# BLOOD CULTURE VALUE IN PATIENTS WITH SEVERE INFECTIONS AFTER LIVER TRANSPLANTATION

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***Keywords:*** *liver transplant, blood culture, infectious complications, germ*

***Abstract:*** *Introduction: Even if the evolution of liver transplantation, as a life-saving surgical procedure, registered lately a major progress in surgical techniques and immunosuppressive therapy, the risk of sepsis still remains a global concern. Objective: Promptly recognizing and testing the bacterial strains, isolated from blood cultures in liver transplanted patients, who presented with sepsis, with or without an apparent origin. Methods: From 2010 until 2012, a retrospective bacteriological study was performed on a group of 195 liver transplanted patients at "Dan Setlacec" General Surgery and Liver Transplantation Centre Fundeni. Aiming at cultivation and qualitative recovery, the positive and negative blood cultures were screened with BACTEC 9050 system (Becton Dickinson). We collected from all pre-transplanted patients, two or three sets of aerobic and anaerobic blood cultures (control). We also collected blood cultures from those who had signs of after-transplantation infection such as bacteremia, severe sepsis, septic shock. Smears and cultures on culture media were performed from positive blood cultures. In order to establish the minimum inhibitory concentration, antimicrobial susceptibility testing was done by disc diffusion and automatic methods. Results: After-transplantation infections are complications with a very high mortality rate. In order to decrease them, it is important to make a bacteriological diagnosis to establish the etiology. To do that, one should perform blood cultures and antimicrobial susceptibility testing. These have major contributions, not only in identifying the cause, but also in choosing the adequate therapy. In our study, 47.3% was Gram-negative bacterial infections, 7.5% was Candida albicans fungal and shown spp. infections and 17.04% were non-compliant samples, reported as contaminated. There have been cases of sepsis without bacterial growing, reported as negative after 7 days of incubation. Conclusions: In order to maintain a lower rate of multidrug-resistant strains and to have an effective treatment, the selection of an antibiotic must be correlated to the etiological profile of the germ.*

***Cuvinte cheie:*** *transplant hepatic, hemocultură, complicaţii infecţioase, germeni*

***Rezumat:*** *Introducere: Evoluţia transplantului hepatic ca procedură chirurgicală de salvare a vieţii pacientului a înregistrat în ultimul timp un progres major din punct de vedere al tehnicilor chirurgicale şi al terapiei imunosupresoare, dar, cu toate acestea, riscul de sepsis rămâne în continuare o preocupare globală. Obiective: Recunoaşterea şi testarea în timp util a tulpinilor bacteriene izolate din hemoculturi la pacientul transplantat hepatic, care a prezentat sepsis cu sau fără origine aparentă. Material şi metodă: Studiul bacteriologic s-a efectuat retrospectiv în perioada 2010-2012 pe un lot de 195 de pacienţi transplantaţi hepatic în Centrul de Chirurgie Generală şi Transplant Hepatic „Dan Setlacec", din cadrul Institutului Clinic Fundeni. Evaluarea hemoculturilor pozitive şi negative s-a efectuat prin screening microbiologic cu sistemul BACTEC 9050 (Becton Dickinson), având ca scop cultivarea şi recuperarea calitativă. S-au prelevat 2 sau 3 seturi de hemoculturi aerobe şi anaerobe la toţi pacienţii din pre transplant (de control) şi la cei care au manifestat semne ale infecţiei posttransplant (bacteriemii, sepsis sever, şoc septic). Din hemoculturile pozitive s-au practicat frotiuri şi culturi pe medii de cultură. Testarea susceptibilităţii germenilor s-a realizat prin metoda difuzimetrică şi automată, pentru determinarea concentraţiei minime inhibitorii. Rezultate: Infecţiile apărute posttransplant sunt complicaţii cu o rată a mortalităţii foarte mare. Pentru scăderea acesteia este importantă stabilirea etiologiei (diagnosticul bacteriologic). În acest scop, trebuie realizate hemocultura și antibiograma la germenele izolat. Aceste acte au o mare contribuție pentru identificarea cauzei, dar și pentru stabilirea tratamentului adecvat. Etiologia bacteriană a fost reprezentată de infecţiile produse de bacili Gram negativi şi a reprezentat 47.3%. Etiologia fungică, reprezentată de Candida albicans şi spp., a avut o frecvenţă de 7.5%. Au existat cazuri de sepsis în cadrul cărora nu s-a detectat creşterea germenilor; acestea s-au raportat ca negative la 7 zile de incubare; 17.04% au reprezentat probe neconforme, raportate contaminate. Concluzii: Alegerea antibioterapiei trebuie adaptată în funcţie de profilul etiologic al germenului, astfel încât să se menţină o rată cât mai mică de tulpini multirezistente și tratamentul să fie, astfel, eficient.*

