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Bacterial complications after liver transplantation. Promising directions for further research

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Abstract

This article is presented in form of a current literature review on bacterial complications of the early post-liver transplantation period and promising areas for studying the effect of bacterial flora in patients after liver transplantation. The paper describes the problem of the emergence, spread, and pathogenesis of various bacterial complications, as well as current concepts of various bacterial complication's impact on the results of liver transplantation. The results of ventilator-associated pneumonia in patients after liver transplantation are given. A theoretical analysis of bacterial complications from the standpoint of microbiota effects on the biliary tree was carried out. The review also highlights a relatively new conceptual approach in examining the results of scientific research using the "Machine Learning Method". The so-called CDC "Big Four" was chosen as the main infectious nomenclature in this article. However, catheter-associated bacterial complications, which pathogenesis has been sufficiently studied to

date, have been replaced by a relatively new group of complications – bacteriobilia. This review also contains a brief statistical data collected in the frames of the NCT04281797 study. Own cohort data consisted of 57 patients who underwent orthotopic liver transplantation from a post-mortem donor. Surgical site infection was the most common bacterial complication of the early postoperative period. The most common causative agent of bacterial infection was Klebsiella pneumonia and Enterococcus.

Keywords: liver transplantation, bacterial complications, pneumonia, urogenital infection, bacteriobilia, bacteremia

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AIH, autoimmune hepatitis

ALD, alcoholic liver disease

ALF, acute liver failure

APS, antiphospholipid syndrome

BI, bloodstream infection

FNH, focal nodular hyperplasia

HCC, hepatocellular carcinoma

IHCh, type II intrahepatic cholestasis

LC, liver cirrhosis

LT, liver transplantation

MLV, mechanical lung ventilation

PBC, primary biliary cirrhosis

PSC, primary sclerosing cholangitis

UTI, urinary tract infection

VH, viral hepatitis

Introduction

Over the recent decades, a tremendous breakthrough has been made in the field of transplantology, and transplantation hepatology has gone far beyond the scope of experimental surgery. Today, 5-year survival after liver transplantation (LT), according to various sources, reaches 85–96% [1–6]. However, complications that occur in the early postoperative period significantly aggravate the course of the convalescence period, often causing repeated hospitalizations, graft dysfunction, further disability and mortality [7–9].

It is known that infectious complications are among significant causes that worsen the natural course of the postoperative period. The most significant and frequent of them are bacterial complications, especially those caused by multidrug-resistant strains, which rates vary widely, from 19% to 33% during the first 100 days after LT [10–14].

Infectious complications still remain one of the main causes of morbidity and mortality in patients who underwent liver transplantation. For example, in a study by R. Shepherd et al. of 2008, which included an analysis of the outcomes of more than 2,000 liver transplantations; more than half of deaths after LT were due to infectious complications [15, 16]. In turn W. Zhang et al. in their analysis based on 499 case reports of LT patients and published in *Annals of Transplantology* in 2020 noted the presence of at least one episode of a bacterial infection in 39.3% of patients, designating bacterial complications as the leading cause of death after LT [9].

This fact suggests that despite the presence of a large number of antibacterial drugs, the strict requirements for their rational administration, and a thorough selection of optimal antibiotic therapy, the problem of bacterial complications is still extremely relevant [12, 17–20]. In particular – last is mostly due to the presence of multiresistant flora, the expansion of the donor organ pool, including through marginal donor grafts, as well as an increased surgical activity of transplant centers. Improvements in surgical care, anesthesiology and resuscitation support has made it possible to perform LT even in patients with deep decompensation and numerous risk factors for the development of infectious complications [17].

For example, in a recent study conducted at the N.V. Sklifosovsky Research Institute for Emergency Medicine, the incidence of infectious complications diagnosed after LT was 65.1% in 2014, 59.5% in 2015, and 49.3% in 2016. And although within 3 years there was a slight trend towards a decrease in the incidence of infectious complications after LT, no statistically significant differences were achieved, according to the authors. In turn, in a study conducted there in 2018, the incidence of infectious complications was as high as 56.5% [21].

