000	.000	.000					
	n	287	287	287	287	287				
Internal control (6)	**r**	.066	**-.220****	**.439****	**.577****	**.454****	1			
	p	.263	.000	.000	.000	.000				
	n	287	287	287	287	287	287			
Luck check (7)	**r**	.027	**.284****	**-.389****	**-.524****	**-.435****	**-.440****	1		
	p	.646	.000	.000	.000	.000	.000			
	n	287	287	287	287	287	287	287		
Important others (8)	**r**	**.785****	**.615****	**.176****	.026	**-.245****	.073	.042	1	
	p	.000	.000	.003	.661	.000	.215	.480		
	n	287	287	287	287	287	287	287	287	

**. significant correlation at p<0.01 level

There is a moderately significant positive relationship between the total chronic disease self-management and the treatment compliance sub-dimension (r=-0.402; p=0.000). As the patients' compliance with their treatment increases during their illness, their chronic disease self-management power increases moderately.

There is a highly significant positive relationship between total chronic disease self-management and the important other locus of control sub-dimension (r=0.785; p=0.000). As the level of patients' relinquishing control over their sick and healthy state to health professionals, family, or friends increases, the degree of chronic disease self-management also increases strongly. No significant relationship was found between the total chronic disease self-management and internal locus of control (r=0.066; p=0.263) and chance locus of control (r=0.027; p=0.646) sub-dimensions.

There is a negative and low-level significant relationship between self-stigmatization and the internal locus of control sub-dimension (r=-0.220; p=0.000). As the patients' belief that they are in control of their own health increases, their self-stigmatization behaviors decrease slightly.

There is a positive, low-level, significant relationship between self-stigmatization and the sub-dimension of luck control (r=0.284; p=0.000). As the patients' belief that luck controls their health increases, their self-stigmatization behaviors increase slightly.

There is a moderately significant positive relationship between self-stigmatization and the important other sub-dimensions (r=0.615; p=0.000). As the level of patients' leaving the control of being sick and healthy to health professionals, family, or friends increases, the level of self-stigmatization increases moderately.

There is a positive and moderately significant relationship between coping with stigmatization and the internal locus of control sub-dimension (r=0.439; p=0.000). As the patients' belief that they are in control of their own health increases, their level of coping with stigmatization increases moderately.

There is a negative and low-level significant relationship between coping with stigmatization and the locus of control sub-dimension of luck (r=-0.389; p=0.000). As the patients' belief that luck controls their health increases, their level of coping with stigmatization decreases slightly.

There is a positive and low-level significant relationship between coping with stigmatization and the important other locus of control sub-dimension (r=0.176; p=0.003). As the level of patients' leaving the control of being sick and healthy to health professionals, family, or friends increases, the level of coping with stigmatization increases slightly.

There is a moderately significant positive relationship between health care effectiveness and the internal control sub-dimension (r=0.577; p=0.000). As the patients' belief that they are in control of their own health increases, their health care efficiency increases moderately.

There is a negative and moderately significant relationship between health care effectiveness and the sub-dimension of chance control (r=-0.524; p=0.000). As the patients' belief that luck controls their health increases, their health care activities moderately decrease.

No relationship was found between health care effectiveness and the important other control sub-dimension (r=0.026; p=0.661).

There is a moderately significant positive relationship between treatment adherence and the internal control sub-dimension (r=0.454; p=0.000). As the patients' belief that they are in control of their own health increases, their compliance with treatment increases moderately.

There is a negative and moderately significant relationship between treatment adherence and the chance control sub-dimension (r=-0.435; p=0.000). As the patients' belief that luck controls their health increases, their adherence to treatment moderately decreases.

There is a negative, low-level significant relationship between treatment adherence and the important other control sub-dimension (r=-0.245; p=0.000). As the patients' level of relinquishing control of being sick and healthy to health professionals, family, or friends increases, their compliance with treatment decreases slightly.

DISCUSSION

Self-management is a comprehensive concept that basically includes treatment of the disease, physical and social consequences, and adaptation to lifestyle changes. Self-stigmatization, coping with stigmatization, the effectiveness of health care, and compliance with treatment are critical elements in chronic disease self-management.[17] In this study, it was observed that the mean total score of the participants obtained from the chronic disease self-management scale was moderate (mean: 64.11±5.4; min: 21; max: 105). Among the sub-dimensions, self-stigmatization (mean: 20.80±4.2 min: 9 max: 33), coping with stigmatization (mean: 16.39±3.4 min: 9 max: 25), and health care effectiveness (mean: 12.73±2.7 min: 8 max: 20) were at a low level, but compliance with treatment (mean: 15.81±4.0 min: 5 max: 25) was at a medium level. Therefore, it was concluded that patients with diabetes had low levels of self-stigmatization, coping with stigmatization, health care effectiveness, a moderate level of treatment compliance, and a moderate level of chronic disease self-management total score.

The locus of control investigates who or what controls the health behavior of individuals. The internal locus of control sub-dimension score of the participants was found to be higher than the other sub-dimensions. According to this result, it is seen that the participants have more internal locus of control beliefs. Therefore, it indicates personality traits that tend to perceive behavioral outcomes and events depending on their own behaviors or personality traits instead of perceiving them depending on fate, luck, and other powerful people and events. In a study conducted by Petricek et al.[21] with type 2 diabetic patients, the internal locus of control was the highest in participants, followed by the locus of control of luck and strong others, respectively. Trento et al.[24] found that the participants' internal locus of control belief was higher than other loci of control.

When the relationship between the chronic disease self-management dimension and its sub-dimensions and the health locus of control sub-dimensions is examined, a strong positive relationship was found between the chronic disease self-management total and important other locus of control sub-dimensions (r=0.785). There is a moderately positive relationship between treatment adherence and the internal control sub-dimension (r=0.454). There is a moderately negative relationship between treatment compliance and the chance control sub-dimension (r=-0.435). There is a low-level negative relationship between treatment adherence and important other control sub-dimensions (r=-0.245). There is a moderately positive relationship between coping with stigmatization and the internal control sub-dimension (r=0.439). A moderately positive relationship was found between health care effectiveness and the internal control sub-dimension (r=0.577). In the study conducted by Morovatisharifabad et al.[16], a positive relationship was found between internal locus of control and adherence to the diabetes regimen, and a negative relationship was found between chance-based locus of control and adherence to the diabetes regimen. Taher et al.[23] in their study on hypertension patients concluded that there is a direct relationship between internal health locus of control and adherence to treatment regimens

in hypertensive patients. Patients with uncontrolled hypertension were also found to have a high locus of control by chance. Therefore, it was observed that patients with internal locus of control beliefs had better compliance with the treatment regimen. Przybylski[22] found that patients with high internal locus of control beliefs had better compliance with treatment. The results obtained are consistent with these studies.

Limitations

The study was conducted with diabetic patients treated in the inpatient ward of the internal medicine department of a public hospital providing secondary health care services. The study can be conducted in a tertiary hospital with a larger sample. In addition, patients receiving treatment and those with chronic diseases other than diabetes can be included.

CONCLUSION

The mean total score obtained by the participants from the chronic disease self-management scale was moderate (mean: 64.11, min: 21–max: 105). Self-stigmatization (mean: 20.80 min: 9-max: 33), coping with stigmatization (mean: 16.39 min: 9-max: 25), and health care effectiveness (mean: 12.73 min: 8-max: 20) are at a low level. On the other hand, adherence to treatment (mean: 15.81, min: 5–max: 25) was at a moderate level.

The internal locus of control score of the participants (mean: 25.08, min: 9.9, max: 36) was found to be higher than the other sub-dimensions. It was concluded that the participants had more internal locus of control beliefs. It can be said that patients are willing to take responsibility for their illnesses themselves instead of attributing them to others. This is a desirable situation. It has been observed that positive results can be achieved when patients are given training and social support about self-management and diseases.

As a result of the correlation analyses performed with respect to individuals' diseases, statistically significant relationships were obtained between the total and sub-dimensions of chronic disease self-management and the sub-dimensions of health locus of control ($p<0.05$). As the health locus of control improves, patients' chronic self-management also increases.

ETHICAL DECLERATION

Ethics Committee Approval: In order to carry out this research, Ethics Committee Approval was received from Kırıkkale University Non-invasive Research (Date: 21.12.2022, Decision No: 2022.12.01)

Informed Consent: A signed, free, and informed consent form was obtained from all participants in this study.

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Review

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Current use of the faricimab in retinal diseases

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ABSTRACT

Faricimab, a novel drug in the field of ophthalmology, has garnered attention because of its promising applications in the treatment of various ocular conditions. This drug, with its dual targeting of angiopoietin-2 and vascular endothelial growth factor (VEGF), is a versatile intervention for the management of neovascular and inflammatory ocular disorders. Developed through meticulous research and clinical trials, faricimab holds promise as a multifaceted solution to longstanding challenges in ophthalmology. This review provides a comprehensive analysis of the current knowledge and clinical use of faricimab.

Keywords: Angiopoietin-2, dual mechanism, faricimab, ophthalmology, retina, vascular endothelial growth factor

INTRODUCTION

Faricimab, a groundbreaking pharmaceutical agent, has emerged as a focal point in ophthalmological therapeutics. As a novel drug, its development and mechanism of action represent a paradigm shift in addressing various ocular conditions. Faricimab is a bispecific monoclonal antibody designed to use intravitreally and faricimab does not only inhibits VEGF but also inhibits Angiopoietin-2. As we delve into the intricacies of faricimab's role in ophthalmology, it becomes evident that its introduction marks a pivotal juncture in the pursuit of more effective and patient-friendly treatments for ocular disorders. This review aims to navigate the current landscape, providing a comprehensive analysis of Faricimab's applications, supported by evidence from recent studies. The subsequent sections will expound on its clinical applications, shedding light on its impact on diverse ophthalmic conditions.

Angiopoietins, a family of growth factors involved in vascular stability, play pivotal roles in angiogenesis. In adults, the Ang/Tie pathway is mainly responsible for the regulation of vascular homeostasis, modulation of vascular permeability, and neoangiogenic and proinflammatory processes.[1,2] Tie-2 is a transmembrane receptor that is especially found in the endothelial cells of blood vessels, and Ang-1 and Ang-2 compete with each other to bind Tie-2. In addition, the binding of either Ang-1 or Ang-2 has different effects on the Tie-2 pathway. Studies have shown that when Ang-1 binds to Tie-2, causing phosphorylation of the receptor and may promote vessel maturation, endothelial cell migration, and initiating its effects of inhibit vascular permeability, it also preserves vascular stability. Ang-1 promotes vascular stabilization and maturation, whereas Ang-2 serves as a dynamic modulator, exerting context-dependent effects on vessel formation. Ang-2 may disrupt the connections between endothelial cells and promote vascular regression, and Ang-2 may promote vascular angiogenesis.[2] Ang-2 has emerged as a key molecular player in ophthalmology. Dysregulation of angiopoietin expression is often implicated in neovascular ocular conditions such as age-related macular degeneration (AMD) and diabetic retinopathy. The intricate interplay between angiopoietins and vascular endothelial growth factor (VEGF) highlights their roles in the pathogenesis of these disorders.

