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ORIGINAL PAPER

Non-Necrotizing Acute Dermohypodermal Infections in Cirrhotic Patients Being Evaluated for Liver Transplantation

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ABSTRACT

Introduction: Infections in cirrhotic patients have a significant impact on morbidity and mortality, but little is known about acute non-necrotizing dermohypodermal infections (erysipelas and infectious cellulitis) in this population. The high mortality in this group also represents a loss of opportunity for liver transplantation, which could be a potential solution for these patients. **Objectives:** This study aims to describe the clinical characteristics, evolution, and outcomes of cirrhotic patients with acute non-necrotizing dermohypodermal infections under evaluation for liver transplant. **Methods:** A retrospective study was conducted on patients hospitalized with cirrhosis and dermohypodermal infections from 2010 to 2012. **Results:** Among 983 patients with liver cirrhosis, leading to 2,046 consultations for decompensated cirrhosis, dermohypodermal infections were identified in 65 (7%) cases. The mean age was 58 years (± 10), with 82% male. Cellulitis predominantly affected the lower limbs (70%), followed by the trunk (21%) and upper limbs (9%). Alcoholic liver disease was the primary etiology (56%), followed by alcohol and hepatitis C (17%), isolated hepatitis C (13%), non-alcoholic steatohepatitis (9%), and hepatitis B (3%). Based on the Child-Pugh score, 8% were classified as class A, 46% as class B, and 46% as class C. The average model for end-stage liver disease (MELD) score was 20 (± 8). Commonly associated infections included urinary tract infection (54%), pneumonia (25%), and spontaneous bacterial peritonitis (21%). Prescribed antibiotics were clindamycin (71%), cephalosporins (40%), oxacillin (18%), penicillin (11%), vancomycin (11%), quinolones (4.5%), and other antibiotics (15.3%). Sepsis occurred in 14% of cases, and the mortality rate was 18.5% (n=12). Among the deceased patients, 67% (n=8) had concomitant infections with cellulitis. Factors significantly associated with mortality were concomitant infections (69 vs. 31%, p = 0.02) and elevated C-reactive protein levels (6 vs. 3 mg/dL, p = 0.03). **Conclusion:** This study highlights the high hospital mortality rate among cirrhotic patients with acute non-necrotizing dermohypodermal infections, especially when concomitant infections are present. The high mortality not only reflects the severity of the condition but also represents a loss of opportunity for potentially life-saving interventions, such as liver transplantation. Further research is needed to improve the management of cirrhotic patients with dermohypodermal infections.

Descriptors: Bacterial Infections; Soft Tissue; Cirrhosis; Immunodeficiency; Mortality.

Infecções Dermo-hipodérmicas em Pacientes Cirróticos em Avaliação para Transplante de Fígado

RESUMO

Introdução: As infecções em pacientes cirróticos têm um impacto significativo na morbimortalidade, porém pouco se sabe sobre as infecções dermo-hipodérmicas agudas não necrosantes (erisipela e celulite infecciosa) nessa população. A alta mortalidade nesse grupo também representa uma perda de oportunidade para o transplante hepático, que poderia ser uma solução potencial para esses pacientes. **Objetivos:** Este estudo tem como objetivo descrever as características clínicas, a evolução e os desfechos de pacientes cirróticos com infecções dermo-hipodérmicas agudas em avaliação para transplante hepático. **Métodos:** Foi realizado um estudo retrospectivo com

pacientes hospitalizados com cirrose e infecções dermo-hipodérmicas no período de 2010 a 2012. **Resultados:** Entre 983 pacientes com cirrose hepática que resultaram em 2.046 atendimentos por descompensação da doença, infecções dermo-hipodérmicas foram identificadas em 65 casos (7%). A média de idade foi de 58 anos (± 10), com predominância do sexo masculino (82%). A celulite afetou predominantemente os membros inferiores (70%), seguida do tronco (21%) e dos membros superiores (9%). A etiologia mais comum da cirrose foi a doença hepática alcoólica (56%), seguida da associação entre álcool e hepatite C (17%), hepatite C isolada (13%), esteato-hepatite não alcoólica (9%) e hepatite B (3%). Quanto à classificação de Child-Pugh, 8% dos pacientes eram classe A, 46% classe B e 46% classe C. A pontuação média no Model for End-Stage Liver Disease (MELD) foi de 20 (± 8). As infecções associadas mais comuns foram infecção do trato urinário (54%), pneumonia (25%) e peritonite bacteriana espontânea (21%). Os antibióticos prescritos incluíram clindamicina (71%), cefalosporinas (40%), oxacilina (18%), penicilina (11%), vancomicina (11%), quinolonas (4,5%) e outros (15,3%). Sepse ocorreu em 14% dos casos, e a taxa de mortalidade foi de 18,5% (n = 12). Entre os pacientes que evoluíram para óbito, 67% (n = 8) apresentavam infecções concomitantes à celulite. Os fatores significativamente associados à mortalidade foram infecções concomitantes (69 vs. 31%, p = 0,02) e níveis elevados de proteína C-reativa (6 vs. 3 mg/dL, p = 0,03). **Conclusão:** Este estudo destaca a elevada taxa de mortalidade hospitalar entre pacientes cirróticos com infecções dermo-hipodérmicas agudas, especialmente na presença de infecções concomitantes. A alta mortalidade reflete não apenas a gravidade da condição, mas também a perda de oportunidade para intervenções potencialmente salvadoras, como o transplante hepático. São necessários mais estudos para aprimorar o manejo desses pacientes.