It is very important to solve the problem of preventing the infection development, including hospital infection, which is still a trigger mechanism for the development of severe postoperative complications [17]. In addition, a growing number of studies in recent years point to the significance of the intestinal microbiota and the so-called gut-liver axis, the imbalance in which system is considered as an independent source of infectious complications after LT [11, 22].

The situation is significantly aggravated by the fact that patients after LT are extremely susceptible to bacterial infection, largely due to such

factors as immunosuppressive therapy, invasive lung ventilation, low nutritional status of patients, previous and(or) repeated surgical interventions, the presence of sarcopenia and many others [16, 23]. It should also be taken into account that LT itself, being an extended intervention on the hepatobiliary system organs, significantly increases the risk of developing severe bacterial complications [12, 24]. In addition, the typical and specific cohort of bacterial complications undergoes significant changes associated with the timing of their occurrence after LT [25].

It is known that infectious complications are conditionally referred to three groups: early (up to 3 months), late (3–6 months), and long-term (over 6 months). Thus, it is known that in the first month after surgery, most infectious complications, including bacterial ones, are associated with the surgical treatment itself and are represented by wound infection, intra-abdominal infection associated with the wound canal, post-transplantation pneumonia, infection of the genitourinary tract, and bacterial contamination of the bloodstream [18]. Although, according to the etiological factor and pathogenetic course, bacterial complications that occur after LT do not differ much from the similar complications that occur after other abdominal operations; and comorbidities, immunosuppression and the complexity of the intervention itself inevitably lead to an increased incidence of their occurrence, more severe course and increased risk of mortality [12, 17]. Meanwhile, most bacterial complications are caused by nosocomial infection or the recipient's own flora subjected to alterations in the physiological biological environment of its existence in a compromised pathological condition of the body, as well as in necessary long-term bacterial and immunosuppressive therapy [26, 27].

In turn, numerous current studies indicate that the highest number of

bacterial complications occurs precisely during this period [3, 12, 17, 28]. For example, the study by E. Gabrino et al. showed that the incidence of early bacterial complications in the first month after surgery is 31 times higher than in subsequent time periods [29].

During the next period, conditionally lasting from 3 to 6 months after LT, the manifested opportunistic infections are more often observed, while the volume of immunosuppressive therapy plays a leading role among the risk factors in this period [12, 14, 26, 30]. Thus, it is known that high doses of the immunosuppression can lead to the development of severe infectious and septic complications [26]. As a rule, during this period, the prognosis of the infectious complication severity largely depends on the need to maintain an "immunosuppressive balance" in the event of an acute rejection, which requires an increased suppression of the immune response, on the one hand, and the need to fight a developing infection, on the other. This opposition of treatment approaches is an extremely difficult task [20, 26, 31, 32].

In the long term after LT, bacterial complications are usually associated with external factors, late biliary strictures, graft functioning, and recipient's concomitant diseases.

In addition, the course of many infectious processes in patients who underwent LT differs significantly from those in the general patient groups, including those who underwent even major non-transplant surgery. For example, pathognomonic signs of lung infiltration revealed by radiography in patients with pneumonia are nonspecific in the diagnosis of post-transplantation pneumonia. Infiltrative processes in the lung tissue under these conditions can reflect various disorders, such as hydrostatic pulmonary edema or adult respiratory distress syndrome. The latter, in some cases, can be combined with post-transplantation pneumonia, masking its

manifestations [17].

In addition, this clinical feature of post-transplant patients is largely due to the use of immunosuppressive drugs “blurring” the usual manifesting disease clinical signs, such as, for example, fever, chills, local symptoms, etc. [12].

