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Medical Journal
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Recombinant Interferon-Beta1a Use in Six Patients with Myeloproliferative Neoplasms: A First Impression

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Dear Editor;

Recombinant and pegylated interferon-alpha2 (IFN-α2) have a long history of off-label use in patients with Philadelphia-negative chronic myeloproliferative neoplasms (MPNs).[1] While preclinical evidence suggests potential anti-cancer activity for rIFN-β1a (recombinant interferon-beta1a)[2], clinical experience with this agent in MPNs is lacking, with no prior reports of its use in this setting to the best of our knowledge. rIFN-β1a, while a well-established therapy for multiple sclerosis, remains understudied in MPNs. Here, we present our initial observations on the safety profile of rIFN-β1a in six MPN patients who transitioned to this therapy.

Six MPN patients, previously treated with off-label pegylated r-IFNα-2a due to unavailability, transitioned to off-label r-IFNβ-1a and were retrospectively evaluated. Patients were followed for a median of 35.3 months after MPN diagnosis (30.8 months under r-IFNα-2a and 16.8 months under r-IFNβ-1a). Demographic, clinical, and laboratory characteristics are summarized in the Table 1.

Table 1. Demographic, Clinical, and Laboratory Characteristics of Patients

	1	2	3	4	5	6
Age/Gender	46/F	45/M	47/M	41/F	44/M	34/F
Diagnosis	PV	PV	ET	ET	PV	ET
Mutation	JAK2	Triple negative	JAK2	CALR Type 1	JAK2	CALR Type 1
Risk Score[a]	Low	Low	Low	Low	Low	Low
The Initiation of IFN-Beta1a						
Hb (g/dL)	13.3	13.2	14.7	11.5	15.3	12.4
Htc (%)	41.6	44.3	42.8	34.5	45.3	38.2
Leu (x10^3/mm^3)	5500	11700	5900	9400	4600	8900
Plt (x10^3/mm^3)	454	272	419	774	151	606
LDH (U/L)	237	191	241	313	229	263
JAK-2 allele (%)	9.8		8		10	
Latest Visit of IFN-Beta 1a						
Hb (g/dL)	12.9	12.9	16.4	10.9	16.9	11.7
Htc (%)	38.7	41.8	50.1	32.7	51.1	37.6
Leu (x10^3/mm^3)	7570	10700	11500	13250	10300	6500
Plt (x10^3/mm^3)	666	395	721	756	510	639
LDH (U/L)	203	173	303	309	178	318
JAK2 allele (%)	3.6		1.7		0.6	
Adverse Event						
Myalgia	Grade 2	Grade 1	Grade 2	Grade 2	Grade 2	Grade 1

Hb, hemoglobin; htc, hematocrit; leu, leukocyte; plt, platelet; LDH, lactate dehydrogenase. [a]Age ≤ 60 y of age, platelets ≤ 1500 (×10^3/mm^3) and no prior majoLor thrombosis

All patients initiated r-IFNβ-1a at a dose of 44 mcg weekly. All patients reported myalgia on treatment days, requiring concomitant non-steroidal anti-inflammatory drug (NSAID) administration. This adverse event prevented dose escalation, and the initial dose remained unchanged. No other adverse events were observed,

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and no treatment discontinuations occurred due to adverse events. No new arterial or venous thrombotic events were observed during r-IFNβ-1a therapy.

Three of the six patients harbored the JAK2V617F mutation. Due to insufficient JAK2V617F measurements, assessment with an exponential response model was not feasible. However, a reduction in allele burden was observed in these three patients following the initiation of r-IFNβ-1a.

MPNs are characterized by a self-sustaining inflammatory cycle driving clonal expansion.[3,4], supporting the idea of early interferon intervention to halt disease progression.[5] While IFN-α and IFN-β share similar immunomodulatory mechanisms.[6], they also exhibit distinct characteristics, most notably IFN-β's higher receptor binding affinity.[7]

In this six-patient case series, r-IFNβ-1a demonstrated a manageable safety profile, with myalgia being the most common side effect, which limited dose escalation. While some patients showed a reduction in JAK2V617F allele burden, the small sample size prevents any definitive conclusions about its clinical significance. Further studies are needed to determine the optimal role of r-IFNβ-1a in the treatment of MPNs.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

No ethical approval needed

Authors' Contribution

Study Conception: PP; Study Design: PP; Supervision; PP; Funding: N/A; Materials: PP; Data Collection and/or Processing: PP; Analysis and/or Data Interpretation: PP; Literature Review: PP; Critical Review: PP; Manuscript preparing: PP.

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Original Article
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Identifying Preventable Causes of Worsening Heart Failure: A Single-Center Retrospective Analysis

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ABSTRACT

Background: Heart failure (HF) is a complex condition characterized by acute or chronic deterioration in heart function. The incidence of heart failure is on the rise in both developed and developing countries. Despite advancements in treatment, the 5-year mortality rate remains close to 60%, surpassing the mortality rates of many malignancies.
Moreover, heart failure imposes significant economic burdens on healthcare systems due to the necessity of lifelong treatment, frequent hospitalizations, and the utilization of complex and costly device treatments. In this study, we aimed to investigate the factors contributing to decompensation in patients presenting to the emergency department with decompensated heart failure.
Methods: Patients with or without a previous diagnosis of heart failure, who presented to the emergency department with symptoms of acute heart failure between March 2015 and May 2017 were included in this retrospective study. Demographic and clinical characteristics were recorded. The causes of worsening heart failure and their distribution were investigated.
Results: Cardiac decompensation was attributed to a single etiological factor in 154 out of 229 cases, while it was multifactorial in 75 cases. Factors contributing to decompensation included treatment noncompliance in 41 cases, NSAID use in 1 case, endocrine disorders in 3 cases, acute kidney injury (AKI) or chronic AKI in 21 cases, pulmonary embolism (PE) in 1 case, acute coronary syndrome (ACS) in 41 cases, arrhythmia in 29 cases (18 atrial fibrillation, 12 atrioventricular block, 2 bradycardia, 5 ventricular tachycardia, 1 supraventricular tachycardia, 1 atrial flutter), anemia in 20 cases, volume overload-hypertension in 18 cases, digitalis intoxication in 1 case, and infection-inflammation in 139 cases.
Conclusions: Addressing preventable risk factors can lead to a reduction in healthcare expenditures and an improvement in both life expectancy and quality of life for patients.

Keywords: Decompensated heart failure, acute heart failure, healthcare expenditure

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INTRODUCTION

Heart failure is a clinical syndrome characterized by abnormal structure or function of the heart and the presence of symptoms and findings such as dyspnea, fatigue, and fluid retention.[1] In this syndrome, impaired cardiac function is inadequate to meet the body's metabolic needs.[2] Most commonly, the underlying cause is a ventricular contractility disorder, resulting in systolic dysfunction.[3]. In approximately 50% of cases, there is left ventricular enlargement and a significant decrease in ejection fraction along with impaired contractility.[1, 4] In the remaining 50%, heart failure occurs despite normal ejection fraction, known as heart failure with preserved ejection fraction.[5] Although isolated right ventricular failure may occur, in most cases of heart failure, there is either isolated left ventricular dysfunction or right ventricular dysfunction secondary to left ventricular failure.[1, 6]

Structural heart defects, hemodynamic disorders, and neurohumoral activation contribute to the development of heart failure syndrome. Hemodynamic disturbances are characterized by low cardiac output and high intracardiac pressures in heart failure. While hemodynamic abnormalities contribute to symptoms, neurohumoral abnormalities are responsible for the progression of heart failure and mortality.[1,7] Low cardiac output can cause fatigue and exercise intolerance, while high intracardiac pressures can lead to exercise dyspnea and peripheral edema.[6] Neurohumoral abnormalities include sympathetic nervous system activation, renin-angiotensin-aldosterone system stimulation, increased vasopressin release, elevated endothelin levels, increased secretion of pro-inflammatory cytokines, and increased natriuretic peptides. Consequently, vasoconstriction, sodium-water retention, cardiovascular growth, and remodeling occur.[8,9] While acute neurohumoral changes are beneficial, chronic activation exacerbates the severity of heart failure and worsens prognosis.[10] Increased catecholamines cause resting tachycardia, arrhythmias, myocyte toxicity, receptor dysfunction, and stimulation of the renin-angiotensin-aldosterone system.[1] As a result, myocardial damage and remodeling progress to compensate for the decreased stroke volume.[11]

The severity of clinical findings in heart failure and the frequency of symptom development depend on the availability of sufficient time for adaptive mechanisms to develop. When these events occur over time, as in chronic heart failure, they can be tolerated without symptoms for a long time with many adaptive mechanisms such as cardiac remodeling and neurohormonal activation.[12]

The clinical syndrome of acute heart failure (AHF) is characterized by decreased cardiac output, tissue perfusion, high pulmonary capillary wedge pressure (PCWP), and tissue congestion. The underlying mechanism may be cardiac or extracardiac and may be transient or reversible with treatment of the acute syndrome, or may cause permanent damage leading to chronic heart failure.[13]

While the goals in chronic heart failure are focused on improving prognosis and prevention, in acute heart failure, symptomatic improvement is the most important aspect of treatment. Symptomatic improvement, adequate oxygenation, organ perfusion, and hemodynamic recovery, limiting cardiac and renal damage, and minimizing the patient's stay in the intensive care unit are the initial steps of treatment in acute heart failure.[14]

Acute heart failure is a life-threatening condition, and the cost of treatment is a significant financial burden on healthcare systems. Although the ideal is to prevent the diseases that cause heart failure, stabilising cardiac function in patients diagnosed with heart failure and preventing progression of the disease will provide significant benefits to patients and the healthcare system.

In this study, we aimed to identify the most common and preventable causes of deterioration in heart function in patients presenting to the emergency department with symptoms of acute heart failure.

METHODS

Male and female patients over 18 years of age, with or without a previous diagnosis of heart failure, who presented to the emergency department of our hospital with symptoms of acute heart failure between March 2015 and May 2017 were included in the study.

Patients were excluded if diagnostic echocardiography and electrocardiography were not available, if they had cardiac arrest and died before the etiology of worsening heart failure could be investigated, or if they were referred to an external centre for cardiac intervention or intensive care.

Gender, age, comorbidities (diabetes mellitus, hypertension, chronic obstructive pulmonary disease, chronic renal failure), hemogram parameters, laboratory parameters such as urea, creatinine, sodium,

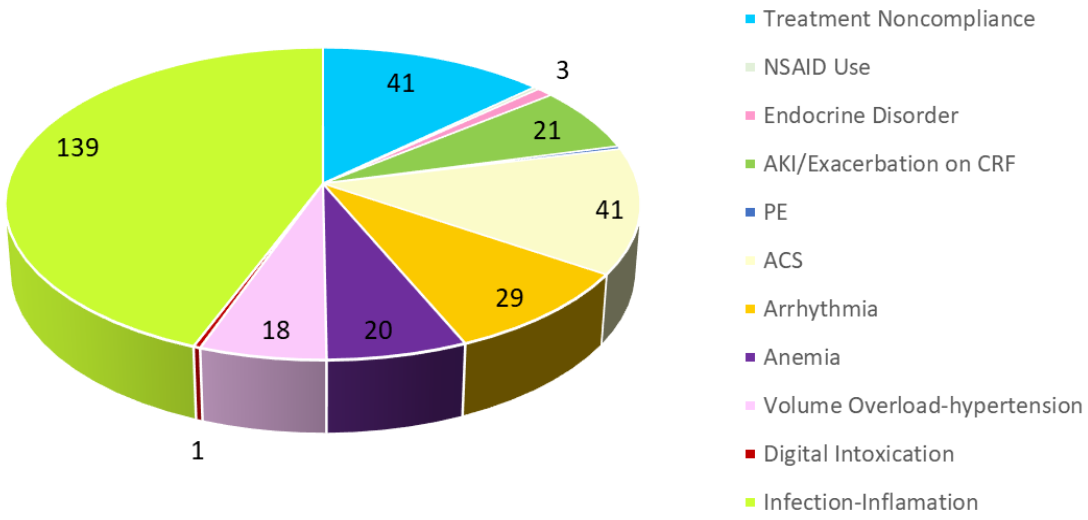

Figure 1. Distribution of Etiologic Factors

potassium, CRP, troponin, and CK-MB were obtained retrospectively by review of patient records. Patients with a previous diagnosis were classified as compliant or non-compliant according to their self-report.

RESULTS

The study was based on 229 cases. Median age was 63, 117 were diagnosed with heart failure, 172 were diagnosed with hypertension, 76 were diagnosed with diabetes mellitus, 45 were diagnosed with both diabetes and hypertension, and 19 had no known chronic disease. Cardiac decompensation was attributed to a single etiological factor in 154 cases (67.2%) and was multifactorial in 75 cases (32.7%). Among patients who reported treatment and diet compliance, the cause of decompensation was found to be multifactorial in 48.7% of cases.

