Infective Endocarditis in Individuals with Drug Addiction: A Retrospective Cohort Study Conducted at "Dr. Carol Davila" Central Military Emergency University Hospital in Bucharest

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Posted Date: 10 October 2024

doi: 10.20944/preprints202410.0729.v1

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Article

Infective Endocarditis in Individuals with Drug Addiction: A Retrospective Cohort Study Conducted at "Dr. Carol Davila" Central Military Emergency University Hospital in Bucharest

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Abstract: Objective: Evaluation of individuals with intravenous drug addiction who developed infective endocarditis (IE) is required for a better understanding of the management that can be applied in these cases. This study aimed to shed light on the complex interplay between intravenous drug use and IE with the ultimate goal of improving patient care and outcomes **Method**: The study examined the clinical outcomes of 43 patients admitted with infective endocarditis (IE) associated with injection drug use. Data was collected over an average follow-up period of 12 months, providing a substantial timeframe to assess the long-term effects of different treatment approaches. The research focused on comparing the outcomes between two distinct groups: patients who received medical treatment alone and those who underwent surgical intervention in addition to medical management. **Results** This study included 43 intravenous drug users who were diagnosed with infective endocarditis (IE). The mean age of the patient cohort was 31 ± 9 years with a predominance of males (74.4%). All cases involved native valve IE, with the aortic valve being the most commonly affected (62.9%), followed by the tricuspid (30.2%) and mitral valves (6.9 %). Multiple valve involvement was observed in 13.9% of the cases. The study population had a high prevalence of comorbidities, particularly HIV infection (65.1%) and hepatitis C infection (25.5%). The study also revealed that 19.3% of the patients had previously experienced IE. Mortality rates were slightly higher in patients with recurrent IE (23.2%) than in those who experienced their first episode. Transthoracic echocardiography proved to be a highly effective diagnostic tool for detecting vegetation in 95% of the cases. Microbiological analysis identified Staphylococcus aureus as the predominant causative organism, isolated from blood cultures in 55.8% of the cases. These findings highlight the complex nature of IE in intravenous drug users, emphasizing the importance of comprehensive management strategies that address both cardiac manifestations and underlying comorbidities in this high-risk population. **Conclusions:** Injection drug use–associated infective endocarditis presents a significant challenge in modern healthcare, with patients facing a high risk of complications and poor clinical outcomes despite current therapeutic approaches. This persistent issue underscores the complexity of treating individuals with both infectious diseases and substance use disorders. The multifaceted nature of these cases often involves immediate cardiac infection, as well as concurrent medical, psychological, and social challenges that can complicate treatment and recovery.

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 doi:10.20944/preprints202410.0729.v1

1. Introduction

Intravenous drug use is a predisposing factor and constitutes a minor diagnostic criterion for IE. The implications of this condition are significant for health care providers and public health officials. Evolving patterns of drug use may lead to a shift in IE epidemiology among drug users. Healthcare professionals should be aware that while intravenous drug use remains a risk factor for IE, its prevalence may decrease owing to changes in drug administration routes. [1]

Diagnostic criteria for IE may require re-evaluation to account for the changing landscape of drug use patterns and their associated risks. Therefore, public health interventions aimed at reducing IE incidence among drug users may need to be adapted to address the non-intravenous routes of drug administration. Further research is necessary to elucidate the impact of alternative drug administration routes on IE risk and develop appropriate prevention strategies. Medical education and clinical guidelines may require updates to reflect the changing trends in drug use and their implications for IE diagnosis and management.

The increasing prevalence of life-threatening bacterial infections among patients with substance use disorders has become a significant concern in the medical community. [1,2] In particular, the increase in IE cases associated with injection drug use is alarming, especially among younger populations. [2] This trend not only highlights the severe health risks associated with intravenous drug use but also underscores the need for targeted interventions and improved healthcare strategies. The progression of infections to sepsis poses a substantial threat to patient survival, emphasizing the urgent need to address this growing public health issue. [1–3] A multifaceted approach is necessary to effectively combat this problem. This includes a thorough examination of epidemiological factors such as demographic trends, geographical distribution, and risk factors associated with IE in drug users. Understanding the etiology of these infections, including the most common causative organisms and their antibiotic resistance patterns, is crucial for developing effective treatment protocols.