Post-transplant pneumonia

Nosocomial pneumonia can be considered one of the most common and severe complications of the immediate postoperative period [2, 33]. Patients after LT are extremely susceptible to respiratory tract infections associated with the surgery duration, mechanical ventilation time, immunosuppressive therapy, difficulties with coughing up the contents of the bronchial tree, due to a large-scale surgical intervention [34-36].

In the general structure of nosocomial infections, the incidence of pneumonia ranges from 20 to 47%. Most studies emphasize the critical role of pneumonia as a causal factor in post-transplant morbidity and mortality. D. Xia et al. reported a post-LT pneumonia-associated mortality rate of 37.5%. In a study by S. Bozbas, upper respiratory tract bacterial infections caused 45.8 % of deaths [37, 38].

With the pneumonia developed 48 hours after transplantation, it is considered as nosocomial pneumonia. Inhalation, aspiration, and hematogenous pathways play the main role in pathophysiology of the nosocomial pneumonia spread [17, 34].

In addition, some studies have demonstrated that increased mechanical lung ventilation (MLV) duration and the length of stay in the intensive care unit can be considered as an independent risk factor for the development of post-transplantation pneumonia [10, 39]. Meantime, we

should note that the most typical causative agent of nosocomial pneumonia is unknown, since even a thorough bacteriological examination fails to identify an infectious agent in 50% of cases [17]. At the same time, gram-negative microorganisms are the most frequently detected flora in bacterial pneumonia [33, 40].

L. Zhong et al., whose study has shown that gram-negative flora acted as an etiological factor in post-transplantation pneumonia in 46% of cases. Meanwhile, 56% of patients were assigned to the group with multidrug-resistant flora [41]. Patients after LT are at increased risk of developing ventilation-associated pathology (VAP) [40]. Thus, it is known that patients on the waiting list often have multiple comorbidities, and stay on prolonged mechanical ventilation, which significantly increases the risk of the VAP development. In a recent study, A. Siniscalchi et al. based on the analysis of case reports of 242 patients who underwent LT, showed that VAP was diagnosed in 7.4% of recipients, while mortality was 22% compared with 4% in patients without VAP [42].

In turn, among recipients operated on while having deep decompensation, the above listed risk factors are especially important, since it is known that the MELD score acts as an independent predictor of an early post-transplantation pneumonia development [43]. Taking into account the fact that LT is now increasingly performed in this category of patients, more and more patients today depend on mechanical respiratory support both in the pre- and post-operative period, thereby further increasing the incidence and likelihood of developing VAP. For example, in a study by H. Petrowsky et al. published in the *Annals of Surgery*, 66% of patients having the MELD score above 40 required ventilation prior to surgery [44].

In turn, given the large variability of risk factors and their

combinations, the methods for predicting the likelihood of this threatening complication still retain their acute relevance. In order to solve the aforementioned, a group of investigators headed by C. Chen et al. in their study completed in 2021 tried to create a system for predicting the pneumonia development after LT using a computer-assisted information and analytical system based on machine learning [39]. The authors based on the analysis of the results of 786 LT entered for verification of results into 6 de novo created software packages. The work of all 6 software packages was verified as part of the AUROC analysis, which showed the statistical significance of the studies. In their research, the authors concluded that the most effective in terms of predicting the development of post-transplant pneumonia was the software program that used the "XGBoost" principle, which showed that post-transplant pneumonia is associated with 14 independent characteristics determined in the preoperative period, including: international normalized ratio, hematocrit, platelets, albumin test, alanine aminotransferase, FIB, erythrocytes, prothrombin, Na+, total bilirubin, anesthesia duration, hospital length of stay (before surgery), amounts of intravenous infused electrolyte solutions, and surgery duration. It is noteworthy that the computer-assisted method did not indicate the MELD score, age, associated surgical interventions, and other previously known factors as independent risk factors for the pneumonia development [39].

