The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 4679-4685

Assessment of Fungal Blood Stream Infection in Patients with Liver Cirrhosis Admitted to The Intensive Care Unit

Enas Faried Abd-ELlatief[*1], Hala Ismail Mohammed Hussein[1], Takwa E. Meawed[2], Heba A. Mohammed[2], Shimaa Abd-Elfattah Awwaad[1], Ahmed Said Mohammed[1]

Departments of [1]Tropical Medicine and [2]Medical Microbiology and Immunology, Faculty of Medicine - Zagazig University, Egypt

***Corresponding author:** Enas Faried Abd-ELlatief, **Mobile:** (+20)01028767219, **Email:** dr.enas.faried@gmail.com

ABSTRACT

Background: Liver cirrhosis (LC) patients are at increased risk for infection due to weakened immune systems and gastrointestinal dysfunction. Therefore, it is crucial to do fungal cultures in LC patients and to keep a high index of suspicion.

Objective: To detect fungal blood stream infection in patients with liver cirrhosis admitted to the intensive care unit.

Methods: In a prospective cross-sectional study that was conducted on 124 subjects were admitted to Zagazig University Tropical department with symptoms and signs suggestive of fungal infections. Using light microscope 40X and 40X for visualization of fungal structures of blood culture.

Results: Our study couldn't detect any case with fungal blood stream infection. Nearly all our patients had leucocytic and inflammatory reaction. Fifty-one patients had HCC, 4 patients had malignant masses: 2 gastric and 2 duodenal masses with no other malignancy. Our patients had mean MELD score of 14.0 ± 3.55. Immune compromising drugs among our patients were completely absent and medical condition that may affect the immunity such as DM were relatively few in our patients.

Conclusions: Liver cirrhosis frequently results in infections. Patients with cirrhosis who are hospitalized to the intensive care unit often get fungal infections, which exacerbate their overall state and can be fatal.

Keywords: Fungal, Liver Cirrhosis.

INTRODUCTION

Liver cirrhosis is an irreversible, systemic condition characterized by the replacement of normal liver cells by regenerating nodules and fibrous septa between them. In response to liver injury, hepatic stellate cells (HSC) are activated and converted into myofibroblasts, a process that is part of the wound healing pathway. Liver cirrhosis is the terminal stage of any liver disease that has persisted over time **(1).**

When cirrhosis progresses to the decompensated stage, survival rates drop from 12 years in the compensated stage to 2 years. The presence of any of the following problems is diagnostic of decompensated cirrhosis: Hepatic failure manifested by ascites, encephalopathy, jaundice, and/or hepatorenal syndrome. Several factors can lead to the decompensation stage being reached, such as: problems with alcohol consumption, infections, and bleeding in the stomach **(2).**

Cirrhosis infections significantly exacerbate the disease's overall course. Cirrhosis problems are another risk factor for getting sick. In cirrhotic individuals, infections can be caused by a number of causes, including immunological failure, bacterial and fungal translocation due to small intestinal bacterial and fungus overgrowth with increased intestinal permeability, and hereditary factors **(3).**

Syndrome of immune dysfunction due to cirrhosis and systemic inflammation is known as cirrhosis associated immune dysfunction (CAIDS). As the primary pathophysiological mechanism behind the emergence of infections in cirrhosis, it warrants special attention **(4).**

About 25% of patients with liver cirrhosis reported an infection, and the mortality rate was roughly four times greater than in the general population. Blood stream infections (BSIs) are a serious problem for people with liver cirrhosis because they lead to more hospitalizations and a higher risk of death **(5).**

Infections caused by bacteria tend to be more common. *Spontaneous bacterial peritonitis* (SBP) accounts for 25% of all bacterial infections, followed by UTIs (20%), pneumonia (15%), bacteremia (12%), and cellulitis (2%-11%) **(6).**

Cirrhosis patients with fungal bloodstream infections are at an extremely low survival risk. Due to its low prevalence, non-specific clinical symptoms, and the time required for an accurate diagnosis, it is often misdiagnosed or detected late **(7).**

