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Early Detection of Invasive Fungal Infections after Liver Transplantation: Single Center Experience

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Abstract: Background: The incidence of invasive fungal infections (IFIs) after solid organ transplantation ranges from 7–42%. Fungal infections after liver transplantation have poor outcome and high mortality rate. The prognosis mainly depends on early treatment for IFIs. Therefore, the diagnosis needs to be prompt depending on the documented risk factors, the duration of operative procedure, the amount of bleeding, the rejection rate and re-transplantation. bAim of work: To determine the incidence of IFIs in liver transplant recipients and to identify various risk factors Material/Methods: This study was performed at the Liver Transplantation Unit, Wadi El Nile Hospital, Egypt during a 2 year period. Fifty consecutive liver transplant recipients were prospectively observed for fungal infections, and the detection of fungal antigen in blood or sterile fluid was done by ELISA. Results: Sixteen patients (32% of the total group) had 19 episodes of fungal infection. Candida was the causative agent in (87.5%) of IFIs and Aspergillus accounted for (31%). Serum creatinine level, dialysis, SBP, MELD and serum bilirubin were significant pre-transplant. risk factors. Operative time, duration of ICU stay, documented bacterial infections were also risk factors. Conclusions: Early detection of fungal infection and prompt treatment is essential for liver transplant recipients.
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Key words: Fungal infection; liver transplantation; risk factors; Egypt.

1. Introduction:

Knowledge about common postoperative infections is essential for improving the care of the liver transplant recipient (1). The incidence of invasive fungal infections (IFIs) is lower than that of bacterial or viral infection, but (IFIs) have the highest mortality rate (2, 3).

Among all transplant groups, liver allograft recipients are at the highest risk of fungal infection, with an incidence of IFI ranging from (7–42%) (4). Candida and Aspergillus species are the most frequently reported fungal pathogens causing infection following liver transplantation (Apergillosis 9–34% vs. Candidiasis 35–91%) (5).

Fungal infections in liver transplant recipients have been associated with mortality rates between 65% to 90% for invasive Aspergillosis and 30% to 50% for invasive Candidiasis (6).

Rational for this study:

As the incidence and mortality rates of (IFIs) after liver transplantation are high, the detection of risk factors in each transplant Center could help the initiation of antifungal prophylactic agents at the appropriate time, and prevent the occurrence of (IFIs). This might improve the prognosis for liver transplant recipients.

Aim of the work:

1-To determine the incidence of invasive fungal infections (IFIs) after liver transplantation in a single Center in Egypt.

2- To identify various risk factors for IFIs. 3- Implement the appropriate treatment modalities to optimize the outcome of liver transplant recipients.

2. Material and Methods:

This study was performed at the Liver Transplantation Unit, Wadi El Nile Hospital, Cairo, Egypt, during a 2 year period. Fifty consecutive patients after liver transplantation were prospectively enrolled and observed for fungal infections.

Collection of data:

Clinical and variables related to surgery were recruited from each patient, and grouped in three different periods. **The preoperative period** was defined as the last month before liver transplantation. During that period, the following data were collected: age, sex, MELD score, surgical procedures within this period, serum creatinine, total bilirubin level, co morbid diseases as (DM, long-term obstructive pulmonary disease), clinical evaluation of respiratory system, type and severity of the underlying liver disease, previous ICU stay (with/ without mechanical ventilation), Cytomegalovirus (CMV) infection, Dialysis, and antibiotic/ antifungal therapy for >7 days. Aspergillus or candida respiratory colonization. in the past 6 months before transplantation were also recorded.

Data were collected in **the intraoperative period** and included urgent clinical status at the time of transplantation, fulminate hepatic failure, re-transplantation, number of packed red blood cells required, and length of graft cold ischemia.

The postoperative period included the first month after transplantation. The following variables were collected: mechanical ventilation time, need of dialysis, intensive care unit stay (ICU stay in days), re- surgical intervention in the first month, prolonged antibiotic therapy (more than 14 days), CMV infection, bacterial infection. fungal prophylaxis. fungal infection.