Although the study was based on a single center cohort, in our opinion, the analysis using machine learning techniques can be considered a convenient and useful analytical method for predicting the development of post-transplant pneumonia, with a high degree of statistical significance.

Urinary tract infection

Another common bacterial complication after LT is urinary tract infection [3, 12, 17, 45–48]. In connection with the improvement in overall survival after LT, the number of surgeries performed on patients having a severe kidney dysfunction which is a frequent complication of chronic progressive liver diseases, also increases [48]. As a result, this category of patients has an increased risk of developing a renal bacterial infection. In addition, many of today's immunosuppressive drugs have significant nephrotoxicity, also increasing the risk of urinary tract infection (UTI). Given the high incidence of this type of complication, a large number of studies today are still devoted to the analysis of UTI risk factors; however, the data from many authors differ greatly, and there is still no single accepted concept that would reflect the type of UTI risk factors. Meanwhile, gender, hospital length of stay, increased body mass index, diabetes mellitus, etc. are most often mentioned among these risk factors [12, 31, 48]. A separate place is given to catheter-associated risk factors for the UTI development. The patients with prolonged catheterization periods for over 24 hours have shown a significantly increased UTI risk [2, 48].

In turn, most UTI cases are asymptomatic in the early stages, and the presence of bacteria in the urine from 10^3 CFU /mL or more is subject to a mandatory blood test for sterility due to the threat of the infection translocation [17].

At the same time, according to many researchers, the use of mycophenolate mofetil, thymocyte globulin and the presence of acute liver graft rejection are also associated with higher risks of developing this type of complication. In a study conducted by G. Pouladfar et al., and based on a multivariate prospective analysis of the medical history records of 485

patients who underwent LT, the above risk factors, such as male gender, diabetes mellitus, and length of hospital stay were verified as prognostically significant in patients who underwent LT. And although the results of the study differed significantly from the data of other authors, no statistical significance was shown [48]. In turn, in this study, gram-negative flora and, in particular, E. coli, were the dominant etiological factors in the UTI development after LT, which coincides with the studies of other authors.

Urinary tract infection is also known as the most significant source of forming antibiotic-resistant bacteria, such as β-*lactamase*-producing *Enterobacteriaceae*, vancomycin-resistant enterococci, and methicillin-resistant staphylococci [2, 49, 50]. In addition, often UTI becomes a source of infection translocation. In a study by M. Wagener from the University of Pittsburgh, UTI was identified as the main cause of bacteremia in patients undergoing LT. At the same time, in patients who underwent LT, the most common bacteremia causes were the biliary tract and abdominal cavity the infections [51].

Bloodstream infections

And although the risks of a bloodstream infection (BI) development are present even in the long term after LT, it most often develops in the immediate postoperative period and, in particular, during the first month after LT [2, 52].

The most specific manifestations of bloodstream infection are hyperthermia, shaking chills, abnormal white blood counts, and often the present local manifestations associated with a potential source of infection. Risk factors for bloodstream infection include: intra-abdominal infection, the need for repeated operations, prolonged use of a urinary catheter, central

venous catheter, graft dysfunction, and acute rejection crisis [2]. Meanwhile, the dominant etiological pathogen differs significantly in various transplant clinics. So, historically, cocci were considered the most common cause of bloodstream bacterial infection; but subsequently, among the etiological causes, a trend towards the predominance of gram-negative flora was noted.

At the same time, nowadays epidemiological studies coming from various centers point to the continued important role of gram-negative flora [12]. The most common microbes that cause BI today include enterobacteria, Staphylococcus aureus, enterococci, and Pseudomonas aeruginosa, which in a study by F. Bert at Beaujon Hospital, were identified in 41%, 20%, 13% and 9% of cases, respectively, which is consistent with the data of other authors [16, 53]. Given a high mortality in patients after LT against the developed BI, reaching 38–40% according to various sources, the infection caused by multidrug-resistant flora is especially significant [12, 16, 53]. Thus, BI caused by carbapenem-resistant *Klebsiella pneumoniae*, as a rule, always leads to death [2].