DUAL MECHANISM OF FARICIMAB ACTION

Faricimab is an antibody engineered to simultaneously bind to and neutralise Angiopoietin-2 (Ang-2) and VEGF-A. Faricimab is an antibody that is engineered to be used intravitreally, designed with a dual mechanism targeting both Ang-2 and VEGF, which may improve the synergistic effects of these pathways. This unique approach positions faricimab as a promising therapeutic

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agent with the potential to address the complexity of neovascularization in ophthalmic pathologies. The integration of Ang-2 inhibition into ophthalmic therapeutics, as seen in faricimab, opens avenues for optimizing treatment regimens. By targeting multiple pathways with a single agent, there is a potential for extended dosing intervals, thereby alleviating the treatment burden on patients and clinics.

Ang-2, in its unbound state, acts as a context-dependent antagonist of Ang-1, promoting the destabilization of blood vessels and fostering conditions conducive to angiogenesis. By blocking Ang-2, Faricimab aims to mitigate this destabilizing influence, contributing to the stabilization of the vascular endothelium. This dual inhibition extends beyond Ang-2, as Faricimab also targets VEGF, a key mediator of angiogenesis and vascular permeability. The synergy between Ang-2 and VEGF inhibition offers more comprehensive control over pathological neovascularization, characteristic of conditions such as age-related macular degeneration (AMD) and diabetic retinopathy. By concurrently addressing two pivotal pathways, faricimab introduced the possibility of extended treatment intervals. This feature is particularly advantageous in reducing treatment burden for patients and optimizing the management of chronic ocular disorders.[1,2]

Clinical Studies with Faricimab in Age-Related Macular Degeneration

The AVENUE study was a phase 2 study of faricimab in treatment-naive nAMD patients, who were treated with five different regimens. The first-arm patients received ranibizumab (0.5 mg every four weeks. In the second arm, the patients received faricimab (1.5 mg every four weeks. In the third arm, the patients received faricimab (6.0 mg every four weeks. In the fourth arm, patients received faricimab, 6.0 mg every 4 weeks until week 12) followed by faricimab, 6.0 mg every 8 weeks). In the fifth arm, patients received ranibizumab 0.5 mg every 4 weeks until week 8, followed by faricimab, 6.0 mg every 4 weeks). Avenue results didn't show statistically significant differences in BCVA and anatomical outcomes between the faricimab arms and the monthly ranibizumab control arm week 36.[3]

The STAIRWAY study was a phase 2 study of faricimab in nAMD patients over 56 weeks. Participants received either 4 monthly 6 mg faricimab as a loading dose and received 6 mg faricimab every 12 or 16 weeks, or 0.5 mg ranibizumab every 4 weeks. The primary endpoint was the change in BCVA at week 40 of the study. The results showed that faricimab administered at 12- and 16-week intervals maintained visual acuity and improved anatomical parameters observed in macular OCT not inferiorly to ranibizumab administered every month.[4]

The TENAYA and LUCERNE trials are pivotal Phase III studies evaluating the efficacy and safety of Faricimab in AMD. These multicenter, randomized, double-masked controlled trials have provided comprehensive insights into the performance of drugs compared to the current standards of care. The primary endpoints included visual acuity, anatomical changes in retinal morphology, and safety profiles. Results from the Tenaya and Lucerne trials demonstrated promising achievements in the primary endpoints. Faricimab was administered monthly for 4 months as loading doses to patients assigned to one of the eight, 12, or 16 weekly dosing groups according to anatomical and visual outcomes. After week 60, the patients' treatment intervals could be extended through a treat-and-extend personalized treatment interval (PTI). Faricimab has shown non-inferiority to aflibercept and met the primary endpoint of clinical trials. The primary endpoint was the mean change in best-corrected visual acuity (BCVA) in the ETDRS from baseline to weeks 40, 44, and 48. These trials showed impressive durability data in patients randomized to receive faricimab. By week 48, nearly 80% of the faricimab-treated patients had a dosing interval of at least 12-week dosing interval. In detail, percentage of patients treated with faricimab with 12-week dosing interval was 34% in TENAYA and 32.9% in LUCERNE; and with 16-week dosing interval was 45.7% in TENAYA and 44.9% in LUCERNE. Approximately 21% of the faricimab-treated patients remained at 8-week intervals. Mean BCVA change from baseline with faricimab was +5.1 and +6.6 letters and with aflibercept +5.1 and +7.8 letters, Tenaya and Lucerne, respectively. The mean change in the central subfoveal thickness (CST) was similar between the treatment groups. For faricimab mean change over weeks 40, 44 and 48 was −136.8 µm in Tenaya and −137.1 µm in Lucerne and for aflibercept treated patients mean change over the same weeks was −129.4 µm in Tenaya and −130.8 µm in Lucerne. The rate of serious ocular adverse events was similar between aflibercept and faricimab, with no evidence of occlusive retinal vasculitis. These findings underscore its potential as a robust treatment option for AMD.[5]

One of the distinguishing features of faricimab is its potential for extended dosing intervals. Clinical studies have explored the feasibility of administering faricimab less frequently than traditional anti-VEGF agents while maintaining therapeutic efficacy. Through week 48, nearly 78% of the patients received injections at least 12 weekly intervals after loading doses. Detailed assessments of anatomical changes, such as reduction in central retinal thickness and improvement in macular morphology, were performed. The changes in CST in

both treatment arms were similar and comparable. The safety profile of faricimab has been the focus of rigorous examination in clinical trials. Analysis of adverse events, ocular and systemic safety parameters, and the incidence of treatment-related complications has provided valuable data to ensure the drug's overall safety and tolerability.[5]

Clinical Studies with Faricimab in Diabetic Retinopathy and Diabetic Macular Edema

The BOULEVARD study was a phase 2 study of faricimab in patients with DME. Patients previously untreated with anti-VEGF agents received 1.5 mg or 6 mg faricimab and 0.3 mg ranibizumab, while non-treatment-naive patients received 6 mg faricimab and 0.3 mg ranibizumab. All groups were injected monthly for the first 20 weeks, and patients were followed up for 16 weeks. In the treatment-naive group, the mean change in faricimab 6 mg treated patients +13.9 letters and +11.7 letters in the 1.5 mg faricimab group. The mean change in the ranibizumab-treated group was +10.3 letter. In both treatment-naive and non-treatment naive patients, a more marked improvement in anatomical parameters and DRSS scores in faricimab regimens was noted compared to the aflibercept arm.[6]

The YOSEMITE and RHINE trials are pivotal Phase III studies evaluating the impact of faricimab on diabetic retinopathy and diabetic macular edema. Clinical studies have systematically assessed Faricimab's efficacy in managing diabetic macular edema, focusing on parameters such as visual improvement and prevention of disease progression.[7] Yosemite and Rhine trials met its primary endpoint. The mean BCVA change for patients who are receiving faricimab is +11.6 and +10.8 ETDRS letters, and +10.1 and 10.3 ETDRS letters for aflibercept patients, Yosemite and Rhine, respectively. The effect of faricimab on diabetic macular edema has been investigated in terms of anatomical changes in central retinal thickness and fluid accumulation. Improvements in CST were significantly greater in faricimab-treated patients than in aflibercept-treated patients after 12 months of treatment. In Yosemite, mean CRT reductions from baseline −196·5 μm (−204·7 to −188·4) in the faricimab PTI and −170.3 μm (−178.5 to −162·2) in the aflibercept groups, and in Rhine, mean CST reductions from baseline −187·6 μm (−195·8 to −179·5) in the faricimab and −170·1 μm (−178·3 to −161·8) in the aflibercept groups. In the PTI Faricimab arm 52.8% in Yosemite and 51% in Rhine achieved 16-week dosing at year 1 year.[7]

Clinical Studies with Faricimab in Macular Edema with Branch and Central Retinal Vascular Occlusion

BALATON and COMINO are randomized, double-blind studies that evaluate the efficacy, safety, and pharmacokinetics of faricimab compared to aflibercept in patients with macular edema secondary to retinal vein occlusion. The Balaton and Comino trials represent significant Phase III clinical studies specifically designed to assess the impact of faricimab on macular edema associated with branch retinal vascular disease. For the first 20 weeks, the patients were randomly assigned 1:1 to receive six monthly injections of either faricimab or aflibercept. From weeks 24 to 72, all patients received faricimab up to every 16 weeks according to a personalized treatment interval dosing based on treat and extend regimen.[8]

The BALATON study was conducted on patients with branch retinal vein occlusion, whereas the COMINO study was conducted on patients with central retinal or hemiretinal vein occlusion. The primary endpoint of each study was the change in best-corrected visual acuity (BCVA) from baseline to 24 weeks. Both studies met the primary end points. Faricimab showed non-inferior visual acuity gains compared to aflibercept. The mean vision gains from baseline in the BALATON were +16.9 EDTRS letters in the faricimab arm, and +17.5, letters in the aflibercept arm at 24 weeks. In the COMINO trial, vision gains were +16.9 letters in, faricimab arm and +17.3 letters in the aflibercept arm at 24 weeks. CST improvements were similar across studies. In the BALATON trial, the improvements were −311.4 μm in the faricimab arm and −304.4 μm in the aflibercept arm. In the COMINO trial, the improvements were −461.6 μm for faricimab and −448.8 μm for the aflibercept arm.