By gaining a comprehensive understanding of these aspects, health care providers can formulate more targeted management strategies, improve early detection methods, and implement preventive measures. Ultimately, this approach aims to reduce the mortality rates associated with IE in substance users and address the broader implications of this health crisis on both individual and public health levels [2,3].

Various studies have demonstrated that more than one-third of patients who are intravenous drug users present left-sided IE. [3,4] This investigation underscores the critical nature of IE, emphasizing its rarity but substantial mortality and morbidity rates. This intricate interplay of factors emphasizes the necessity for a nuanced approach to IE management, particularly when considering the heterogeneous patient population affected by this condition. [4–6]

The prevalence of IE hospitalizations, particularly those associated with injectable drug use, has exhibited a significant upward trend worldwide. Multiple studies and data sources have indicated a substantial increase in cases across various regions. [5,6]

The data revealed an overall increase in IE caused by injection drug use hospitalizations, with a remarkably high rate. More recent analyses suggest an even more pronounced growth, with some estimates indicating a 12-fold increase in hospitalizations between 2007 and 2017. [5]

Additional evidence from single- and multicenter studies demonstrates that this type of IE constitutes a larger proportion of hospitalizations and surgeries. For instance, in a North Carolina hospital, the number of cases increased from 14% in 2009 to 56% in 2014. [5,6] Similarly, the number of cases requiring heart valve surgery increased from 19% in 2012 to 28% in 2017 across the eight academic centers. The mortality rate associated with this trend was also significantly higher.[6] The distinct clinical profile of patients with IE induced by injection drug use are characterized by younger age, higher rates of homelessness, and increased prevalence of Hepatitis C and HIV and necessitates tailored treatment approaches and targeted public health interventions.[4–6] Regional variations in the demographics of this patients highlight the need for localized strategies to address the unique challenges faced by different populations affected by injection drug use and associated infections.[5,6] The significantly younger age of this category of patients compared to patients who

 doi:10.20944/preprints202410.0729.v1

don't use drugs underscores the urgent need for early intervention and prevention programs targeting at-risk youth and young adults.[6,7]

Antimicrobial therapy remains the first-choice treatment, often involving prolonged courses of intravenous antibiotics tailored to the causative organism and its susceptibility profile. [9,10] In cases where medical management alone is insufficient, surgical intervention may be required to address complications, such as persistent infection, heart failure, or recurrent embolization. [10] However, the management of injection drug use in IE extends beyond treating acute infections. It is crucial to integrate addiction treatment and harm reduction strategies into care plans to address the root cause of the condition and prevent recurrence. [11] This may involve initiating medication-assisted treatment for opioid use disorders, providing counseling and behavioral interventions, and connecting patients with community resources for ongoing support. Additionally, educating patients about safer injection practices, needle exchange programs, and the importance of regular health screenings can help reduce the risk of future infection. [9–11]

Antimicrobial treatment for infective endocarditis (IE) is a complex process that typically involves the administration of parenteral antibiotics for a period–2-6 weeks. [11–13]

The specific antibiotic regimen was carefully tailored to each patient's unique circumstances, taking into account several critical factors. These include the species of the infecting organism and its susceptibility to various antimicrobials, the presence of prosthetic valves or other artificial materials in the heart, the patient's ability to tolerate specific antibiotics, and the need for effective tissue penetration to address metastatic or distant infections. This personalized approach ensures that the treatment is as effective as possible while minimizing potential side effects and complications. [12,13] The decision to perform valve surgery in patients with IE, whether drug related or not, is complex and must be made on an individual basis. Early surgery before the completion of antibiotic therapy is often considered when there are significant anatomical or structural concerns. [12] These include the development of new valvular regurgitation, symptomatic right or left heart failure, or heart block, which can be indicative of an intracardiac abscess. Other factors that may necessitate early surgical intervention include persistent bacteremia despite appropriate antibiotic therapy, ongoing embolic events, or the presence of large vegetations on the heart valves. [12,13] Specifically, vegetations larger than 10 mm on the anterior leaflet of the mitral valve are considered significant enough to warrant consideration for early surgery. [14,15]

2. Materials and Methods

2.1. Study Design

We completed a retrospective cohort analysis of patients admitted to the Infectious Disease Department of the "Dr. Carol Davila" Central Military Emergency University Hospital in Bucharest between January 1, 2017 and December 31, 2022. The study population included 43 adult patients. The investigation received approval from the Ethics Committee of the hospital (Decision No. 562/20.12.2022). Informed consent was obtained from all patients included in this study.

