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POST LIVER TRANSPLANT INFECTIONS — EXPERIENCE AT A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT **Background:** Liver Transplantation (LT) is a standard treatment option for End-stage Liver Disease (ESLD). However, Post liver transplant infections remains a major concern. This study aimed to identify the most common microorganisms that cause such infections in a tertiary care Hospital. **Methods:** A total of 30 patients who had undergone LT during the period (2016-2017) was observed. The pre-transplant and post-transplant clinical samples were analysed for the presence of infectious organisms. Additionally, complete blood investigations along with chemiluminescent microparticle immunoassay (CMIA) were performed to estimate the levels of immune-modulatory agents. **Results:** The recipients did not have any infections at the time of transplant and were followed-up for infections following LT. Bacterial infections such as Urinary Tract Infection (UTI) (8; 26.6%), bacterial-pneumonia (4; 13.3%), surgical site infections (SSI) (4; 13.3%), and Central-venous-catheter related blood stream infections (8; 26.6%) was observed. The common gram-negative organisms such as Escherichia coli, Klebsiella pneumoniae and gram-positive organism such as Enterococcus species and methicillin-resistant Staphylococcus aureus (MRSA) were observed in postoperative period. Moreover, 4 patients were found to have UTI and SSI caused by fungal species such as Candida albicans and Aspergillus species respectively. Viral infection was observed in two patients, which was due to Epstein-Barr virus, a common virus associated with post-transplant lymphoproliferative disease (PTLD). Acute graft rejection (6; 20%) was observed and they were treated with high doses of intravenous corticosteroids. **Conclusion:** Infections after LT is the major cause of morbidity and mortality. A better understanding of the common causative infectious organisms and early initiation of therapy may improve the survival rate of recipients.

KEYWORDS : Bacterial infection, End-stage liver disease, Escherichia coli, Klebsiella pneumoniae, Liver transplantation.

INTRODUCTION

Liver transplantation (LT) is a standard therapeutic procedure for end-stage liver disease (ESLD) and acute liver disease. It is a surgical replacement that removes a non-functional liver and replaces it with the liver from a deceased donor or a portion of liver from healthy donor. According to the Global Health Observatory (GHO) data from the World Health Organization (WHO), the burden of liver disease in India is relatively high with 22.2 deaths per 100,000 population attributed to cirrhosis.[1] In India, it is estimated that at least 20,000 people requires liver transplantation annually. Yet currently, only about 800-1000 transplants were performed in every year with 80% of living donor and 20% of deceased donor.[2] Though the liver transplant is an outstanding procedure, the immunological rejection remains a significant clinical problem. To overcome this rejection, the recipient requires immunosuppressive therapy. The immunosuppressant is required in solid organ transplant to prevent the cellular rejection, thus increasing the survival rate. There are different kinds of immunosuppressive drugs with various mechanism of action, that include, inhibitors of calcineurin, mTOR (mammalian target of rapamycin), RAS mitogen activated protein (MAP) kinase and nuclear factor kappa B (NF-kB) pathways, which inhibit the transcription of cytokines like IL-2 (Interleukin 2) and proliferation of T cells. In general, Calcineurin inhibitor (CNI), together with Corticosteroids and antimetabolites were first used as immunosuppressive agent after transplantation to avoid rejection.[3,4]

Despite advances in surgical techniques, post-transplant care, antimicrobial prophylaxis and immunosuppressant, the incidence of infectious complications after liver transplantation is still a major cause of morbidity and mortality than any other organ transplantation.[5-7] This is due to the intricacy of the surgical procedure and long-term use of immunosuppressive drugs. Post liver transplant infection is predictable to occur in 80% of the recipients. In which, bacterial infections (70%) are more accountable followed by viral (20%) and fungal (8%) infections[7,8]. Bacteria is the most common cause of infections that include surgical site infection, bacteraemia, pneumonia, catheter-related infections, Respiratory Tract Infections (RTIs) and UTIs after liver transplant.[9]