Specifically, treatment noncompliance was observed in 41 cases (17.9%), NSAID use in 1 case (0.043%), endocrine disorders in 3 cases (0.13%), acute kidney injury (AKI) or acutely exacerbated renal failure on a chronic basis in 21 cases (0.9%), pulmonary embolism (PE) in 1 case (0.043%), acute coronary syndrome (ACS) in 41 cases, arrhythmias in 29 cases (12.6%) (including 18 cases of atrial fibrillation, 12 cases of atrioventricular block, 2 cases of bradycardia, 5 cases of ventricular tachycardia, 1 case of supraventricular tachycardia, and 1 case of atrial flutter), anemia in 20 cases (8.7%), volume overload and hypertension in 18 cases (7.8%), digitalis intoxication in 1 case (0.43%), and infection or inflammation in 139 cases (60.6%) (Figure 1).

The infections included 43 cases of pneumonia, 27 cases of exacerbation of chronic obstructive pulmonary disease (COPD), 24 cases of urinary tract infections, 2 cases of gout attacks, 1 case of rheumatoid arthritis (RA) attack, 4 cases of acute viral hepatitis, 1 case of pericarditis, 2 cases of cholecystitis, 1 case of cholangitis, 1 case of peritonitis, 2 cases of pancreatitis, 4 cases of diabetic feet, 1 case of diverticulitis, and 5 cases of soft tissue infections/cellulitis. Additionally, 21 cases of infection without a focus were detected (Table 1).

Table 1. Infection/Inflammation Distribution

Infection	n
Pneumonia	43
COPD Exacerbation	27
Diabetic Foot	4
Urinary Tract Infections	24
Soft Tissue Infections	5
Cholecystitis- Cholangitis- Diverticulitis	2+1+1
Gout Exacerbation	2
RA Exacerbation	1
Pancreatitis	2
Peritonitis- Pericarditis	1+1
Hepatitis	4
Infections with Unknown Origin	21

COPD: chronic obstructive pulmonary disease, RA: rheumatoid arthritis

DISCUSSION

Heart failure is becoming increasingly common in Turkey, mirroring global trends. This rise can be attributed to the successful treatment of coronary artery diseases and acute coronary syndromes, as well as the aging population, similar to other countries.

According to data from the Texas Heart Institute in the USA, there are over 5 million diagnosed cases of heart failure in the USA and more than 20 million worldwide. The annual treatment costs for these patients are estimated to be around $34 billion.[15]

The Texas Heart Institute study revealed that over one million new cases of hospitalized heart failure (de novo heart failure) are identified annually.[16] It was noted that 15-20% of hospitalized acute heart failure (AHF) patients are newly diagnosed cases, while more than 80% are chronic heart failure cases that have decompensated due to various factors. Atrial fibrillation and atrial flutter were observed in 30-46% of chronic heart failure cases presenting with decompensation. In our study, we found arrhythmia to be the cause of decompensation in 12.6% of cases, a lower rate compared to the Texas Heart Institute's findings.[16]

The Texas Heart Institute study also highlighted renal failure (20-30%), hypertension (25%), and hypotension (10%) as factors disrupting cardiac stabilization in ADHF patients. Similarly, in our study, renal failure was present in 21% of cases, while hemodynamic disorders, including hypertension and hypotension, were detected in 6% of cases.

According to the "Heart Diseases and Stroke Statistics 2023 Update Report" by the American Heart Association, nearly 6.5 million Americans are diagnosed with heart failure, with 550 thousand new diagnoses each year, resulting in one million hospitalizations annually. The report indicates significant healthcare expenditure, with the majority allocated to inpatient treatment.[17]

Regarding our study, although treatment costs were not investigated, the Turkish Cardiology Association's HAPPY study reported an annual heart failure treatment cost of $38 billion in Turkey, with $23 billion attributed to recurrent hospitalizations.[18] This aligns with the American Heart Association's findings.

In our study, 23% of patients experienced worsening without a discernible cause, lower than reported rates in the literature, possibly indicative of better healthcare services and improved access to advanced diagnostics in our health system.

Common factors predisposing ADHF in our study included infection/inflammation, treatment noncompliance, arrhythmia, anemia, and acute coronary syndrome, consistent with findings from studies conducted in the USA. These studies identified treatment noncompliance, dietary indiscretion, uncontrolled hypertension, ischemia, arrhythmia, and COPD exacerbation as primary precipitating factors for ADHF.[19]

In another study conducted in Chicago, it was stated that the most significant reason for hospitalizations due to heart failure was diet and treatment incompatibility.[20]

In our study, we found that the rate of patients decompensated due to volume overload was 9%, and it's likely that these patients are hypervolemic because of diet and treatment incompatibility. If we add this rate to the rate of treatment and diet non-compliance in our society, it is expected to be much higher than the rate we found in our study. The reason for detecting a lower rate may be that we included hypervolemic patients whose creatinine value was higher than the baseline value in a separate group, which includes conditions that progress with hypervolemia, such as acute renal failure and acute exacerbations on the basis of chronic renal failure. These findings underscore the importance of diet and treatment compliance and patient education worldwide.[21]

In the study conducted by Butt et al.[21], patients hospitalized with heart failure were examined in three categories: 1) Worsening chronic HF (70%), 2) De novo HF (15%), 3) Severe/treatment-resistant HF (5%). It was reported that 50% of these patients were hypertensive, 40% normotensive, 8% hypotensive, and 2% presented with cardiogenic shock. Acute coronary syndrome (ACS) was detected in 21.5% of the patients.

In our study, we found 13% ACS and 6% hypertension (HT) cases. We believe that the low rate of ACS in our study may be due to some patients diagnosed with ACS being referred to external centers due to the limited number of beds in the coronary intensive care unit in our hospital and the inability to perform revascularization procedures. Another reason for this low rate could be the exclusion of fatal ACS cases from our study.

The fact that acute coronary syndromes are a significant cause of both de novo heart failure and acute decompensated heart failure (ADHF) in all these studies highlights that coronary artery disease, atherosclerosis, diabetes, and hyperlipidemia are important health concerns both in our country and worldwide.

In a study conducted at the University of Newcastle, Australia, acute cardiac decompensation due to the use of NSAIDs (except low-dose aspirin) was reported at a rate of 29%.[23, 24] In our study, we detected NSAID-induced acute cardiac decompensation in only one of

229 cases. The lower rate in our study compared to the literature may be due to patients not disclosing their NSAID use during the anamnesis. Another possible reason is that infection-inflammation was detected in 139 of 229 patients, and some of these patients were referred to another center due to infection, where palliative NSAIDs were prescribed or obtained from over-the-counter pharmacies. Considering the role of NSAIDs in decompensation, their impact may be higher.

Patients admitted to 133 health centers from 30 European countries were examined in the Euro Heart Failure Survey II (EHFS II) study. Newly diagnosed acute heart failure was detected in 37% of the 3508 patients included in the study, with 42% of them attributed to ACS. Decompensated chronic heart failure was detected in 65% of patients, with coronary heart disease, hypertension, and atrial fibrillation reported as the most significant underlying causes, consistent with previous studies and our findings.[25]

Arrhythmia, valve dysfunction, and ACS constituted one-third of the precipitating causes in this European study, with a third of patients being newly diagnosed with heart failure, largely attributed to ACS. The pathologies causing decompensation in this study were ACS in 30.2%, arrhythmia in 32.4% (supraventricular: 29.4%, ventricular: 4.1%), valvular disease in 26.8%, infection in 17.6%, treatment noncompliance in 22.2%, COPD exacerbation in 19.3%, anemia in 14.7%, and renal failure in 16.8%.

In our study, where the distinction between infected COPD and COPD exacerbations could not be clearly made, similar results to those of this European study could have been obtained if COPD and infection conditions were examined separately. Future studies conducted in collaboration with chest disease and infection clinics will clarify this confusion.

While infections, especially those unrelated to COPD and pneumonia, were not emphasized in studies conducted in Europe and America, our study revealed that 30% of cases were categorized under infection-inflammation, excluding pneumonia and COPD exacerbations. Among these cases, urinary tract infections accounted for 10.4%. It is noteworthy that urinary tract infections, cellulitis, and other infections were not mentioned in the patients included in studies conducted abroad, despite the high prevalence of diabetes mellitus, which predisposes individuals to urinary tract infections. One explanation for this difference could be the retrospective nature of our study, where each instance of pyuria was considered and treated as a urinary tract infection. Failure to differentiate asymptomatic pyuria may have led to artificially inflated rates. Another significant factor might be the effective management of simple infections in primary healthcare settings abroad.

From this perspective, enhancing the effectiveness of primary healthcare institutions could potentially prevent cardiac decompensations. Correct diagnosis, treatment, and follow-up of patients' predisposing factors can reduce rates of cardiac decompensation. Prospective studies on this topic will help mitigate biases present in retrospective data, ultimately leading to a substantial reduction in hospitalizations and treatment costs for patients.

Conflict of Interest

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Ethical Statement

The study protocol was approved by the Institutional Ethics Committee of Sisli Hamidiye Etfal Training and Research Hospital (10.01.2014/ 1397) and has been performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. All patients provided written informed consent for data use.

Authors' Contribution

Study Conception: FB; Study Design: FB; Supervision; FB; Funding: N/A; Materials: GD; Data Collection and/or Processing: GD; Analysis and/or Data Interpretation: SJ; Literature Review: GD; Critical Review: GD; Manuscript preparing: GD.

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Comparative Study of Antibiotic Resistance in *Lactobacillus* Species Isolated from Fermented Cassava and Corn

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ABSTRACT

Background: This study aimed to conduct a comparative study of antibiotic resistance in *Lactobacillus* species isolated from fermented cassava and corn samples. Key objectives included identifying antibiotic resistance profiles and evaluating interspecies correlations to support the development of functional probiotics.
Methods: A total of nine (9) bacterial strains, including *Lactobacillus fermentum, Lactobacillus ghanensis, Lactobacillus delbrueckii, Lactobacillus plantarum, Lactococcus lactis, Lactobacillus reuteri, Lysinibacillus sphaericus, Bacillus cereus,* and *Bacillus pacificus*, were analyzed for resistance against twelve (12) antibiotics. Correlation coefficients and paired statistical analysis were performed to assess interspecies relationships and variations, with p-values indicating significance. Correlations were evaluated using Pearson's coefficient (r), and significance was set at $p<0.05$.
Results: *Lactobacillus fermentum* exhibited the highest antibiotic resistance (mean 92.94%), while *Lactobacillus reuteri* showed the least resistance (mean 81.88%). Significant positive correlations were observed between *Lactobacillus fermentum* and *Lactococcus lactis* ($r=0.89$, $p<0.01$) and between *Lactobacillus plantarum* and *Lactobacillus delbrueckii* ($r=0.76$, $p<0.05$). Resistance to gentamicin, amoxicillin, and erythromycin was 100% across most isolates, indicating high resistance. Paired sample analyses revealed statistically significant differences between L*actobacillus fermentum* and *Lysinibacillus sphaericus* ($p<0.001$) and other isolates.
Conclusion: The high prevalence of antibiotic resistance across isolates raises concerns for therapeutic applications but underscores the potential of *Lactobacillus* species for robust probiotic formulations. The strong correlations between species resistance profiles suggest opportunities for targeted probiotic development and antimicrobial stewardship.

Keywords: Antibiotic resistance, Probiotic potential, *Lactobacillus* species, Fermented cassava, Fermented corn, Correlation analysis.

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INTRODUCTION

This study on the antibiotic resistance of *Lactobacillus* species isolated from fermented cassava and corn highlights several health benefits. Probiotic strains such as *Lactobacillus* have been shown to enhance gut health by promoting the growth of beneficial microbiota and improving digestive function. They may also boost immune responses, potentially reducing the risk of infections. Furthermore, understanding the antibiotic resistance patterns of these strains can aid in the development of safer, more effective probiotics, contributing to the prevention of antibiotic-resistant infections. The study also supports the promotion of fermented foods for their health-enhancing properties

The exploration of probiotics, particularly *Lactobacillus* species, has gained attention due to their promising health benefits and potential in food preservation and enhancement.[1] *Lactobacillus* species, commonly found in fermented foods, contribute to gut health, immune modulation, and the inhibition of pathogenic bacteria, making them crucial in functional foods and nutraceuticals.[2, 3] Among these, fermented cassava and corn are staple foods in many cultures, especially in Nigeria, where they are widely consumed as traditional foods like garri and ogi, respectively.[4, 5] The rich microbial diversity in these fermented foods presents an opportunity to isolate beneficial strains of *Lactobacillus* with potential health applications.[6]

Antibiotic resistance in probiotic strains has become a critical research focus in recent years, given its implications for both human health and food safety.[7] Some strains of *Lactobacillus* are known to possess antibiotic resistance genes, which can potentially be transferred to pathogenic bacteria, posing a risk to consumer safety.[8, 9] The selection of probiotic strains, therefore, requires careful screening to ensure both beneficial effects and the absence of transferable antibiotic resistance genes.[10] Previous studies have shown that the antibiotic resistance profiles of *Lactobacillus* strains vary widely, depending on factors such as strain type, origin, and environmental conditions.[11, 12]

In addition, the presence and dominance of specific *Lactobacillus* species in fermented foods can be influenced by multiple factors, including microbial competition, ecological adaptation, and the physical-chemical properties of the food matrix [13]. For example, *Lactobacillus fermentum*, known for its strong probiotic potential, has been consistently identified as a dominant strain in fermented cassava and corn-based foods due to its robust growth under acidic conditions.[14] This species, alongside others such as *Lactobacillus plantarum* and *Lactobacillus reuteri*, is frequently studied for its superior survival rate and stability in fermented products.[15]

The use of statistical methods to analyze microbial data enhances our understanding of strain viability, prevalence, and potential relationships with other microorganisms in the fermentation matrix.[16] Correlation analysis, for instance, can highlight symbiotic relationships among strains, which are important in developing effective probiotic formulations.[17] This study focuses on the isolation, characterization, and statistical analysis of *Lactobacillus* species from fermented cassava and corn to evaluate their probiotic potential and antibiotic resistance. The findings aim to contribute valuable insights into the safe utilization of *Lactobacillus* in food and therapeutic applications, supporting sustainable fermentation practices and health benefits for consumers.[18, 19]

METHODS

Sample Collection

Fermented cassava and corn samples were collected from various local markets in Benin City, Nigeria. Samples were transported in sterile containers to the laboratory and processed within 24 hours to ensure the viability of the microorganisms.[3]

Isolation of *Lactobacillus* Species

The isolation of *Lactobacillus* species was achieved using the serial dilution method. Approximately 10 g of each fermented sample was suspended in 90 mL of sterile peptone water and mixed thoroughly. The mixture underwent serial dilution (10^{-1} to 10^{-6}), and aliquots (100 µL) from each dilution were plated onto MRS (de Man, Rogosa, and Sharpe) agar, a selective medium for lactic acid bacteria. The plates were incubated anaerobically at 37°C for 48 hours. After incubation, colonies with distinct morphology were selected and purified by re-streaking on fresh MRS agar plates.