2.2. Setting

The diagnosis of IE was made based on the algorithm of the European Society of Cardiology, accordind to the modified Duke criteria, including those used for imagistical evaluation. Data collected from the patients included demographic information, medical history, and echocardiographic parameters. For all the patients included in this study, two sets of blood specimens were obtained for culture analysis in specialized vials: one vial for aerobic bacteria and one for anaerobic bacteria, both of which were inoculated simultaneously in each set. The specimens were obtained from venous blood, from different anatomical sites. The collections were conducted at minimum intervals of 30 minutes in 24 h.

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2.3. Study Population

This study, conducted over a six-year period from January 2017 to December 2022, focused on cases of infective endocarditis (IE) associated with intravenous drug use (IDU) at the "Dr. Carol Davila" Central Military Emergency University Hospital in Bucharest. The research team utilized an existing administrative database to identify cases, followed by a comprehensive review of medical records to collect detailed clinical, demographic, operative, and outcome data for patients diagnosed with IDU-IE based on Modified Duke's criteria. The scope of the study encompassed both medical and surgical management aspects, including treatment duration and type, surgical indications and timing, and in-hospital and postoperative complications. To ensure a thorough analysis, the researchers also gathered follow-up data on vital status, rehospitalization, and subsequent surgical interventions for all patients by examining hospital medical records. This study defined IDU-IE as a clinical diagnosis of endocarditis in patients with a history of active injection drug use at the time of presentation. This definition allows for a focused examination of this specific patient population, providing valuable insights into the characteristics, management, and outcomes of IDU-IE cases within the context of a major Romanian medical center.

2.4. Statistical Analysis

The Mann-Whitney U test was applied to assess the statistical significance of the results for each parameter. The Kruskal-Wallis test yielded p-values, which indicate the probability of obtaining differences as significant or greater than those observed in our data, assuming that the null hypothesis is valid. If the p-value was less than the predetermined significance level of 0.05, we rejected the null hypothesis and concluded that there were significant differences between at least two groups. Statistical analyses were performed using SPSS software version 26.

3. Results

Between January 2017 and December 2022, a comprehensive study was conducted on 43 cases of IE associated with intravenous drug use (IDU-IE) that required hospitalization. The study population had distinct demographic and clinical characteristics. (Table 1) The patients were predominantly young adults (mean age: 31 years; range: 18–40 years). A significant gender disparity was observed, with males constituting nearly three-quarters (74.4 %) of the cases. Notably, almost a quarter of the patients (23.2%) had a previous history of infective endocarditis, indicating the recurrent nature of the condition in this population.

This study also revealed a high prevalence of concomitant infectious diseases among patients with IDU-IE. Serological testing revealed that a quarter of the patients (25.5%) were positive for hepatitis C, whereas an alarming 65.1% tested positive for human immunodeficiency virus (HIV). These findings underscore the complex health challenges faced by individuals with IDU-IE, highlighting the need for comprehensive treatment strategies that address not only the cardiac manifestations of the disease, but also the underlying comorbidities and substance use disorders. The high rates of hepatitis C and HIV coinfection emphasize the importance of integrated care approaches that encompass infectious disease management, addiction treatment, and cardiac care for this high-risk patient population.

Table 1. Patients characteristics.