CONCLUSION

In the field of ophthalmology, the exploration of faricimab has unfolded as a narrative of its transformative potential, offering a multifaceted solution to various ocular disorders. The distinctive mechanism of dual inhibition by faricimab, which targets both angiopoietin-2 and vascular endothelial growth factor, represents a paradigm shift in ophthalmic therapeutics. This innovative approach addresses the complexity of angiogenesis and vascular regulation, offering a comprehensive solution for the pathological processes in various ocular disorders. Considering age-related macular degeneration, diabetic macular edema, or macular edema secondary to retinal vein occlusion, faricimab consistently demonstrates its potential to improve visual outcomes, stabilize retinal morphology, and potentially reduce the treatment burden through extended dosing intervals. Intravitreal faricimab minimally improved vision even in eyes with treatment-resistant neovascular AMD. In addition, longer dosing intervals have advantages over ranibizumab or aflibercept.[9] Regarding toxicity, intraocular events are

present; however, there seem to be fewer instances of serious inflammatory events observed with the use of faricimab when compared to the toxicities associated with brolucizumab.[10] Faricimab's adaptability caters to the nuances of individual patient profiles, optimizes therapeutic interventions, and potentially enhances patient compliance. Beyond controlled trials, real-world evidence studies and long-term follow-up investigations will provide valuable insights into the practical applicability of faricimab.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

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Review

TRANSLATIONAL&PRACTICAL MEDICINE

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Type 2 diabetes mellitus: current diagnosis and treatment

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ABSTRACT

Type 2 diabetes mellitus is a globally prevalent chronic disease caused by obesity, a sedentary lifestyle, hereditary and environmental factors, and multifactorial causes. The prevalence of diabetes has increased worldwide, and its complications cause high morbidity and mortality. With the increase in diabetes and its complications, treatment costs are also increasing. Early diagnosis of type 2 diabetes, timely initiation of treatment, and prevention of complications are crucial. Management of type 2 DM is multifaceted and includes lifestyle changes, pharmacotherapy, and close monitoring of blood glucose levels. In obese individuals, weight loss has been shown to improve glycemic control and reduce the risk of complications. Pharmacologic treatment is tailored to individual needs and may include oral antidiabetic agents, injectable drugs such as insulin, and newer classes of drugs that target specific pathways involved in glucose regulation. Glycemic control is of paramount importance to reduce the risk of microvascular and macrovascular complications associated with T2DM. In conclusion, the diagnosis and treatment of type 2 diabetes require an integrated approach focusing on lifestyle changes, regular follow-up, and personalized pharmacotherapy. Implementing early interventions and maintaining optimal glycemic control are vital to preventing complications and improving the overall condition of individuals with type 2 DM.

Keywords: Type 2 diabetes mellitus, diagnosis, treatment

INTRODUCTION

The prevalence of obesity and the associated prevalence of type 2 diabetes mellitus (type 2 DM) are increasing worldwide. Type 2 DM and obesity are independent risk factors for cardiovascular diseases. Hypertension, dyslipidemia, atherosclerotic heart disease (ASHD), musculoarticular problems, chronic kidney disease (CKD), and peripheral arterial disease are more common in diabetics and obese people. Therefore, diabetes creates a serious financial and moral burden both with its treatment and with the treatment of the complications it brings. Up to 80% of people with type 2 diabetes are obese. When people with a body mass index (BMI) >35 kg/m² were compared with those with a BMI <22 kg/m², the incidence of diabetes was found to increase 80-fold over a 10-year period. In other words, the risk of developing diabetes increases as BMI increases. This shows that in order to achieve lasting success in type 2 DM patients, almost all of whom are obese, perhaps one of the most important goals, besides blood glucose regulation, should be to bring patients to their ideal weight. Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia that develops as a result of peripheral resistance to insulin action, insufficient secretion of insulin, or both. The main clinical symptom of diabetes is hyperglycemia. However, DM is also associated with insulin deficiency and/or insulin resistance, abnormalities in lipid and protein metabolism, and mineral and electrolyte disorders. The International Diabetes Federation (IDF) estimates that the number of type 1 and type 2 diabetic patients worldwide was 463 million in 2019, and this number is estimated to reach 700 million in 2045. The number of type 1 DM patients aged 0-19 years worldwide in 2019 was 1.110.100, and the annual number of new cases was 128.900. In the 2010 TURDEP-II study, the prevalence of DM in Turkey was found to be 13.4%. According to the 2018 Health Statistics Yearbook of the Republic of Turkey Ministry of Health, the prevalence of DM in individuals aged 20-79 years in Turkey was calculated at 12.1%. According to IDF 2019 data, the prevalence of diabetes worldwide is 9.3%.[1-7]

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SYMPTOMS

Diabetes often develops slowly and may not be recognized in its early stages. Common symptoms of diabetes include polyuria, polydipsia, polyphagia, loss of appetite, weakness, fatigue, dry mouth, and frequent nighttime urination (nocturia). Rare symptoms include blurred vision, unexplained rapid weight loss, persistent infections, sores, recurrent infections, numbness, tingling (peripheral neuropathy), and itching. Diabetes can be mildly symptomatic or asymptomatic in its early stages. For this reason, especially at-risk individuals should have regular health checks and examinations for early diagnosis and treatment.[1-3,8-10]

PREDIABETES

Prediabetes refers to a condition prior to the development of diabetes in which blood glucose is higher than normal but does not reach the diagnostic limits for type 2 diabetes. Prediabetes is defined as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and HbA1c in the range of 5.7-6.4%. It is characterized by increased risk for diabetes and its complications and is characterized by metabolic disorders such as dyslipidemia, physical inactivity, hypertension, obesity, insulin resistance, procoagulant status, oxidative stress, and chronic inflammation. Increased insulin resistance and impaired β-cell function are the most important pathological mechanisms leading to prediabetes and subsequent diabetes. The progression of prediabetes to diabetes can be halted and normoglycemia restored, leading to a reduction in both macrovascular and microvascular complications. Lifestyle changes, a healthy diet, regular physical activity, and weight management play an important role in the prevention and management of prediabetes progression to diabetes. In prediabetes patients with increased insulin resistance, metformin and pioglitazone, which increase insulin sensitivity, may be preferred in medical treatment.[1-3,8,11-14]

DIAGNOSIS OF TYPE 2 DM

The diagnosis of DM is based on plasma glucose (fasting and postprandial) levels, a 75-gram oral glucose tolerance test (OGTT), and HbA1c. If there are no severe symptoms of diabetes, the diagnosis should be confirmed at a later date, preferably with the same method. Impaired fasting glucose (IFG) is defined as fasting plasma glucose (FPG) between 100-125 mg/dl, and impaired glucose intolerance (IGT) is defined as 2nd-hour plasma glucose between 140-199 mg/dl after the oral glucose tolerance test (OGTT). DM is diagnosed if FPG is ≥126 mg/dl, 2nd hour glucose on OGTT is ≥200 mg/dl, or plasma glucose value in randomly drawn blood is ≥200 mg/dl with polyuria, polydipsia, ketonuria, and weight loss.[1-3,12,15-20]

TREATMENT OF TYPE 2 DIABETES

In the treatment of diabetes, where treatment options were limited in the past few years, the options are gradually increasing with the new drugs that are released every day. The treatment of type 2 diabetes should not only be aimed at lowering blood sugar levels; the development of complications should be prevented, and treatment plans should be made for obese diabetics to return to their ideal weight. The patient should be evaluated comprehensively, and treatment should be planned individually. Microvascular complications decrease with lowering HbA1c; however, strict glycemic control has not been proven to prevent macrovascular disease.[1-3,17-19,21]

All patients diagnosed with type 2 diabetes and prediabetes should be counseled about lifestyle changes, including diet and exercise. Many drug options are

Table 1. Antidiabetic drugs

Insulin secretagogues Sulfonylureas Meglitinides
Drugs that increase insulin sensitivity Biguanides Thiazolidinedione derivatives
Alpha glucosidase inhibitors
Sodium glucose co-transporter-2 inhibitors (SGLT2-i)
Insulinomimetic drugs Amylin analogues (pramlintide) Incretin-based treatments [dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon-like peptide 1 (GLP1) analogues]
Insulins Short-acting Intermediate-acting Long-acting Mix insulins

available (Table 1). Metformin is the first choice, unless there is a contraindication. In cases where metformin treatment is not sufficient, a second drug should be selected according to the patient's characteristics. In young patients without comorbidities and complications, the HbA1c target is <7% (or even <6.5%), whereas in elderly patients with multiple comorbidities and limited life expectancy, higher values can be targeted with an HbA1c of 8-8.5%. In elderly patients with a life expectancy of more than 15 years with no comorbidities, the HbA1c target can be set at <7%. In many patients, pharmacologic treatment is initiated if HbA1c >7.5-8% at diagnosis. In patients with HbA1c <7.5%, lifestyle modification can be tried for 3-6 months if the patient is motivated. If HbA1c <8.5%, monotherapy is initiated. Sodium glucose co-transporter-2 (SGLT-2) inhibitors should be considered for patients with cardiovascular risk. If HbA1c is 8.5-10%, double combination is started; if not sufficient, triple combination is planned. Basal or mixed insulin or GLP1 analogs may also be added, and insulin and incretin-based therapies may be an option from the beginning, depending on the patient's characteristics. In patients with high BMI, SGLT-2 inhibitors and GLP1 analogs should be planned to be added to the treatment from the beginning, unless there is a contraindication. If HbA1c is >10%, insulin and/or GLP1 analogs are added to oral therapy.[1-3,16,17,19,21-26]

INSULIN SECRETAGOGUES

Sulfonylureas

They bind to SUR1 receptors in pancreatic beta cells. They increase insulin release from beta cells by inhibiting ATP-dependent potassium channels of the receptor. Beta-cell function is required for them to be effective. These drugs are not effective if C-peptide is severely low in patients who have been followed up for a long time with a diagnosis of diabetes. Today, 2nd-generation sulfonylureas are used. Glibenclamide, Glipizide, Gliclazide, and Glimepiride are commonly used sulfonylureas. Their advantages are that they lower HbA1c by 1-2%, and they are potent and cheap drugs. In the treatment of type 2 diabetes, sulfonylureas can be combined with other oral antidiabetics and insulins; however, they are not given together because they have the same mechanism of action as the meglitinide group. Concomitant use is not recommended when switching to intensified insulin therapy due to the high risk of hypoglycemia. They are effective in patients with maturity-onset diabetes of the young (MODY). The most important side effects are hypoglycemia and weight gain. Patients with irregular diets should be educated about hypoglycemia. They may cause cross-reactions in patients with sulfonamide allergies. They may cause nausea, elevated liver enzymes, and hematologic side effects. They bind tightly to albumin in the circulation and interact with warfarin, sulfonamides, fibrates, and acetaminophen. They may accelerate beta cell loss, and patients' transition time to insulin may be shortened.[1-5,16,21,22,27]