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## INTRODUCTION

Liver transplantation is a high amplitude surgical intervention done to a patient with severe hepatic disease in terminal phase (according to MELD with a prediction of mortality at 3 months).(1)

Frequently, such patients also present with other dysfunctions of organs and systems (renal dysfunction, hepato-renal syndrome, hematological enlarged spleen (hyper spleen) – leucopenia, thrombocytopenia, major coagulation disorders, etc.). This increases the risk of after-transplantation complications, including the infectious ones. For example, in administering multiple blood products in massive bleedings, the patient is at risk to develop spontaneous bacterial peritonitis.(2)

Multiple hospitalizations lead to the contamination of different sites which, after transplant, can became the major source of infections.(3)

Maintenance or antibiotic treatments administered before transplantation increase the risk of bacterial infections and especially of nosocomial infections.(4)

Laborious surgical interventions can result in surgical complications which, in turn, can be the starting point in abdominal sepsis. Also, intensive therapy procedures are the starting point in pulmonary sepsis or of other origin. Active sepsis is an absolute contraindication for liver transplantation.(5)

Sepsis is a systemic inflammatory response syndrome (SIRS) caused by bacterial and/or fungal infection; this is characterized by disequilibrium of the hemodynamic balance with endothelial dysfunction which, in turn, severely compromises the cardio-circulatory system, as well as intracellular homeostasis. Cellular hypoxia and apoptosis contribute to dysfunction and death. The occurrence of infectious signs such as bacteremia, SIRS, severe sepsis, septic shock can lead to the death of the patient.(6)

Management of septic shock implies three inseparable components: treatment of the infection, cardiovascular resuscitation and immunomodulation. Acute blood infection can be primary or secondary, community acquired or nosocomial and remains one of the most severe form of infection. Frequently observed in critical and immunocompromised patients, this is rarely asymptomatic and can be associated with multiple organ failure.(7) The term “acute blood infection” includes all forms of confirmed or unconfirmed bacteremia and fungaemia.(8)

Nosocomial germs are the main source of morbidity and mortality which require the evaluation of some new systems of prevention, diagnostic, rapid and adequate treatment. Data are limited to after transplantation bacterial infections. The progressive resistance of germs to antimicrobials and their spreading to the organism can lead to graft rejection by triggering after transplant complications.(9)

In a severe infection, blood culture remains the key procedure to germ isolation and testing. Respecting the work protocols and sampling techniques leads to favourable results. Just tracing an infection since before transplantation can be a prevention technique started from immediate after-transplantation time.(10)

Bacterial diagnosis, through germ detection in blood culture and prompt antibiotic administration techniques, remains a global priority in regard to survival.(11)

Indications on etiological value of these germs will be given through constant isolation in repeated blood cultures. This is what we proposed to do in our study.

## METHODS

This microbiological study was done on a group of 195 liver transplanted patients (adults and children) in “Dan Setlacec” General Surgery and Liver Transplantation Centre They were microbiologically evaluated in 2010-2012 at The Bacteriology Research Laboratory, Fundeni. All patients were tested prospectively against infection.

The frequency of germs that caused bacterial and fungal infections and the phenotypic evolution of bacterial strains under the antimicrobial influence are the subjects of the current study.

**Type of infection**

In this study, we tried to identify all infections that occurred in the liver transplanted patients. We sorted these by such criteria as: time of developing, site of infection, type of isolated germ, severity of infection. For defining infections included in this study, we adhered to a package of criteria. Among these, bacteremia, soft tissue infection (cellulites), peritonitis, abscess, cholangitis, pneumonia, urinary infections and invasive fungal infections were associated with a very high rate of septic shock.

Mortality due to infection occurred when the patient was still under multiple antibiotic and antifungal therapies with no response to the treatment.

**Harvesting blood cultures**

Depending on the type of postoperative infection, sampling bacteriological balance was decided, which included blood culture beside other samples. We studied a number of positive blood cultures (true and false positives), negative (true and false negative) and contaminated (by different sources). The total batch of aerobic and anaerobic samples analyzed and observed was 1074 in 3 years (table no. 4).