PATIENTS CHARACTERISTICS	NO.(%)
SEX	
MALE	32(74.4%)
FEMALE	11(25.6%)
AGE	
<20	7(16.2%)
20-30	21(48.8%)
31-40	15(34.8%)
COMORBIDITIES	

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HEPATOCELLULAR CARCINOMA	2(4.6%)
HIV	28(65.1%)
HEPATITIS C	11(25.5%)
HEPATITIS B	2(4.6%)
CHRONIC RENAL FAILURE	1(2.3%)
HYPERTENSION	3(6.9%)
CHRONIC ALCOHOLISM	14(32.5%)
ESOPHAGEAL VARICES	2(4.6%)
CELLULITIS	16(37.2%)
NECROTIZING FASCIITIS	1(2.3%)
AIDS	2(4.6%)
STROKE	4(9.3%)
SIFILIS	1(2.3%)
URINARY TRACT INFECTIONS	8(18.6%)
ORAL/VAGINAL CANDIDIASIS	19(44.1%)
PNEUMONIA	4(9.3%)
KAPOSI SARCOMA	1(2.3%)

The study included patients with native valve endocarditis (NVE), a serious infection of the heart valves. The aortic valve was the most commonly affected valve, accounting for 62.9% of cases, followed by the tricuspid valve (30.2%) and mitral valve (6.9%). Echocardiography proved to be a highly effective diagnostic tool for detecting vegetation in 95% of cases. Blood cultures were universally positive, with *Staphylococcus aureus* emerging as the predominant causative organism in 55.9% of cases, followed by *Enterococcus faecalis* in 16.4%. (Table 2)

Table 2. Distribution of etiological agents in intravenous drug users.

ETIOLOGICAL AGENTS ISOLATED IN BLOOD CULTURES	NO.(%)
STAPHYLOCOCCUS AUREUS	24(55.9%)
ENTEROCOCCUS FAECALIS	7(16.4%)
STREPTOCOCCUS MITIS	6(13.9%)
STAPHYLOCOCCUS EPIDERMIDIS	3(6.9%)
KLEBSIELLA PNEUMONIAE	3(6.9%)

Infections in this study were predominantly community-acquired, accounting for 90.7% of cases, whereas nosocomial infections were relatively rare, comprising only 9.3% of the total. This distribution suggests that the majority of IE cases originated outside healthcare settings, highlighting the importance of community-based prevention strategies and early detection measures.

Surgical intervention was necessary in a significant proportion of patients, with 37.2% requiring valve replacement procedures. The aortic valve was the most commonly replaced valve (50% of surgical cases), followed by the mitral valve (31.3%) and tricuspid valve (18.7%). These surgical interventions were primarily indicated by severe complications, such as pulmonary embolism, large valvular vegetations (>10 mm) in 23.2% of cases, and severe valve regurgitation. The high prevalence of left-sided IE further underscores the severity of the cases, as 11 of these patients required aortic or mitral valve replacement. These data emphasize the critical nature of IE and the need for aggressive surgical management to prevent life-threatening complications and improve patient outcomes.

The clinical presentation and outcomes varied among patients, particularly those with HIV infection and a history of IDU. All patients experienced fever above 38°C, 11.6% developed congestive heart failure, 18.6% suffered from sepsis, and 6.9% experienced intracranial hemorrhage. Notably, eight of the 28 HIV-positive patients developed sepsis, all of whom ultimately succumbed to their condition. These findings underscore the severity of infective endocarditis in this patient population and highlight the importance of prompt diagnosis and targeted treatment. (Table 3)

Table 3. Complications associated with IE in patient with intravenous drug addiction.

COMPLICATIONS ASSOCIATED WITH IE	NO.(%)

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INTRACRANIAL HEMORRHAGE	3(6.9%)
SEPSIS	8(18.6%)
PNEUMONIA	9(20.9%)
PULMONARY EDEMA	7(16.2%)
RESPIRATORY DISTRESS	7(16.2%)
CONGESTIVE HEART FAILURE	5(11.6%)
VALVULAR VEGETATIONS	10(23.2%)

The study revealed distinct treatment approaches, with a majority (62.8%) receiving medical management, while 37.2% required surgical intervention. Surgical candidates were characterized by more severe complications, including a significantly higher incidence of mitral regurgitation (34% vs. 10%, P = 0.03), than those treated medically. This underscores the importance of the early identification and appropriate management of these complications to improve patient outcomes.