Meglitinides

They bind to a different site of the SUR1 receptor and act through short-term inhibition. They are especially used to lower postprandial blood glucose. They are pharmacologically different from sulfonylureas and can be used in patients with sulfonamide allergies. Meglitinides have a faster onset of action and a shorter duration of action compared to sulfonylureas. Their rapid and short-acting nature allows flexibility in dosing, and the risk of hypoglycemia is lower than with sulfonylureas. Two drugs are available, repaglinide and nateglinide. They are used three times a day, before each meal. Since repaglinide is metabolized by the liver, it can be used in renal failure. It can be given in low doses to patients with a GFR of 20-40 ml/min. It should not be used in patients with a GFR <20 ml/min. Nateglinide undergoes hepatic metabolization, and its renal metabolites are also active. Therefore, caution should be exercised in both renal and hepatic impairment. They cause less hypoglycemia than sulfonylureas and have similar weight-gain effects. Since they bind to the same receptors, concomitant use with sulfonylureas is not recommended.[1-5,16,18,28]

INSULIN SENSITIZERS

Biguanides (Metformin)

Biguanides are widely used in the treatment of type 2 DM. The most widely used first-line treatment is metformin. Biguanides decrease glucose production by the liver, increase glucose sensitivity in cells, and decrease glucose absorption from the intestine. Metformin can be used fast, with or without food; the daily dose is 500-2550 mg (2-3 times a day); the daily dose of metformin in extended-release form is 500-2000 mg (1-2 times a day). It inhibits glucose output from the liver by suppressing gluconeogenesis. The conversion of lactate to pyruvate is also reduced. Metformin also suppresses hepatic gluconeogenesis and lipogenesis by increasing the activation of the AMP protein kinase enzyme. Due to its side effects on the gastrointestinal system and by increasing GLP1 to some extent, it decreases appetite and causes moderate weight loss (0-6 kg). It has cardiovascular protective properties (decrease in total cholesterol, LDL, and VLDL; neutral or increase in HDL; decreases oxidative stress; lowers blood pressure; decreases platelet aggregation). They do not cause hypoglycemia and have their most important

side effects on the gastrointestinal system. Metallic taste in the mouth, loss of appetite, nausea, vomiting, burning in the stomach, bloating, soft stools, and diarrhea occur. Gastrointestinal side effects are less frequent and milder when starting with 500 mg and gradually increasing the dose. A vitamin B12 deficiency may develop. Lactic acidosis may occur, especially in patients with impaired peripheral circulation, heart failure, and severely impaired renal function (9/100.000). Metformin should not be used in shock, hypoxia, COPD, acute decompensated heart failure, and severe renal failure. It should not be started if GFR <45 ml/min; it should be discontinued if GFR <30 ml/min. Contraindications include liver failure, chronic alcoholism, peripheral arterial disease, pregnancy and lactation, major surgical intervention, and advanced age (over 80). It is recommended to discontinue 24 hours before contrast-enhanced procedures (such as angiography, etc.) and restart 24 hours later if creatinine measurement is normal. Can be combined with other diabetes medications and insulins. It does not cause weight gain, hypoglycemia and is inexpensive. It should be continued as long as there are no contraindications.[1-5,16,18,21,29-31]

Thiazolidinedione Derivatives (Pioglitazone)

Glitazones act by increasing insulin sensitivity and decreasing insulin resistance. They decrease glucose production in the liver and increase peripheral insulin sensitivity. It activates peroxisome proliferator-activated receptor (PPAR) gamma. Activation of PPAR-γ increases insulin sensitivity in adipose tissue, skeletal muscle, and the liver. The most commonly used form of glitazone is pioglitazone. The starting dose of pioglitazone is 15-30 mg; the maximum dose is 45 mg, once daily. If edema does not develop for 1-3 months at a low dose and the glycemic response is inadequate, the dose is increased. It has a high effect on reducing HbA1c (0.5-1.4% decrease in HbA1c). It is metabolized in the lung and excreted with bile. They do not cause hypoglycemia, are generally well tolerated, increase HDL levels, decrease triglycerides, reduce secondary cardiovascular events, and lower blood pressure. They reduce insulin resistance by acting primarily on adipose tissue. Benefits have been shown in non-alcoholic fatty liver disease, first choice. They may prevent the progression to diabetes in prediabetics. Glitazones as a group have been shown to significantly reduce the risk of type 2 diabetes, even more so than with metformin. However, despite these findings, the use of glitazones in prediabetic patients is not recommended because the potential side effects such as fluid retention, weight gain, exacerbation of heart failure, osteoporotic fractures, and bladder cancer are greater than the benefits obtained, and the cost of use is quite high. It should not be used in the presence of congestive heart failure (CHF), as it increases sodium reabsorption and associated water retention. The risk of edema is higher in insulin users, women, obese patients, patients with pre-existing edema, and patients with congestive heart failure. Salt restriction is applied, and diuretics are used if necessary. CHF and anasarca edema leading to hospitalization may rarely be seen; they may also cause anemia, weight gain, an increase in liver enzymes, and worsen Graves' ophthalmopathy. May increase the risk of fractures in postmenopausal women and older men and increase respiratory infections. It should not be given to patients with bladder cancer or unexplained hematuria. It is also contraindicated in patients with elevated ALT (if 2.5 times the upper limit of normal), CHF class I-IV according to the New York Heart Association classification, chronic severe renal failure, pregnancy, type 1 DM, risk of macular edema, adolescents, and children.[1-5,7,14,16,21,32]

ALPHA GLUCOSIDASE INHIBITORS

Alpha-glucosidase inhibitors work by slowing down the digestion and absorption of carbohydrates in the small intestine, thus reducing the rise in blood glucose levels after meals. Acarbose is the only agent available in our country, available in 50-100 mg tablets (dosage 50 or 100 mg tablets 3 times a day). The tablets are swallowed with some liquid before a meal or chewed with the first bites during a meal. They inhibit carbohydrate absorption by blocking the breakdown of polysaccharides into monosaccharides in the intestine. Metabolized by intestinal flora, absorption is minimal, and metabolites are inactive. They are weakly effective, reducing HbA1c by 0.5-1.3%. They can provide glycemic control without weight gain, do not cause hypoglycemia, and may prevent the progression to diabetes in prediabetics. Side effects may include bloating, diarrhea, abdominal pain (10-25%) and rarely iron deficiency. Although they do not cause hypoglycemia in monotherapy, they may cause hypoglycemia when used in combination with sulfonylurea, glinide, or insulin. Hepatotoxicity may be seen rarely. The main contraindications include inflammatory bowel disease, chronic ulceration, malabsorption, partial intestinal obstruction, cirrhosis, pregnancy, and lactation.[1-5,33,34]

SODIUM GLUCOSE CO-TRANSPORTER-2 (SGLT-2) INHIBITORS

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are new-generation oral antidiabetic drugs that have been in use in the treatment of diabetes for the last few years. In Turkey, dapagliflozin, empagliflozin, and the combination of empagliflozin and metformin are available. They have a very important place in

diabetes treatment as they can be combined with all oral antidiabetics, insulins, and GLP1 analogs, and they cause weight loss and hypoglycemia in type 2 DM patients, most of whom are obese. These drugs, called glucoretics or gliflozins, reduce glucose reabsorption in the renal proximal tubules by 30-50% and lower blood glucose levels independently of insulin-mediated mechanisms. In diabetic patients, the reabsorption threshold of the kidney is increased, and renal glucose absorption capacity is increased. This new group of drugs increases glucosuria by inhibiting SGLT-2. Since they act independently of insulin, they can be used in all stages of diabetes. They provide moderate weight loss and, in combination with GLP1 analogs, are the first choice in patients in whom weight loss is desired, unless contraindicated. They have a low risk of hypoglycemia, reduce blood pressure by 2-4 mmHg, and reduce uric acid levels and albuminuria. They reduce cardiovascular mortality, are nephroprotective, and reduce hospitalization for heart failure; therefore, interest in these drugs has increased, and they have started to be used by cardiologists and nephrologists. Phase studies are ongoing in type 1 diabetes but have not yet been approved. They should not be used in ketosis-prone patients because they increase the frequency of ketosis. Side effects include genitourinary infections, fluid loss, dehydration, dizziness, and hypotension. Female patients are more at risk for genitourinary infections. Care should be taken in terms of urosepsis and pyelonephritis. It may cause mild dehydration, and caution should be exercised when used with drugs that may trigger acute kidney injury (such as nonsteroidal anti-inflammatory drugs, ACE inhibitors, angiotensin II receptor blockers, and diuretics). In elderly patients, caution should be exercised in terms of hypotension, dizziness, and falls due to fluid loss, and patients should be informed. If the risk is thought to be high, it should not be given. They increase serum creatinine to some extent; this increase is temporary and may cause a minimal increase in LDL. Euglycemic ketoacidosis may develop; ketones should be checked if nausea and vomiting occur. It should not be started if the GFR is <20 ml/min.[1-5,16,21,22,35,36]

INSULINOMIMETICS DRUGS

Amylin Analogues

Pramlintide is a synthetic analog of amylin. It is used by subcutaneous injection three times a day. It slows gastric emptying, decreases glucagon secretion, and causes weight loss, yet this drug is not available in our country.[1-3]

Incretin Effective Drugs

DPP4 inhibitors: Inhibition of the DPP-4 enzyme, which enables rapid degradation of the GLP-1 molecule in the postprandial period, is a new group of antidiabetic drugs that increases the levels of GLP-1 and GIP, which are endogenous and natural incretins. DPP4 inhibitors, also known as gliptins, increase insulin secretion in a glucose-dependent manner. Sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin are drugs in this group. They decrease glucagon secretion. They are weight-neutral and have no gastrointestinal side effects. Treatment costs are high. They reduce HbA1c by 0.6-1.1%. They can be used in combination with other oral antidiabetics, such as insulin, and may contribute to a reduction in insulin requirement, which indirectly helps the patient lose weight. They can be used in combination with metformin in elderly patients, as the risk of hypoglycemia is higher in the sulfonylurea combination. They have good tolerability, do not cause hypoglycemia, and improve islet cell function by increasing pancreatic alpha and beta cell function. They do not increase the risk of cardiovascular disease. There are data on saxagliptin and alogliptin alone that increase hospitalization for heart failure. The most important side effects are headache, nasopharyngitis, upper respiratory tract infection, gastrointestinal side effects (acute pancreatitis), urinary tract infections, hepatic dysfunction, inflammatory bowel diseases, skin reactions, arthralgia, and myalgia. Linagliptin is eliminated from the enterohepatic system and can be used in chronic renal failure without dose modification. In others, the dose is halved when GFR is <45 ml/min and 75% dose reduction when GFR is <30 ml/min.[1-5,16,21,37]

GLP1 receptor analogues: GLP-1, a member of the family of incretin hormones, is a molecule produced from the intestine that increases insulin secretion from the pancreas in a glucose-dependent manner. This group of drugs, which are GLP-1 receptor agonists, also suppresses glucagon synthesis from alpha cells in the pancreas, slows gastric emptying, and increases the feeling of satiety. Since they act glucose-mediatedly, their hypoglycemia effect is low, and they reduce HbA1c by 0.5-2.5%. Exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide, and tirzepatide are drugs in this group. In addition to the treatment of diabetes mellitus, their use is especially prominent in the treatment of obesity. Favorable effects have been shown in patients at high risk of cardiovascular disease and in patients with nonalcoholic steatohepatitis. Short-acting GLP-1 RAs such as exenatide are more effective on postprandial glucose, allow blood glucose regulation at lower insulin doses, and reduce the weight gain effect of insulin treatment. Liraglutide and semaglutide are used to treat obesity in patients without DM. Relatively longer-acting drugs administered once daily or once weekly have a stronger effect (liraglutide, exenatide XR, dulaglutide, and semaglutide). They are not preferred as

initial treatment because of their high cost, and the fact that they are administered as injections limits their use.