The time of occurrence of infection after LT is divided as early (1 month of LT), intermediate (between 1 and 6 months of LT) and late (beyond 6 months) infection. Majority of infections that occurs during the first month of post LT which is caused by nosocomial organisms or normal flora of patients. During the next period of post LT, opportunistic infections may occur, depending on the intensity of the immunosuppression. After 6 months of LT, the infection is related to an environmental exposure, biliary complications, sepsis, UTI, intra-abdominal infection etc. due to minimal immunosuppression.[7,10] Frequent administration of prophylactic antibiotics before surgery make the recipients vulnerable to Multi-Drug Resistant Organisms (MDRO) that include methicillin resistant S.aureus (MRSA), Vancomycin resistant Enterococci (VRE), extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae and carbapenem resistant Enterobacteriaceae (CRE).[6,8] The fungal species like Candida, Aspergillus, Cryptococcus, Coccidioides species are also a major cause of morbidity and mortality among post LT patients. Viruses such as Cytomegalovirus (CMV), Epstein - Barr virus (EBV), Herpes simplex virus (HSV) are found to be opportunistic pathogen often related to over exposure of immunosuppression, contributing to risk of rejection. Therefore, the rate of infection after liver transplantation is

usually a reflection of state of immunosuppression.[6,11] The diagnosis and treatment of these infections are not easy enough as the induction of immunosuppression therapies blunted the inflammatory response and the clinical symptoms of infection leading to a devastating consequence.[9] Therefore this study was aimed to investigate the post liver transplant infections caused by the microorganisms in a tertiary care teaching Hospital.

MATERIALS & METHODS

This study was caried out in the Diagnostic laboratory, Institute of Surgical Gastroenterology (SGE) and Liver Transplantation, Government Stanley Medical College and Hospital, during the study period (2016–2017). The follow-up study included a total of 30 donors and 30 recipients who had undergone liver transplantation.

Pre-transplantation samples (throat swab, nasal swab, blood, and urine) and post-transplantation samples (central venous catheter tip, body fluids, wound swab) were processed in the laboratory. The samples were inoculated on the MacConkey agar and Blood agar plate. Urine samples were inoculated on cystine lactose electrolytes deficient agar (CLED). The plates were incubated (aerobically) overnight at 37ºC. The obtained isolates were identified by its colonial morphology, Gram staining and conventional biochemical characteristics. Antibiotic Susceptibility Test (AST) was performed by modified Kirby-Bauer method. The tested antibiotics (Hi-media) include aminoglycosides (amikacin and gentamycin), Cephalosporin (cefatoxime and ceftazidime), quinolones (ciprofloxacin, norfloxacin, levofloxacin), Carbapenem (meropenem, imipenem), nitrofurantoin, tigecycline and colistin for gram negative bacteria. Penicillin, ampicillin, bacitracin, vancomycin (Minimum inhibitory concentration for Staphylococcus aureus), doxycycline, teicoplanin and linezolid for a gram-positive bacterium.

Additional investigations such as complete blood count, serum electrolytes, liver function test (LFT), renal function test (RFT) and coagulase profile were performed. Tacrolimus and Cyclosporine assay were performed using chemiluminescent microparticle immunoassay (CMIA) to measure its level in whole blood.

The data of complete blood investigation during discharge of the recipients were collected and analysed with IBM.SPSS statistics software 23.0 Version. For the descriptive statistics: frequency analysis, percentage analysis was used for categorical variables and the mean & Standard deviation (S.D) were used for continuous variables.

RESULTS

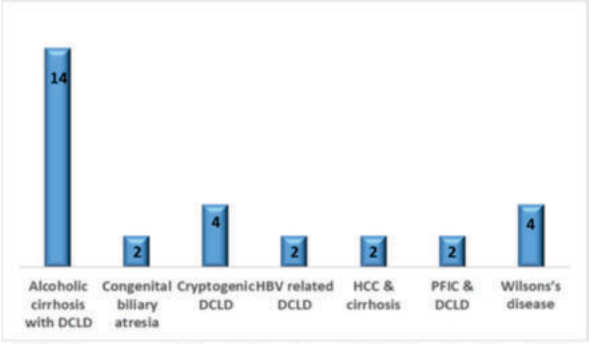
In the study of 30 recipient and donor, the recipient (28 male and 2 female) with the mean age of 38 (range: 15 to 58 years) did not show significant microbial growth in pre-transplantation samples. Among the donors, β - haemolytic Streptococci (6, 20%), MRSA (2, 6.6%) and Candida albicans (2, 6.6%) was isolated from various pre-transplantation samples.