Descritores: Infecções Bacterianas; Tecido Mole; Cirrose; Imunodeficiência; Mortalidade.

INTRODUCTION

Cirrhosis is the final stage of the progressive hepatic fibrosis in chronic liver disease. This stage is characterized by hepatic architectural distortion and the formation of regenerative nodules that cause lobular and vascular disorganization of the liver.[1] This final pathway of chronic liver disease does not depend on its etiological agent, whether alcoholic, viral, autoimmune, biliary, drugs, venous flow obstruction, or cryptogenic.[1] Indeed, the advanced stage of the disease is irreversible, making liver transplantation its definitive therapy.

Cirrhotic patients are vulnerable to many complications that significantly reduce their life expectancy. Such complications include upper gastrointestinal bleeding, ascites, hepatorenal syndrome, jaundice, hepatocellular carcinoma, encephalopathy, and infections associated with high mortality rates.[2-6] The most frequent infections reported in medical literature are spontaneous bacterial peritonitis (SBP) (25-31%), urinary infection (20-25%), and pneumonia (PNM) (15-21%).[4-7]

Skin infections also are at risk to develop; however, there are few reports, especially about non-necrotizing acute dermohypodermal infections (NNADHI).[4,8,9]

NNADHI in cirrhotic patients, which includes erysipelas and infectious cellulitis, arises due to bacteria entering through openings in the skin's protective barrier. This disease is an acute form of infection affecting the skin and superficial lymphatic vessels. Numerous etiological studies have demonstrated that in both conditions, group A streptococcus (*Streptococcus pyogenes*) is the most common etiological agent, while *Staphylococcus aureus* is responsible for approximately 15% of cases.[10-17,18]

The typical presentation of dermohypodermatitis is exemplified by erysipelas, characterized by an abrupt onset with fever and chills, followed by the development of an erythematous, edematous, warm, and painful plaque with well-defined borders, often located in the lower extremities (in approximately 80% of cases), although it can also occur on the face, upper extremities, and trunk.

On the other hand, atypical dermohypodermatitis presents as infectious cellulitis, typically associated with a more nonspecific clinical picture, with or without fever. In this case, the erythematous plaque is warm, with less defined borders, and variable pain.

Clinical differentiation between these two conditions is not always feasible, and it is preferable to use a term that encompasses both, namely, "acute non-necrotizing dermohypodermatitis."[18] While serious complications such as abscesses or sepsis are uncommon, the recurrence of the infection is a significant concern.[19]

This retrospective study evaluates cellulitis in cirrhotic patients admitted for liver transplant evaluation in a tertiary university hospital and describes their clinical characteristics, evolution, and outcome.

METHODS

This analysis was approved by the Research Ethics Committee of Faculdade de Medicina de São José do Rio Preto (FAMERP), Brazil. The research was carried out using electronic medical records of patients with an episode of cellulitis upon admission to the Liver Transplantation Unit and the Gastrohepatology Service at Hospital de Base (FUNFARME/FAMERP), resulting in a retrospective review of the records.

This study included all cirrhotic patients who presented with cellulitis upon hospital admission in the period from July 1, 2010 to December 31, 2012. The diagnostic criteria for NNADHI included the following clinical findings: an area of skin with redness (well defined in erysipelas and less well defined in infectious cellulitis); edema (swelling) that may spread beyond the red area; skin that is hot to the touch; pain or sensitivity; and, possibly, fever.