Short-acting exenatide is administered subcutaneously twice a day: liraglutide lixisenatide once a day; albiglutide; dulaglutide; exenatide XR; and semaglutide once a week. In type 2 DM patients with obesity, the use of GLP1 RA in combination with insulin is effective in both sugar regulation and weight loss. Gastrointestinal side effects such as nausea and vomiting are less common when starting with a low dose of the drug, slowly increasing the dose, and achieving tolerance. Cases of pancreatitis and gallstones have been reported with GLP1A drugs, and this group of drugs has been monitored in this respect. If acute pancreatitis is suspected, the drug should be discontinued immediately. It should also be used with caution in patients with a history of gallstones. C-cell hyperplasia in the thyroid has been reported with liraglutide, and further investigation is recommended in the presence of suspected thyroid medullary carcinoma. Worsening of diabetic retinopathy has been reported with semaglutide, and caution is advised in this respect. Exenatide dose reduction is required if eGFR is <30 ml/min/1.73 m^2, while dose reduction is not required for other drugs in this group. Liraglutide has been shown to be useful in diabetic nephropathy. Since GLP1A and dipeptidyl peptidase-4 (DPP4) inhibitors act through the same mechanism, their combined use is not recommended.[1-5,21,24,38-41]

Table 2. GLP1A, half-lives, dosage

	GLP-1RA	Method of Use
Short impact	Exenatide	5-10 mcq / 2 times a day
	Lixisenatide	10-20 µg / once a day
	Liraglutide	0.6-1.8 µg / 1 time a day
Long impact	Dulaglutide	0.75-1.5 µg / once a week
	Semaglutide	0.5-1 mg / once a week
	Exenatide-LAR	2 mg / once a week
	Albiglutide	30-50 µg / once a week

INSULINS

Insulin was discovered in 1921 by Benting and colleagues after long studies. Insulin, which is considered a life-saving treatment, especially in patients with type 1 DM, improves the quality of life in all patients with diabetes. Animal (dog, pig) pancreases were used in the first studies on obtaining insulin. Subsequent and ongoing studies have aimed to increase the effects of insulin, make it more effective for longer periods of time, and use it at the most ideal and stable doses without hypoglycemia. These developments are also factors affecting costs and transportation. Insulin treatment decreases patient compliance due to the difficulties and laboriousness of administration. For this reason, treatment should be planned taking into account the patient's compliance with treatment, and the choice of treatment should be based on the patient's age, comorbidities, presence of diabetic complications, risk of hypoglycemia, work, and daily routine. Insulin therapy is applied to patients with insulin deficiency or who require insulin support.

Indications for insulin therapy; patients with type 1 diabetes mellitus, patients with type 2 diabetes mellitus (HbA1c above 10), pregnancy and lactation, emergency hyperglycemic conditions (diabetic ketoacidosis and hyperglycemic hyperosmolar state) who cannot achieve sugar regulation with non-insulin anti-hyperglycemic therapy, the presence of severe hyperglycemic symptoms, acute coronary syndrome, allergy to non-insulin agents, severe hepatic-renal failure, major surgical operations, acute febrile and systemic disease.

Human insulin and insulin analogs developed by recombinant DNA techniques are used in treatment. Insulin is usually administered subcutaneously.

Insulins are grouped as very fast acting, fast acting, short acting, intermediate acting, long acting, and very long acting. Their onset of action and duration of action are important in the organization of treatment. Prandial (short-, fast-, and very fast-acting) and basal insulin (intermediate-, long-, and very long-acting) use

Table 3. Commonly used insulins

Insulin type	Impact Initiation	Peak time	Duration of impact
Lispro, Aspart, Glulisin	3-15 min	45-75 min	2-4 hours
Regular	30 min	2-4 hours	5-8 hours
NPH	2 hours	4-12 hours	8-18 hours
NPA/Asp 70/30	6-12 min	1-4 hours	18-24 hours
Insulin glarjin	2 hours	Peakless	24 hours
Insulin detemir	2 hours	3-9 hours	6-24 hours*
Insulin glarjin U300	2 hours	Peakless	<36 hours
Insulin degludek	2 hours	Peakless	>40 hours
Insulin deg/Asp 70/30	14-72 min	2-3 hours	>24 hours

suppresses gluconeogenesis and ketogenesis and corrects hyperglycemia. In addition to long-acting insulins, long-acting concentrated insulins have been developed for use in patients who are regulated with high doses of insulin. Fast-short-acting insulins can be used intramuscularly (i.m.) and intravenously (i.v.), but i.m. and i.v. use of medium-long-acting insulins is contraindicated. The types of insulins and their modes of action are given in Table 3.

Insulin is usually administered subcutaneously, and the rate of absorption is affected by ambient temperature (faster in heat, slower in cold) and injection site (from fast to slow; abdomen, arm, thigh, buttock). During insulin therapy, complications such as hypoglycemia, an increase in body weight, edema, immunogenicity (the development of antibodies against insulin preparations), lipohypertrophy and atrophy at the injection site, bleeding, oozing, and pain may occur. In patients with type 2 diabetes, if adequate blood glucose regulation cannot be achieved with oral anti-diabetic therapy, basal insulin (0.1-0.2 U/kg) or NPH is added once daily. Basal insulins are preferred over NPH because they are longer-acting and cause less hypoglycemia. When basal insulin is not sufficient, twice-daily mixed insulin or basal-bolus therapy may be administered. Ready-made combinations of basal insulin and GLP1 analogs are also a form of treatment administered once daily, with dose titration based on basal insulin dose and fasting blood glucose. Basal-bolus (multiple dose) treatment is administered to patients with type 1 diabetes, pregnant patients who cannot be regulated despite diet, and patients with type 2 diabetes who cannot be adequately regulated with other treatments. Fast-short-acting insulin (bolus) is administered 3 times a day before meals and medium-long-acting insulin (basal) 1-2 times a day. The physical activity, body mass index, presence of diabetic complications, and previous insulin use determine the insulin requirement. A maintenance dose of 0.4-1.0 IU/kg/day is required in type 1 diabetics and 0.3-1.2 IU/kg/day in type 2 diabetics. In basal-bolus insulin treatments, approximately half of the total daily insulin requirement is basal, and the remaining half is bolus. Fast-acting insulins can be used 5 minutes before a meal, short-acting insulins 15 minutes before a meal, and very fast-acting insulins with a meal.[1-5,42-44]

CONCLUSION

The prevalence of obesity and type 2 DM is increasing. Treatment is individualized; an appropriate treatment approach should be chosen for each patient, and weight reduction treatment should be prioritized in obese patients.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

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Review

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Pneumonies

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ABSTARCT

Pneumonia is an inflammation of the alveolar space distal to the terminal bronchiole in the lung parenchyma. The inflammation seen in pneumonia is mostly caused by microorganisms such as viruses, bacteria, and fungi, but can also be caused by non-infectious causes (toxic substance inhalation, radiation damage, hypersensitivity reaction-pneumonitis, autoimmunity). Pneumonia can be observed in three forms: community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP). Patients with pneumonia usually present with cough, fever, sputum, chest pain, dyspnea, and hemoptysis. In addition, patients may have nonspecific symptoms. CAPs are caused by typical (*Streptococcus pneumoniae*) and atypical (*Chlamydia pneumoniae, Mycoplasma pneumoniae,* and *Legonella pneumoniae*) agents. On presentation, fever, pulse rate, respiratory rate, oxygen saturation, blood pressure, and auscultation should be performed. Typical chest radiographic findings in the diagnosis of CAP include lobar consolidations, interstitial infiltrates, and/or cavitations. Acute-phase reactants may be elevated in response to infection and inflammation in pneumonia. The first decision to be made in cases of pneumonia is the determination of the need for hospitalization and the choice of antibiotherapy. If possible, cultures should be taken before antibiotics are started on the patient for whom hospitalization is planned. After 72 hours, in patients with no symptom improvement, the reason for treatment non-response should be evaluated, and antibiotherapy should be changed if necessary.

Keywords: Antibiotherapy, community-acquired pneumonia Pneumonia, hospital-acquired pneumonia

INTRODUCTION

Pneumonia is an inflammation of the alveolar space distal to the terminal bronchiole in the lung parenchyma. The inflammation seen in pneumonia is mostly caused by microorganisms such as viruses, bacteria, and fungi, but can also be caused by non-infectious causes (toxic substance inhalation, radiation damage, hypersensitivity reaction-pneumonitis, autoimmunity). Leukocytes and fibrinous exudate getting into the alveolar space can make it hard for the lungs to work, which could mean they need invasive mechanical ventilation and intensive care.[1]

Pneumonia can be observed in three forms: community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP).[2,3]

Community Acquired Pneumonia

Pneumonia caused by community-acquired pathogens in people without a diagnosis of immunodeficiency is considered community-acquired pneumonia.

Hospital-Acquired Pneumonia

It is defined as pneumonia that develops within 48 hours before hospitalization and within the first 48 hours after discharge of the patient who was not in the picture of pneumonia.

Ventilator Associated Pneumonia it is defined as pneumonia that develops 48 hours after intubation in a patient under invasive mechanical ventilation support without pneumonia before intubation.