Table 1. Descriptive Statistics Of Complete Blood Investigations For The Recipients During Discharge

DESCRIPTIVE STATISICS					
Data's	No. of Recipients	Minimum	Maximum	Mean	SD
Age	30	15	58	38	15.09
Platelet count	30	214000	266000	181093	56976.83
WBC count	30	5400	12700	8440	2083.54
Neutrophils	30	60.00%	86.00%	74.93%	7.7318%
Lymphocytes	30	11.00%	86.00%	19.80%	6.0143%
Baso/Mono/ Esono	30	2.00%	12.00%	5.73%	3.3905%
PCV	30	24.00%	35.00%	30.00%	3.7123
MCV	30	76.0	96.0	87.0	4.376
MCH	30	26.0	36	31.0	2.98
MCHC	30	30.0	38	35.0	2.27
Hb	30	9.0	12	10.0	1.12
INR	30	1.0	1.60	1.30	0.173
Blood Glucose	30	92.0	162.0	124.4	20.618
Urea	30	28.0	42.0	35.5	3.998
Creatinine	30	0.5	1.30	0.90	0.249
Total Bilurubin	30	0.7	1.90	1.1	0.267
Direct Bilurubin	30	0.18	0.40	0.25	0.0806
AST	30	32.0	50.0	41.5	5.655
ALT	30	24.0	80.0	50.0	12.043
SAP	30	160.0	280.0	228.0	37.291
Total Protein	30	4.8	7.0	6.0	0.729
Albumin	30	3.0	5.0	4.0	0.509
Globulin	30	0.6	2.90	1.9	0.541
Sodium	30	130.5	150.0	140.3	4.934
Potassium	30	3.2	5.0	4.4	0.494
chloride	30	95.0	110.0	103.0	4.623
Calcium	30	8.5	12.	10.0	0.976
Magnesium	30	2.0	2.8	2.4	0.203
Phosphorous	30	3.6	5.2	4.5	0.506

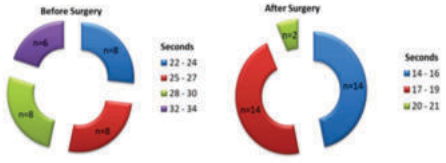
Abbreviation: SD-Standard Deviation; WBC-White Blood Cells; PCV-Packed Cell Volume; MCV-Mean Corpuscular Volume; MCH-Mean Corpuscular Hemoglobin; MCHC-Mean Corpuscular Hemoglobin concentration; Hb-Haemoglobin; INR-International Normalized Rate; AST-Aspartate Aminotransferase; ALT-Alanine transaminases; SAP-Serum Alkaline Phosphatase.

Figure 1. Underlying diagnosis of 30 recipients for liver transplantation.



DCLD - Decompensated Chronic Liver Disease; HBV - Hepatitis B Virus; HCC - Hepatocellular Carcinoma; PFIC - Progressive Familial Intrahepatic Cholestasis.

Figure 2. Prothrombin time of the recipients before and after surgery (during discharge).

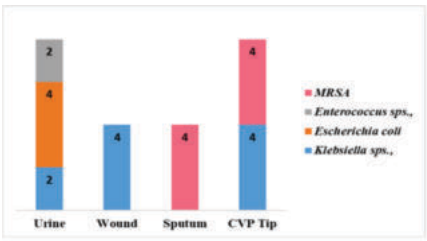


The images show that, the prothrombin time of the recipients before surgery is prolonged due to improper function of liver, as the liver plays a vital role of making blood clotting proteins. After surgery, at the time of discharge, the prothrombin time falls at a normal range which shows a normal function of transplanted liver. n-number of patients.