All patients were treated with (cyclosporine or tacrolimas) and corticosteroids after transplantation.

Methods:

1- Standard laboratory evaluation for liver transplant recipients.

2- For the diagnosis of co-existing bacterial infections, different specimens were incubated aerobically on blood agar, chocolate agar and MacConkey agar and anaerobically on blood agar for isolation of aerobic and anaerobic bacteria for 24–72 hours at 37°C. The growing organisms were identified by conventional biochemical reactions.

3- Detection of Aspergillus and Candida antibodies (IgG –IgM) in patient serum before and after transplantation by ELISA.

4- Cytomegalovirus (CMV) infection was defined by the presence of a positive CMV polymerase chain reaction result (≥ 64 copies/ml white blood cells) after transplantation.

5- Diagnosis of invasive fungal infections (IFIs)

The diagnosis of IFIs was based on the detection of fungus from a normally sterile site. This included:

(1) Blood cultures were taken from peripheral veins. Blood cultures were incubated for 7 days. At the end of the incubation (for negative samples) or at the time of a positive signal (for positive samples), the blood cultures were subcultured onto specific media for fungal detection and maintained in culture at 25°C under ordinary atmospheric conditions until the growth of fungi was observed. In cases with no growth, the culture was observed for 14 days and then considered to be negative.

(2) Microscopy and culture of needle aspirates or biopsies from normally sterile sites; (ascitic fluid, sputum, bile, urine, transtracheal aspirate, endotracheal tube, pleural fluid and bronchial lavage) on fungal media, which are Brain heart infusion agar, Malt extract agr, Potato–dextrose agar and Sabouraud dextrose agar.

(3) Detection of Aspergillus antigen using an immunoenzymatic sandwich microplate assay for the detection of *Aspergillus* galactomannan antigen in adult and pediatric serum samples and bronchoalveolar lavage (BAL) fluid samples (The Platelia™ *Aspergillus* Ag).

(4) Detection of the mannan antigen of *candida* in human serum or plasma by immunoenzymatic assay (Platelia™ *Candida* Ag Plus).

(5) Radiological examination by X-ray and high-resolution CT are useful in the detection of fungal infections. Pulmonary lesions with central cavitation, pulmonary nodules, infiltration, and halo or air-crescent signs are characteristic of pulmonary fungal infections (7).

6- Definition of infections:

Fungal infection was considered a proven fungal infection when there was a positive culture and fever >38^{0}C. Probable/possible fungal infection was diagnosed when there was a positive mannan antigen or Aspergillus galactomanan antigen testing, and the patient was febrile in spite of using broad-spectrum antibiotics (8).

Platelia™ Aspergillus Ag:

The Platelia™ *Aspergillus* Ag is a one-stage immunoenzymatic sandwich microplate assay which detects galactomannan in human serum and BAL fluid. The assay utilizes rat EBA-2 monoclonal

antibodies directed against the *Aspergillus* galactomannan. Positive results obtained with the Platelia™ *Aspergillus* Ag should be considered in conjunction with other diagnostic procedures such as microbiological culture, histological examination of biopsy samples and radiographic evidence.

Monoclonal antibody- galactomannan - monoclonal antibody/peroxidase complex forms in the presence of galactomannan antigen. The absorbance (optical density) of specimens and controls is identified by a spectrophotometer set at 450 and 620/630 nm wave length.

Reagents:

Platelia™ *Aspergillus* Ag: product No. 62794 (96 Tests). Store the kit at 2-8°C. Bring all reagents to room temperature (18-25°C) for at least 30 minutes before use. Return all reagents to 2-8°C immediately after use.

Specimen Collection:

The test is done on serum or BAL fluid.

I- Serum

Collect blood samples according to standard laboratory procedures. Serum samples must be uncontaminated with fungal spores and/or bacteria. Transport and store samples in sealed tubes, unexposed to air. Unopened samples can be stored at 2-8°C for up to 5 days prior to testing. After initial opening, samples may be stored at 2-8°C for 48 hours prior to testing. For longer storage, store the serum at -70°C. Serum samples could be subjected to maximum of 4 freezing / thawing cycles.