COMMUNITY-ACQUIRED PNEUMONIA

Pneumonia caused by community-acquired pathogens in individuals without a diagnosis of immunodeficiency is defined as community-acquired pneumonia (CAP).[4] Community-acquired pneumonia (CAP) is responsible for a significant portion of mortality and morbidity worldwide.[5] Newly developing infiltrations on chest radiography, together with appropriate clinical and laboratory findings, are the gold standard for diagnosis.[6] The clinic is characterized by the acute onset of fever,

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cough (with or without sputum), and dyspnea. In some cases, pleuritic chest pain may also accompany. Less common symptoms include gastrointestinal complaints (nausea, vomiting, diarrhea, and abdominal pain) and loss of appetite. In older patients, fever may be absent or mental status changes may be the only presenting symptom.[7] Identification of the responsible microorganism is important for treatment, but since it is often not possible to identify the causative agent, it is necessary to start empirical treatment as soon as possible by correctly estimating the possible agents. For this reason, it is important to evaluate the patient's clinical picture, lung radiographic findings, the patient's risk factors, and, if possible, the results of sputum gram staining. Table 1 shows the risk factors associated with specific pathogens in CAP.[8]

Table 1. Risk factors associated with specific pathogens in community-acquired pneumonia

Alcoholism	*Streptococcus pneumoniae,* Oral anaerobes, *Klebsiella pneumoniae, Acinetobacter* species, *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae, Pseudomonas aeruginosa, Legionella* species, *S. pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae*
Aspiration	Gram-negative enteric oral anaerobes pathogens, oral anaerobes
Lung abscess	MRSA, oral anaerobes, endemic fungal pneumonia, *M. tuberculosis*, atypical mycobacteria
Exposure to bat or bird droppings	*Histoplasma capsulatum*
Feeding birds	*Chlamydia psittaci*
Feeding rabbits	*Francisella tularensis*
Keeping farm animals or cats	*Coxiella burnetti* (Q fever)
HIV infection (early)	*S. pneumoniae, H. influenzae, M. tuberculosis*
HIV infection (late)	Pathogens listed for early infection *Pneumocystis jirovecii, Cryptococcus, Histoplasma, Aspergillus,* Atypical mycobacteria (especially *Mycobacterium kansasii*), *P. aeruginosa, H. Influenzae*
Hotel or air-conditioned accommodation	Legionella species
Structural lung disease (e.g. bronchiectasis)	*P. aeruginosa, Burkholderia cepacia, S. aureus*
Injection drug use	*S. aureus,* Anaerobes, *M. tuberculosis, S. pneumoniae*
Endobronchial obstruction	Anaerobes, *S. pneumoniae, H. |influenzae, S. aureus*

Risk Factors

Advanced age, the presence of comorbid diseases, malnutrition, immunosuppressive conditions, the presence of cognitive disease, and smoking all increase the risk of developing pneumonia. The most common comorbidities are COPD, hypertension, cerebrovascular diseases, heart failure, and malignancies.[9]

Clinic

Patients with pneumonia usually present with cough, fever, sputum, chest pain, dyspnea, and hemoptysis. In addition, patients may have nonspecific symptoms (nausea and vomiting, sore throat, myalgia, headache, etc.). CAPs are caused by typical (*Streptococcus pneumoniae*) and atypical (*Chlamydia pneumoniae, Mycoplasma pneumoniae,* and *Legonella pneumoniae*) agents. These agents have different clinical manifestations. In typical pneumonia, acute onset, fever, cough, chest pain (pleuritic), lobar infiltrations on chest radiography, and leukocytosis-neutrophilia in the complete blood count are present. In atypical pneumonias, subsegmental infiltrations, scattered patchy infiltrations, reticular opacities, and a normal leukocyte value in the complete blood count are observed on chest radiography, with nonspecific findings including subacute onset, subfebrile fever, myalgia, and headache.[4,6,9]

Physical Examination

On presentation, fever, pulse rate, respiratory rate, oxygen saturation, blood pressure, and auscultation should be performed. Pneumonia may present with tachycardia, tachypnea, and hypoxemia on physical examination.

Auscultation findings vary according to stage and extent.

*Thin rales (crepitant rales) at the end of inspiration in the exudation phase,

*Bronchial respiration during the consolidation phase (tuber sufl),

*In the resolution phase, fine rales are heard again.[10]

Radiology

Two-way chest radiography should be performed in patients with a suspected diagnosis of pneumonia, unless there is an obstacle. Posteroanterior and lateral chest radiographs are sufficient for diagnosis in most patients with suspected CAP. Imaging is a necessity for hospitalized patients.[7] Typical chest radiographic findings in the diagnosis of CAP include lobar consolidations, interstitial infiltrates, and/or cavitations. Findings on x-rays can help doctors figure out what caused pneumonia (for example, lobar consolidations can mean an infection with common bacterial pathogens), but they can't always tell the difference between them.[11]

Chest radiography is guiding both the diagnosis and the detection of a condition mimicking pneumonia. It is not possible to make a definite etiologic diagnosis with radiologic appearance, but it may be useful in the differential diagnosis of certain diseases such as tuberculosis and cancer.[12] It is also helpful in the detection of complications of pneumonia (e.g., parapneumonic effusion, empyema, abscess) and in the evaluation of alternative or concurrent diagnoses (e.g., heart failure, malignancy).[7] Lung imaging is also useful to determine the severity of pneumonia (such as multilobar involvement). Lobar (Figure 1), segmental, bronchopneumonic, and interstitial involvement (Figure 2) can be seen on chest radiography. When chest radiography is performed within the first 4 hours in patients with suspected pneumonia, mortality is significantly reduced due to the acceleration of diagnosis and the initiation of effective treatment.[4]

After the diagnosis of pneumonia and the initiation of treatment, radiologic control varies according to the clinical status of the patient and the presence of complications. While it is sufficient to see the patient once the treatment is completed in pneumonias with response, in cases of delayed resolution (no radiologic improvement after 4-6 weeks despite clinical response), recurrent pneumonias (at least two pneumonias in a year or at least three pneumonias in a lifetime), lung radiography follow-up and thoracic computed tomography evaluation may be required in terms of complications.[12]

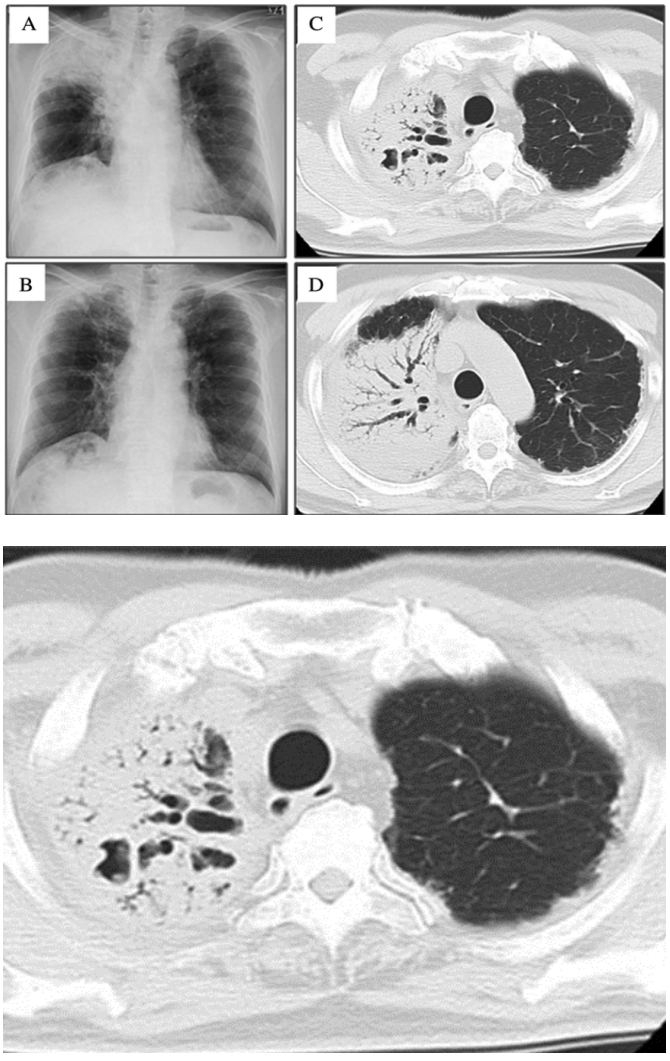

Figure 1. Lobar pneumonia, chest radiography, and lung computed tomography findings (air bronchograms)

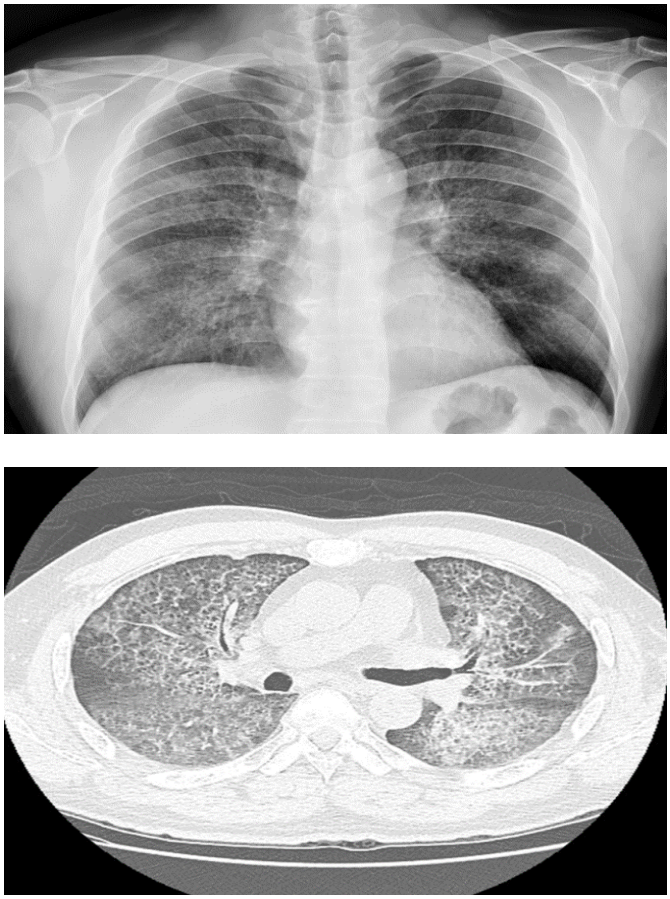

Figure 2. Chest radiography and lung computed tomography findings in interstitial pneumonia

It should be kept in mind that chest radiography may appear normal in the first 24 hours of pneumonia, in elderly patients, in the presence of neutropenia, in dehydration, and in *Pneumocystis jiroveci* pneumonia.[13]

High-resolution computed tomography (HRCT) is more sensitive than chest radiography in the detection of pneumonia.[5] It may help differentiate pneumonia complications and some pneumonia agents (e.g., invasive fungal infections, pneumocyst pneumonia, bacterial pathogens), especially in immunocompromised patients.[14] Thoracic CT imaging may be performed in patients with no improvement or deterioration in the clinic or in patients in whom other accompanying pathologies, such as tumors, are suspected.