There was a total of 223 positive blood cultures, respectively one single bacterial strain isolated per aerobic bottle (223 bacterial strains). There were cases (0.1%) when, in the same blood culture, were detected 2 to 3 consecutive germs without clinical significance.

Blood cultures with false positive results were due to the way of sampling, respectively of contamination. There were cases of false positive because of changes in the incubation temperature of the automated analyzer, but classical cultures at 48h proved to be negative.

True negative blood cultures were demonstrated through classical cultures, negative at 48h. In some cases there was a discrepancy between negative blood cultures and patient’s clinical state (sepsis), which made it difficult to diagnose. Immediate sampling after the first dose of antibiotic and, often, on the same catheter of administration led to false negative results during sepsis.

**Microbiological techniques**

We monitored the frequency of germs producing bacterial and fungal infections and also the phenotypic evolution of bacterial strains under the antimicrobial influence on a batch of 223 positive blood cultures from a total of 1074 samples (table no. 4).

For this, the bacteriological balance was sampled (blood culture was mandatory) before and after transplantation. There were inoculated 8 to 10 ml blood / vial (aerobe, anaerobe, and mycosis) in aseptic conditions, with automatic incubation at $37^{\circ}C$; periodic reading was performed by BACTEC 9010 system. In order to study the bacterial morphology and mobility, microscopic examination of positive blood culture was performed through interpretation of smears stained with Methylene Blue, Gram, China Ink; this is of major importance in diagnostic and therapeutic orientation. Bacterial and fungal cultures were grown on nonselective agar media, Columbia Agar with 5% ram blood incubated in aerobic, anaerobic and $CO_2$ atmosphere and on other media – CLED, Lactose Agar, Chrom Agar, Sabouraud Agar.

Identification of germs was performed by the automatic Phoenix (B. Dickinson) system for which the producer supplied us with the direct germ isolation method: from positive blood cultures, were done sub-inoculums in ID broth with immediate re-inoculation on the biochemical identification card for Gram-negative bacilli; with the microbiological results obtained at 18-24h, the therapeutic reorientation scheme was decided.

For more accurate results on bacterial typing, the identification and susceptibility testing was done by Micronaut Skan (Merlin/Virotech) system in cards with biochemical and enzymatic substrate (IDS 6h-Merlin) with an identification time of 6h. Bacterial susceptibility was explored through classical diffusion method on Mueller Hinton media with standard 0.5 McFarland inoculums; detection of minimal inhibitory concentration (CMI) was done with E test strips (Liofilchem) and automatic with the aid of systems described above; The susceptibility results (sensitive, intermediary, resistant) were interpreted according to international standards CLSI 2011-M100-S21.(20)

Results were communicated according to international protocols of interpretation, that is: positive blood culture with "X" germ or "negative blood culture at 7 days".

## RESULTS

Infections are complications of liver transplantation with a very high mortality rate. To decrease the mortality rate, it is important to determine the etiology of infections (microbiological diagnosis). Blood culture has great significance within the management of infections and, moreover, within establishing antibiotic and antifungal treatment (susceptibility testing for bacteria and the yeast). The incipient establishment of infectious etiology from an outbreak, the germ detection and identification leads to improvements in patient's clinical status.

Avoiding as much as possible bacterial and fungal infections and, therefore, prolonged antibiotic treatment, it is a method of preventing nosocomial infections. In 2010, from a total of 440 blood culture samples, 94 were positive and 332 were reported as negative at 7 days from incubation (table no. 1, figure no. 1). Isolated germs from positive blood culture presented, in general, with multi-drugs resistance and were considered nosocomial. Incorrect sampling maneuvers (for example, sampling on catheters) led to contaminations in a percent of 3.28%. In 2010, positive blood culture differential count was 22.3%.

**Table no. 1. Strains isolated and tested in 2010**

| Isolated and tested strains in 2010 | Number of positive cases |
|---|---|
| MRSA | 26 |
| MSSA | 6 |
| Pseudomonas aeruginosa | 8 |
| Acinetobacter baumannii / spp. | 15 |
| Candida albicans/ spp. (glabrata, dubliniensis, krusei) | 6 |
| E. coli | 5 |
| Klebsiella pneumoniae / spp. | 7 |
| Enterococcus faecalis / spp. | 4 |
| Enterobacter / spp. | 1 |
| Stenotrophomonas maltophilia | 2 |
| Contaminations | 14 |
| Total | 94 |

In 2011, from 322 samples, 59 were positive and 251 were negative; a percentage of 3.33% represented contaminations (table no. 2, figure no. 2). In 2011, positive blood samples differential count was 16.3%.