II. BAL fluid

Collect BAL fluid samples according to standard laboratory procedures. BAL fluid samples must be collected in sterile saline and may be tested as is or supernatants from centrifuged samples (10,000 rpm for 10 min) before proceeding to treat the sample. Transport and store samples in sealed tubes, unexposed to air. After initial opening, samples may be stored at 2-8°C for up to 24 hours. For longer storage, store the BAL samples frozen (-20°C or less) up to 5 months. BAL samples can be subjected to a maximum of 4 freezing/ thawing cycles.

Interpretation of Results:

The presence and absence of galactomannan antigen in the test sample is determined by calculating an index for each patient specimen. The Index (I), is the Optical Density (OD) value of the specimen divided by the mean optical density of the wells containing Cut-off Control Serum.

Interpretation of sera/BAL fluid with index < 0.50:

Sera/BAL fluid with an index < 0.50 are considered to be negative for galactomannan antigen. Repeat testing is recommended if the result is negative, but the disease is suspected.

Interpretation of sera /BAL fluid with an index ≥ 0.50

Sera /BAL fluid with an index ≥ 0.50 are considered to be positive for galactomannan antigen. For all positive patients, it is recommended that a new aliquot of the same sample (serum/BAL) be repeated.

Platelia™ Candida Ag Plus Detection Of The Mannan Antigen Of Candida In Human Serum Or Plasma By Immunoenzymatic Assay:

Platelia™ *Candida* Ag Plus is an immunoenzymatic sandwich microplate assay for the detection of the circulating mannan *Candida* antigen in human serum or plasma. Platelia™ *Candida* Ag Plus (code 62784) was used. Mannan is a polysaccharide non-covalently bound to the yeast cell-wall and represents more than 7% of the dry weight of *C. albicans*. It is found to be one of the main biomarkers for the diagnosis of invasive candidiasis.

Principle of the Procedure:

Platelia™ *Candida* Ag Plus is a one-stage immunoenzymatic sandwich microplate assay, allowing the detection of the circulating mannan *Candida* antigen in human serum or plasma. The assay uses the rat monoclonal antibody (MAb), EBCA-1.

The EBCA1 MAb is used to:

- Coat the microplate wells and bind the mannan antigen.
- Detection of the antigen bound to sensitized microplate (conjugate reagent: peroxidase labelled MAb).
- Serum or plasma samples are heat-treated in the presence of EDTA in order to dissociate the immune complexes which could possibly interfere with the immunoassay reaction. The treated samples of serum or plasma and the conjugate are added to the wells of the microplate coated with the anti-mannan monoclonal antibody.
- The absorbance (optical density) of human samples and calibrator is determined with a spectrophotometer at 450/620 nm wave length.

Interpretation of the results:

- Samples with concentrations less than 62.5 pg/mL (C < 62.5) are considered to be «negative» for mannan antigen.
- Samples with concentrations between 62.5 and 125 pg/mL (62.5 ≤ C < 125) are considered to be «intermediate» for mannan antigen.
- Samples with concentrations that are equal or greater than 125 pg/mL (C ≥ 125) are considered to be «positive» for mannan antigen.

Statistical analysis:

Patients with and without post-transplantation IFIs were compared as follows: Continuous variables (age, bilirubin and serum creatinine levels, duration of ICU stay, MELD, etc.) were expressed as the mean ±

standard deviation (SD) and compared using the Student's *t*-test. Categorical variables data (underlying liver disease, presence or absence of CMV, dialysis, antibiotic use, etc.) were compared using the Chi-square test of Fisher's exact probability test. Differences were considered significant if the *P* value was less than 0.05.

3. Results:

This prospective study included 50 liver transplant patients (38 male and 12 females). They were classified into adults (≥ 18 years) and pediatric age group (<18 years). The mean age of the adult group was 54.5±8.5 years (range: 23 – 70). The mean age of the pediatric group was 4.3±2.5 years (range: 2-10).

The incidence of invasive fungal infection was seen in (figure 1).