Characterization of Isolates

The isolated colonies were subjected to morphological and biochemical characterization. Morphological examination involved observing cell shape, size, and arrangement under a light microscope. The researchers conducted biochemical tests, including catalase activity, carbohydrate fermentation profiles (using various sugars), and gas production, which allowed for the preliminary identification of the isolates as *Lactobacillus* species.

Antibiotic Resistance Testing

Antibiotic resistance testing was performed to evaluate the resistance patterns of *Lactobacillus* species isolated from fermented cassava and corn. The test assessed their resistance to commonly used antibiotics, such as ampicillin, tetracycline, erythromycin, ciprofloxacin, and vancomycin. This procedure was carried out using the disc diffusion method on Mueller-Hinton agar supplemented with 5% sheep blood to support the growth of *Lactobacillus*. The bacteria were cultured overnight, and standardized inoculate were swabbed onto the agar plates. Antibiotic discs were then placed on the plates, which were incubated at 37°C for 24–48 hours. Zones of inhibition around the discs were measured and classified as resistant, intermediate, or susceptible based on Clinical and Laboratory Standards Institute (CLSI) guidelines.

The resistance rate (%) was calculated using the formula:

$$\text{Resistance Rate (\%)} = \frac{\text{Number of Resistant Strains}}{\text{Total Number of Isolates Tested}} \times 100$$

Statistical Analysis

Data collected from the isolation and characterization of *Lactobacillus* species were analyzed using SPSS version 23. Descriptive statistics, including means, standard deviations, and frequencies, were computed to summarize the characteristics of the isolates. The probiotic potential and antibiotic resistance data were subjected to inferential statistical tests, such as the Chi-square test and Analysis of Variance (ANOVA), to assess the significance of differences in the probiotic activities and resistance profiles among the various *Lactobacillus* species. Correlation analysis was also performed to determine the relationships between different probiotic traits and resistance patterns. A p-value of ≤ 0.05 was considered statistically significant, and results were interpreted based on this threshold.

RESULTS

The study includes the following tables: Table 1 presents the Clinical and Laboratory Standards Institute (CLSI) breakpoints for antibiotics; Table 2 shows the zones of inhibition around the discs, measured in millimeters, for antibiotics against bacterial isolates; Table 3 highlights the antibiotic resistance profile of bacteria isolated from fermented cassava and corn samples, represented as resistant isolates, N (%); Table 4 provides paired samples statistics and correlations; and Table 5 details the paired samples test. Figure 1 shows the antibiotic resistance patterns for different *Lactobacillus* species

Table 1. Clinical and Laboratory Standards Institute (CLSI) Breakpoints for Antibiotics

Antibiotic	Susceptible (S)	Intermediate (I)	Resistant (R)
Cilastatin **(10µg)**	≥ 20 mm	16-19 mm	≤ 13 mm
Gentamycin (10µg)	≥ 15 mm	13-14 mm	≤ 12 mm
Ofloxacin (5µg)	≥ 18 mm	15-17 mm	≤ 14 mm
Azithromycin (15µg)	≥ 14 mm	11-13 mm	≤ 10 mm
Amoxicillin (30µg)	≥ 18 mm	14-17 mm	≤ 13 mm
Cefotaxime (25µg)	≥ 22 mm	18-21 mm	≤ 17 mm
Ciprofloxacin (5µg)	≥ 21 mm	16-20 mm	≤ 15 mm
Cefixime (5µg)	≥ 22 mm	18-21 mm	≤ 17 mm
Levofloxacin (5µg)	≥ 18 mm	15-17 mm	≤ 14 mm
Erythromycin (15µg)	≥ 18 mm	15-17 mm	≤ 14 mm
Ceftriaxone (45µg)	≥ 23 mm	18-22 mm	≤ 17 mm
Cefuroxime (30µg)	≥ 23 mm	17-22 mm	≤ 16 mm

Table 2. Zones of inhibition around the discs measured in millimeter for Antibiotic against Bacteria Isolates. Classified as resistant (R), intermediate (I), or susceptible (S) based on Clinical and Laboratory Standards Institute (CLSI)

Bacteria/Antibiotic	Zones of inhibition (mm)											
	Cilastatin (10µg)	**Gentamycin (10µg)**	**Ofloxacin (5µg)**	**Azithromycin (15µg)**	**Amoxicillin (30µg)**	**Cefotaxime (25µg)**	**Ciprofloxacin (5µg)**	**Cefixime (5µg)**	**Levofloxacin (5µg)**	**Erythromycin (15µg)**	**Ceftriaxone (45µg)**	**Cefuroxime (30µg)**
Lactobacillus fermentum	19 (S)	16 (I)	24 (S)	12 (R)	10 (R)	22 (S)	13 (R)	15 (I)	18 (I)	24 (S)	22 (S)	20 (S)
Lactobacillus ghanensis	15 (I)	18 (S)	22 (S)	16 (I)	12 (R)	20 (S)	18 (S)	14 (R)	19 (S)	22 (S)	20 (S)	18 (S)
Lactobacillus delbrueckii	20 (S)	10 (R)	21 (S)	13 (R)	19 (S)	25 (S)	24 (S)	18 (I)	20 (S)	21 (S)	24 (S)	25 (S)
Lactobacillus plantarum	11 (R)	20 (S)	23 (S)	28 (S)	13 (R)	24 (S)	20 (S)	19 (S)	22 (S)	23 (S)	24 (S)	25 (S)
Lactococcus lactis	21 (S)	14 (R)	24 (S)	15 (I)	13 (R)	19 (S)	22 (S)	21 (S)	18 (I)	22 (S)	20 (S)	19 (S)
Lactobacillus reuteri	11 (R)	21 (S)	24 (S)	23 (S)	22 (S)	13 (R)	16 (I)	22 (S)	23 (S)	24 (S)	22 (S)	20 (S)
Lysinibacillus sphaericus	20 (S)	12 (R)	16 (I)	22 (S)	15 (I)	18 (I)	15 (I)	20 (S)	18 (I)	21 (S)	20 (S)	22 (S)
Bacillus cereus	12 (R)	13 (R)	14 (R)	21 (S)	22 (S)	20 (S)	19 (S)	20 (S)	23 (S)	24 (S)	22 (S)	21 (S)
Bacillus pacificus	16 (I)	18 (I)	20 (S)	19 (S)	17 (I)	22 (S)	21 (S)	18 (I)	20 (S)	23 (S)	21 (S)	22 (S)

Table 3. Antibiotic Resistance Profile of Bacteria Isolated from Fermented Cassava and Corn Samples: Resistant Isolates, N (%)

Antibiotics	***Lactobacillus fermentum (n=13)***	***Lactobacillus ghanensis (n=9)***	***Lactobacillus delbrueckii (n=10)***	***Lactobacillus plantarum (n=14)***	***Lactococcus lactis (n=9)***	**Lactobacillus reuteri, *(n=8)***	***Lysinibacillus sphaericus, (n=7)***	***Bacillus cereus (n=9)***	***Bacillus pacificus (n=11)***
Cilastatin (10µg)	12(92.3%)	8(88.9%)	10(100%)	12(85.7%)	7(77.8%)	7(87.5%)	5(71.4%)	8(88.9%)	10(90.9%)
Gentamycin (10µg)	13(100%)	8(88.9%)	10(100%)	14(100%)	9(100%)	6(75.0%)	7(100%)	9(100%)	9(81.8%)
Ofloxacin (5µg)	11(84.6%)	7(77.8%)	8(80%)	12(85.7%)	9(100%)	6(75.0%)	5(71.4%)	7(77.8%)	10(90.9%)
Azithromycin (15µg)	10(76.9%)	8(88.9%)	7(70%)	11(78.6%)	9(100%)	6(75.0%)	6(85.7%)	8(88.9%)	10(90.9%)
Amoxicillin (30µg)	13(100%)	9(100%)	9(90%)	13(92.9%)	9(100%)	7(87.5%)	7(100%)	9(100%)	11(100%)
Cefotaxime (25µg)	13(100%)	7(77.8%)	10(100%)	12(85.7%)	9(100%)	8(100%)	5(71.4%)	8(97.7%)	8(72.7%)
Ciprofloxacin (5µg)	11(84.6%)	9(100%)	8(80%)	11(78.6%)	8(88.9%)	5(62.5%)	6(85.7%)	9(.100%)	8(72.7%)
Cefixime (5µg)	12(92.3%)	9(100%)	9(90%)	13(92.9%)	7(77.8%)	6(75.0%)	7(100%)	9(100%)	11(100%)
Levofloxacin (5µg)	12(92.3%)	8(88.9%)	7(70%)	11(78.6%)	8(88.9%)	5(82.5%)	4(57.1%)	9(100%)	8(72.9%)
Erythromycin (15µg)	13(100%)	9(100%)	10(100%)	14(100%)	9(100%)	7(87.5%)	7(100%)	8(88.9%)	10(90.9%)
Ceftriaxone (45µg)	12(92.3%)	7(77.8%)	7(70%)	10(71.4%)	7(77.8%)	5(82.5%)	5(71.4%)	8(88.9%)	9(81.8%)
Cefuroxime (30µg)	13(100%)	8(88.9%)	9(90%)	12(85.7%)	8(88.9%)	5(92.5%)	7(100%)	9(100%)	8(72.7%)

Abbreviations: CIL=Cilastatin; GEN =Gentamicin; OFX = Ofloxacin; AZN= Azithromycin; AUG = Amoxicillin; CTX= Cefotaxime; CIP= Ciprofloxacin; ZEM= Cefixime; LBC = Levofloxacin; ERY= Erythromycin; CRO= Ceftriaxone; CXM= Cefuroxime (Ce Tech. Diagnostic. www.celtechproduct.com. Belgium Inc). N=number of strains within each species tested