**Figure no. 1. Frequency of isolates in 2010**

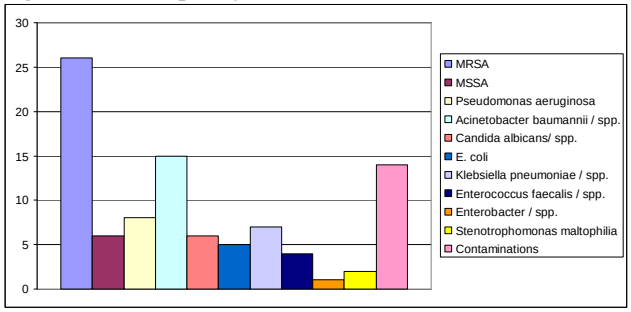
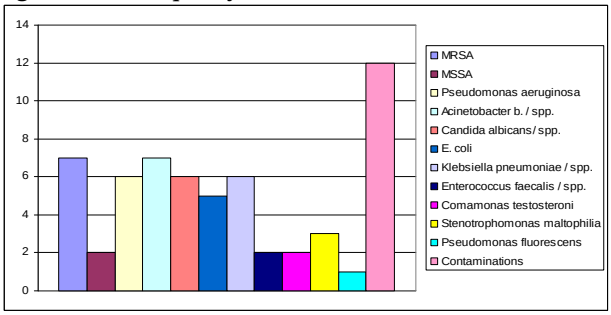



**Table no. 2. Strains isolated and tested in 2011**

| Strains isolated and tested in 2011 | Number of positive cases |
|---|---|
| MRSA | 7 |
| MSSA | 2 |
| Pseudomonas aeruginosa | 6 |
| Acinetobacter b. / spp. | 7 |
| Candida albicans / spp.(krusei, glabrata) | 6 |
| E. coli | 5 |
| Klebsiella pneumoniae / spp. | 6 |
| Enterococcus faecalis / spp. | 2 |
| Comamonas testosterone | 2 |
| Stenotrophomonas maltophilia | 3 |
| Pseudomonas fluorescens | 1 |
| Contaminations | 12 |
| Total | 59 |

**Figure no. 2. Frequency of isolates in 2011**



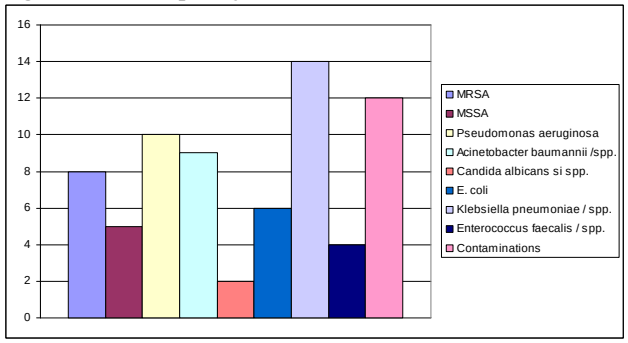

In 2012, from a total of 312 tested samples, 70 were positive and 230 were negative; contamination represented 4%. The incidence of Gram-negative bacilli (23.3%) was lower this year compared to the previous year (table no. 3, figure no. 3). In 2012, positive samples differential count represented 23.3%, with the prevalence of enterobacteriaceae and nonfermenting germs.

**Table no. 3. Strains isolated and tested in 2012**

| Strains isolated and tested in 2012 | Number of positive cases |
|---|---|
| MRSA | 8 |
| MSSA | 5 |
| Pseudomonas aeruginosa | 10 |
| Acinetobacter baumannii /spp. | 9 |
| Candida albicans si spp.(glabrata) | 2 |
| E. coli | 6 |
| Klebsiella pneumoniae / spp. | 14 |
| Enterococcus faecalis / spp. | 4 |
| Contaminations | 12 |
| Total | 70 |

In these 3 years, the average number of positive samples was 20.6%. Enterobacteriaceae and nonfermenting germs represented 47.98%, staphylococci and enterococci 28.69% and fungi 6.27%. Anaerobic bacteria were not detected in collected anaerobic vials.