Cirrhosis of the liver is associated with a 10-13% incidence of fungal BSI. Bacterial infections are sometimes present as well. Risk factors for fungal BSI include renal insufficiency, antibiotic overuse, and invasive procedures **(8).**

About 10% of BSI is caused by *Candida species*, which are frequently isolated from cirrhotic patients in the intensive care unit. Therefore, the most common fungal BSI in such individuals is candidemia **(9).**

This study objective was Detection of fungal blood stream infection in patients with liver cirrhosis admitted to the intensive care unit and its relation to morbidity in those patients.

Received: 26/11/2022
Accepted: 28/01/2023

SUBJECTS AND METHODS

In a prospective cross-sectional study that was conducted on 124 subjects were admitted to Zagazig University Tropical department with symptoms and signs suggestive of fungal infections.

Inclusion Criteria:

Patient's ≥ 18 years of both sexes, proved to have liver cirrhosis (through clinical, laboratory and imaging data), admitted to ICU due to cirrhosis related complications.

Exclusion Criteria:

Patients <18 years, with alcohol misuse and alcoholic hepatitis, those who were on antifungal medications or received antifungal medications during one month before ICU admission, Patients on immune modulatory medications, Patients on probiotics within the last 3 months, Patients with other organ failure were excluded from the study.

Methods:

1. **Complete history, and detailed clinical examination.**
2. **Lab investigations:**

Complete blood cell count (RBCs, HB, platelets, WBCs total and differential), Biochemical liver tests (serum bilirubin, serum amino-transaminases, total serum proteins & serum albumin) on (Synchron CX5 auto-analyzer of Beckman), Viral markers (HBsAg, HBcAb and anti-HCV), Kidney function test (blood urea and serum creatinine) using (auto-analyzer cobas-Roch diagnostic), Coagulation profile (prothrombin time in seconds and international randomization ratio, INR) on (Synchron CX5 auto-analyzer of Beckman). Random blood sugar, Hemoglobin A1c (HbA1C) for diabetic patients, CRP and ESR, Na, K level and PH.

Evaluation of the severity of liver disease according to Modified Child-Pugh and MELD score [10]. MELD score was calculated by this equation: $9.57\times\log_e(\text{creatinine}) + 3.78\times\log_e(\text{total bilirubin}) + 11.2\times\log_e(\text{INR}) + 6.43$.

3. **Pelvi-abdominal ultrasonography**
4. **Blood culture:**

Five millilitres of blood were extracted aseptically and placed in blood culture vials (Salix, Egypt). Bottles containing patient information were incubated at 37 degrees Celsius. When growth was suspected or on a regular basis (every 2–5 days), blood culture vials were used to conduct subcultures. Subcultures were grown in 25°C and 37°C incubators on Sabouraud's dextrose agar and brain heart infusion agar, respectively. Differentiating fungal colonies was aided by growth rate, surface features, reversal, colour, and form. The presence of mould should be suspected if the initial inspection indicated fluffy, cottony, or woolly aerial mycelia. Smooth, creamy, or viscous surfaces are also indicators that yeast may be present. The structures of fungi can be observed using a 40X and 40X light microscope: Wet mount, and Lactophenol cotton blue stained film.

Budding yeast cells can be either round or oval in shape. In the meanwhile, it's important to classify hyphal filaments based on their uniformity, septation (or lack thereof), angle of division, and presence of spores.

Ethical approval:

This experiment was ethically approved by the Zagazig University's. After being fully informed, all participants provided written consent. The study was conducted out in line with the Helsinki Declaration.

Statistical analysis

Statistics were analysed using SPSS 20 (Statistical Package for the Social Services). It was found that using visual aids like tables and graphs helped best express the results. The quantitative information was displayed as the mean, median, standard deviation, and confidence intervals. Stats like frequency and % were used to help illustrate the data's quality. When dealing with quantitative independent variables, the student's t-test (T) is employed to evaluate the data. Mann Whitney test, for abnormally distributed quantitative variables, to compare between two studied categories. Chi-Square for Linear Trend (X^2) and Pearson Chi-Square were used to evaluate the linear independence of qualitative data. For statistical significance, a P value of 0.05 or less was established.