Meanwhile, as well as in relation to the incidence, in recent years there has been a tendency for an increase in gram-negative flora in the spectrum of multi-resistant bacteria that cause bacteremia. Thus, the prevalence of gram-negative flora with β-lactamase is estimated at 13%. Many studies also note a progressive increase in the multiresistance development among habitual bacterial organisms. According to P. Ischai, multiresistance to quinolones was noted in 47%, which, according to the author, is associated with antibiotic prophylaxis before LT, as well as with a standard treatment for spontaneous bacterial peritonitis and other infections associated with liver cirrhosis. A number of authors have reported the incidence of detecting multi-resistant flora being 62.5% for *Acinetobacter*

baumannii, 54% for *Stenotrophomonas maltophilia*, and 51.5% for *Klebsiella spp.* [31, 54].

In turn, among glucose-non-fermenting gram-negative bacteria, *Pseudomonas aeruginosa and A. baumannii* can be considered the most significant; with their dissemination the mortality reached 37-50% [13, 30, 55, 56]. The most frequent "endogenous" bacterial complications associated with LT are described above; their occurrence significantly aggravates the prognosis of the post-transplant period. However, in our opinion, there are a number of other bacterial complications of the post-transplantation period, which are of great importance in practical transplantation, but which are currently given insufficient attention in the scientific literature.

Bacteriobilia

The very difference in terminology (bacteriobilia and bacterial cholangitis) largely explains the reason for the lack of a large number of scientific papers and randomized control trials (RCTs) on this issue, even despite the fact that the problem of biliary complications is still very urgent after both living-related donor and cadaveric LT. Thus, the interpretation of the cholangitis bacterial nature still remains difficult in clinical practice; the main reason for this is the fact that bacterial contamination of the biliary tree or bacteriobilia is not always accompanied by the development of cholangitis [57]. This statement became fundamental in a study conducted in Kyoto in 2018. The authors of that study assessed the development of cholangitis after liver transplantation in 274 patients allocating them into three groups: the 1st group consisted of patients without bacteriobilia, the 2nd group included the patients with asymptomatic bacteriobilia, and the 3rd group included those with developed cholangitis against the presence of

bacteriobilia ($p<0.03$). Comparison analysis of the three groups showed quite interesting results: patients with developed post-transplant cholangitis had significantly worse short-term and long-term graft survival due to a higher incidence of early graft dysfunction (HR 0.28; CI 95%; 0.28−0.53; $p<0.001$). In addition, the frequency of patient rehospitalizations for recurrent cholangitis was also significantly higher in the second and third groups ($p<0.001$). However, a statistically significant difference in the rates of graft loss was noted only in group 3 ($p<0.01$) [57].

It is known that the vertical orientation of the bile outflow, the bacteriostatic activity of bile components, as well as immunoglobulin A secreted by the liver, together with the biliary tract mucosa that prevents the fixation of bacteria, make it possible to keep the biliary tree sterile [58]. However, an impaired bile flow in the post-transplant period, the presence of calculi or clots in the biliary tree can cause the bacteriobilia development with subsequent colonization of the entire biliary tree. In addition, cases of bacteria spontaneous migration through a functioning sphincter of Oddi are not uncommon, which, in case of a compromised immune system, can become a dominant factor followed by further dissemination of bacteria. In turn, a number of studies in recent years, indicating the presence of bacteria in the biliary tree as a physiological component in a healthy body, today can be considered untenable. This fact was confirmed on the basis of the biliary tree microbiome study conducted by Franchesco D'Amico in 2021 [59]. In their study, the authors collected bile from the biliary tree from liver donors by puncture of the common bile duct before organ harvesting and before hepatectomy in liver recipients. It is noteworthy that in order to avoid the misinterpretation of the results or bile contamination, the authors excluded from the study patients with the previous history of ERCP and (or) any

concomitant biliary tree conditions. In addition, in order to determine the contamination of bile, instead of culturing, the sequencing of 16S ribosomal RNA [59] was used, which made it possible to significantly increase the accuracy of the study. The listed facts point to an extremely high relevance of the study of the biliary bed and its "interactions" with bacterial agents today.