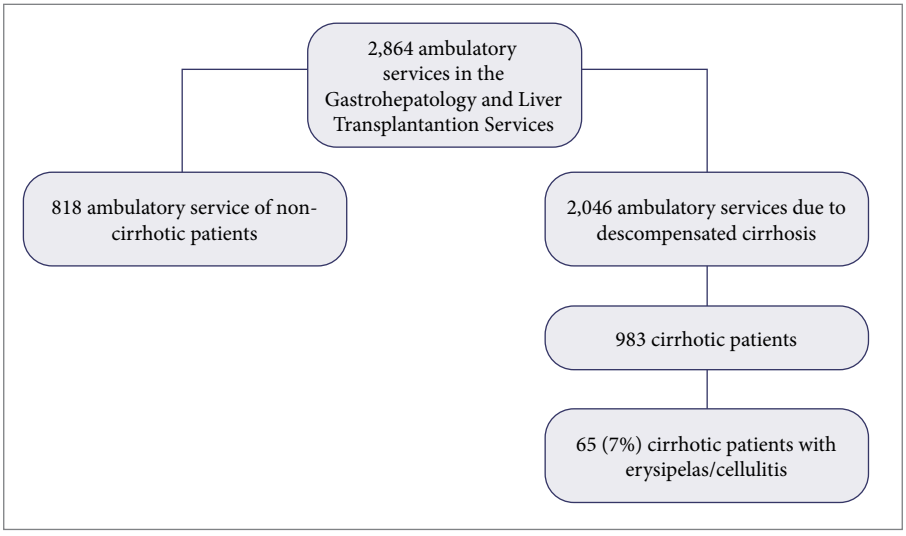
The primary exclusion criterion ruled out patients with doctor's report insufficient data, and the second exclusion criteria rule out those whose initial diagnosis of erysipelas or cellulitis was not confirmed during hospitalization.

The evaluated parameters included patient identification, cirrhosis etiology, Child-Pugh classification, model for end-stage liver disease score (MELD), associated comorbidities, associated infections, C-reactive protein (CRP) levels, prescribed antibiotics, and the patient outcomes.

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS®) program. Each category was explored through descriptive evaluation of data, combined with the interpretation of quantitative variables using its medians and standard deviations, and percentages. Comparative analysis was carried out using the chi-square test, Fisher's exact test, Student t test, and Mann-Whitney test.

RESULTS

From July, 1st 2010, to December 31, 2012, there were 2,864 outpatient consultations at the Liver Transplantation Unit and Gastrohepatology Service. Of these, 2,046 were motivated by decompensated cirrhosis, identifying the care of 983 different cirrhotic patients during this period. Among them, 7% (65) of the patients had cellulitis and formed the studied group in the study (Fig. 1).



Source: Elaborated by the author.

Figure 1. Selection criteria.

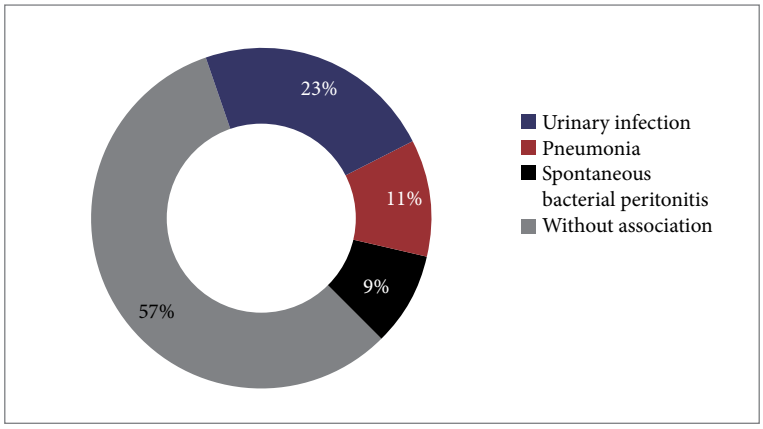
The epidemiological analysis revealed an average age of 58 years (± 10), with a predominance of male patients (82%). The most common etiology of cirrhosis was isolated alcoholic liver disease, followed by other causes, as detailed in Table 1. Sixty-three patients had sufficient data for hepatic dysfunction assessment using the Child-Pugh and MELD scores, with distribution across Classes A, B, and C and an average MELD score of 20 (± 8). The median CRP level was 4 mg/dL (0.2-25). The most frequent infection site was the lower limbs, followed by the trunk and upper limbs (Table 1).