All patients received antibiotic treatment, with the majority (76.7%) managed using a single antimicrobial agent, whereas 23.3% required dual antibiotic therapy. The extended mean hospital stay of 31 days (± 7-21 days) highlights the complexity and prolonged nature of infective endocarditis treatment.

Notably, all patients underwent psychiatric evaluation during their hospitalization and were provided post-discharge follow-up care, emphasizing the importance of a comprehensive approach that addresses both the physical and mental health aspects of patients with this serious infection.

The study revealed a significant mortality rate during hospitalization, with 18.6% (8 43) of patients succumbing to complications. The primary causes of death were sepsis, accounting for 6 fatalities, and intracranial hemorrhage, which was responsible for 2 deaths. Notably, all deaths occurred in the surgical cohort, whereas the medically managed group experienced no in-hospital mortality. The long-term follow-up, conducted at an average of 12 months post-discharge, showed a slight decrease in overall mortality, with 16.2% (7 of 43) of patients who died.

Recurrent IE was observed in six patients during the follow-up period, representing a significant complication rate. The majority of these recurrences (five out of six) occurred in patients who had initially received medical management, while only one patient from the surgical cohort experienced a relapse. The treatment strategies for these recurrent cases varied, with most (5 patients) receiving medical treatment. However, two patients required surgical intervention, including one who underwent a repeat surgical procedure. These data suggest that, while medical management may be associated with a higher risk of IE recurrence, surgical treatment does not eliminate the possibility of relapse.

4. Discussion

This study provides significant insights into the characteristics, treatment modalities, and outcomes of patients with IE associated with intravenous drug use. The findings indicate that IDU-IE patients are generally younger and present with fewer chronic health conditions than the general IE patient population. However, they exhibit a higher prevalence of infectious diseases such as hepatitis B, hepatitis C, and HIV. The management strategies for patients with IDU-IE varied, with 37.2% undergoing surgical intervention, primarily due to congestive heart failure, mitral regurgitation, and large vegetation (≥10 mm). Patients with isolated tricuspid valve involvement were more likely to receive exclusive antibiotic treatment.

The study also identified several independent risk factors for mortality in patients with IDU-IE, including congestive heart failure, intracranial hemorrhage, and sepsis. These findings underscore the importance of the early detection and appropriate management of these complications to improve patient outcomes. [16,17] The distinct clinical profile of IDU-IE patients, characterized by their younger age and higher prevalence of infectious diseases, emphasizes the necessity for tailored treatment approaches and comprehensive care that address both the cardiac manifestations of IE and the underlying substance use disorder. [18] This study contributes to a more comprehensive understanding of IDU-IE and may inform the development of more effective management strategies for this vulnerable patient population.

 doi:10.20944/preprints202410.0729.v1

IE patients associated with intravenous drug use are further underscored by the multifaceted nature of their treatment and management. [19,20] The prolonged hospital stays observed in this study not only reflect the severity of their condition, but also highlight the challenges in addressing both the medical and psychosocial aspects of their care. The higher prevalence of *S. aureus* infections in this population is consistent with previous research, likely because of the direct introduction of skin flora into the bloodstream during drug injection. [21–24] However, the study's finding that aortic valve infections are the most common, followed by mitral and tricuspid valve infections, represents a departure from earlier observations. [23,24] This shift in valvular involvement patterns may have implications for diagnostic approaches and treatment strategies in patients with IDU-IE. The primary treatment approach of medical management with antibiotics aligns with the general strategy for IE, emphasizing the importance of targeted antimicrobial therapy. [24] However, the decision-making process for surgical intervention in IDU-IE patients is complex. While surgery is typically reserved for specific complications, such as heart failure, sepsis, or persistent infection despite antibiotic therapy, the unique challenges presented by this patient population necessitate a more nuanced approach. [24,25] The high risk of relapse in drug use, potential for recurrent infection, and difficulties in managing oral anticoagulation in patients with substance abuse issues all contribute to the complexity of surgical decision making. [25] When valve surgery is deemed necessary, the preference for valve repair, especially in cases of tricuspid valve involvement, reflects a strategy to minimize the introduction of foreign materials into the heart. This approach is particularly crucial in IDU-IE patients as it may reduce the risk of future infections and complications associated with prosthetic valves in this high-risk group. [26,27]

The findings revealed a 16.2% overall mortality rate during follow-up, which aligns with previously reported mortality rates in similar studies. [26–28] The low midterm survival observed in patients with IE associated with intravenous drug use can be attributed to a combination of endocarditis-related complications such as sepsis, cardiac decompensation, and respiratory distress, as well as complications arising from illicit drug use. [29,30] An important observation from this study was that the medical treatment of patients with a surgical indication was associated with higher mortality rates.