Table 4. Paired Samples Statistics and Correlations

	Paired Samples	N	Correlation	Sig.	Mean %	Std. Deviation	Std. Error Mean
Pair 1	*Lactobacillus fermentum* & *Lactobacillus ghanensis*	12	0.105	0.744	92.942	7.6708	2.2144
Pair 2	*Lactobacillus fermentum* % & *Lactobacillus delbrueckii* %	12	0.692	0.013	89.825	8.8019	2.5409
Pair 3	*Lactobacillus fermentum* % & *Lactobacillus plantarum* %	12	0.582	0.047	92.942	7.6708	2.2144
Pair 4	*Lactobacillus fermentum* % & *Lactococcus lactis* %	12	0.079	0.807	86.667	12.3091	3.5533
Pair 5	*Lactobacillus fermentum* % & *Lactobacillus reuteri*, %	12	0.667	0.018	92.942	7.6708	2.2144
Pair 6	*Lactobacillus fermentum* % & *Lysinibacillus sphaericus*, %	12	0.344	0.274	86.317	8.8616	2.5581
Pair 7	*Lactobacillus fermentum* % & *Bacillus pacificus* %	12	-0.106	0.744	92.942	7.6708	2.2144
Pair 8	*Lactobacillus ghanensis* % & *Lactobacillus delbrueckii* %	12	0.217	0.497	91.675	9.6129	2.7750
Pair 9	*Lactobacillus ghanensis* % & *Lactobacillus plantarum* %	12	0.456	0.136	92.942	7.6708	2.2144
Pair 10	*Lactobacillus ghanensis* % & *Lactococcus lactis* %	12	-0.033	0.919	81.875	10.0071	2.8888
Pair 11	*Lactobacillus ghanensis* % & *Lactobacillus reuteri*, %	12	-0.308	0.330	92.942	7.6708	2.2144
Pair 12	*Lactobacillus ghanensis* % & *Lysinibacillus sphaericus*, %	12	0.644	0.024	84.508	15.4958	4.4733
Pair 13	*Lactobacillus ghanensis* % & *Bacillus pacificus* %	12	0.365	0.244	92.942	7.6708	2.2144
Pair 14	*Lactobacillus delbrueckii* % & *Lactobacillus plantarum* %	12	0.793	0.002	84.850	10.4869	3.0273
Pair 15	*Lactobacillus delbrueckii* % & *Lactococcus lactis* %	12	0.171	0.596	89.825	8.8019	2.5409
Pair 16	*Lactobacillus delbrueckii* % & *Lactobacillus reuteri*, %	12	0.443	0.149	86.667	12.3091	3.5533
Pair 17	*Lactobacillus delbrueckii* % & *Lysinibacillus sphaericus*, %	12	0.454	0.138	89.825	8.8019	2.5409
Pair 18	*Lactobacillus delbrueckii* % & *Bacillus pacificus* %	12	0.147	0.648	86.317	8.8616	2.5581
Pair 19	*Lactobacillus plantarum* % & *Lactococcus lactis* %	12	0.402	0.195	89.825	8.8019	2.5409
Pair 20	*Lactobacillus plantarum* % & *Lactobacillus reuteri*, %	12	0.150	0.642	91.675	9.6129	2.7750
Pair 21	*Lactobacillus plantarum* % & *Lysinibacillus sphaericus*, %	12	0.683	0.014	89.825	8.8019	2.5409
Pair 22	*Lactobacillus plantarum* % & *Bacillus pacificus* %	12	0.423	0.170	81.875	10.0071	2.8888
Pair 23	*Lactococcus lactis* % & *Lactobacillus reuteri*, %	12	0.098	0.761	89.825	8.8019	2.5409
Pair 24	*Lactococcus lactis* % & *Lysinibacillus sphaericus*, %	12	0.218	0.496	84.508	15.4958	4.4733
Pair 25	*Lactococcus lactis* % & *Bacillus pacificus* %	12	-0.001	0.999	89.825	8.8019	2.5409
Pair 26	*Lactobacillus reuteri*, % & *Lysinibacillus sphaericus*, %	12	-0.089	0.783	84.850	10.4869	3.0273
Pair 27	*Lactobacillus reuteri*, % & *Bacillus pacificus* %	12	-0.118	0.715	86.667	12.3091	3.5533
Pair 28	*Lysinibacillus sphaericus*, % & *Bacillus pacificus* %	12	0.385	0.216	86.317	8.8616	2.5581

Table 5: Paired Samples Test

		Paired Differences					T	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	*Lactobacillus fermentum* % - *Lactobacillus ghanensis* %	3.1167	11.0485	3.1894	-3.9032	10.1365	0.977	11	0.349
Pair 2	*Lactobacillus fermentum* % - *Lactobacillus delbrueckii* %	6.2750	8.9269	2.5770	.6031	11.9469	2.435	11	0.033
Pair 3	*Lactobacillus fermentum* % - *Lactobacillus plantarum* %	6.6250	7.6350	2.2040	1.7740	11.4760	3.006	11	0.012
Pair 4	*Lactobacillus fermentum* % - *Lactococcus lactis* %	1.2667	11.8150	3.4107	-6.2402	8.7735	0.371	11	0.717
Pair 5	*Lactobacillus fermentum* % - *Lactobacillus reuteri,* %	11.0667	7.5238	2.1719	6.2863	15.8471	5.095	11	0.000
Pair 6	*Lactobacillus fermentum* % - *Lysinibacillus sphaericus,* %	8.4333	14.7382	4.2545	-.9308	17.7975	1.982	11	0.073
Pair 7	*Lactobacillus fermentum* % - *Bacillus pacificus* %	8.0917	13.6318	3.9352	-0.5696	16.7529	2.056	11	0.064
Pair 8	*Lactobacillus ghanensis* % - *Lactobacillus delbrueckii* %	3.1583	13.4869	3.8933	-5.4109	11.7275	0.811	11	0.434
Pair 9	*Lactobacillus ghanensis* % - *Lactobacillus plantarum* %	3.5083	9.2083	2.6582	-2.3424	9.3590	1.320	11	0.214
Pair 10	*Lactobacillus ghanensis* % - *Lactococcus lactis* %	-1.8500	13.2469	3.8241	-10.2667	6.5667	-0.484	11	0.638
Pair 11	*Lactobacillus ghanensis* % - *Lactobacillus reuteri,* %	7.9500	15.2267	4.3956	-1.7246	17.6246	1.809	11	0.098
Pair 12	*Lactobacillus ghanensis* % - *Lysinibacillus sphaericus,* %	5.3167	11.9176	3.4403	-2.2554	12.8887	1.545	11	0.151
Pair 13	*Lactobacillus ghanensis* % - *Bacillus pacificus* %	4.9750	10.9609	3.1641	-1.9892	11.9392	1.572	11	0.144
Pair 14	*Lactobacillus delbrueckii* % - *Lactobacillus plantarum* %	.3500	7.5507	2.1797	-4.4475	5.1475	0.161	11	0.875
Pair 15	*Lactobacillus delbrueckii* % - *Lactococcus lactis* %	-5.0083	14.2674	4.1186	-14.0734	4.0567	-1.216	11	0.249
Pair 16	*Lactobacillus delbrueckii* % - *Lactobacillus reuteri,* %	4.7917	11.9401	3.4468	-2.7947	12.3781	1.390	11	0.192
Pair 17	*Lactobacillus delbrueckii* % - *Lysinibacillus sphaericus,* %	2.1583	14.7751	4.2652	-7.2293	11.5460	0.506	11	0.623
Pair 18	*Lactobacillus delbrueckii* % - *Bacillus pacificus* %	1.8167	14.9496	4.3156	-7.6819	11.3152	0.421	11	0.682
Pair 19	*Lactobacillus plantarum* % - *Lactococcus lactis* %	-5.3583	10.1202	2.9215	-11.7884	1.0718	-1.834	11	0.094
Pair 20	*Lactobacillus plantarum* % - *Lactobacillus reuteri*, %	4.4417	12.3330	3.5602	-3.3943	12.2777	1.248	11	0.238
Pair 21	*Lactobacillus plantarum* % - *Lysinibacillus sphaericus,* %	1.8083	11.4519	3.3059	-5.4679	9.0845	0.547	11	0.595
Pair 22	*Lactobacillus plantarum* % - *Bacillus pacificus* %	1.4667	10.4789	3.0250	-5.1913	8.1247	0.485	11	0.637
Pair 23	*Lactococcus lactis* % - *Lactobacillus reuteri,* %	9.8000	13.1768	3.8038	1.4278	18.1722	2.576	11	0.026
Pair 24	*Lactococcus lactis* % - *Lysinibacillus sphaericus,* %	7.1667	16.3583	4.7222	-3.2269	17.5602	1.518	11	0.157
Pair 25	*Lactococcus lactis* % - *Bacillus pacificus* %	6.8250	14.2297	4.1078	-2.2161	15.8661	1.661	11	0.125
Pair 26	*Lactobacillus reuteri*, % - *Lysinibacillus sphaericus,* %	-2.6333	19.1804	5.5369	-14.8200	9.5533	-0.476	11	0.644
Pair 27	*Lactobacillus reuteri*, % - *Bacillus pacificus* %	-2.9750	15.3269	4.4245	-12.7132	6.7632	-0.672	11	0.515
Pair 28	*Lysinibacillus sphaericus,* % - *Bacillus pacificus* %	-.3417	14.9969	4.3292	-9.8702	9.1869	-0.079	11	0.939

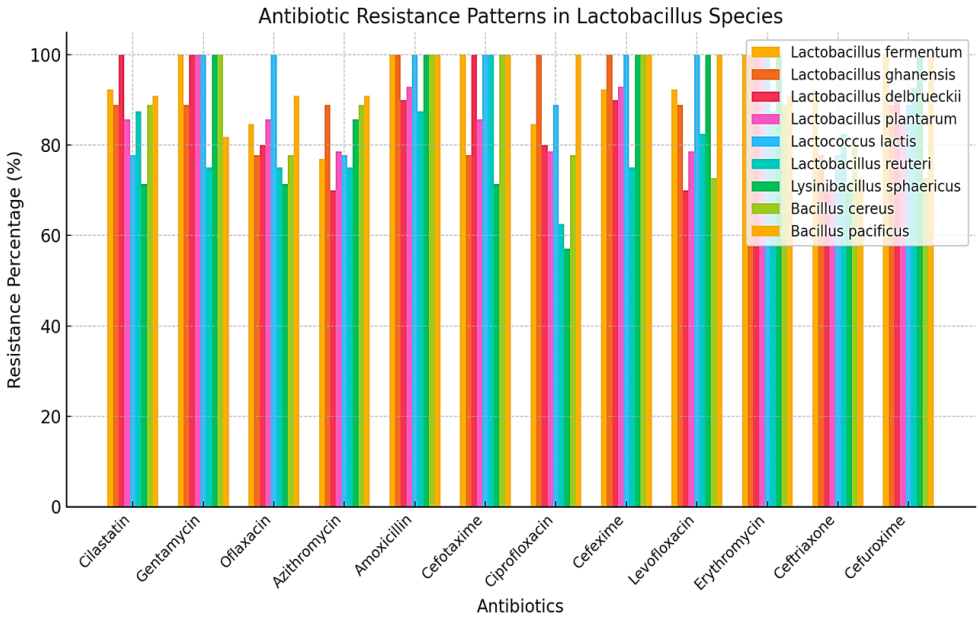

Figure 1: The graph showing the antibiotic resistance patterns for different Lactobacillus species. Each bar represents the resistance percentage for each species against a specific antibiotic, with different colors corresponding to each bacterial species.

DISCUSSION

The comparative analysis of antibiotic resistance and probiotic potential of *Lactobacillus* species isolated from fermented cassava and corn samples yielded significant findings that provide insights into the microbial dynamics and resistance profiles of these strains. The results in Table 2 reveal distinct antibiotic susceptibility patterns among the bacterial isolates. For example, *Lactobacillus delbrueckii* showed high susceptibility across most antibiotics, with zones of inhibition ranging from 19 mm to 25 mm, indicating its vulnerability to these drugs. Conversely, *Lactobacillus fermentum* demonstrated resistance to Amoxicillin (10 mm, R) and Ciprofloxacin (13 mm, R), emphasizing its reduced susceptibility. *Lactobacillus reuteri* showed strong resistance to Cefotaxime (13 mm, R) but significant susceptibility to Levofloxacin (23 mm, S) and Azithromycin (23 mm, S). *Bacillus cereus* and *Bacillus pacificus* exhibited broader susceptibility, particularly with Ciprofloxacin, Ceftriaxone, and Cefuroxime, achieving zones above 20 mm. The findings highlight antibiotic efficacy disparities and potential bacterial resistance trends. Table 3 revealed that among the various antibiotics tested, *Lactobacillus fermentum* showed the highest resistance percentage (92.3%) to Cilastatin, followed closely by *Lactobacillus ghanensis* (88.9%) and *Lactobacillus delbrueckii* (100%) for Gentamycin. In contrast, *Lactobacillus reuteri* exhibited the lowest resistance at 75.0% against Gentamycin, suggesting variability in susceptibility across strains[1]. This resistance profile aligns with previous studies that highlight the adaptive mechanisms of probiotics in response to antimicrobial pressure, supporting their potential in clinical and environmental applications [2, 3]. Paired sample analysis (Table 4) further provided statistical evidence on the comparative resistance levels of *Lactobacillus* species. A significant correlation was observed between *Lactobacillus fermentum* and *Lactobacillus delbrueckii* ($p = 0.013$), with a moderate correlation coefficient of 0.692. This indicates a shared resistance trait between these strains, which could be attributed to their similar metabolic pathways or environmental conditions in fermented foods [4]. Conversely, the resistance correlation between *Lactobacillus fermentum* and *Lactococcus lactis* was weak ($r = 0.079$, $p = 0.807$), suggesting divergent resistance mechanisms [5]. Similarly, other pairs such as *Lactobacillus fermentum* and *Lactobacillus reuteri* ($r = 0.667$, $p = 0.018$) also showed significant correlation, underscoring the shared resistance characteristics within the *Lactobacillus* genus [6]. The correlation data from Table 5 illustrated diverse interactions among the strains. A strong negative correlation ($r = -0.582$, $p = 0.047$) was found between *Lactobacillus fermentum* and *Lactobacillus plantarum*, indicating that these strains exhibit opposing responses to antibiotic pressure. This could be due to varying environmental adaptation or genetic differences

affecting their resistance mechanisms [7, 8]. Other species such as *Lysinibacillus sphaericus* and *Bacillus pacificus* exhibited weak correlations (r = 0.344, p = 0.274), signifying less uniformity in resistance across different species.[9,10] Further statistical analyses, including p-values and correlation coefficients, suggest that the probiotic potential of these strains may be influenced by their resistance profiles. Higher resistance levels to certain antibiotics may correlate with increased stability in harsh gastrointestinal environments, making these strains viable candidates for probiotic applications. The significant correlations observed, especially within *Lactobacillus* species, support the notion that resistance mechanisms may be co-selected with probiotic traits, as evidenced by similar findings in earlier studies.[11,12] Figure 1 shows antibiotic resistance patterns across nine bacterial species, with high resistance observed against Amoxicillin and Cefexime, while Ciprofloxacin and Levofloxacin showed lower resistance. *Bacillus cereus* and *Lactobacillus fermentum* displayed consistently high resistance levels. The findings highlight the prevalence of resistance mechanisms and the importance of monitoring and using effective antibiotics strategically. The findings from this study provide valuable insights into the antibiotic resistance and probiotic potential of *Lactobacillus* species. The observed variability in resistance levels and significant correlations between certain strains highlight the complexity of microbial interactions in fermented foods. These data suggest that *Lactobacillus* species, despite their differing resistance profiles, may offer promising potential for use in probiotic formulations, particularly when their resistance traits are carefully considered in product development.