Comorbidities were observed in 29 (45%) patients and were caused by acquired metabolic diseases in 28 patients. Metabolic syndrome (which includes abdominal obesity, insulin resistance, high blood pressure, dyslipidemia, and elevated fasting blood sugar levels) was observed in 11 cases (17%). Cellulitis and other infections occurred simultaneously in the following proportions: urinary tract infection (UTI) in 15 cases (54%), PNM in seven (25%), and SBP in six (21%) (Fig. 2). The most prescribed antibiotics were clindamycin (71%), cephalosporins (40%), oxacillin (18%), penicillin (11%), vancomycin (11%), quinolones (4.5%), and others in 15.3% (Fig. 3). Nine patients (14%) developed sepsis. The total death outcome was 12 (18.5%), represented by four deaths (33%) of patients who had only cellulitis and eight (67%) in those who had cellulitis and other concomitant infections (Fig. 4). It is important to note that cirrhotic patients who died with erysipelas did not have the opportunity for liver transplantation.

Table 1. Characteristics of evaluated patients.

Characteristics	
Age (years)	58 ± 10
Sex, n (%)	
Male	53 (82)
Location, %	
Lower limbs	70
Trunk	21
Upper limbs	9
Etiology, n (%)	
Alcohol	35 (56)
Hepatitis C + alcohol	11 (17)
Hepatitis C	8 (13)
Non-alcoholic steatohepatitis	6 (9)
Hepatitis B	2 (3)
Others	1 (2)
Child-Pugh, n (%)	
A	5 (8)
B	29 (46)
C	29 (46)
MELD	20 ± 8

Source: Elaborated by the author.



Source: Elaborated by the author.

Figure 2. Erysipelas and associated infections.

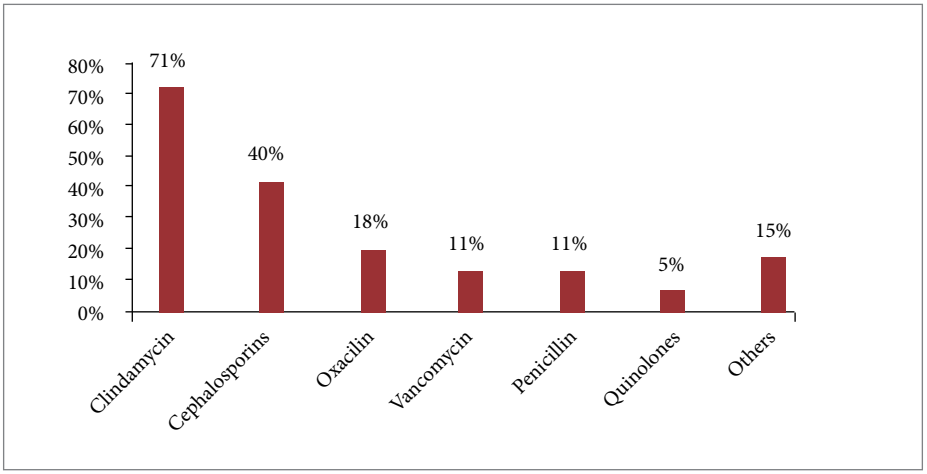


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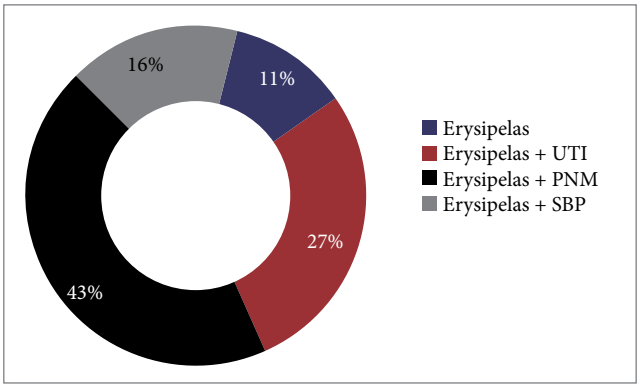
Figure 3. Prescribed antibiotics.

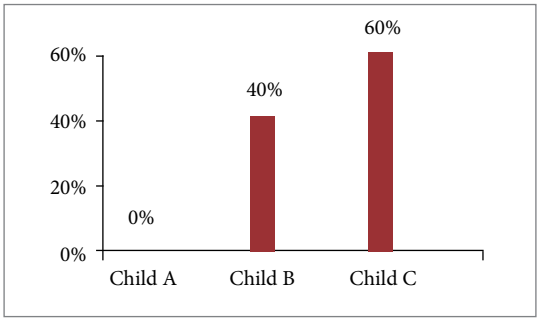


Source: Elaborated by the author.