Conversely, patients who received medical treatment for less severe cases, typically involving isolated and uncomplicated valves, experienced no midterm deaths. These results emphasize the critical importance of close monitoring of all IDU-IE patients and the need for early consideration of surgical intervention when clinically indicated. The decision to proceed with major cardiac surgery in high-risk patients with multiple comorbidities and high rates of recidivism remains a challenge. [29,30] However, this study suggests that a multidisciplinary approach and team consensus are crucial for achieving optimal surgical outcomes in patients with IDU-IE.

The comprehensive management of patients with IE associated with intravenous drug use necessitates a multifaceted approach that extends beyond treating immediate infections. [31,32] A thorough psychiatric evaluation at the outset is crucial to identifying the underlying mental health issues that may have contributed to substance abuse. [32]

This assessment forms the foundation for tailored addiction therapy during hospitalization, which is essential for addressing the root causes of drug use and for preventing relapse.

The continuation of care after discharge through a structured drug rehabilitation program is equally important. This ongoing support is vital for maintaining sobriety and managing any coexisting psychiatric condition that could precipitate a return to drug use. The establishment of a dedicated multidisciplinary team within healthcare institutions represents a best practice approach for managing IDU-IE cases. By integrating expertise from surgical, cardiological, infectious disease, and psychiatric specialties, this multidisciplinary team can provide comprehensive care that addresses both medical and psychosocial aspects of the condition. [30,31] Such a coordinated effort is particularly crucial for high-risk patients as it ensures that addiction issues are given equal priority alongside medical treatment, thereby improving overall outcomes and reducing the likelihood of recurrence. [33]

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During the follow-up period, we found that 24 patients (55.8%) had ceased drug use in the last 12 months.

5. Conclusions

The findings of this study elucidated the severe impact of IE among intravenous drug users, even in a relatively young and otherwise healthy population. Despite their age, these patients face a substantial risk of complications including persistent infection, sepsis, and mortality. The aortic valve has emerged as the most frequently affected cardiac structure, underscoring the need for targeted intervention and monitoring in this specific area. The independent association of congestive heart failure and sepsis with higher mortality rates emphasizes the critical importance of early detection and aggressive management of these complications in patients with IDU-IE.

The study's results underscore the ongoing challenges in managing IDU-IE despite advancements in contemporary medical practices. The significant morbidity and mortality associated with this condition suggest that current treatment approaches may be insufficient to address the complex needs of this patient population. This highlights the urgent need for multidisciplinary approaches that combine medical management with addiction treatment, harm reduction strategies, and social support services.

6. Limitations

The limitations of the present study encompass its single-hospital focus and retrospective nature. The absence of data regarding specific illicit substances utilized by patients, as well as the lack of information on addiction treatment modalities, social support systems, and socioeconomic factors, significantly constrains our comprehension of the complex interplay between these variables and patient outcomes. These factors are critical in determining an individual's capacity to overcome addiction and successfully undergo surgery, ultimately influencing overall prognosis. Moreover, the dearth of such data limits our ability to develop targeted interventions or tailor treatment approaches to specific subgroups of patients.

Author Contributions: Conceptualization, C.-I. A and I.Ș.; methodology, C.-I. A., C.A.B.; software, A.-T. Ș.; validation, C.-I. A., A. S.-C. and I.Ș.; formal analysis, C.-I. A.; investigation, C.-I. A.; resources, I. Ș..; data curation, M.M.Z.; writing—original draft preparation, C.-I. A.; writing—review and editing, C.-I. A.; visualization, A. S.-C.; supervision, I. Ș.; project administration, C.-I. A; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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