At the same time, it is known that in patients with bacterial contamination as a result of various causes, bile cultures usually reveal enterococci, Klebsiella, and Escherichia coli. However, their ratio differs significantly in case of cholangitis development [60, 61]. The so-called vicious circle in the treatment of patients with biliary complications after LT can also be interesting, in which precisely the bacterial process can be considered the fundamental link. So, as an example, we can cite the need for endobiliary stenting in patients with developed stricture of the biliary anastomosis, in which the anastomotic stricture itself is an independent risk factor for the development of biliary contamination, and the performed stenting aimed at resolving the anatomical narrowing actually produces it. In this case, the biliary tree is inevitably contaminated, which creates the prerequisites for the initiation of lithogenic processes that comes full the vicious circle due to own potential to maintain the microbiological environment [57]. This clinical situation is by no means uncommon in the practice of clinicians and often turns into a prolonged and complex process with an outcome difficult to predict. These patients typically experience multiple episodes of hospitalization, recurrent cholangitis, and exacerbation of anastomotic stricture, followed by the development of chronic post-transplant calculous cholangitis often leading to repeated reconstructive interventions.

In addition, the studies of recent years are of interest, pointing to the impact of the intestinal microbiota on the incidence of post-transplant complications, both infectious, and also immunological ones [11, 22, 62, 63].

Statistics of our own

Given the above, it becomes clear that the problem of bacterial complications in the early post-transplant period still remains highly relevant. At the same time, the epidemiological data reported by various authors sometimes differ considerably. Thus, according to a number of authors, the incidence of early bacterial complications after LT reaches 30.2% [64], and 14.1% according to other authors [65]. Undoubtedly, this variability is largely due to geographical, clinical and epidemiological and other features, however, we considered it appropriate to provide our own brief clinical and epidemiological picture of bacterial complications in the early post-transplantation period. Thus, in the first half of 2022, we performed 57 LTs from a cadaveric donor to patients suffering from focal lesions and end-stage liver diseases of various etiological groups. The age of the patients ranged from 12 to 74 years (median 49.2; SD 13.2). There were 17 men (20%) and 40 women (70%). Most often, LT was performed for viral hepatitis resulted in the liver cirrhosis development (Figure).