RESULTS

Forty-seven patients (37.9%) were females and 77 (62.1%) were males. The mean age of studied cases was 62.52 ± 8.20 SD with range (45-85) years. Most of our patients had HCV as cause of cirrhosis 112 (90.3%) while 12 patients (9.7%) had mixed etiology of HCV and bilharziasis. No one of our patients had HBV. Thirty-four patients (27.4%) had DM, 4 patients (3.2%) had CKD and 51 patients (41.1%) had HCC. No one of our patients had HIV. There were 42 (33.9%) had HE as cause of the admission, 13 patients (10.5%) had jaundice, abdominal pain and vomiting, 36 patients (29.0%) had tense ascites with LL edema, 57 patients (46.0%) had hematemesis and melena.

Table (1): Distribution of the studied cases according to demographic data, etiology of liver cirrhosis, associated comorbidities and cause of admission:

				Cases NO. (124)
Sex	**Female**	**No.**		47
		%		37.9
	Male	**No.**		77
		%		62.1
Age (years)		**Range**		45.0 – 85.0
		Mean ± SD		62.52 ± 8.20
		Median		62.50
				Cases NO. (124)
Etiology of liver cirrhosis	**HCV**		**No.**	**112**
			%	**90.3**
	HCV& bilharziasis		**No.**	**12**
			%	**9.7**
				Cases NO. (124)
Morbidity	**Diabetes Mellitus(DM)**		**No.**	**34**
			%	**27.4**
	Chronic Kidney Disease(CKD)		**No.**	**4**
			%	**3.2**
	Hepatocellular carcinoma(HCC)		**No.**	**51**
			%	**41.1**
				Cases NO. (124)
Cause of admission	**HE**		**No.**	**42**
			%	**33.9**
	Jaundice, abdominal pain and vomiting		**No.**	**13**
			%	**10.5**
	Tense ascites with LL edema		**No.**	**36**
			%	**29.0**
	Hematemesis and melena		**No.**	**57**
			%	**46.0**

Nine patients (7.3%) had Child-Pugh class A, 36 patients (29.0%) had Child-Pugh class B and 79 (63.7%) had Child-Pugh class C. The mean MELD score of studied cases was 14.0 ± 3.55 SD with range (6.44 – 24.75). Sixty- one patients (49.2%) had moderate ascites, 36 patients (29.0%) with marked ascites, 27 patients (21.8%) underwent therapeutic abdominal paracentesis, 57 patients (46.0%) had upper GI bleeding, 49 patients (39.5%) had upper GI endoscopy, while 8 patients couldn't have upper GI endoscopy because they weren't fit for endoscopy (they had hepatic encephalopathy or HB ≤ 6.0 g/dl). Focal colonization was detected in 4 patients (3.2%) with esophageal moniliasis.

Table (2): Distribution of the studied cases according to Child-Pugh class and MELD and presence of predisposing factors of IFI:

			Cases NO. (124)	
Child-Pugh class	**A**	**No.**	9	
		%	7.3	
	B	**No.**	36	
		%	29.0	
	C	**No.**	79	
		%	63.7	
MELD score		**Range**	6.44 – 24.75	
		Mean ± SD	14.0 ± 3.55	
		Median	13.72	
				Cases NO. (124)
Ascites	**No**		**No.**	9
			%	7.3
	Mild		**No.**	18
			%	14.5
	Moderate		**No.**	61
			%	49.2
	Marked		**No.**	36
			%	29.0
Therapeutic paracentesis	**Abdominal**	**No**	**No.**	97
			%	78.2
		Yes	**No.**	27
			%	21.8
	Pleural		**No.**	6
			%	4.8
Upper GI bleeding	**No**		**No.**	67
			%	54.0
	Yes		**No.**	57
			%	46.0
Focal colonization	**No**		**No.**	120
			%	96.8
	Esophageal moniliasis		**No.**	4
			%	3.2
Central venous catheter (CVC)	**No**		**No.**	110
			%	88.7
	Yes		**No.**	14
			%	11.3
Urinary catheter	**No**		**No.**	8
			%	6.5
	Yes		**No.**	116
			%	93.5
Nasogastric tube (NGT)	**No**		**No.**	74
			%	59.7
	Yes		**No.**	50
			%	40.3
Endoscopy	**No**		**No.**	75
			%	60.5
	Yes		**No.**	49
			%	39.5