Figure 4. Infection distribution among deaths.

Among the 12 patients who died, MELD and Child-Pugh scores could not be calculated for one patient due to insufficient laboratory data. Of the remaining patients, four (33.3%) were classified as Child-Pugh B, and seven (58.3%) were classified as Child-Pugh C. The MELD scores ranged from a minimum of 14 to a maximum of 37, with a median of 20. The deaths were notably acute: six patients (50%) died within 7 days of symptom onset, five patients (41.6%) died between 8 and 21 days after the onset of symptoms, and only one patient (8.3%) survived until the 38th day before passing away.

Cross-referencing the mortality rates with the Child-Pugh classification, Class A had no such outcomes; however, Classes B and C accounted for 40 and 60% of deaths, respectively (Fig. 5). The average MELD score of hospital-discharged patients was 19 (± 7), and for those who evolved to death, it was 23 (± 9), representing no statistical significance ($p > 0.05$). The group with death as an outcome compared to the group with hospital discharge as an outcome has their concerning parameters of age, male sex, MELD, associated infections, and CRP represented in Table 2.



Source: Elaborated by the author.

Figure 5. Child-Pugh distribution among deaths.

Table 2. Variables analysis according to outcome.

	Death	Hospital discharge	*p*-value
Age (years)	55	58	0,36
Sex, male (%)	73	83	0,41
MELD	23	19	0,16
Child-Pugh (%)	10	9	0,39
Associated infection (%)	69	31	0,02
CRP, median	6	3	0,03

Source: Elaborated by the author.

DISCUSSION

Bacterial infection is a frequent complication in cirrhotic patients with an incidence ranging from 25 to 57% being responsible for approximately 30 to 50% of the deaths due to hepatic cirrhosis.[4,6,7,20] The frequency of skin infections was estimated at 2 to

11%, mainly caused by continuity solution areas in the skin and subcutaneous tissue leading to bacterial penetration associated with fluid retention (edema).[4,6,7]

Among 983 cirrhotic patients admitted to the tertiary university hospital, this study demonstrated a prevalence of 65 (7%) patients with NNADHI associated or not with other infections. The frequency of other infections in cirrhotic patients was not analyzed.

We encountered 37 (57%) patients presenting only NNADHI and 28 (43%) presenting erysipelas or cellulitis with another associated infection in those 65 patients. It was that found 15 (23%) patients had NNADHI associated with UTI, seven (11%) associated with PNM, and six (9%) associated with SBP.

Overall, the causes of this higher vulnerability to bacterial infections in cirrhotic patients are multifactorial and concomitant. The existing systemic port shunt leads to lower hepatic depuration of endotoxins and bacteria coming from the portal circulation. Beyond that, cirrhosis is associated with a decrease in the endothelial reticulum system activity and a decrease in the bactericidal activity of phagocytic cells. There is also impairment of the opsonization process and reduction of the complement system factors and C-protein levels.[6,7] According to Bunchorntavakul et al.,[7] some factors are more specifically related to NNADHI, such as bacterial translocation, fragile, thin and emaciated skin, poor hygiene, malnutrition, frequent hospital admissions, hypoalbuminemia, high MELD score, and hepatic encephalopathy.

Several studies state that the prevalence of infections grows even more as hepatic dysfunction worsens, mainly caused by immunological system dysfunction. Comparing with the Child-Pugh classification, this study resulted in 92% of cirrhotic patients classified in classes B and C responsible for 100% of deaths in the group, with no deaths occurring in class A. Indeed this study is in accordance with literature rates.[3,4,6]

The death rate encountered was 12 (18.5%). Four patients (33%) had only NNADHI while eight deaths (67%) had erysipelas/cellulitis and another concomitant infection. Thus, crossing the rate of NNADHI concomitant with other infections and the patient outcome lead to a significant result: 69% evolved to death while 31% received hospital discharge (p = 0.02). Indeed Pleguezuelo et al.[21] related the mortality associated with infections being twenty times higher in cirrhotic patients compared to the general population. Other studies claim that infections are responsible for 25% of deaths in the cirrhotic population.[4,6]