Sixteen patients out of 50 (32%) developed invasive fungal infections. Those 16 patients had 19 episodes of fungal infection, including three patients with two fungal infections. Ten male patients had 12 fungal infection episodes (eight episodes of Candida and four Aspergillus) and 6 female patients had 7 fungal infection episodes (six episodes of Candida and one Aspergillus). There was no significant difference between male and female patients regarding the incidence of IFIs **(Table 1)**.

Table (1): Invasive fungal infections in liver transplant recipients

Variable	**All patients** (N= 50)	**Male patients** (N= 38)	**Female patients** (N= 12)
No. with fungal infections (%)	16 (32%)	10(26%)	6(50%)
Episodes of fungal infection per patient	19/50 (38%)	12/38(31.6%)	7/12 (58%)
Deaths, all causes.	3/50(6%)	3/38 (7.9%)	0/12(0%)
P value: 0.162 not significant.			

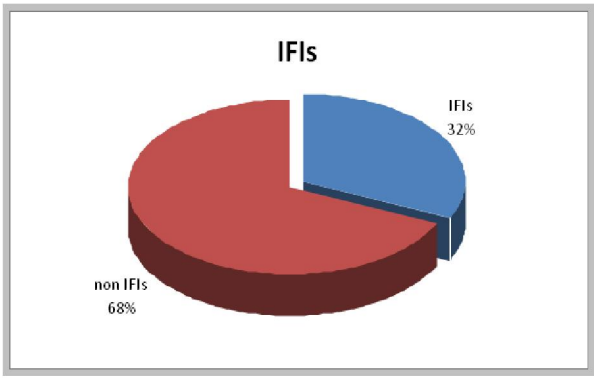

Figure (1): Incidence of invasive fungal infections (IFIs) after liver transplantation

Table (2): Invasive fungal infection in adult & pediatric age groups

Variable	**All** (N=50)	**Group 1 (Adults)** (N=42)	**Group 2 (Pediatrics)** (N=8)
No. with fungal infections (%)	16(32%)	10(24%)	6(75%)
Episodes of fungal infection per patient	19/50 (38%)	12/42(28.6%)	7/8(87.5%)
Deaths, all causes	3/50 (6%)	3/42 (7.1%)	0/8(0%)
P value: 0.009 (very significant).			

Table (3): Types of invasive fungal infections (IFIs) and mean time of onset after liver transplantation

IFIs type	**No. = 16**	**Percentage**	**Mean time of onset of fungus infection**
Aspergillosis	5 / 16	31 %	105 days
Candidiasis	14/16	87.5%	41.7 days

Of the 16 patients diagnosed invasive fungal infection by positive Aspergillus & Candida galactomanan, only 6 were diagnosed by routine fungal culture, two had positive yeast fungus in sputum and ascetic fluid culture, one had Aspergillus fumigatus in sputum, two had Candida albicans in sputum & urine and one had Aspergillus Niger in sputum.

Of all fungal infection episodes, 79% (15/19) occurred in the first month after transplant, and 21% occurred after the first month. Among the Candidal

infections 12/ 14 and among the Aspergillus infections 3/5 were detected four weeks after transplantation.

As regards the age, table (2) shows the comparison between adult and pediatric age in getting fungal infections after transplantation. Six children of eight (75%) got seven episodes of infections (six Candida infections and one Aspergillus). Ten adults out of 42 (24%) got 12 episodes of fungal infections (eight episodes of Candida and four Aspergillus). There was a significant correlation between age and IFIs (P value =0.009).

Candida was the causative agent in (87.5%) of IFIs and Aspergillus accounted for (31%). Fourteen episodes of Candida and five episodes of Aspergillus were reported in the current study. Candida isolated was Candida albicans and Apergilus were fumigatus and niger **(Table 3)**.

The relation between fungal infection and underlying liver disease was shown in table (4), where all patients with primary biliary atresia developed fungal infections, the four patients got five episodes of fungal infections (p= 0.007). Six patients out of 25 with HCV (24%) got seven episodes of fungal infection, 4/14 of HCC patients (29%) developed five episodes, as regards cryptogenic cause, no patient got infection and two of "other" causes /3 (66.7%) got fungal infection, and this indicates significant correlation between the underlying cause of liver cirrhosis and risk of fungus infection (P= 0.012) (Table 4).