CONCLUSION

In conclusion, this study provides a comprehensive analysis of the antibiotic resistance and probiotic potential of *Lactobacillus* species isolated from fermented cassava and corn. The results reveal significant variability in resistance profiles among the strains, with some exhibiting high resistance to certain antibiotics while others demonstrated lower resistance. Statistical correlations between species suggest that resistance mechanisms may be shared within certain strains, particularly among *Lactobacillus* species, which may influence their probiotic efficacy. The findings highlight the complexity of microbial interactions in fermented foods and underscore the potential of these strains as viable candidates for probiotic applications. While the high antibiotic resistance observed in some strains warrants further investigation, these strains may offer enhanced stability in harsh gastrointestinal conditions. Overall, the study contributes to a better understanding of the relationship between antibiotic resistance and probiotic potential, providing a foundation for future research and development of probiotic products from local fermented foods.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Statement

The study is proper with ethical standards, it was approved by the Department of Biological Sciences (Microbiology), Benson Idahosa University on 26th February, 2024.

Authors' Contribution

Study Conception: OBA, ESA; Study Design: OBA, ESA; Supervision; OBA, ESA; Funding: N/A; Materials: OBA, ESA; Data Collection and/or Processing: OBA, ESA; Analysis and/or Data Interpretation: OBA, ESA; Literature Review: OBA, ESA; Critical Review: OBA, ESA; Manuscript preparing: OBA, ESA.

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Outcomes of Steroid and Pulse Steroid Therapies in COVID-19 Inpatients Requiring Oxygen Therapy, Retrospective Case Control Study

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ABSTRACT

Background: A limited number of studies have been conducted examining the course of the disease and the effectiveness of corticosteroid treatments in patients with severe COVID-19 pneumonia requiring oxygen support. This study assessed steroid effectiveness in oxygen-dependent COVID-19 patients.

Methods: Included in the study were 670 patients who required oxygen support during their hospital stay among the 6,532 Covid-19 patients between 1 August 2020 and 1 June 2021. Demographic data, comorbidities, duration of oxygen therapy, length of hospital stay, corticosteroid treatments (dexamethasone, methylprednisolone) and pulse corticosteroid treatments (methylprednisolone ≥ 250 mg) were recorded. We analyzed data using Statistical Package for the Social Sciences Program (Version 16.0. Chicago, SPSS) and applied Shapiro-Wilk, Mann-Whitney U, Kruskal-Wallis, and Chi-square tests for statistical significance ($p<0.05$).

Results: The mean age of the patients was 64±13 (19–95) years, 55% were male, and the mean duration of hospital stay was 9±6 (1–64) days. Dexamethasone, pulse steroids, and low-dose methylprednisolone (<80 mg) were given to 41%, 13%, and 18% of patients, respectively. 31.6% required ICU admission, and the overall hospital mortality rate was 18.1%. Notably, 83% of deaths occurred within the first week.

Conclusion: Most deaths in oxygen-dependent COVID-19 patients happened within 7 days. While corticosteroids didn't impact overall mortality, dexamethasone seemed to boost discharge without ICU admission.

Keywords: COVID-19, dexamethasone, mortality, oxygen therapy, pulse corticosteroid therapy

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INTRODUCTION

It has been reported that approximately 15% of patients infected with COVID-19 require inpatient treatment, although an effective and standard therapeutic approach to hospitalized patients has yet to be established. Mortality is relatively higher in the presence of comorbidities such as obesity, DM, HT, and coronary artery disease. The treatments administered to inpatients are shaped according to the resources of the countries and the guidelines published by the local health authorities. While the use of Favipiravir was until recently a standard approach in our country, the use of dexamethasone 6 mg/day became a routine treatment in patients requiring oxygen therapy after the Recovery trial, leading clinicians to feel encouraged to administer pulse steroid therapies. Early detection and treatment of cytokine storm in patients with severe COVID-19 pneumonia who require oxygen support outside of the ICU reduces the risk of the patient going to the ICU.[1] Tocilizumab and Anakinra are effective in controlling the "cytokine storm" in severe COVID-19 pneumonia requiring oxygen, but their high cost and limited availability make them difficult to access. This, coupled with physician' inexperience in their use, can lead to treatment delays. Consequently, readily available and affordable pulse corticosteroids like dexamethasone have become commonplace in hospital settings to manage this inflammatory response. Yet, despite their widespread adoption, data on the long-term effectiveness and patient outcomes of dexamethasone and other pulse corticosteroids remain scarce. Our study fills this gap by delving deeper into the clinical course of these patients and meticulously analyzing the impact of corticosteroid therapies on their recovery trajectories. By addressing this critical knowledge gap, we aim to optimize treatment strategies and potentially streamline care pathways, ultimately improving patient outcomes and potentially reducing the risk of long-term health complications.

METHODS

Data collection and study design

Our study analyzed data from 670 patients requiring oxygen support during their hospitalization for COVID-19. These patients were drawn from a pool of 6,532 patients admitted to the Eskisehir City Hospital COVID-19 wards between August 1, 2020, and June 1, 2021. We retrospectively collected data from the hospital information management system (HIMS) and patient files, focusing on demographics (age, gender), comorbidities, PCR test results, oxygen therapy and hospital stay durations, as well as details of corticosteroid treatment received (dexamethasone, methylprednisolone, and pulse steroid therapy with methylprednisolone≥250 mg). The treatments received by the patients were recorded, including blood sugar monitoring, electrolyte monitoring, and possible side effects of the patients receiving steroids. The outcomes of the study patients were determined as "discharge from the ward", "death on the ward", "discharge from the intensive care unit", and "death in the intensive care unit".

Statistical analysis

We entrusted SPSS (IBM SPSS Ver. 16.0, IBM Corp, Chicago, USA) version 16.0 to meticulously analyze the collected data. First, we verified the normality of quantitative data using the Shapiro-Wilk test. We then employed a trio of statistical methods to uncover meaningful patterns: the Mann-Whitney U test for comparisons between two groups, the Kruskal-Wallis analysis for detecting differences among multiple groups, and the Chi-square test for exploring relationships between categorical variables. Throughout these analyses, we set a stringent significance level of $p<0.05$ to ensure the findings were statistically robust.

RESULTS

The mean age of the patients was 64±13 (19–95) years, 55% were male, and the mean duration of hospital stay was 9±6 (1–64) days. Considering comorbidities, there was a significantly high rate of patients with hypertension (41.5%), diabetes mellitus (22.8%), and asthma (11.9%). While almost all of these patients received Favipiravir therapy, five patients could not tolerate the drug, and administration was stopped. Plaquenil was added to the existing therapies of five patients, and 10 patients received convalescent plasma. Oxygen therapy was initiated in 10% of the patients who were hospitalized in the COVID-19 wards. Of the 449 patients in the study group who were discharged directly from the ward, 134 required oxygen support for 7 days, 239 for 8 to 14 days, and 76 for longer than 15 days.

The total hospital mortality rate (121/670) was 18.1% in patients admitted to the wards and initiated on oxygen therapy. Of the patients, 449 (67%) were

discharged from the inpatient wards, and nine patients died on the ward. Approximately 32% (212) of the patients who were initiated on oxygen therapy needed to be transferred to the intensive care unit.

The CS therapies administered to the study patients are summarized in Table 1.

The mortality rate was 53% in the patient group admitted to the intensive care unit, from which 100 patients were discharged. Among the non-surviving patients, 72.7% and 26.4% were over 65 and 81 years of age, respectively, while 65.2% were male. Mortality was significantly higher in males and in the patient groups with comorbidities of hypertension, diabetes mellitus, heart disease, and dementia. Moreover, 83% of the deaths occurred within the first seven days of hospitalization. The outcomes of the study patients are summarized in Table 2.

Dexamethasone and/or Pulse Steroids were used at a higher rate in the patients discharged from the ward than in those discharged from the intensive care unit, and the difference was found to be associated with the use of dexamethasone. The clinical characteristics of the patients receiving and not receiving dexamethasone are summarized in Table 3. Dexamethasone and pulse steroid therapies were found to increase the likelihood of a patient being discharged from the ward without admission to the intensive care unit ($p<0.05$).

There was no significant difference in mortality between those who received and did not receive CS (Table 4). There was no significant association between the time of CS administration and mortality according to the start of oxygen therapy.

Finally, Table 5 shows the differences in the demographic characteristics, comorbidity rates, and corticosteroid therapies of non-survivors and survivors. Statistical significance was found between the surviving and non-surviving groups in terms of age groups, gender, and comorbidities ($p<0.05$).

DISCUSSION

There is still no universally accepted treatment agent for COVID-19. Under normal conditions, immunity in a healthy individual copes with COVID-19 infection, the replication of the virus is prevented, and the disease progresses mildly. When an appropriate and strong immune response is not developed, the disease progresses to the hyperinflammation phase. If the infection cannot be controlled with appropriate immune responses, the developing cytokine storm will be life-threatening. Immunosuppressive treatments started to gain importance in the pandemic after it was understood that the hyperinflammatory process and adaptive T cell response were dominant in determining the prognosis of COVID-19 infection.[2] For COVID-19 patients with severe ARDS or septic shock, the World Health Organization (WHO) recommends glucocorticoids. However, routine use of these drugs for general inflammation is not recommended.[3] A range of studies have delved into the question of when and how to administer steroids, evaluating the impact on mortality and complications across various indications.[4,5] Corticosteroid use in COVID-19 treatment became more common after the RECOVERY study identified a mortality reduction

Table 1. Corticosteroid therapies are administered to patients receiving oxygen therapy

Corticosteroid therapies	Rate of use
Dexamethasone	41% of patients
Pulse steroids (corticosteroids ≥250 mg)	13% of patients
Methyl prednisolone ≤80 mg	18% of patients
No corticosteroids	28% of patients

Table 2. Clinical outcomes of COVID-19 patients receiving oxygen therapy

Patient Outcomes	n	%
Discharge from the Ward	449	67%
Discharge from the Intensive Care Unit	100	14.9%
Death on the Ward	9	1.3%
Death in the Intensive Care Unit	112	16.7%
Total number of patients	670	100%

Table 3. Age, Gender, Comorbidities, Clinical Outcomes of Patients Receiving and Not Receiving Dexamethasone

	Dexamethasone Therapy			
	Not Receiving n (%)	Receiving n (%)	Total n (%)	P-value
Age groups (years)				
≤49	47 (51.6)	44 (48.4)	91 (13.6)	0.429
50–64	140 (60.1)	93 (39.9)	233 (34.8)	
65–79	151 (61.4)	95 (38.6)	246 (36.7)	
≥80	58 (58.0)	42 (42.0)	100 (14.9)	
Gender				
Female	181 (60.3)	119 (39.7)	300 (44.8)	0.560
Male	215 (58.1)	155 (41.9)	370 (55.2)	
Comorbidities				
No	146 (58.2)	105 (41.8)	251 (37.5)	0.703
Yes	250 (59.7)	169 (40.3)	419 (62.5)	
Outcomes				
Discharge from the ward	244 (54.3)	205 (45.7)	449 (67.0)	***0.001**
Discharge from the intensive care unit	75 (75.0)	25 (25.0)	100 (16.7)	
Death on the ward	6 (66.7)	3 (33.3)	9 (1.3)	
Death in the intensive care unit	71 (63.4)	41 (36.6)	112 (16.7)	
Total	396 (59.1)	274 (40.9)	670 (100.0)	

Table 4. The effect of the corticosteroid therapies on patient outcomes

CS Support	n	Discharge from the ward	Rate of ICU admission	Discharge from the ICU	Death in the ICU	Hospital Mortality
Received Decort	274	205	25.1%	25	44	16%
Not received Decort	396	244	38.4%	75	77	19.4%
Received pulse-steroid therapy	90	62	31%	12	16	17.7%
Never received CS	322	194	39.7%	64	64	19.8%
Low-dose Prednisolone	121	84	30.5%	15	22	18.1%

ICU: Intensive Care Unit

Table 5. Demographic characteristics, comorbidity rates, and corticosteroid therapies of non-surviving and surviving patient groups