Microbiological Investigations

Routine microbiologic examinations are not recommended for patients scheduled for outpatient follow-up. Microbiological investigations are instructive in patients who are scheduled for hospitalization and in patients with a history of colonization due to lung parenchymal injury. In patients requiring hospitalization, microbiologic investigations should be performed before antibiotherapy is started, if possible. Sputum culture samples should be evaluated together with gram staining, considering the possibility of colonization. It is recommended that blood cultures be sent separately from both arms during the febrile period.[4,10]

Microscopy of sputum and lower respiratory tract samples, blood, and sputum cultures are guiding the choice of treatment. However, it should be known that culture results are obtained in 24-48 hours under the best conditions. For this reason, it is not recommended to wait for culture results, even for patients who are sent for culture. Empirical antibiotherapy for the possible agent should be initiated at the time of diagnosis according to the clinical characteristics of the patient.[12]

In each patient, a microbiologic examination should be decided by evaluating the time and cost of proving the pathologic agent.

a. Evaluation of sputum by gram staining method; in microscopy of a quality sputum sample, the number of squamous epithelial cells seen with a small magnification objective (10x) should be less than 10, and the number of polymorphonuclear leukocytes (PNL) should be above 25. It is an important diagnostic method for the detection of the causative microorganism and the determination of antibiotic susceptibility. The sample must be obtained before antibiotic treatment is started. Sputum culture should be evaluated with gram staining.

b. Blood culture and PCR tests; rapid nasal PCR or culture tests are used in patients with risk factors for methicillin-resistant Staphylococcus aureus (MRSA).

c. In every hospitalized patient, two sets of blood cultures (one aerobic blood culture bottle + one anaerobic blood culture bottle) should be taken before antibiotic treatment is started and, if possible, during the febrile period.

d. In patients with parapneumonic pleurisy, pleural fluid cell count, biochemical examination of the fluid (pH, LDH, glucose, ADA, etc.), gram staining examination and cultures should be performed.

e. Molecular tests; viruses and bacteria are common infectious agents. Some of the bacteria causing respiratory tract infections cannot be grown in culture, and special media are needed for their growth (e.g., *Chlamydia pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae*). Since viruses cannot be diagnosed by bacteriological culture, nucleic acid tests for viruses have been developed. Urine antigen tests for *Streptococcus pneumoniae*, polymerase chain reaction [PCR] for *Legionella* spp., or alternatively, urine antigen tests, and appropriate tests for COVID-19 can be performed.

Laboratory

Acute-phase reactants may be elevated in response to infection and inflammation in pneumonia. Acute-phase reactants and biomarkers may guide the differentiation between infectious and noninfectious diseases and the prognosis. A complete blood count, serum electrolytes, and renal and liver function values have a limited contribution to the diagnosis. However, they should be considered in prognosis, hospitalization evaluation, antibiotherapy selection, and dose adjustment. Blood gas measurement is recommended in the presence of COPD, hypotension, dyspnea, tachypnea, and confusion.[15]

Routine blood tests: Hemograms and biochemical tests are usually used to help confirm the diagnosis of CAP and determine the need for hospitalization.

a. Leukocytosis: Leukocytosis and left shift are most common in CAP. Leukopenia (<4000 cells per mm^2) is less common but usually means a worse prognosis. Similarly, thrombocytopenia (platelet count <100.000 cells per mm^2) is an uncommon finding, but like leukopenia, thrombocytopenia is associated with a poor prognosis.

b. Acute elevation of creatinine and BUN also implies a poor prognosis and often indicates the need for hospitalization. Abnormal liver function tests may be elevated in sepsis, requiring intensive care.

c. Serum biomarkers C-reactive protein (CRP) and procalcitonin support clinical and radiographic evaluation in the diagnosis of pneumonia.

Management of CAP Patients

The first decision to be made in cases of pneumonia is the determination of the need for hospitalization and the choice of antibiotherapy. Hospitalization is mainly related to the predicted prognosis. There are various scoring systems for determining the prognosis. Among these, CURB-65 and PSI (pneumonia severity index) are most commonly used (Table 2, Table 3, Table 4,, Table 5).[16,17]

Table 2. CURB-65 scoring
Confusion
Urea >42.8 (BUN >20 mg/dl or 7 mmol/l)
Respiratory rate >30/min
Blood pressure systolic <90 or diastolic <60 mmhg
Age >65
Each of the above criteria is a score → 0-1 low risk, 2 medium risk, 3-5 high risk

Table 3. Mortality risk level according to the CURB-65 score and assessment for hospitalization

Score	30-day mortality risk	Treatment location
0	<1%	Outpatient
1	3%	Outpatient but individual assessment required*
2	13%	Hospital
3	17%	Hospital
4	42%	Hospital - evaluation in terms of intensive care unit hospitalization required
5	57%	Assessment for hospital-intensive care unit hospitalization required

*Patients with inadequate home care support, patients with doubts about regular use of medications and adequate nutrition, and patients with criteria other than age in CURB-65 scoring may be hospitalized.

Table 4. Pneumonia associated severity score (PSI)

PSI score components	
Factor	**Score**
Patient age	
Male	Age
Female	Age-10
Long-term care facility resident	+10
Accompanying disease	
Neoplastic disease	+30
Liver Disease	+20
Congestive Heart Failure	+10
Cerebrovascular disease	+10
Chronic kidney disease	+10
Symptoms at diagnosis	
Acute psychosis	+20
Breathing rate >30/min	+20
Systolic pressure <90mmHg	+15
Body temperature <35 or >40	+15
Heart rate >125/min	+10
Laboratory measurements	
Arterial blood pH<7.35	+30
BUN >30mg/dl	+20
Serum sodium <130 mEq/L	+20
Serum glucose >250 mg/dl	+10
Hb<9gm/dl (hematocrit <%30)	+10
Atmospheric arterial blood gas (PaO_2)<60 mmHg	+10
SaO_2<90%	+10

Patients who do not require hospitalization, according to PSI and CURB-65 (Group 1), are followed and treated as outpatients. The group requiring hospitalization is evaluated according to the suitability of ward follow-up or intensive care unit follow-up (Group 2). Patients in Group 3 must be followed up in centers with intensive care. The approach according to disease severity is shown in Table 6.

Table 5. Assessment of mortality risk and hospitalization according to the PSI score

Risk Group	PSI score	30-day mortality risk	Treatment location
I-II	<70	<1%	Outpatient
III	71-90	1-3%	Outpatient, but individual assessment is required
IV	91-130	8-12%	Hospital
V	>130	27-31%	Assessment for hospital-intensive care unit hospitalization required

Table 6. Approach according to disease severity

	Disease severity	Treatment location	Microbial research
Mild	PSI: I or II or CURB-65:0	Outpatient treatment	COVID-19 testing during the pandemic Influenza testing (when incidence is high) Otherwise, the search for the causative pathogen is usually not necessary.
Middle	PSI: III or IV or CURB-65: 1-2	Hospitalization (ward)	Blood cultures Sputum Gram stain and culture urine streptococcal antigen *Legionella* test Respiratory viral panel during respiratory virus season COVID-19 test HIV screening
Severe	PSI: V or CURB-65>3	Hospitalization in the intensive care unit	Blood cultures sputum Gram stain and culture urine streptococcal antigen test *Legionella* test respiratory viral panel Bronchoscopy specimens for Gram stain, fungal stain, aerobic fungal culture, and molecular tests (when available) COVID-19 test for HIV screening

The criteria for the need for intensive care are given in Table 7.

Treatment

Early diagnosis and treatment of CAP are important in reducing mortality and morbidity. The choice of empirical antibiotherapy is determined according to patient groups. In pneumonia, patients are divided into three groups.

Group 1: Patients with a CURB65 score below 2 or PSI I-III who are followed as outpatients. Group 1 is divided into two groups. Patients without chronic disease are evaluated as Group la, and those with chronic disease are evaluated as Group lb.[17]

Table 7. Criteria for hospitalization in the intensive care unit
Major
The need for invasive mechanical ventilation
Septic shock requiring vasopressors
Minor
Respiratory rate >30/min
Pao2/fio2 <250
Multilobular infiltrates on chest radiograph
Uremia (BUN >20mg/dl)
Leukopenia (leukocytes <4000/mm³) Thrombocytopenia (platelets <100000/mm³)
Hypothermia (<36c)
Hypotension requiring intensive fluid loading
In the presence of one of the major risk factors or at least three of the minor risk factors, intensive care unit monitoring is recommended.

Possible pneumonia agents in group la are *Streptococcus pneumoniae, Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae*. While penicillin/amoxicillin treatment is sufficient in the clinical picture of typical pneumonia, if atypical pneumonia is considered, it is recommended to add a macrolide group to penicillin/ampicillin.[9,17,18]

In group 1b, possible agents increase due to the presence of chronic disease. *Haemophilus influenzae* and enteric Gram-negative bacilli are added to the agents in group 1a. In treatment, 2nd-3rd generation oral cephalosporin alone or combined with macrolide or doxycycline, amoxicillin clavulanic acid alone or combined with macrolide or doxycycline, and monotherapy with respiratory quinolone alone can be applied.[9,17,18] (Table 8)

It should be emphasized that patients with a treatment plan should be readmitted if there is no clinical improvement (decrease in fever, regression in symptoms) after 72 hours.