Table (4): Relationship of invasive fungal infections (IFIs) to pre-transplant liver pathology

Diagnosis	Number/percentage	Fungal episodes per patient	Percentage of patients with fungal infections
Post-hepatitis C	25/50(50%)	7/25 (28%)	6/25 (24%)
HCC	14/50(28%)	5/14(35.7%)	4/14 (28.6%)
Cryptogenic cirrhosis	4/50(8%)	0/4(0%)	0/4 (0%)
Extrahepatic billiary atresia *	4/50(8%)	5/4(125%)	4/4 (100%)
Other causes ¶	3/50(6%)	2/3(66.7%)	2/3 (66.7%)
Total	50	19/50 (38%)	16/50 (32%)

* Extrahepatic biliary atresia patients compared with all other patients (p<0.007).
¶ one patient with primary hyperoxaluria, one patient had Grigler Najjar syndrome and one patient had fulminant hepatitis.

Table (5): Comparison of pre-transplantation, operative and post-transplantation variables in patients with and without IFIs following liver transplantation.

Variable	Patients with fungal infection (N = 16)	Patients without fungal infection (N = 34)	P. Value
Sex **- *Male*** **- *Female***	 10(62.5%) 6(37.5%)	 28 (82.4%) 6(17.6%)	 0.16
MELD and PELD score	17.7± 9.3	12± 6.1	0.012*
SBP	5 (31 %)	2 (5.9%)	0.02 *
Mean value of serum creatinine	1.7± 2.13	1.0 ± 0.36	0.04*
Mean value of Serum bilirubin	11.0 ±12	4.3 ±5.9	0.011*
CMV infection	1 (6%)	4 (12%)	0.2
Asp. & Cand. Colonization in past 6 months	7 (43.8%)	10 (29.4%)	0.3
Dialysis	3 (18.8%)	0(0%)	0.02*
Long-term obstructive. pulmonary disease	0(0%)	2 (6%)	1
Serum Albumin (g/dL, mean value ± SD)	3.0±0.8	3.0±0.6	0.9
Neutrophils (x 10^9 /L, mean value ± SD)	3.8±1.9	3.1±2.4	0.3
ALT	91±101.8	90±285.3	0.9
Operation time in hours, (mean value ± SD)	13.1 h	8.1 h	0.02*
No. of units of packed RBCs transfused	9.0±9.7	6±5.4	0.18
Other organ transplantation	3 (19%)	0(0%)	0.02*
Days in ICU (mean ± SD)	8 ± 6	5 ±4	0.04*
CMV infection	2 (12.5%)	1 (3%)	0.23
Bacterial infection	14 (87.5%)	18 (53%)	0.03*
Immunosuppression			
Tacrolimus	11 (69%)	18 (53%)	0.36
Cyclosporin	5 (31%)	16 (47%)	0.36

Note: *Significant (P value <0.05)

Risk factors for IFIs are shown in table (5). As regards pre-transplantation variables, serum creatinine level, dialysis, SBP, MELD and serum bilirubin were significant risk factors (p value <0.05 for each).

Regarding operative variables, the mean value of operative time in hours was significantly longer in those who had invasive fungal infections when compared to those without (13.1 versus 8.1). No association between blood transfusion and IFIs could be found in our results. The mean duration of ICU stay (in days) after transplantation surgery was significantly longer in the group of patients who developed IFIs compared to those who did not (8 versus 5) (P = 0.04). Of the 16 patients with fungal infections, 14 (87.5%) had one or more documented bacterial infections. Of the 34 patients without fungal infection, 18 (53%) had bacterial infections (P=0.026).

Among the bacterial infections, the most frequent organism was ESBL (Extended spectrum beta-lactamase) in 44%. The second most common isolated organism was E.coli followed by Pseudomonas, Klebsiella. Acinetobacter baumannii and Alpha haemolytic streptococci. The common sites of pathogen isolation were blood, bile, urine and sputum.