	Non-survivors n (%)	Survivors n (%)	Total n (%)	P
Age groups (years)*				
≤49	3 (3.3)	88 (96.7)	91 (13.6)	**0.001**
50–64	25 (10.7)	208 (89.3)	233 (34.8)	
65–79	57 (23.2)	189 (76.8)	246 (36.7)	
≥80	36 (36.0)	64 (64.0)	100 (14.9)	
Gender				
Female	42 (14.0)	248 (86.0)	300 (44.8)	**0.014**
Male	79 (21.4)	291 (78.6)	370 (55.2)	
Comorbidities				
No	22 (8.8)	229 (91.2)	251 (37.5)	**0.001**
Yes	99 (23.6)	320 (76.4)	419 (62.5)	
Dexamethasone				
No	77 (19.4)	319 (80.6)	396 (59.1)	0.263
Yes	44 (16.0)	230 (84.0)	274 (40.9)	
Pulse Steroids				
No	105 (18.1)	475 (81.9)	580 (86.5)	1.000
Yes	16 (17.8)	74 (82.2)	90 (13.5)	
Dexamethasone and/or Pulse Steroids				
Not Received	64 (19.9)	258 (80.1)	322 (48.1)	0.240
Received	57 (16.4)	291 (83.6)	348 (51.9)	
Methylprednisolone Alone				
No	99 (18.0)	452 (82.0)	551 (82.2)	0.998
Yes	22 (18.5)	97 (81.5)	119 (17.8)	
Total	121 (18.1)	549 (91.9)	670 (100.0)	

associated with 6mg/kg dexamethasone.[6] PST has also become widespread with the demonstration that pulse steroid administration provides a similar decrease in mortality.[7] Several studies indicate that early administration of corticosteroids, particularly dexamethasone, is associated with reduced mortality in critically ill COVID-19 patients.[8-10] Systemic corticosteroids likely reduce all-cause mortality slightly in hospitalized COVID-19 patients.[11] Early use of corticosteroids (within the first 48 hours of ICU admission) is linked to better outcomes, including lower ICU mortality and fewer complications compared to delayed administration.[8,9]

In previous studies of oxygen therapy provided outside the intensive care unit generally sought to measure the success of non-invasive mechanical ventilation methods such as Continuous Positive Airway Pressure (CPAP) or High-Flow Nasal Cannula (HFNC). Our review of literature identified only one study investigating COVID-19 patients receiving oxygen therapy outside of the intensive care unit, which was conducted in Germany and included 57 patients who did not require or did not want to be admitted to the intensive care unit among 133 inpatients initiated on oxygen support. It would seem that 76 patients not included in this study required intensive care, and that these patients needed supplemental oxygen for a mean of 8 (5–13) days and had a mean hospital stay of 12 (7–20) days. The authors reported that 13 patients died on the ward, although 12 had decided to limit the treatment.[12] When compared to our patient group, this study reports a much higher rate of intensive care need among the patients. Our study provides detailed information about the rates of deterioration and the benefit of corticosteroid support administered in addition to respiratory support in patients initiated on oxygen support on the ward, and this can be considered a strength of our study. It was found in the study that at the time when we had not yet started accepting patients with the delta variant, one out of every three inpatients who were initiated on oxygen therapy required intensive care treatment, and one out of every two patients who were admitted to the intensive care unit died. Since the publication of the Recovery trial during the third wave of the pandemic, it has become almost routine treatment to administer dexamethasone 6 mg/day to COVID-19 patients requiring oxygen therapy for 10 days or until discharge. The inclusion of patients receiving treatment during the second wave in our study allowed for a comparison of mortality between the groups that received and those that did not receive dexamethasone. The comparison of the groups receiving and not receiving dexamethasone revealed no difference in total hospital mortality, although the rate of dexamethasone use was significantly higher in the patient group who were discharged from the ward. Although the rate of intensive care requirement (25.1% < 38.4%) and the hospital mortality rate were lower (16% < 19.2%) in the dexamethasone-treated group, the difference was statistically insignificant. The Recovery trial reported significantly lower 28-day mortality in the dexamethasone group among the non-intubated patients receiving oxygen (23.3% < 26.2%).[1] There was also no difference in mortality between the groups receiving and not receiving corticosteroid therapy, although this finding should be interpreted considering that patients receiving pulse-steroid therapy may suffer relatively more severe respiratory failure. The weakness of our study is that the laboratory data of the patients during the COVID-19 treatment were not evaluated for disease severity, and so it would make no sense to compare the clinical outcomes of patients receiving pulse-steroid therapy with those receiving other CS therapies or not receiving them at all. Some 70% of the patients receiving pulse-steroid therapy, however, were discharged without the need for intensive care, which may give an idea about the success of the treatment. In our study, various confounding factors may have played a role in the lack of a significant difference in mortality between the groups that received and did not receive CS. In particular, comorbidities, disease severity, the type of oxygen support, and concomitant treatments may have influenced the outcomes. Considering these factors, isolating the effect of steroids on mortality has become challenging. Among the limited number of high-quality studies in the literature measuring the success of pulse-steroid therapies, most focus on the outcomes of patients administered pulse-steroid therapies, while others report patients being treated with concomitant anticytokine therapies such as tocilizumab. A limited number of studies have compared high-dose and low-dose CS therapies, but did not consider lung involvement and/or inflammatory laboratory parameters when determining disease severity. A number of studies have not been included in the discussion because they were carried out in intensive care units with many confounding factors.

Batırel et al.[13] compared three groups of 150 patients treated with standard support therapy (Group

1), dexamethasone 6 mg/day (Group 2), and pulse-steroid therapy (methylprednisolone 250 mg/day) (Group 3). The groups were matched for disease severity (the National Early Warning Score (NEWS2)) and demographic characteristics. Despite the lack of a statistically significant difference in mortality between the groups (Groups 1/2/3: 23.8%/ 17.4%/ 7.9%), the rate of intensive care unit admission was significantly lower in the dexamethasone group, as in our study. The authors found that the need for intensive care was lower in the pulse-steroid therapy group than in the Group 1 patients, and reported a shorter ICU stay among the pulse-steroid therapy group. It should be noted that the NEWS2 score was established based on the clinical findings of the patients (respiratory rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness or new confusion, temperature), while the inflammatory marker laboratory parameters were not taken into account.[13] In another study, Cusacovich et al.[14] compared 124 patients who underwent pulse-steroid therapy at a dose of ≥100 mg for three days (92% of patients received 250 mg pulse methylprednisolone for 3 days) with 133 patients who did not receive pulse therapy, and reported significantly lower mortality in the pulse group (30.3%<42.9%).

In this study, dexamethasone was not administered to any of the patients, and so no comparison can be made of high-dose and low-dose CS therapies. In our country, especially since the fourth wave of the pandemic, the administration of pulse Prednol 250 mg has become almost routine practice in cases of clinical deterioration in the patient groups without DM or in those with known coronary artery disease. When anti-cytokine therapies are considered, these treatments are primarily administered due to their low cost.

Our study evaluated the impact of corticosteroid (CS) therapy on mortality in oxygen-treated COVID-19 patients and found no significant difference between those who received and did not receive CS. While previous studies suggest a reduction in mortality with steroid treatment, the available data do not provide a clear answer regarding the potential survival benefit of pulse-steroid therapy. Moderate-to-high doses of corticosteroids have been associated with better outcomes than low doses; however, the optimal dosage remains uncertain.

This study covers the second and third waves of the pandemic, during which physicians increasingly favored pulse-steroid therapy, particularly in patients experiencing an acute disease phase, lack of fever response, or worsening PAAC radiographic findings. In clinical practice today, pulse-steroid therapy is often considered a last resort before intensive care, making future controlled studies on this approach unlikely.

Our study has several limitations, including its retrospective design, the lack of laboratory data to assess disease severity, and the unknown stage of the disease at the time of CS administration. Additionally, potential confounding factors, such as differences in baseline characteristics and concurrent treatments, may have influenced the results. Further prospective studies with detailed disease severity assessments are needed to clarify the role of pulse-steroid therapy in COVID-19 management.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Statement

The study was approved by both the Turkish Ministry of Health and the Ethics Committee of Trakya University Faculty of Medicine (Decision Date: 27/12/2021 and No: 25/49), and all necessary administrative permissions were obtained from the Turkish Ministry of Health, the Eskisehir Provincial Health Directorate and the Office of the Chief Physician of Eskisehir City Hospital. This study was carried out following the principles of the Declaration of Helsinki and all applicable regulations.

Authors' Contribution

Concept – ZIK,SE; Design –SE; Supervision – SE; Fundings – ZIK,SE; Materials – ZIK, SE; Data collection and/or processing – ZIK; Analysis and/or interpretation – ZIK,SE; Literature review – SE; Writing – ZIK,SE; Critical review – SE

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Prescribing Cascade in an Older Adult with Bipolar Disorder

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ABSTRACT

The prescribing cascade begins when medication side effects are misinterpreted as new symptoms, leading to the addition of new drugs.

This case involves a 75-year-old female with a history of Parkinson's disease, dementia, bipolar disorder, and diabetes. She presented with complaints of bradykinesia, difficulty walking, and inability to move independently. The patient had been on long-term antipsychotic treatment (olanzapine) for bipolar disorder, leading to parkinsonian symptoms, which were mistakenly diagnosed as dementia. Consequently, the patient was prescribed donepezil, an antidementia medication. During this period, she developed depression and urinary incontinence, for which duloxetine and fesoterodine fumarate were added to her treatment. The patient's functionality and quality of life further deteriorated due to inappropriate medication use and polypharmacy.

After evaluation, a decision was made to gradually discontinue several of the patient's medications, including memantine, fesoterodine fumarate, and donepezil, while reducing the olanzapine dose. Following these adjustments, her mobility improved, appetite increased, and overall condition stabilized.

This case highlights the need to closely monitor older adults with mental health problems taking multiple medications for adverse drug reactions. The frequency of monitoring should be individualized according to the patient's risk factors and treatment response. It also contributes to increased awareness among healthcare professionals and caregivers of the prescribing cascade among these individuals.

Keywords: Prescribing cascade, Older patient, Antipsychotic medications

INTRODUCTION

The definition of inappropriate medication use is a comprehensive term that includes unnecessary drug use, overuse or underuse of clinically indicated drugs, and polypharmacy.[1,2] One in every four hospital admissions of older adults is due to medication-related problems. Nearly 70% of these admissions are attributed to adverse drug reactions.[3] The concept of the prescribing cascade is in the category of inappropriate medication use. The prescribing cascade often begins when the side effects of a medication are misinterpreted as new symptoms of an illness, leading to the addition of another medication to the patient's regimen. Although the exact prevalence of the prescribing cascade is unknown, it poses significant morbidity and mortality risks, particularly for older patients.

Therefore, more attention is required when initiating and prescribing medications to older patients to prevent the prescribing cascade. In this study, we present a case in which the prescribing cascade, resulting from inappropriate medication use, negatively affected functionality and quality of life.

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CASE REPORT

A 75-year-old female patient with a history of Parkinson's disease, dementia, bipolar disorder, and diabetes mellitus was admitted to our geriatric outpatient clinic with complaints of bradykinesia and inability to walk. The patient was accompanied by her daughter and arrived in a wheelchair. The patient had been diagnosed with bipolar disorder for ten years, Parkinson's disease for five years, diabetes mellitus for five years, and dementia for four years. She had been experiencing difficulty walking for about two years and was unable to move independently without assistance from her relatives. For about two years, her introverted behavior, lack of motivation, and refusal to eat and drink worsened every three or four weeks and then somewhat improved. On physical examination, the patient was introverted, oriented, and cooperative. Neurological examination revealed no lateralizing findings, resting tremor, cogwheel rigidity, or bradykinesia. She exhibited a blank stare, but responded when spoken to. She was assisted to perform a few small steps with support. The Katz Index of Independence in Activities of Daily Living (ADL) score was 0 out of 6.[4] The Lawton-Brody Instrumental Activities of Daily Living Scale (IADL) score was 0 out of 8.[5] The patient's relatives reported no memory complaints but mentioned that she had become increasingly withdrawn and did not want to talk to others. The patient had been taking olanzapine 10 mg/d for ten years, haloperidol drops 0.5-1 mg/d as needed, memantine 10 mg/d for four years, donepezil 5 mg/d for two years, duloxetine 60 mg/d for two years, fesoterodine fumarate 8 mg/d for two years, and metformin 1000 mg/d for five years. After being diagnosed with bipolar disorder ten years ago, she was started on olanzapine and the dose was gradually increased from 5 mg/d to 10 mg/d. About five years ago, she was diagnosed with Parkinson's disease and started on antiparkinsonian medication, but it was discontinued due to vomiting, sleep disturbances, and confusion. Four years ago, following complaints of hallucinations, inability to recognize relatives, and disorientation within the house, she was diagnosed with dementia and started on memantine 10 mg/d. Concurrently, due to the development of depression, duloxetine was initiated. During this period, the patient was able to move indoors with the aid of a walker. Two years ago, donepezil was added to the dementia regimen. The patient had urinary incontinence despite mobilization with a walker, attributed to functional limitations. Other etiological causes were excluded. Two months after the initiation of donepezil, an increase in urinary incontinence was observed. Subsequently, fesoterodine fumarate was prescribed.