The studied patients had elevated values of WBC count (19.00 ± 4.30 SD), inflammatory markers such as CRP and ESR of studied cases was ranged from 17.90 – 180.9 and 40.0 – 110.0 respectively. Parameters of liver function test were affected such as serum albumin of studied cases was (2.66 ± 0.47 SD), INR was (1.53 ± 0.37 SD) and serum bilirubin was 0.50 – 30.50.

Table (3): Laboratory parameters of the studied patients:

Laboratory investigations	**Min. – Max. (Median) Mean ± SD**
Complete blood count (CBC)	
WBC(x10^9/l)	19.00 ± 4.30
HB(g/dl)	9.18 ± 1.52
Platelet count(x10^3/cmm)#	12.0 – 291.0 (125.5)
Liver function test (LFT)	
Serum albumin(g/dl)	2.66 ± 0.47
Serum bilirubin(mg/dl)#	0.50 – 30.50 (2.70)
Kidney function test (KFT)	
Urea#	18.30 – 267.0 (83.0)
Serum creatinine (mg/dl)#	0.30 – 7.90 (2.50)
International normalized ratio (INR)	1.53 ± 0.37
Inflammatory markers	
CRP#	17.90 – 180.9 (37.90)
ESR#	40.0 – 110.0 (70.0)

Min. – Max, Median: Non-parametric test

Blood culture revealed *Staph. aureus* in 4 patients (3.2%) and *Klebsiella pneumonia* in 2 patients (1.6%), levofloxacin was the most prescribed antibiotic in 64 patients (51.6%) patients, followed by ceftriaxon in 55 patients (44.4%), the mean duration of ICU stay was 5.08 ± 2.25 SD, there were 8 patients (6.5%) died mostly due to HCC related causes.

Table (4): Distribution of the studied cases according to different intensive care unit parameters (n = 124):

	No.	**%**
Blood culture		
Staph. aureus	4	3.2
Klebsiella pneumonia	2	1.6
Admission antibiotic		
Cefepime	6	4.8
Levofloxacin	64	51.6
Cefobid	24	19.4
Tienam	8	6.5
Cefotax	24	19.4
Ceftriaxon	55	44.4
Meropenem	30	24.2
Averozolid	2	1.6
Steroids	0	0.0
ICU stay (days)		
Min. – Max.	3.0 – 13.0	
Mean ± SD.	5.08 ± 2.25	
Median	5.0	
No. of admission		
Min. – Max.	0.0 – 4.0	
Mean ± SD.	2.14 ± 1.21	
Median	2.0	
Death		
No	116	93.5
Yes	8	6.5
Cause of death		
No	116	93.5
Malignant gastric mass	2	1.6
HCC related causes	6	4.8

DISCUSSION

Patients with cirrhosis who are hospitalized to the intensive care unit have a lowered resistance to IFI because of various factors. These patients are at a higher risk of infection due to the spread of CAIDS. Other external means include the use of intrusive devices or procedures, the continuous use of antibiotics for treatment or prevention, and frequent hospitalizations [(11)]. *Candida spp.*, especially *C. albicans*, but also *non-albicans spp.*, indicate increased prevalence over the past decade, as have been reported in earlier investigations. Aspergillus spp., the causal fungal in IA, is the second fungi reported in cirrhotic individuals. In other instances, Cryptococcus neoformans was also isolated [(12)]. Fifty-four point four percent of all Candida species are *C. albicans*, followed by *C. glabrata* (14.5 percent), *C. parapsilosis* (14.1 percent), *C. tropicalis* (5.8 percent), *C. kruzei* (2.5 percent), and *C. dubliniensis* (0.4 percent). About (8.3%) of reported cases had infection by more than one species of candida [(13)]. While around (21.4%) of patients with severe cirrhosis had detectable levels of Aspergillus [(12)].