Group 2 is a group of patients with a CURB-65 score of 2 and above or PSI IV-V who do not meet intensive care criteria. Requires ward follow-up. Group 3 includes patients with a CURB-65 score of 2 and above or between PSI IV-V who meet intensive care criteria.[18,19]

Risk factors for resistant infection should be taken into consideration when choosing empiric antibiotherapy in groups 2 and 3. Isolation of resistant bacteria in the respiratory tract in the last 6 months, hospitalization in the last 3 months, and history of antibiotic use in the last 3 months are risk factors for resistant infection.[19]

The antibiotherapy selection is similar for both groups. Patients without resistance risk factors are primarily recommended betalactam-betalactamase inhibitors without anti-Pseudomonas activity or macrolide

Table 8. Group 1 treatment algorithm		
	Possible factors	**Recommended antibiotics**
Group 1a (without chronic diseases)	-*Streptococcus pneumonia* -*Mycoplasma pneumonia** -*Chylamadolphylia pneumonia** - viruses	-amoxicillin -amoxicillin + macrolide / doxycycline **
Group1b (those with chronic diseases)	Group 1a bacteria *Haemophilus influenzae* Enteric gram-negative bacilli	-2nd-3rd generation oral cephalosporin -2nd-3rd generation oral cephalosporin + macrolide / doxycycline ** -amoxicillin clavulanic acid -amoxicillin clavulanic acid + macrolide / doxycycline ** - monotherapy with respiratory quinolone ***
*Some bacteria can cause pneumonia alone or together with another bacteria (mixed infection) **Decision should be made by showing a syndromic approach. *** In patients considering a combination of beta-lactam + macrolide/doxycycline, if there is a history of gastrointestinal problems, drug allergies, or a history of beta-lactam use in the last 3 months, it is more appropriate to use a respiratory fluoroquinolone alone instead of this combination. Quinolones should not be used in patients with clinical or radiographic evidence of tuberculosis.		

combinations with 3rd generation cephalosporins (cefotaxime and ceftrisxone) without anti-Pseudomonas activity, while macrolide combination therapy with broad-spectrum anti-*Pseudomonas* active antibiotics is recommended for patients with risk factors. The only difference between the two groups is that while respiratory quinolone monotherapy is appropriate in patients hospitalized in the ward, one of the options of beta-lactam+macrolide or beta-lactam+respiratory quinolone is recommended in patients hospitalized in intensive care due to the lack of sufficient data on the efficacy of quinolone monotherapy.[17,20](Table 9)

Priority parenteral antibiotherapy is recommended in cases of pneumonia requiring hospitalization. In order to reduce the cost, complications, and hospitalization of parenteral treatment, a transition to oral treatment is recommended for patients who respond to treatment (Table 10). This requires a fever-free period of at least 24 hours, resolution of tachycardia, tachypnea, hypotension, and hypoxemia, regression of leukocytosis and CRP levels, and no problems with oral intake and gastrointestinal absorption. Antibiotics can be discontinued after the fever subsides and the patient is clinically stable, provided that the total duration of treatment is not shorter than 5 days (7 days in resistant infections).[20]

Table 9. Group 2 and Group 3 treatment algorithm

Patients without risk factors for the resistant agent	Possible factors	Recommended antibiotics
Patients without risk factors for the resistant agent	-*Streptococcus pneumonia* -*Legionella pneumophilia* -*Haemophilus influenza* -enteric gram-negative bacilli -*Staphylococcus aureus* -*Mycoplasma pneumonia* -viruses	*3rd generation anti-pseudomonas non-cephalosporin (3ksef)+macrolides *betalactam + betalactamase inhibitor (bl+bli)+ macrolide *respiratory fluoroquinolone (patients hospitalized in the ward) 3k sef or bl + bli+ respiratory fluoroquinolone (patients hospitalized in the ICU)
Patients with risk factors for a resistant agent	-Factors in patients without risk factors -pseudomonas aeruginosa -Enteric gram-negative bacilli producing extended spectrum beta lactamase (gsbl)	*anti-*Pseudomonas* beta lactam*+ ciprofloxacin Anti-pseudomonas beta lactam*+ aminoglycoside +macrolide

The presence of these bacteria isolated from respiratory samples within the last year, antibiotic use in the last 3 months, and hospitalization history in the last 3 months
In hospitalized patients, risk factors for resistant infection are common, and there is no significant difference in antibiotic choices, regardless of the need for ICU admission (severity of pneumonia). However, in the absence of data on the efficacy of respiratory quinolone monotherapy in severe pneumonia requiring intensive care, combination therapy is recommended.
*In patients in whom broad-spectrum antibiotic treatment has been initiated, bacteriologic examination results should be monitored, and in cases where a bacterium is isolated, treatment should be rearranged according to the antibiogram result, and de-escalation should be performed if possible (the spectrum should be narrowed).
*3rd generation cephalosporin (ceftazidime), 4th generation cephalosporin (cefepime), carbapenems(imipenem, meropenem), beta-lactamase inhibitor anti-pseudomonas drugs (piperacillin + tazobactam, cefoperazone + sulbactam)
* Patients on ciprofloxacin do not need to add a macrolide.

Table 10. Antibiotics used in sequential treatment

IV/ With the same antibiotic orally	IV/ With oral different antibiotics
Cefuroxime / cefuroxime axetil Amoxicillin-clavulanic acid Clarithromycin Ciprofloxacin Levofloxacin Moxifloxacin Clindamycin Metronidazole	Cefotaxime/cefuroxime axetil . Cefotaxime/cefixime Ceftazidime/ciprofloxacin - Ceftriaxone/cefixime Ampicillin-sulbactam/ Amoxicillin-clavulanic acid

Treatment non-response is the absence of improvement in fever and other symptoms 72 hours after the initiation of antibiotherapy. Treatment non-response, patient compliance, appropriateness of antibiotherapy, development of complications such as empyema or abscess, and additional diseases or conditions that may make recovery difficult should be reviewed.[18]

HOSPITAL-ACQUIRED PNEUMONIA

Pneumonia that develops 48 hours after hospitalization or within 48 hours after discharge is called hospital-acquired pneumonia (HAP). Pneumonia that develops 48 hours after intubation in patients who do not have pneumonia during intubation is called ventilator-associated pneumonia (VAP).[21] HAP is the 2nd most common nosocomial infection in our country as well as in the whole world.[22]

When the diagnosis of HAP/VIP is made, empirical antibiotherapy should be initiated immediately. The evaluation of mortality risk factors and resistant infection risk factors in the selection of antibiotherapy and appropriate treatment is summarized in tables 11 and 12.[21]

Table 11. Empirical treatment of hospital-acquired pneumonia

In patients without risk factors for multidrug resistance	In cases with multidrug resistance risk and/or mortality risk*
Ceftazidime Cefepime Piperacillin - Tazobactam Cefoperazone - Sulbactam Imipenem Meropenem	Piperacillin - Tazobactam + Ciprofloxacin Cefoperazone - Sulbactam + Levofloxacin Imipenem** Amikacin Meropenem **

Table 12. Empirical treatment of ventilator-associated pneumonia

Standard treatment approach		
Piperacillin - Tazobactam Cefoperazone - Sulbactam Imipenem Meropenem Cefepime Ceftazidime	+	Ciprofloxacin or Levofloxacin Aminoglycoside Sulbactam Colistin *
Standard recommended treatment if Acinetobacter baumannii prevalence is high		
Cefoperazone - Sulbactam Imipenem Meropenem	+	Ciprofloxacin or Levofloxacin Aminoglycoside Sulbactam Colistin *

* One of Linezolid, Teicoplanin, or Vancomycin should be added to the treatment regimen of patients whose Gram-stained slides show Gram-positive cocci with staphylococcal morphology.

* A single risk factor may lead to unnecessary antibiotic use. Increasing the number of risk factors increases the likelihood of multidrug resistance.
* Colistin-containing combinations should be preferred in hospitals with a high prevalence of Gram-negative bacteria resistant to carbapenems.

High mortality risk factors include advanced age, two or more organ failures, the presence of a high APACHE score, underlying disease, bacteremia, late antibiotic initiation, and the need for mechanical ventilation.[21,23]

Risk factors for multidrug-resistant infection include IV antibiotic use within 90 days, the presence of septic

shock, hospitalization for 5 days or more before VAP, a history of acute renal replacement therapy, and the presence of ARDS before VAP.[23]

In both HAP and VAP, the recommended optimal duration of treatment for infections developing with susceptible pathogens whose causative agents are isolated and who do not have antibiotic resistance problems is 7 days on average. The determinant here is clinical, laboratory, and radiologic improvement.[23] In patients with MRSA growth, the optimal treatment is 14 days. In HAP caused by bacteria such as Acinetobacter, *Pseudomonas*, and *Stenotrophomonas*, the duration of treatment can again be extended to 14 days.[23]

COVID-19 PNEUMONIA

In late 2019, a new coronavirus called SARSCoV-2 (severe acute respiratory syndrome coronavirus) was identified in Wuhan province, China, with a severe pneumonia clinic. The disease, named COVID-19 by the World Health Organization, spread rapidly all over the world and in our country shortly after.

Clinical Findings

The disease can range from asymptomatic cases to acute respiratory distress syndrome. Patients with COVID-19 typically first progress from a mild upper respiratory tract infection (e.g., pharyngitis, runny nose) to a lower respiratory tract infection (e.g., cough, fever), flu-like symptoms (e.g., fever, chills, headache, myalgia), or gastroenteritis (e.g., nausea, vomiting, diarrhea). Loss of smell and taste may also occur, with loss of smell typically reported early in the disease. If dyspnea develops, it tends to occur four to eight days after the onset of symptoms, but it can also occur after 10 days. In addition, even where the prevalence of COVID-19 is high, the possibility of other symptom etiologies should be considered.[24]

Laboratory Findings

Common laboratory findings among COVID-19 patients include lymphopenia, elevated aminotransaminase levels, elevated lactate dehydrogenase levels, elevated inflammatory markers (for example, ferritin, C-reactive protein, and erythrocyte sedimentation rate), and abnormalities in coagulation tests (elevated D-dimer).

Imaging Findings

1.Chest radiographs: Chest radiographs may be normal in early or mild disease; common abnormal radiographic findings are consolidation and ground-glass opacities with bilateral, peripheral, and lower lung zone distributions; lung involvement increases over the course of the disease, with a peak in severity 10 to 12 days after symptom onset.

2.Thorax CT: Thoracic computed tomography (CT) is more sensitive than chest radiography. Some CT findings may be specific to COVID-19, but no finding can completely rule out the possibility of COVID-19.

Common CT findings:

*Ground glass opacifications

*Mixed consolidation frosted glass opacities

*Adjacent pleural thickening

*Interlobular septal thickening

*Expressed as air bronchograms.

Management in COVID-19 Patients

Direct detection of SARS-CoV-2 RNA, most frequently by reverse transcription polymerase chain reaction (RT-PCR), is the typical method for making the diagnosis of COVID-19 in patients with the aforementioned symptoms.

If the initial test is negative but suspicion of COVID-19 persists (e.g., suggestive symptoms without an obvious alternative cause) and confirmation of the presence of infection is important for management or infection control, PCR testing may be repeated.

Patients are assessed for previous chronic illnesses, smoking, and degree of dyspnea, and a decision is made whether to treat the patient on an outpatient or inpatient basis depending on the presence or absence of these conditions.

IMPORTANT POINTS

In patients with suspected pneumonia, chest radiography in the first 4 hours is effective in reducing mortality because it saves time in making the diagnosis. After the diagnosis of pneumonia is made, it is important to first determine the group to which the patient belongs and start appropriate empirical antibiotherapy. If possible, cultures should be taken before antibiotics are started on the patient for whom hospitalization is planned. After 72 hours, in patients with no symptom improvement, the reason for treatment non-response should be evaluated, and antibiotherapy should be changed if necessary.

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