

**Experience of using anidulafungin for the treatment of invasive  
candidiasis in a patient after liver transplantation**

**(Case report)**

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*This paper is a case report of a successful treatment of the invasive fungal infection, and bacterial infection caused by multidrug-resistant pathogen after liver transplantation.*

**Keywords:** candidiasis, bacterial infection, liver transplantation, anidulafungin.

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Currently, the incidence of invasive fungal infections in the first year after solid organ transplantation makes approximately 3% and still remains one of the causes of severe clinical manifestations and mortality. According to a number of studies, the annual mortality rates from invasive aspergillosis, candidiasis, and cryptococcosis have made 40%, 34%, 27%, respectively [1-3].

After liver transplantation, the risk of invasive mycosis persists for many years and it actually develops in 4.7% of cases [1]. The epidemiology of fungal infections may be influenced by the donor organ quality, comorbidities, the severity of the recipient's condition, and postoperative

complications. The risk of developing invasive fungal infections increases with initially severe condition of the recipient, the presence of chronic viral infections (hepatitis C and B, cytomegalovirus), leucopenia. Risk factors in the postoperative period include a massive antibacterial therapy, and the mucosal contamination with pathogenic fungi, and also a pulse therapy for acute rejection crisis. [4]. In the recent years, much attention has been paid to donor organs as a potential source of infection with pathogenic fungi [5]. An invasive fungal infection in an organ donor makes a contraindication to organ harvesting for transplantation, but its diagnosis makes certain difficulties. This is especially true for endemic fungal infections and cryptococcosis that often exist in a latent form. Sometimes unexplained symptoms in organ donors become clear only in the retrospect with the mycosis developing in the recipient [6-15]. Uniform recommendations on donor screening for endemic mycosis have not been developed yet [16].

Well-known are the cases of infecting the recipient with various *Candida* spp. derived from the donor organ. This may occur at the stage of donor management and organ harvesting, as well as in organ transplantation [17-19].

Some researchers have noted a certain time period of a potential fungal infection development after organ transplantation. Specifically, invasive candidiasis may occur in a period of a few weeks to several months following liver transplantation [2]. It is known that candidiasis is the most common form of invasive fungal infections with the incidence of 50-60% among all types of fungal infections [1]. Fungal colonization with *Candida* species, especially *Candida albicans*, occurs via the gastrointestinal tract, skin, airways, and genitourinary tract of a patient.

The purpose of the paper was to show the case of a successful treatment for invasive candidiasis caused by *Candida parapsilosis* and *Candida albicans* in a patient who underwent a liver transplantation.

Patient S., a man of 48 years old with the diagnosis of "liver cirrhosis resulted from hepatitis C, hepatocellular carcinoma, hepatocellular failure, hepatorenal syndrome," underwent a cadaveric liver transplantation. At preoperative assessment of the patient's condition the Child-Pugh score was 10, MELD score was 24, focal hepatocellular carcinoma lesions were falling within the Milan Criteria.

Intraoperative period was stable in conditions of a multicomponent balanced general anesthesia with the use of Sevoran in the low fresh gas flow. Of particular note were the decrease in the urine output to less than 50 ml/h during hepatectomy and in the anhepatic phase, and also the use of dopamine in a dose of 8-10 mcg/kg/min and norepinephrine in a dose of 200-300 ng/kg/min to stabilize the mean blood pressure (MBP) at a level higher 70 mm Hg during the anhepatic period and in the first minutes of venous reperfusion. An estimated blood loss volume made 1600 mL, meanwhile 450 mL of washed autologous red blood cells were reinfused using a specialized Blood Salvage Machine.

The patient was extubated in the intensive care unit at 6 hours after surgery. Immunosuppression scheme included Daclizumab (20 mg intraoperatively after haemostasis before suturing the laparotomy wound, and 20 mg on the 4<sup>th</sup> postoperative day), tacrolimus, everolimus and mycophenolic acid.

The peak elevations of cytolytic enzyme levels (ALT and AST) were registered on the 1<sup>st</sup> postoperative day making 470 and 730 units, respectively. Hepatorenal syndrome was the cause of the renal failure in the

early postoperative period. By the 3rd postoperative day, the patient's severity was attributed to the increases in the serum creatinine level over 200  $\mu\text{mol/L}$ , and urea of more than 30  $\text{mmol/L}$ , to the presence of oliguria and overhydration as diagnosed at control chest X-ray. That required to undertake two veno-venous hemodiafiltration sessions on the 3<sup>rd</sup> and 5<sup>th</sup> postoperative days that resulted in the recovery of a normal kidney function.

The patient received a prophylactic antibacterial (*Ceftriaxone*) and antifungal therapy (*Fluconazole*). By the 7th postoperative day, all drain tubes had been removed, and sterile blood cultures for bacteria and fungi were obtained, including those from removed draining tubes. A moderate leukocytosis of  $10 \times 10^9/\text{L}$  with an increase in stabs to 6% retained.