Our study done in a group of 124 Egyptian patients with cirrhosis. The mean age of the studied population was 62.52 years with male predominance 62.1%, the most common cause of cirrhosis in our patients were HCV 90.3%. At the end of our study, we cannot detect any case with IFI. Because of this result, features and underlying risk factors could not be statistically analyzed.

Among previous studies, in a **Habib *et al.*** [(15)] study found that 1-2% of cirrhotic patients admitted to the intensive care unit experienced IFI [(14)] according to a **Theocharidou *et al.*** study, up to 9 percent [(15)].

The most common type of IC is candidemia, which is the fourth most common nosocomial blood stream infection in the intensive care unit. Seven to ten percent of all blood stream infections in cirrhotic hospitalised patients are caused by candidemia. From January 2011 to March 2020, Chang and coworkers 2022 retrospectively studied 460 individuals with blood stream infections and discovered that 35 of them had candidemia (bacteremia found in 425 cases) [(16)].

Despite its low incidence, IFI has a higher fatality rate due to the complications that arise when a diagnosis is missed or put off. Patients with cirrhosis who also had fungemia had a mortality rate greater than 50% after 30 days, according to a study by **Bajaj *et al.*** [(8)]. In addition, **Verma *et al.*** [(12)] found that the death rate from fungemia was approximately 55%, from invasive candidiasis it was 55.3%, and from invasive aspergillosis it was 81.8%. When compared to controls with either a bacterial infection or no illness, this rate is 1.7–2.9 times higher.

The autopsy investigation by **Saffo *et al.*** [(17)], found that 18% (17 patients) had IFI, and that 35% of IFI patients were not diagnosed before death but were found on autopsy. Therefore, they concluded that IFI is a common consequence of decompensated cirrhosis that is often not detected clinically until it is too late.

Four patients had SFP, two had fungemia, and one had a disseminated infection, according to a study by **Hassan *et al.*** [(7)] conducted at Assiut University Hospital (AUH) and reporting IFI.

Several of the criteria we list below may help explain why our outcome was negative.

At first glance, the low incidence of fungal infections in cirrhotic patients may be attributed to the availability of enough numbers of functioning neutrophils required for conventional fungal host defense. Some research on patients with persistent neutropenia have found that IFI is a prevalent consequence among those with hematologic malignancies (leukaemia, lymphoma, and myelodysplastic syndrome) [(7)]. Between 30 and 50 percent of people with candidemia also have cancer [(18)]. No instances of blood cancers were found in our sample.

Secondly, compared to **Hassan *et al.*** [(7)], where the mean MELD score was 26(± 11.7 SD) and elevated MELD were strongly related with fungal infections in cirrhotic patients, the mean MELD score of our examined cases was 14.0 (±3.55 SD), which is low.

Third, the median length of stay in our patients' ICU was shorter (5.08 ± 2.25 SD) than that reported by Chang *et al.*, (21.9 ±31.9 SD for the candidemia group and 4.9± 32.6 SD for the bacteremia group) **(16).** ICU length of stay was found to be a predictor of candidemia.

In our study, 39.5% of patients underwent EGD, 22.6% had OV banding performed without invasive manoeuvres, 1.6% underwent colonoscopy, and 10.5% underwent ERCP. In 11.3% of situations, we also used CVC. These numbers are lower than those reported by **Bartoletti *et al.*** [(19)], who found that the use of a central venous catheter (CVC) and a history of invasive procedures (gastrointestinal endoscopy and biliary procedures) independently predict the development of candidemia in patients with liver cirrhosis (34 percent of them for TPN).