Regarding Immunosuppression, 11/16 who acquired IFIs after transplantation received tacrolimas and 5/16 received cyclosporine. There was no significant difference between two groups regarding incidence of IFIs (P=0.3).

Mortality rate:

Three out of total 50 patients (6%) died during the follow-up period. There was no significance difference in the mortality rate between those with IFIs (2/16, 12.5%) and those without (1/ 34, 2.9%) (P = 0.2). One patient with Aspergillus infection died. One patient with Candida infection died.

4. Discussion:

Despite the advances in surgical techniques which reduce the intra-operative requirements of blood and surgical time in recent years, the incidence of IFI still ranges from 5% to 20% (9, 10). The use of immunosuppressants decreases the host immunity, making recipients more susceptible to viral and fungal infections, and increases the death rate, after OLT (10, 11).

In the current study, IFIs were observed in 32% of liver transplant recipients, 58% of them was receiving tacrolimas and 42 % receiving cyclosporine as an immunosppressive agent. Invasive Candidiasis was reported in 87.5 % and Aspergillosis was reported in 31% in the current study. Charles et al. (12) showed (42%) IFIs in 62 liver transplant recipients. This is not different from our findings (16/50 or 32%) but if compared to the figures reported from a study at the University of Rochester Medical Center (17.7%). (13), which lower than our study. This lower incidence may be attributed to the use of fluconazole as antifungal prophylaxis after transplantation. However, in our study, the recipients did not receive antifungal prophylaxis.

Raghuram et al. (13) claimed that Candida infections predominated and accounted for 47 of the 58 IFIs (81%), this is also proved in the current study (87.5 %), as well as, in the study done by Silveira and Husain (5). Similarly, Marzaban et al (14) in Egypt demonstrated that Candida was the most common fungal infection (17/23 patients; 73.9%). In contrast to Candida, Aspergillus, is not an endogenous organism and is probably acquired from the physical environment. In the present study, Aspergillus was the second most common fungal infection (31%), which was similar to other reports like Shi et al. (15) (32.4%) and Marzaban et al (14) (6/23; 26.1%). However, it was higher than that of Fortún‘s et al. (16) (1–9.2%) of liver transplant recipients.

Three out of total 50 patients (6%) died during the follow-up period in the current study. This is an improvement in survival over that seen in the past studies. This is may be due to early diagnosis and the earlier recognition of the high-risk patient. In the current study, there was no significance difference in the mortality rate between those with IFIs (2/16, 12.5%) and those without (1/ 34, 2.9%) (P = 0.2). Similary, Marzaban et al (14) reported that the mortality was not significantly different between those with fungal infection (5/ 23; 21.7%,) and those without (21/117; 17.9%) (p=0.8).

Utsumi et al. (17) diagnosed 15/ 153 patients (9.8%) as IFIs with Candida spp. (n = 10), and Aspergillus spp. (n = 4). Of those patients with IFIs, 7 patients (46.7%) died despite treatment.

Many studies have detected a number of risk factors associated with IFIs after liver transplantation. Dialysis, rejection treatment, cytomegalovirus (CMV) viremia or disease, acute hepatic insufficiency, early graft failure, increased the operation time, retransplantation, prolonged preoperative hospitalization, preoperative use of antibiotics, intra-operative infusions of blood products, fungal colonization, and re-exploration after transplantation (18-20). Our work documented that an elevated serum creatinine level and requirement of dialysis were significant risk factors for IFIs. Renal dysfunction is prone to secrete more Th2 cytokines and enhance susceptibility to all kinds of infections, including fungal infection in liver recipients (21).

The patients who developed a fungal infection were more likely to have received antibiotics in the 2 weeks before transplantation. We concluded that preoperative antibiotic therapy does predispose to subsequent fungal infection. In contrast to previous

report (22). However, our result did not validate blood products during surgery as a risk factor for IFIs after LT. longer operative time was a risk factor in the present study. Longer operative time may reflect technical problems at surgery and results in longer exposure of the operative field to the environment.

Multivariate analysis indicate that MELD score of 23-30 or more than 30 associated with a 2.1-fold or 3.1-fold increase in relative risk of IFIs, so the liver transplant patients with MELD score >20 are candidates for antifugal prophylaxis (23). This is also proved in the current study.