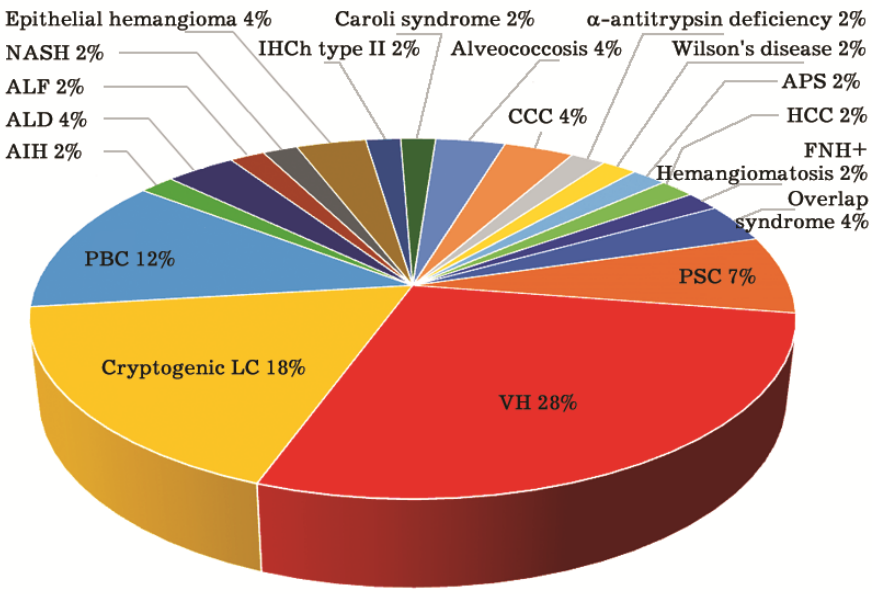

Figure. Distribution of patients by nosological groups

VH, viral hepatitis; Cryptogenic LC, liver cirrhosis of unspecified etiology; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; ALD, alcoholic liver disease; ALF, acute liver failure; CCC cholangiocellular carcinoma; IHCh, type II intrahepatic cholestasis; APS, antiphospholipid syndrome; HCC, hepatocellular carcinoma; FNH, focal nodular hyperplasia; PSC, primary sclerosing cholangitis

The incidence of bacterial complications in the early post-transplant period in our clinic did not differ from the data reported by other authors. Thus, bacterial complications confirmed by relevant studies, occurred in 14 (24.6%) of 57 patients. The infection of the surgical area was most frequently noted, complicating the course of the post-transplant period in 13 patients (22.8%). The most frequent pathogens were: *K . pneumoniae in* 4 (30.8 %) and *Enterococcus in* 4 (30.8%). It is noteworthy that, according to the phenotypic growth nature, the moderate growth of flora prevailed in 4 cases (30.8%) (Table 1).

Table 1 Characteristics of bacterial infection after liver transplantation

Type and nature of bacterial infection	Patients	% of bacterial complications	% in total cohort
Infection complicated the course	**14**	–	**24.6**
Surgical site infection	**13**	**92.9**	**22.8**
Klebsiella pneumoniae	4	30.8	–
Enterococcus faecalis	2	15.4	–
Enterococcus faecium	1	7.7	–
Enterococcus spp.	1	7.7	–
Staphylococcus epidermidis	2	15.4	–
Escherichia coli	1	7.7	–
Pseudomonas aeruginosa	1	7.7	–
Staphylococcus aureus	1	7.7	–
Flora growth in surgical site infection			
Massive flora growth	2	15.4	–
Moderate flora growth	4	30.8	–
Scarce flora growth	2	15.4	–
Sporadic flora growth	3	23.1	–
Bloodstream infection	**2**	**14.3**	**3.5**
Enterococcus faecalis	1	7.1	–
Staphylococcus aureus	1	7.1	–
Urogenital infection	**1**	**7.1**	**1.8**
Klebsiella pneumoniae spp. Pneumoniae (Moderate flora growth)	1	**7.1**	–
Respiratory tract infection	1	**7.1**	**1.8**
Klebsiella pneumoniae (Single growth)	1	**7.1**	

Despite the observational and retrospective nature of our study, its limitations in terms of a small sample size and a short follow-up period, our data do not differ from those of most currently published studies. They can be considered as preliminary results of the population analysis.

Conclusion

From the foregoing, it becomes obvious that in recent years, despite the breakthrough achieved in the field of surgical technology, as well as in the field of related clinical disciplines, a large number of unresolved

problems have still remained, and the treatment results in patients with developed bacterial complications may not be considered satisfactory yet.

In addressing this issue, great hopes are placed on recently initiated studies on the importance of the intestinal microbiota and its role in the development of infectious complications after liver transplantation. In this regard, the definition of the role and place of the intestinal microbiota in the aspect of the so-called gut–liver axis in patients after liver transplantation is an extremely urgent task. Undoubtedly, a promising trend is the development of modern methods for risk stratification of the development of these complications through the use of "artificial intelligence" and machine learning. Thus, it is obvious that further studies in this area of clinical medicine are relevant, and the use of modern diagnostic tools and methodologies is necessary.

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