Finally, no cases of HBV or HIV were observed in our investigation; however, we did find diabetes in 27.4%, chronic kidney disease in 3.2%, and hepatocellular carcinoma in 41.1% of our patients who had liver cirrhosis. Fungal infections in liver cirrhosis are relatively common; 47% of patients were shown to have DM as a contributing cause [(8)].

None of our patients were prescribed corticosteroids. Thirteen percent of prednisolone-treated patients developed serious infections, compared to seven percent of non-prednisolone-treated patients, according to research by **Thursz *et al.*** [(20)].

Poor clinical symptoms, difficulty and delayed diagnosis, and difficulty differentiating fungal colonization from IFI all contribute to the challenge that doctors have when trying to diagnose IFI. There are, therefore, a number of concerns brought up during research on the incidence of invasive candidiasis and candidemia. The sensitivity of most blood culture

techniques for diagnosing IFI is just around 50%, which is one of them. The volume of blood culture, the amount of blood sample, the blood culture equipment, and whether or not the patient is taking antifungal drugs all affect the findings of a blood culture. **De Pauw *et al.* [(21)]** found that a three-time blood culture (with two blood cultures collected each time using 10 mL of blood) was the best way to diagnose IC (totally 60 mL). In our investigation, we used a single blood sample in a single blood culture vial.

Other diagnostic tests, such as β-D- glucan and mannan/anti-mannan, are recommended by European guidelines but are not usually employed, leading to an underestimate of candidemia rates **[(22)].** Since β-DG's sensitivity and specificity depend on the cut-off value of kits used for diagnosis, the results are not accurate and not sure for the existence of IFI. As a result, misdiagnosis and inadequate care with antifungal medicines are common, both of which contribute to the spread of resistance **[(23)].**

Host variables, clinical symptoms, mycological evidence, and indirect tests (β-DG and mannan/anti-mannan) were all part of the EORTC/definition MSG's of probable IFI. Only host variables and clinical suspicion are necessary for an IFI diagnosis **[(24)].**

CONCLUSION

Liver cirrhosis frequently results in infections. Patients with cirrhosis who are hospitalised to the intensive care unit often get fungal infections, which exacerbate their overall state and can be fatal.

We found no cases of IFI in cirrhotic patients in the intensive care unit, and other research in the field found the same. Nosocomial IFI, like many healthcare-related illnesses, has been on the decline as of late. This could be a result of the careful implementation of post-covid-19 infection control methods, as well as general and special hygiene precautions. The leucocytic reaction indicates that our patients' immune system is somewhat retained despite the presence of liver cirrhosis.