With the development of new diagnostic tools to detect fungal components, such as fungal antigens and fungal nucleic acids, which sometimes are the only diagnostic tools for IFIs (24, 25), it is becoming necessary to use these tools in the current study. In patients with IFIs, the ELISA test usually gives positive results before the clinical symptoms and signs become detectable (26). In this study, *Aspergillus* was mostly detected in blood. Only 2 patients had *Aspergillus* in sputum, confirmed by CT chest. This was contrary to several previous studies that stated pulmonary infection was the most common *Aspergillus* clinical presentation (90%) (27), and that the lungs are the definite or probable primary site of invasive Aspergillosis in most patients (28).

Conclusion:

Our preliminary data emphasize the importance of galactomanan antigen assay in the early diagnosis of IFIs. The optimal management of fungal infection depend on early detection of the causative agent. The present study recommended that the combined use of culture, GM ELISA resulted in an earlier and more definite diagnosis of IFIs. Antifungal prophylaxis should be given to high-risk liver transplant patients, such as patients with pre-transplant high MELD score, those with renal failure or prolonged ICU stay.

References:

1. Patel G, Huprikar S: Infectious complications after orthotopic liver transplantation. Semin Respir Crit Care Med, 2012; 33(1): 111–24.
2. Neofytos D, Fishman JA, Horn D, Anaissie E, Olyaei A and Marr KA: Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transpl Infect Dis 2010; 12(3): 220–29.
3. Liu X, Ling Z, Li L, Ruan B. Invasive fungal infections in liver transplantation. International Journal of Infectious Diseases 2011; 15: e298–e304.
4. Winkler M, Pratschke J, Zheng S, Zhang M and Li W, Lu M, Sgarabotto D, Sganga G, Kaskel P, Chandwani S, Ma L, Petrovic J, and Shivaprakash M: Caspofungin for post solid organ transplant invasive fungal disease: results of a retrospective observational study. Transpl Infect Dis. 2010; 12(3): 230–37.
5. Silveir FP and Husain S: Fungal infections in solid organ Transplantation. Med. Mycol 2007; 45 (4): 305– 20.
6. Sganga G, Bianco G, Frongillo F, Lirosi M C, Nure E, Agnes S. Fungal Infections After Liver Transplantation: Incidence and Outcome. Transplantation Proceedings 2014; 46(7): 2 314-2318.
7. Greene RE, Schlamm HT, Oestmann JW, Stark P, Durand C, Lortholary O, Wingard JR, Herbrecht R, Ribaud P, Patterson TF, Troke PF, Denning DW, Bennett JE, de Pauw BE, Rubin RH. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis 2007; 44(3): 373–79.
8. Ascioglu S, Rex JH, De Pauw B, Bennett JE and Bille J**:** Invasive Fungal Infections. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002; 34:7-14.
9. Pappas P G, Alexander BD. Andes DR. Hadley S, Kauffman CA, Freifeld A, et al. “Invasive fungal infections among organ transplant recipients: results of the transplant-associated infection surveillance network (TRANSNET),” Clinical Infectious Diseases 2010; 50(8): 1101–1111.
10. Pacholczyk M J, Lagiewska B, Lisik B, Wasiak D and Chmura A. “Invasive fungal infections following liver transplantation— risk factors, incidence and outcome,” Annals of Transplantation 2011.; 16(3): 14–16.
11. Yang C-H, He X.-S, Chen J, Ouyang B, Zhu X-F, Chen M-Y et al. “Fungal infection in patients after liver transplantation in years 2003 to 2012,” Annals of Transplantation 2012; 17(4): 59–63.
12. Wajszczuk CP, Dummer JS, Ho M, Van Thiel DH, Starzl TE, Iwatsuki S, Shaw B Jr. Fungal infections in liver transplant recipients. Transplantation. 1985; 40(4): 347–353.
13. Raghuram A, Restrepo A, Safadjou S, Cooley J, Orloff, M.; Hardy D, Butler S and Christine EK: Invasive Fungal Infections Following Liver Transplantation: Incidence, Risk Factors, Survival, and Impact of Fluconazole-Resistant Candida parapsilosis. Liver Transplantation 2012; 18 (9):1100-1109.
14. Marzaban R, Salah M, Mukhtar AM, Dwedar RA, Abdel-Latif W, Mahmoud I. Fungal