**Figure no. 3. Frequency of isolated strains in 2012**




If we trace the total number of samples each year, we observe a decrease from 440 cases (94 positive) in 2010 to 312 cases (70 positive) in 2012; this is due to the improvement of working protocols and adaptation of antibiotic and antifungal therapy (for example, antibiotic de-escalation program in critical patient, modern laboratory methods of germ isolation and identification et al.) (table no. 4).

**Table no. 4. Summary of results during 2010-2012**

| BACTEC Hemocultures | Year 2010 No. | Year 2011 No. | Year 2012 No. |
|---|---|---|---|
| Positive | 94 | 59 | 70 |
| Contaminations | 14 | 12 | 12 |
| Negative | 332 | 251 | 230 |
| Total | 440 | 322 | 312 |

**Antibiotic and antifungal multiresistance**

Due to microorganism variability in regard to antibiotics, constant increase of nosocomial strains was observed. The majority of isolated strains (e.g. nonfermenting Gram-negative bacilli) presented with antibiotic multiresistance to: ceftazidim (10.5%), cefoperazone (10.2%), imipenem (8.5%), aztreonam (8.8%), amikacine (22.5%), netilmicine (26.5%),ciprofloxacine (16.5%), tobramicine (6.5%), gentamicine (12%) (tabele no. 5).

*Pseudomonas aeruginosa* strains were sensible to cefoperazone-sulbactam, meronem, cefepim, piperciline-tazobactam, colistin.

In *Acinetobacter baumannii,* sensibility was demonstrated, "in vivo" as well as "in vitro", for colistin, tigecicline, rifampicine, ampiciline-sulbactam. Administration of colistin or tigecicline in some cases of after-transplantation sepsis resulted in remission of infectious signs.

Strains of *Klebsiella sp. pneumonaie* presented sensibility to meronem, colistin, tigecicline, cefoperazone-sulbactam, amikacine.

In the case of Meticiline Resistant *Staphylococcus aureus* strains, these presented an increased resistance, "in vivo" as well as "in vitro", towards teicoplanine, linezolid, ceftaroline fosamil, vancomicine.

Infection with *Candida albicans* under long term empiric or prophylactic treatment with antibiotics and/or antifungals, with or without the evidence of microbiological cultures, led to the appearance of *C. non-albicans* strains resistant to fluconazol. Testing sensibility towards antifungals proved, "in vivo" as well as "in vitro", the efficiency of antifungals such as: caspofungin, anidulafungin or voriconazol.

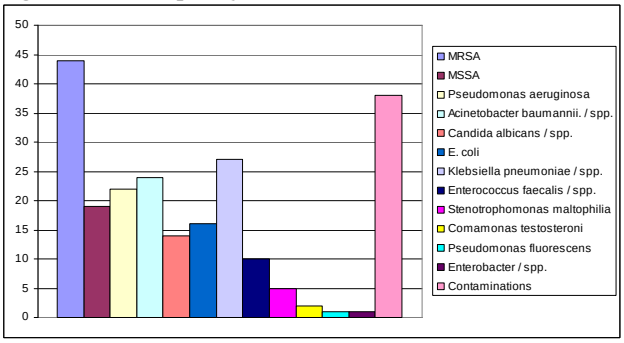
In liver transplanted patients with pulmonary sepsis (e.g. intubations, catheterizations), abdominal sepsis (e.g. interventions for massive bleedings, abscesses, fistulas, vascular reconstructions, de-thrombosis etc.) or with other starting locations, de-escalation therapy was ideal for survival. This consisted in: meronem or imipenem, teicoplanine or linezolid, caspofungin or voriconazol or anidulafungin. The appearance of microbiological cultures, the isolation and identification of germ, as well as, the determination of bacterial and fungal susceptibility redirected the antibiotic and antifungal scheme.

Selection of multi-resistant strains, both bacterial and fungal, still remains a problem of general interest.