Strauss[22] observed that the fatality rate among cirrhotic patients with infections is significantly higher than that recorded in patients with severe hepatic decompensation who do not have infections. Currently, bacterial infections are recognized as the primary cause of death in patients with decompensated cirrhosis. In this context, infections such as erysipelas and cellulitis, although often treatable successfully, have shown particularly high mortality rates. A recent retrospective case-control study corroborated this concern by revealing that patients with these infections had a much higher 3-month mortality rate compared to those without infections (23 vs. 4%). Furthermore, the analysis of the cohort in this study, comprising patients who died from erysipelas or cellulitis, revealed an acute mortality pattern, consistent with Strauss's findings. Among the 12 death cases analyzed, six patients (50%) died within 1 week of symptom onset, while another five patients (41.6%) succumbed between 8 and 21 days after the initial manifestation of symptoms. Notably, only one patient (8.3%) survived until the 38th day after the onset of symptoms before passing away.

In cases of NNADHI, any examination would reveal evidence of a bacterial infection, characterized by an increase in neutrophils and elevated levels of CRP.[19] Regarding this, only the comparison between CRP levels and patient outcomes revealed a significant association concerning laboratory data evaluation. The group with death as an outcome had a median CRP level of 6 mg/dL, while it was at 3 mg/dL in the hospital discharge outcome group (p = 0.03). This data shows that the cirrhotic patients with cellulitis and CRP higher than 6 mg/dL must be treated with an antibiotic scheme as aggressively as possible.

Studies demonstrate that NNADHI is primarily caused by streptococci. Additional bacteria such as *S. aureus*, *Pseudomonas aeruginosa*, and enterobacteria can be present, but their role in erysipelas/cellulitis development is unclear.[19] As suggested in the literature, erysipelas/cellulitis treatment must be performed using antibiotics with good coverage against streptococcus and staphylococcus, such as first-generation cephalosporins, amoxicillin with clavulanate, or clindamycin. If the patient had recent use of antibiotics, the recommended treatment is third-generation cephalosporins associated with vancomycin. The most used antibiotics reported in this study is align with the medical literature recommendations and the prescription had the following frequencies: clindamycin (71%); third- and fourth-generation cephalosporines (ceftriaxone 34% and cefepime 6%); oxacillin (18%); penicillin (11%); vancomycin (11%); quinolones (4.5%), and others in 15.3%.[4,6,7,17,20]

There are studies that confirm no definitive conclusion could be drawn regarding the most effective antibiotic treatment for acute dermohypodermal infections based on the data presented. There was no superiority of one antibiotic over another, including cephalosporin versus penicillin. Glycopeptide, oxazolidinone, and daptomycin did not demonstrate superiority either. Combination therapy did not show better outcomes in the study. Limited data and previous studies support the use of oral therapy for erysipelas/cellulitis, as it appeared to be more effective than intravenous (IV) treatment. The optimal duration of antibiotic therapy could not be determined, with only one trial specifically examining duration and no evidence supporting antibiotic

therapy longer than 5 days. Trials investigating an antibiotic targeting methicillin-resistant *S. aureus* (MRSA) in cellulitis did not show any advantage, further supporting the notion that cellulitis is primarily caused by streptococcal infection.[23]

From the 65 patients studied, two cases had no record of antibiotic use in the electronic report; in that group one patient evolved to death soon after the hospital admission. A total of 47 patients were treated with an isolated antibiotic, 11 were treated with an association of two antibiotics, and five patients were treated with an association of three antibiotics. Nine (19%) deaths reported were among those using antibiotic monotherapy. Of these, six patients had both erysipelas/cellulitis and another infection. However, the design of our study cannot attribute therapeutic failure to antibiotic monotherapy or blame for the association between infections for such an outcome.

CONCLUSION

In conclusion, the in-hospital mortality of cirrhotic patients with NNADHI who were evaluated for liver transplantation was high, and the presence of another concomitant infection increased the risk of death. Finally, the approach to cirrhotic patients with erysipelas or cellulitis requires additional investigation, given that the high mortality rate in these cases may prevent individuals eligible for liver transplantation from receiving the organ.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Santos VCM, Cretelli OS, Valsechi LC, Meirelles MB; **Conception and design:** Silva-Fucuta P, Silva EC, Santos VCM; **Data analysis and interpretation:** Marcatto G, Silva-Isepon LB, Itimura P; **Article writing:** Santos VCM, Cretelli OS, Valsechi LC; **Critical revision:** Santos VCM, Silva R; **Final approval:** Santos VCM.

DATA AVAILABILITY STATEMENT

All data were generated or analyzed in this study.

FUNDING

Not applicable.

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