Infections in Liver Transplant Patients Admitted to the Intensive Care Unit. Ann Transplant, 2014; 19: 667-673.
15. Shi X-JJ, Lü S-CC, He L, Lu F, Liang YR, Luo Y, Ji WB, Zhao ZM.: Diagnosis and treatment of fungal infection after liver transplantation. Chin Med J (Engl) 2011; 124(7): 1015–17.
16. Fortún J, Martín-Dávila P, Moreno S, De Vicente E, Nuño J, Candelas A, Bárcena R, García M.: Risk factors for invasive aspergillosis in liver transplant recipients. Liver Transpl. 2002; 8 (11): 1065–70.
17. Utsumi M, Umeda Y, Yagi T, Nagasaka T, Shinoura S, Yoshida R, Nobuoka D, Kuise T, Fuji T, Takagi K, Takaki A, and Fujiwara T. Risk Analysis for Invasive Fungal Infection after Living Donor Liver Transplantation: Which Patient Needs Potent Prophylaxis? Dig Surg 2019;36:59–66.
18. Osawa M, Ito Y, Hirai T, Isozumi R, Takakura S, Fujimoto Y, et al. Risk factors for invasive aspergillosis in living donor liver transplant recipients. Liver Transpl 2007;13:566–70.
19. Shi SH, Lu AW, Shen Y, Jia CK, Wang WL, Xie HY, et al. Spectrum and risk factors for invasive candidiasis and non-Candida fungal infections after liver transplantation. Chin Med J (Engl) 2008;121:625–30.
20. Rosenhagen M, Feldhues R, Schmidt J, Hoppe-Tichy T, Geiss HK. A risk profile for invasive aspergillosis in liver transplant recipients. Infection 2009;3 7:313–9.
21. Sun HY, Singh N, Wannstedt C, Wagener MM and Steele C: Dysregulated expression of T-helper cell responses and susceptibility to infections in high-risk liver transplant recipients. Transpl. Immuol (2008); 20:68–72.
22. Singh N, Gayowski T and Wagener MM: Post transplantation dialysis-associated infections: morbidity and impact on outcome in liver transplant recipients. Liver Transpl. 2003; 7:100–5.
23. Saliba F, Delvart V, Ichaۥ P, Kassis N, Botterel F, Mihaila L, Azoulay D, Adam R, Castaing D, Bretagne S, Samuel D. Fungal infections after liver transplantation: outcomes and risk factors revisited in the MELD era. Clin Transplant 2013: 27: E454–E461.
24. Yeo SF and Wong B: Current status of nonculture methods for diagnosis of invasive fungal infections. Clin Microbiol Rev 2002; 15:465- 484.
25. Cuenca-Estrella M, Matteo B, Lass-Florl C, Raci Z and Thomas RR: Detection and investigation of invasive mould disease. J Antimicrob Chemother 2011; 66 (Suppl 1):i15-24.
26. Sulahian A, Boutboul F, Ribaud P, Leblanc T, Lacroix C and Derouin F: Value of antigen detection using and enzyme immunoassay in the diagnosis and prediction of invasive aspergillosis in two adult and pediatric hematology units during a 4-year prospective study. Cancer 2001; 91:311-318.
27. Singh N and Husain S: The AST Infectious Community Diseases of Practice: Invasive aspergillosis in solid organ transplant recipients. Am J Transplant 2009; 9 (Suppl.4): S180–91.
28. Linden PK, Coley K, Fontes P, Fung JJ, Kusne S: Invasive Aspergillosis in Liver Transplant Recipient: Outcome Comparison of Therapy with Amphotericin B Lipid Complex and a Historical Cohort Treated with Conventional Amphotericin B. Clin Infect Dis 2003; 37: 17–25.

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