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

REFERENCES

1. **Nusrat S, Khan M, Fazili J *et al.* (2014):** Cirrhosis and its complications: Evidence based treatment. World Journal of Gastroenterology, 20(18): 5442-5460.
2. **Mansour D, McPherson S (2018):** Management of decompensated cirrhosis. Clin Med (Lond), 18(2): 60-65.
3. **Piano S, Singh V, Caraceni P *et al.* (2019):** Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. Gastroenterology, 156(5): 1368-1380.
4. **Irvine K, Ratnasekera I, Powell E *et al.* (2019):** Causes and consequences of innate immune dysfunction in cirrhosis. Frontiers in Immunology, 10: 293. doi: 10.3389/fimmu.2019.00293
5. **Ekpanyapong S, Reddy K (2019):** Infections in cirrhosis. Current Treatment Options in Gastroenterology, 17(2): 254-270.
6. **Gomes C, Renata G, Silva V *et al.* (2019):** Bacterial infections in patients with liver cirrhosis in an internal medicine department. GE-Portuguese Journal of Gastroenterology, 26(5): 324-332.
7. **Hassan E, Abd El-Rehim A, Hassany S *et al.* (2014):** Fungal infection in patients with end-stage liver disease: Low frequency or low index of suspicion. International Journal of Infectious Diseases, 23: 69-74.
8. **Bajaj J, Kamath P, Reddy K (2021):** The evolving challenge of infections in cirrhosis. New England Journal of Medicine, 384(24): 2317-2330.
9. **Bartoletti M, Rinaldi M, Pasquini Z *et al.* (2020):** Risk factors for candidemia in hospitalized patients with liver cirrhosis: A multicenter case-control-control study. Clinical Microbiology and Infection, 27(2): 276-282.
10. **Mccormick P, Jalan R (2018):** Hepatic Cirrhosis. Sherlock's Diseases of the Liver and Biliary System. Wiley-Blackwell, pp. 107-126. https://onlinelibrary.wiley. com/ doi/book/ 10.1002/9781119237662
11. **Bartoletti M, Giannella M, Lewis R *et al.* (2016):** Bloodstream infections in patients with liver cirrhosis. Virulence, 7(3): 309-319.
12. **Verma N, Singh S, Singh M *et al.* (2022):** Global epidemiological burden of fungal infections in cirrhosis patients: A systematic review with meta-analysis. Mycoses, 65: 266-284.
13. **Bassetti M, Peghin M, Carnelutti A *et al.* (2017):** Invasive candida infections in liver transplant recipients: clinical features and risk factors for mortality. Transplantation Direct, 3(5): 1-7.
14. **Theocharidou E, Agarwal B, Jeffrey G *et al.* (2016):** Early invasive fungal infections and colonization in patients with cirrhosis admitted to the intensive care unit. Clinical Microbiology and Infection, 22(2): 1-7.
15. **Habib S, Yarlagadda S, Carreon T *et al.* (2020):** Fungal infection in acutely decompensated cirrhosis patients: value of model for end-stage liver disease score. Gastroenterology Res., 13(5):199-207.
16. **Chang Y, Chen J, Yin C *et al.* (2020):** Candidemia in hospitalized cirrhotic patients with bloodstream infection: A retrospective analysis and brief summary of published studies. Journal of the Chinese Medical Association, 85(3): 295-303.
17. **Saffo S, Jain D, Sanchez H *et al.* (2022):** Invasive fungal infections are underdiagnosed in hospitalized patients with decompensated cirrhosis: an autopsy study. Gastro Hep Adv., 1(5): 803-806.
18. **Alves J, Alonso-Tarrés C, Rello J (2022):** How to identify invasive candidemia in ICU—a narrative review. Antibiotics, 11(12): 1804. doi: 10.3390/antibiotics11121804
19. **Bartoletti M, Rinaldi M, Pasquini Z *et al.* (2020):** Risk factors for candidemia in hospitalized patients with liver cirrhosis: A multicenter case-control-control study. Clinical Microbiology and Infection, 27(2): 276-282.
20. **Thursz M, Richardson P, Allison M *et al.* (2015):** Prednisolone or pentoxifylline for alcoholic hepatitis. New England Journal of Medicine, 372(17): 1619-1628.
21. **De Pauw B, Walsh T, Donnelly J *et al.* (2008):** Revised definitions of invasive fungal disease from the European organization for research and treatment of cancer/invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (EORTC/MSG) consensus group. Clinical Infectious Diseases, 46(12): 1813-1821.
22. **Enoch D, Yang H, Aliyu S *et al.* (2017):** The changing epidemiology of invasive fungal infections. Methods Mol Biol., 1508: 17-65.
23. **Yang Z, Song Y, Li R (2021):** A ten-year retrospective study of invasive Candidiasis in a tertiary hospital in Beijing. Biomedical and Environmental Sciences, 34(10): 773-788.
24. **Brauns E, Gustot T (2019):** Infection in cirrhosis. Evidence-based Gastroenterology and Hepatology. John Wiley & Sons, Ltd., pp. 384-394. DOI:10.1002/9781119211419

.