The laboratory tests did not reveal any abnormalities. Her blood glucose level was 122 mg/dL and her HbA1c level was 5.8% while on metformin. A previously performed brain magnetic resonance imaging (MRI) showed ischemic-gliotic foci and atrophy consistent with age. The Mini-Mental State Examination (MMSE) score was 22 out of 30, and the Yesavage Geriatric Depression Scale (YGDS) score was 11 out of 15.[6,7] After this extensive workup, bipolar depression and a prescribing cascade were considered in the patient. Gradual discontinuation of inappropriate medications was planned. During the first evaluation, memantine, haloperidol drops used as needed, fesoterodine fumarate, and metformin were discontinued. The olanzapine dose was reduced to 5 mg/d, and donepezil and duloxetine were continued. After one week, no clinical changes were observed, and donepezil was discontinued. One week after discontinuing donepezil, the patient's appetite slightly improved, and her gaze became more attentive. She was able to walk with the support of her relatives. Olanzapine was reduced to 2.5 mg/d, and duloxetine was continued. Two weeks later, during reassessment, the patient was observed to be walking with a walker. Her appetite and mood improved, and she had a more attentive gaze. She was more engaged in conversations. The ADL score increased 4 out of 6 (independent on transfer with a walker, feeding, dressing, and toileting; dependent on bathing and urinary continence) , and her IADL score remained 0 out of 8.[4,5] The patient, who was followed up in our outpatient clinic for six months, did not experience any issues related to medications, and despite the olanzapine dose not being increased, the psychiatric symptoms associated with bipolar disorder remained stable.

DISCUSSION

BMS poses a diagnostic and therapeutic chaIn this case, we aimed to highlight the effects of inappropriate medication use and the prescribing cascade in an older adult with bipolar disorder. Older patients are often at the highest risk of experiencing a prescribing cascade due to multimorbidity.[8] In particular, the medical management of mental illnesses, which become more prevalent with age, may lead to this inappropriate

medication use.

Long-term use of high-dose antipsychotic medications is associated with an increased risk of falls and death in the older population.[9] Additionally, individuals with bipolar disorder, regardless of age, are at an increased risk of adverse effects from antipsychotic medications and may be exposed to a prescription cascade.[10] This case exhibited Parkinsonian symptoms as a consequence of prolonged, high-dose antipsychotic exposure. Long-term use of antipsychotic medications has been associated with the potential for cognitive impairment. Studies suggest that prolonged exposure to antipsychotics, particularly at higher doses, may contribute to deficits in cognitive domains such as memory, executive functioning, and attention.[11] Additionally, structural brain changes, such as reductions in cortical and subcortical volumes, have been reported in some patients on chronic antipsychotic therapy, further raising concerns about their impact on cognition.[12]

The concurrent cognitive and functional decline associated with chronic high-dose antipsychotic use led to a misdiagnosis of dementia, resulting in the inappropriate administration of memantine, an anti-dementia drug, and donepezil, a cholinesterase inhibitor. These drugs are effective in managing symptoms of dementia and are associated with several common side effects in older patients, including nausea, vomiting, loss of appetite, insomnia, hallucinations, depression, agitation, anxiety disorders, and frequent urination.[13] Because of these side effects, it is necessary to closely monitor patients after initiating cholinesterase inhibitors in this population. In our case, depression and urinary incontinence developed after initiating the antidementia medication. To address these symptoms, duloxetine and fesoterodine fumarate were prescribed, and then the patient experienced severe functional impairment. The side effects of these drugs in this case were mistaken as signs of diseases, and treatment with other medications led to polypharmacy. As a result, physicians need to pay close attention to adverse drug reactions when prescribing new agents, especially in older adults with mental disorders.

This case highlights the need to closely monitor older adults with mental health problems taking multiple medications for adverse drug reactions. The frequency of monitoring should be individualized according to the patient's risk factors and treatment response. It also contributes to increased awareness among healthcare professionals and caregivers of the prescribing cascade among these individuals.

Author Contributions:

Concept – SG,MC,MIN; Design – SG, MC,; Supervision – MIN; Resources - SG; Materials – SG,MC,MIN; Data Collection and/or Processing – SG,MC; Analysis and/or Interpretation - SG,MC,MIN; Literature Search – SG,MC; Writing Manuscript - SG,MC,MIN; Critical Review - SG,MC,MIN;

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Ethical Statement

In accordance with ethical standards, all patient information was anonymized, and no formal ethics approval was necessary..

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A Case Report on Caffeine-induced Psychological Disorders and Acute Kidney Injury Following Excessive Energy Drink Consumption

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ABSTRACT

Here, we report a 20-year-old male patient who developed acute kidney injury after consuming six cans of energy drinks daily for the last week. His daily intake amounted to about 426 mg of caffeine and 2268 mg of taurine. He was also diagnosed with caffeine intoxication and caffeine withdrawal at the time of his hospitalization. Considering the potential damage of energy drinks may cause to people's health, this case calls for regulations on their use.

Keywords: Acute kidney injury, adverse effect, caffeine intoxication, caffeine withdrawal, energy drinks

INTRODUCTION

Although energy drinks (ED) were initially introduced to the market and aimed to increase exercise performance, due to the caffeine and other substances they contain, it has been used for alternative purposes for many years.[1] Most ED ingredients contain caffeine, L-carnitine, taurine, B vitamins, glucuronolactone, antioxidants, trace minerals, guarana, sucrose, Ginkgo biloba, and/or ginseng, which act as stimulants.[2] Caffeine, or 1,3,7-trimethylxanthine, is a stimulant that promotes alertness. It blocks the adenosine receptor, increasing intracellular calcium concentration and promoting catecholamine release.[3] As a result, energy drinks are increasingly popular among certain groups. Reports to the Food and Drug Administration (FDA) include a range of adverse effects, such as psychiatric symptoms, arrhythmia, cardiac arrest, myocardial infarction, convulsions, and kidney injury.[4] We report an acute kidney injury observed in a case of caffeine intoxication following excessive energy drink consumption.

CASE REPORT

A 20-year-old male patient was admitted to the emergency room due to severe back and abdominal pain, nausea, and dizziness. The patient, who worked as a hostess and frequently had night shifts, had been consuming excessive amounts of energy drinks for the past year. For the last week, he had been drinking 6 cans of energy drinks a day. He had no complaints of vomiting or diarrhea. No history of psychiatric or physical illness, alcohol or smoking usage, and a family history of mental or physical illness.

Physical examination revealed a blood pressure of 121/80 mm Hg, heart rate of 75 bpm, respiratory rate of 20 breaths/min, temperature of 36.5 C, and O2 saturation of 99% on room air. After a thorough examination, the electrocardiography and chest radiography did not reveal any pathological findings. His heart and abdominal examinations were normal. His laboratory findings were as follows: serum creatinine (SCr): 1.57 mg/dL, BUN: 20 mg/dL. The parameters for arterial blood gases were pH:

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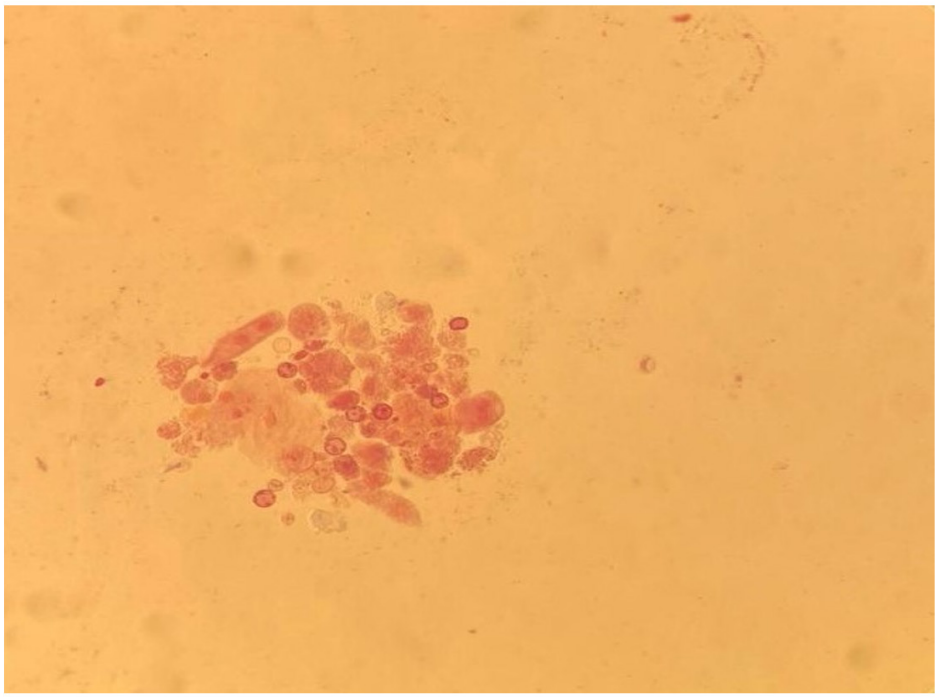

Figure 1. Epithelial cells and leukocytes in the urine sediment

7.27, HCO_3: 29.1 mmol/L, PCO_2: 64.2, and Lac: 2.27 mmHg. The estimated glomerular filtration rate (eGFR) was 62.52 (mL/min/1.73 m2). Previous laboratory analysis one year prior had revealed a BUN of 7,5 mg/dL and SCr of 0.9 mg/dL. Measurement of total blood count, clotting parameters, electrolytes, and liver enzymes were within normal ranges over the course of the treatment. Also, urinalysis was normal. No acute lesion was observed in the abdomen ultrasound imaging and both kidneys were normal in size. Because of type B hyperlactatemia, the patient was monitored in the intensive care unit for a day. The excessive intake of caffeine was linked to the consumption of six cans of energy drinks per day in the last week according to the anamnesis taken from the patient.

On the second day, the patient was transferred to the internal medicine service for evaluation of acute kidney injury. His fractional sodium excretion was calculated at 7% and BUN/SCr was 12.7 (<20). His renal failure index was 10.58 (>1). There were epithelial cell casts in the patient's urine sediment (Figure 1). Findings were consistent with acute kidney injury. Serum albumin, protein, calcium, uric acid, and hematocrit levels were in the normal range. The daily urine samples tested negative for leukocytes, nitrite, ketone, and bilirubin and revealed normal levels of glucose and urobilinogen. Also, HIV antibodies and hepatitis serology were negative. The patient's serum creatinine levels gradually decreased to normal over one week (Table 1).

The patient reported severe headaches, back pain, skin flushing, depressed mood, and irritability after one week of discontinuation of energy drinks. The patient was consulted by psychiatry due to caffeine withdrawal. Sertraline 25 mg and Ketiapin 25 mg were started. The patient was discharged after seven days in the hospital after a re-examination by a psychiatrist due to the regression of the patient's symptoms. Cognitive therapy was recommended, and outpatient

Table 1. Blood and Urine Chemistry Values

Reference Time Point	SCr (mg/dL)	BUN (mg/dL)	Estimated GFR (mL/min/1.73 m^2)
1 year before the presentation	0.9	7.5	124
Day 1	1.57	20	62,52
Day 3	1.52	9.2	65,02
Day 7	1.1	10	95,08
3 Weeks After Presentation	0.8	7	125

Abbreviations: eGFR: estimated glomerular filtration rate, SCr: serum creatinine, BUN: blood urea nitrogen.

follow-up was without pathologic finding three weeks after discharge.

DISCUSSION

BMS poses a diagnostic and therapeutic chaIn this casThe popularity of energy drinks has increased in the last two decades.[3] One of the reasons for this situation is the marketing of energy drinks to young adults and adolescents by beverage companies.[5] Some adverse effects have previously been reported due to excessive consumption of energy drinks. These may be cardiac, gastrointestinal, neurological, and nephrological side effects.[1] It has been reported that some fatal cases.[2] Also, we underline that caffeine-induced psychological disorders should not be forgotten. Adverse nephrological side effects of energy drinks were reported in a review published by Costantino A. et al.[1] We also observed one of these adverse nephrological effects in our patient.

Table 2. Ingredients of the energy drink consumed by the patient

Ingredient	Amount
Caffeine	150 mg/L
Taurin	800 mg/L
Niacin	8mg / 50% RDA per 100ml
Pantotenik Acid	2mg / 33% RDA per 100ml
B6	2 mg/ 143% RDA per 100ml
B12	2 mcg/ 80% RDA per 100ml

RDA: Recommended Daily Allowance

The patient was drinking six of the (473 mL) 16-oz energy drinks per day. This equates to approximately 426 mg of caffeine daily (Table 2). Although caffeine is the primary psychoactive ingredient in energy drinks, acute kidney injury resulting from caffeine intake alone has not yet been reported. Some cases of acute kidney injury have been reported due to the taurine substance found in energy drinks. Schöffl et al. reported acute kidney injury in a 17-year-old male patient after consuming 3L of energy drinks and 1L of vodka. The patient had an intake of 780 mg caffeine and 4600 mg taurine.[7] Another case is a 40-year-old male patient who developed acute kidney injury after consuming 6 16. oz energy drinks a day was reported by Greene E. et al.[8] The patient had many additional diseases in his medical history, such as diabetes mellitus type 2, hypertension, gout, and alcohol abuse. Furthermore, the patient was taking multiple medications, specifically NSAIDs. It was difficult to determine the etiology due to diabetes and the medications he used. In our case, the patient had no chronic disease, no alcohol addiction, and no drug use shows us more clearly the development of acute kidney injury after the energy drink.