**Table no. 5. Etiologic agents with clinical importance isolated in 2010-2012**

| Ethologic agents; period 2010-2012 | Number of cases / Frequency % |
|---|---|
| MRSA | 44 / 23.7 |
| MSSA | 19 / 10.2 |
| Pseudomonas aeruginosa | 22 / 11.9 |
| Acinetobacter baumannii. / spp. | 24 / 12.9 |
| Candida albicans / spp. | 14 / 7.5 |
| E. coli | 16 / 8.6 |
| Klebsiella pneumoniae / spp. | 27 / 14.5 |
| Enterococcus faecalis / spp. | 10 / 5.4 |
| Stenotrophomonas maltophilia | 5 / 2.7 |
| Comamonas testosteroni | 2 / 1.08 |
| Pseudomonas fluorescens | 1 / 0.5 |
| Enterobacter / spp. | 1 / 0.5 |
| Contaminations | 38 / 17.04 |
| Total | 223 / 20.16 |

**Figure no. 5. Frequency of isolates in 2010-2012**




## DISCUSSIONS

Through this study, we tried to give a detailed description of the frequency in blood cultures of the pathogens causing infections in liver-transplanted patients. Blood culture remains a bacteriological diagnostic marker for infections with Gram-negative and Gram-positive germs, aerobic and anaerobic bacteria, fungi and mushrooms. Applying targeted antibiotic therapy according to sensitivity testing leads to the increase of the patient's survival rate. Microbiological monitoring, before and after transplantation, through sampling, remains paramount in the detection and timely treatment of infections. Infections occurred after liver transplantation still remains a cause of mortality. In our study mortality because of infections after liver transplantation accounted for more than 42.9% (22/195) (e.g. multiresistant Gram-negative nonfermentative bacilli combined with MRSA, *Candida albicans* and *non-albicans*). At these patients, were isolated, from blood culture, bacteria with strong pathogenic character and phenotypic multiresistance (table no. 5)

Studies of Kusne, et.al show that overall mortality was 26/101 (26%) and 23 to 26 deaths (88%) were associated with infection.(11) Summarizing the results of our study, in the period 2010-2012, we observed that the number of strains isolated from positive blood cultures and associated with infection was significantly less as the evolution changes. (table no. 4). Thus, it is observed a decline in mortality (42.9%) versus an increase in survival, while technical advances in surgery and other medical branches continuously advance.

Lately, according to international and United States' studies, enterobacteria developed antibiotic resistance; these show a frequency of infections with nosocomial Gram-negative germs over 63%.(12) In our study, the frequency of infections with fermentative and non-fermentative multiresistant Gram-negative bacteria was of 47.8%, a ratio according to other studies.

In 20-40% of liver transplanted patients, septic shock was due to infections with Gram-negative bacteria. Most nosocomial infections with Gram negative bacilli and coco bacilli appeared after surgical and intensive therapy maneuvers.(13) In our study, for example, infections with *Acinetobacter baumanii* represented 12.09%, close to data from literature. Sensitivity towards colistin and tigecicline remains tributary in the case of these infections and still stays in observation in the era of modifications of bacterial genetic conformation.

Despite recent epidemiological changes in MRSA strains, the clinical use of new antibiotics and the improvement of sustaining therapy make the mortality caused by infections to be 30%. Clinically, infections with *Staphylococcus aureus* appear especially in the first 3 months after transplantation and lead to: pneumonia, infections of surgical plagues, bacteremia and septic shock (detected most frequently in blood culture).(14) In our study, 23.7% of MRSA strains were isolated from blood culture.

According to some studies, invasive infections with *Candida albicans* or *non albicans* in liver transplant have a mortality rate between 5-77% and an incidence of 4-42%.(15,16) In our study, systemic infections with fungi represented 7.5%.

Wisplinghoff H, et al. presents the *Candida species* as the most frequent nosocomial pathogens, which significantly contribute to morbidity and mortality rates. Longitudinal data in regard to systemic epidemiological infections with *Candida* are still limited.(17,18) All echinocandidas shown a good activity for *Candida spp*., including *C. parapsilosis*, but only 38.1% of *C. glabrata* species tested were sensitive to caspofungine.(19) Sensibility to echinocandidas (caspofungin, anidulafungin, voriconazol etc.) was proven for *Candida glabrata* and other species.(20,21) In our study, isolates of *Candida albicans* and *spp*. had an increased efficiency to antifungals, "in vivo" as well as "in vitro" (e.g. CMI-caspofungin-0.064 μg/dl, anidulafungin 0.094 μg/dl for species of *Candida glabrata*).

## CONCLUSIONS

Bacteriological diagnosis through germ detection from blood culture, as well as administration of antibiotic and antifungal therapy on time remains a global priority in regard to survival. The use of new performing systems of microbiologic sampling, isolation, identification and susceptibility testing in the new era of modern antibiotics and antifungals can lead to the improvement of the life quality of the liver transplanted patient.

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