The fluid therapy, preventive antibacterial and antifungal therapy were continued. Despite the administered therapy, the patient's condition demonstrated negative dynamics. Tachycardia of up to 110 bpm and oliguria (400 ml urine per 24 hours) were noted at postoperative day 22. Ultrasonographic examination revealed a fluid collection in a subhepatic area and enteroparesis. Hematology study demonstrated anemia (hemoglobin of 78 g/L, erythrocyte count of  $3.83 \times 10^{12}/\text{L}$ , leukocytosis of  $12.87 \times 10^9/\text{L}$  with the differential formula shift to the left to myelocytes (3), thrombocytopenia with platelets of  $78 \times 10^9/\text{L}$ ). Hypocoagulation (INR=1.86) was noted in the blood clotting system.

Blood biochemistry showed hyperbilirubinemia (total bilirubin of 35  $\text{mmol/L}$ ), hyperazotemia (with creatinine of 184  $\text{mmol/L}$ , urea of 29  $\text{mmol/L}$ ), hypoalbuminemia (albumin of 29 g/L).

The clinical pattern of sepsis made the indication for relaparotomy. Abdominal surgical exploration revealed a defect in the area of choledocho-choledochal anastomosis; an inflammation with purulent discharge and

sequestration were noted in the zone of pancreatic head, the isthmus of the gland, and in the surrounding fatty tissue. During the surgery, the sequestrectomy around the isthmus of the pancreas was undertaken followed by the drainage. After relaparotomy, the endoscopic retrograde cholangiography, papillosphincterotomy and stenting of the common bile duct were performed.

Microbiology study of abdominal contents revealed a multidrug-resistant (MDR) pathogen *Acinetobacter sp.* having an intermediate sensitivity only to cefoperazone/sulbactam. The study for fungal flora revealed *Candida spp.*

The polymerase chain reaction (PCR) assays detected *Candida parapsilosis* and *Candida albicans* in blood, sputum, and intestinal content specimens (Figure).

On the basis of the obtained data, the patient was administered cefoperazone/sulbactam in the maximal dose of 8 g/day intravenously and anidulafungin in the dose of 100 mg/day. An intensive therapy was undertaken including renal replacement therapy in a continuous mode, plasmapheresis and LPS-adsorption. For the drainage of the parapancreatic abscess area, the draining tubes were attached to suction-irrigation system. The patient was extubated on the 4<sup>th</sup> day after relaparotomy, and put to a non-invasive ventilation mode via a face mask. The administered therapy resulted in the improvement of clinical and laboratory parameters over time.

Neither *Candida parapsilosis*, no *Candida albicans* were seen at PCR assays of blood, sputum, urine, and intestinal secretions after 14 days of anidulafungin therapy.

It should be emphasized that the occurrence of bacterial and invasive fungal infections is a major cause of severe clinical manifestations and lethal

outcomes after liver transplantation. The recipient's condition, and the impact of external factors predetermine the risk of invasive candidiasis development. In our observation, the fungal invasion was related to the intensity of colonization that was stimulated by the exposure to broad spectrum antibiotics, corticosteroids, aggravated by concomitant diabetes mellitus, a prolonged ICU stay. The negative impact in this case heightened due to the damage of mucosal and skin barriers, a prolonged use of intravascular catheters, a longer surgery duration, radiation and immunosuppressive therapies.

A key factor for the survival of patients with life-threatening bacterial infections would be an early administration of targeted antibiotic therapy. Current principles of treatment for such conditions imply an immediate administration of reserve broad spectrum antibiotics, or a combination of several drugs potent against the majority of potential pathogens. In infectious diseases and complications caused by multidrug-resistant pathogens, antibiotics are recommended for use in the maximum daily doses [21]. However, a massive antibiotic therapy would be a risk factor for invasive fungal infections, especially in the patients on an immunosuppressive therapy. Such complications are characterized by the severe clinical manifestations and very high mortality rates [22].

In our observation, the use of antibiotic therapy with increasing drug doses proved effective in the treatment of bacterial infections. However, this therapy gave the ground for the development of invasive candidiasis. This, probably, in turn, led to the postoperative incompetence of bilio-biliary anastomosis with a biliary fistula formation.

According to the Russian National Guidelines [22], in case the antifungal preventive therapy with fluconazole appears inadequate in liver

transplant recipients, they should be switched to a drug from the . We successfully used anidulafungin belonging to this class and having a number of advantages if compared to other antifungals. First of all, it can be used in patients with hepatic and renal insufficiency, it poses no effect on blood plasma concentrations of cyclosporine and tacrolimus, it is characterized by few or negligible known drug-drug interactions, no cytochrome P450 interactions. Also, it is indicated as a prophylaxis during a renal replacement therapy, relaparotomy, retransplantation, and in a patient on a prolonged mechanical ventilation (over 48 hours).

The patient was discharged in a satisfactory condition on the 73<sup>rd</sup> day after liver transplantation.

Conclusion: liver transplantation, a postoperative complex intensive therapy including extracorporeal detoxification methods, the use of antibacterial and antifungal agents, provided the recovery of a severely ill patient.



**Figure. Oral candidiasis.**

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