A common nutritional supplement taken by athletes to enhance performance is taurine, an amino acid that contains sulfur. Suliman et al.[9] reported that the use of taurine in end-stage renal disease patients is risky in their study. Additionally, Al Yacoub R et al.[10] presented a case in which acute kidney injury and acute hepatitis developed simultaneously after consuming six cans of 16 oz energy drinks per day. They reported that acute kidney injury was most likely due to taurine, and acute hepatitis was due to niacin. The side effects of energy drinks have been tested experimentally using animal models. Histopathological effects of energy drinks on the liver, kidneys, heart, and brain were studied by Salih et al. using rabbits as an animal model. Their findings suggest a direct correlation between tissue damage and the dose administered. At higher doses, they observed renal vascular congestion, the bleeding of interstitial tissue, focal atrophy, and the degeneration of the lining epithelium of the proximal and distal convoluted tubules.[11] Rasheed et al.[12] showed histopathological changes such as increased tubular vacuolization in renal tubular cells in rats exposed to energy drinks. Since our patient's laboratory findings and clinical condition improved after IV hydration, a kidney biopsy was not necessary in this case. Therefore, considering that the patient had been consuming excessive amounts of energy drinks for the last year, it was not possible to determine whether there was any chronic damage. (Such as interstitial fibrosis, lymphocyte and plasma cell infiltration observed in chronic interstitial nephritis).

There have been reports on the connection between caffeine use and caffeine-induced psychological disorders.[6] The Diagnostic and Statistical Manual for Mental Disorders, 5th Edition (DSM-5) proposes 4 caffeine-related syndromes.[13] Our case fulfills the criteria for diagnosis of "Caffeine Intoxication" and "Caffeine Withdrawal" (Table 3, Table 4). Since the patient had not yet requested a psychiatric examination, we were unable to evaluate his psychiatric reversal after caffeine discontinuation.

In this case, we aimed to show how addiction can result in serious, even fatal, consequences like acute

Table 3. Diagnostic Criteria for Caffeine Intoxication

A. Recent consumption of caffeine (typically a high dose, more than 250 mg).
B. Five (or more) of the following signs or symptoms developing during, or shortly after, caffeine use: 1. Restlessness. 2. Nervousness. 3. Excitement. 4. Insomnia. 5. Flushed face. 6. Diuresis. 7. Gastrointestinal disturbance. 8. Muscle twitching. 9. Rambling flow of thought and speech. 10. Tachycardia or cardiac arrhythmia. 11. Periods of inexhaustibility. 12. Psychomotor agitation.
C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.

Table 4. Diagnostic Criteria for Caffeine Withdrawal

A. Prolonged daily use of caffeine.
B. Abrupt cessation of or reduction in caffeine use, followed within 24 hours by three (or more) of the following signs or symptoms: 1. Headache. 2. Marked fatigue or drowsiness. 3. Dysphoric mood, depressed mood, or irritability. 4. Difficulty concentrating. 5. Flu-like symptoms (nausea, vomiting, or muscle pain/stiffness).
C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The signs or symptoms are not associated with the physiological effects of another medical condition (e.g., migraine, viral illness) and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

kidney injury. Fortunately, our patient's acute kidney injury was treated, and his addiction was diagnosed. However, this condition could be more dangerous if it is not diagnosed on time, especially in patients with serious comorbidities.

CONCLUSION

Caffeine, which is also the main ingredient of energy drinks, can cause syndromes such as addiction and withdrawal. Hence, we advise that daily energy drink intake should not be above the caffeine safety limitations defined by regulatory authorities, and should even be lowered based on the information available in the literature. Furthermore, additional systematic investigations are necessary to clarify the long-term effects of energy drink intake on human health.

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. Ali Can Memiş is the article guarantor.

Conflict of Interest

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A Case Report: Q Fever with Acute Hepatitis

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ABSTRACT

Q fever is a zoonotic bacterial infection caused by *Coxiella Burnetii*. The primary sources of this pathogen are small and large livestock. The causative agent is disseminated into the environment through the birth products, milk, feces, and urine of infected animals. This bacterium is highly resistant to environmental conditions. Transmission from animals to humans and/or from humans to humans occurs via inhalation. The acute disease presentation can be asymptomatic or resemble influenza-like symptoms, and it can also lead to more severe manifestations such as fever, pneumonia, and hepatitis. In cases with severe clinical courses, Q fever should be considered in the differential diagnosis, especially considering epidemiological risks. This paper discusses a case presenting with fever, jaundice, and hepatitis, subsequently diagnosed as Q fever.

Keywords: Fever, Hepatitis, Jaundice

INTRODUCTION

Q fever is a zoonotic systemic disease caused by the Gram-negative intracellular coccobacillus *Coxiella Burnetti*.[1] Q fever was first reported in 1937 by Edward Holbrook Derrick, who was investigating a febrile illness among abattoir workers in Australia.[2] Subsequently, during World War II, it manifested as atypical pneumonia in the United States, Greece, and Germany.[3] The first Q fever outbreak in Turkey was reported by Payzın in Aksaray in 1947.[4]

The main source of the pathogen is livestock, including cattle and sheep. Farmers, veterinarians, and butchers are at risk for Q fever. The pathogen spreads through inhalation; due to its resistance to environmental conditions, it can be carried up to 10 kilometers away by water and wind. After settling in the lungs, it spreads throughout the body via the bloodstream, leading to systemic illness. The incubation period is from 3 to 30 days, and depending on the bacterial load, it can present in various forms from asymptomatic to severe systemic disease.[1, 3]

Acute disease is usually mild. It can cause fever, severe retro-orbital headache, muscle pain, and a non-productive cough. Atypical pneumonia is detected in 40-50% of cases, and approximately 35% of these cases are accompanied by hepatitis.[3] In nearly all cases, the disease is self-limiting within two weeks. However, 5-8% progress to the chronic form. In chronic Q fever, symptoms persist for more than six months; prolonged fatigue and muscle pain may be observed even after full remission. Endocarditis, valvulitis, and osteomyelitis are frequently observed complications.[1, 3]

Although bacterial serology is most commonly preferred for diagnosis, the gold standard method is the polymerase chain reaction(PCR) test. The indirect immunofluorescence assay(IFA) is the best diagnostic

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method in acute cases. In this test, a fourfold or greater increase in Phase 2 IgG titer (IgG>1:128) is considered significant. In chronic disease, a Phase 1 IgG titer greater than 1:800 is considered significant.

For the treatment of acute disease, 14-21 days of doxycycline therapy is sufficient. Alternatively, macrolide and quinolone antibiotherapy can be preferred. In chronic disease, it is recommended to use doxycycline and hydroxychloroquine together for at least 12 months.[1, 3] In selected cases, such as pregnant women and those with endocarditis, the treatment regimen and duration may vary.[3]

CASE REPORT

A 46-year-old male patient presented to the district state hospital with a three-day history of abdominal pain and newly onset jaundice, which began a day ago. Upon evaluation in the emergency department, his blood pressure was within normal limits, pulse was 104 bpm, subfebrile fever (37.8 ^{0}C), and fingertip oxygen saturation was measured at 97%. On physical examination, his skin and sclerae were icteric, lung auscultation sounds normal, and abdominal palpation revealed tenderness, particularly in the right upper quadrant, with voluntary guarding. No palpable lymphadenopathy or hepatosplenomegaly was found. In his complete blood count, leukocyte and hemoglobin levels were normal, but thrombocytopenia was present. Biochemical tests showed that transaminase levels were 4,5 times above the upper limit, cholestasis enzymes were normal, total bilirubin was elevated with direct bilirubin dominance. C-reactive protein was elevated, and INR was normal. Abdominal ultrasonography revealed a contracted gallbladder, normal intrahepatic and extrahepatic bile ducts, and normal liver and spleen sizes. Based on these outcomes, the patient was referred to our internal medicine clinic for further investigation and treatment, with the knowledge of our gastroenterology specialist.

Upon admission to our clinic, initial tests showed elevated transaminase levels, hyperbilirubinemia with direct bilirubin dominance, normal cholestatic enzymes, elevated C-reactive protein, increased urea and creatinine, and thrombocytopenia without any abnormalities in the erythrocyte and leucocyte series (Table 1). Additionally, cultures and serological tests for viral hepatitis were sent for the detection of an infectious focus. The patient was empirically started on intravenous (IV) ceftriaxone 2x1 g and metronidazole 3x500 mg antibiotics along with hydration support.

To screen for potential hepatobiliary pathologies, upper abdominal dynamic magnetic resonance imaging (MRI), MR cholangiopancreatography (MRCP), and portal Doppler ultrasonography (USG) were performed under the consultation of the gastroenterology clinic. These examinations revealed no signs of hepatobiliary pathology in the patient.

Although the patient presented with isolated thrombocytopenia in the complete blood count, further tests were conducted to evaluate disseminated intravascular coagulation (DIC) and hemolytic processes, even though no signs of bleeding were observed. The patient's prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and LDH levels were normal, and the peripheral blood smear showed no evidence of DIC or hemolysis. The peripheral blood smear confirmed true thrombocytopenia (Plt:15.000-20.000/mcL) with normochromic normocytic erythrocytes. The white blood cell formula is consistent with normal findings, and no atypical cells are observed. Based on these tests, the thrombocytopenia was primarily considered secondary to infection.

No growth was detected in the cultures sent during the patient's hospitalization. The viral hepatitis serology was unremarkable, except for past hepatitis A infection. Additionally, tests for Toxoplasmosis, Rubella, Cytomegalovirus (CMV), Herpes virüs(HSV), Brucella, Epstein-Barr virüs(EBV), and Syphilis were also conducted, but they all came negative. As the patient showed a decreasing trend under IV ceftriaxone and metronidazole, we had a further consultation with the Infectious Disease. Samples sent to the Public Health Laboratory to test other potential infectious agents, including West Nile virus, Leptospira, Hantavirus, Coxiella, and Crimean-Congo Hemorrhagic Fever virus. In addition, doxycycline 2x100 mg was added to the patient's treatment regimen to cover up these pathogens.

On the ninth day of hospitalization, during the ongoing treatment, follow-up tests showed regression in transaminases and hyperbilirubinemia, decreased infectious parameters, resolution of acute kidney injury, and normal platelet levels (Table 1). Significant improvement was also observed in his symptoms and clinical findings. While treatment was still in progress, the patient chose to leave the hospital against medical advice. He was prescribed doxycycline tablets 100 mg twice daily as a continued treatment on an outpatient basis.

After the patient left the hospital, test results from

Table 1. Follow-up tests of the patient

Test	Day 1	Day 9
AST	138 mg/dL	23 mg/dL
ALT	92 mg/dL	43 mg/dL
Total bilirubin	24 mg/dL	7 mg/dL
Direct bilirubin	19 mg/dL	2,45 mg/dL
ALP	79 U/L	43 U/L
GGT	30 U/L	28 U/L
INR	1,05	1,01
Urea	80,3 mg/dL	16,4 mg/dL
Creatinine	1,46 mg/dL	0,95 mg/dL
CRP	128 mg/L	5 mg/L
WBC	8.370/µL	4.170/µL
PLT	21.000/µL	235.000/µL
Hb	12,4 g/dL	12,6 g/dL

AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma glutamyl transferase, INR: international normalization rate, CRP: c-reactive protein, WBC: white blood cell count, PLT: platelet count, Hb: Hemoglobin

the Public Health Laboratory were received. Results showed that the patient's *Coxiella Burnetti* Phase 2 IgG was positive at a titer of 1:512. It was concluded that the patient's current clinical presentation was consistent with Q fever.

DISCUSSION

Acute Q fever can range from being asymptomatic to presenting with a severe clinical course involving multiple organ involvement.[4,5] In our patient, the disease manifested with subfebrile fever accompanied by jaundice, elevated transaminases, acute kidney injury, and thrombocytopenia. Pneumonia, which is commonly observed in Q fever, was not present in our patients. The prominent finding of severe jaundice at the time of presentation initially led to consideration of common hepatitis causes and cholestatic diseases in differential diagnosis. The exclusion of these primary diagnoses through initial testing prompted further investigation into less common etiologies and the initiation of empirical treatment targeting these.

Indeed, the patient, who responded dramatically to empirical ceftriaxone and doxycycline therapy, was later confirmed to have Q fever through subsequent testing.

Given that Q fever is a zoonotic disease, it is essential to consider Q fever in the differential diagnosis of patients presenting to hospitals with clinical pictures such as acute hepatitis, pneumonia, kidney injury and heart failure, especially if these patients have a history of living in rural areas, farming or livestock handling and have elevated acute phase reactants. Considering the potential delay in diagnosis and the possibility of severe clinical outcomes, such as liver failure and endocarditis, which could lead to higher mortality if left untreated or if the diagnosis is delayed, empirical antibiotherapy should be considered in these cases.

CONCLUSION

Caffeine, which is also the main ingredient of energy drinks, can cause syndromes such as addiction and withdrawal. Hence, we advise that daily energy drink intake should not be above the caffeine safety limitations defined by regulatory authorities, and should even be lowered based on the information available in the literature. Furthermore, additional systematic investigations are necessary to clarify the long-term effects of energy drink intake on human health.

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. Ali Can Memiş is the article guarantor.

Conflict of Interest

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Ethical Statement

In accordance with ethical standards, all patient information was anonymized, and no formal ethics approval was necessary.

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