Incidence of postoperative infections

The bacterial species that cause infection at various sites was observed after LT. The infection such as, Catheter associated UTI (26.6%), bacterial pneumonia (13.3%), SSI (13.3%) and Central – venous – catheter related bloodstream infections (26.6%).

Figure 3. Common bacterial species that cause infections at various sites after LT.



CVP Tip - central venous pressure tip; MRSA – Methicillin-Resistant *Staphylococcus aureus*

Table 2. Antibiotic sensitivity pattern for the gram-negative bacilli isolated from various clinical samples.

Sample	No. of Organisms	Organisms	Antibiotics used for antibiotic susceptibility test										
			AK	GEN	CAZ	CTX	NIT	NOR	CIP	IMP	MRP	TGC	CS
Urine	Four E. coli	E. coli 1	S	R	R	R	S	R	-	S	R	S	S
		E. coli 2	S	S	R	R	S	S	-	S	S	S	S
		E. coli 3	S	R	R	R	S	S	-	R	R	S	S
		E. coli 4	S	S	R	R	S	R	-	S	R	S	S
	Two K.pneumoniae	K.pneumoniae 1	S	S	R	R	S	R	-	S	R	S	S
		K.pneumoniae 2	S	S	R	R	S	R	-	S	R	S	S
Wound	Four K.pneumoniae	K.pneumoniae 1	S	S	R	R	-	-	R	S	R	S	S
		K.pneumoniae 2	R	R	R	R	-	-	R	R	R	S	S
		K.pneumoniae 3	R	R	R	R	-	-	R	S	R	S	S
		K.pneumoniae 4	S	R	R	R	-	-	R	R	R	S	S
CVP tip	Four K.pneumoniae	K.pneumoniae 1	S	S	R	R	-	-	R	S	R	S	S
		K.pneumoniae 2	S	S	R	R	-	-	S	S	S	S	S
		K.pneumoniae 3	R	R	R	R	-	-	R	S	R	S	S
		K.pneumoniae 4	S	R	R	R	-	-	R	R	R	S	S

Abbreviation: AK-Amikacin, GEN-Gentamicin, CAZ-Ceftazidime, CTX-Cefotaxime, NIT-Nitrofurantoin, NOR-Norfloxacin, CIP-Ciprofloxacin, IMP-Imipenem, MRP-Meropenem, TGC-Tigecycline, CS-Colistin; R-Resistant, S-Sensitive.

Table 3. Antibiotic sensitivity pattern for the gram-positive bacteria isolated from various clinical samples.

Sample	No. of Organisms	Organisms	Antibiotics used for antibiotic susceptibility test												
			AK	PEN	AMP	HLG	B	CX	NIT	NOR	E	CD	VAN	LZ	LEV	TEC
Urine	Two Enterococci sp.,	Enterococci 1	S	R	S	S	S	-	S	S	-	-	S	S	-	-
		Enterococci 2	R	R	S	S	S	-	S	R	-	-	S	S	-	-
Sputum	Four MRSA	MRSA 1	S	R	-	-	S	R	-	-	R	R	S	S	S	S
		MRSA 2	S	R	-	-	R	R	-	-	S	S	S	S	R	S
		MRSA 3	S	R	-	-	R	R	-	-	R	R	S	S	R	S
		MRSA 4	R	R	-	-	S	R	-	-	S	R	S	S	R	S
CVP Tip	Four MRSA	MRSA 1	S	R	-	-	R	R	-	-	S	S	S	S	R	S
		MRSA 2	S	R	-	-	S	R	-	-	S	S	S	S	S	S
		MRSA 3	R	R	-	-	S	R	-	-	R	S	S	S	S	S
		MRSA 4	S	R	-	-	R	R	-	-	S	R	S	S	R	S

Abbreviation: MRSA-Methicillin-Resistant Staphylococcus aureus; AK-Amikacin, PEN-Penicillin, AMP-Ampicillin, HLG-High level gentamicin, B-Bacitracin, CX-Cefoxitin, NIT-Nitrofurantoin, NOR-Norfloxacin, E-Erythromycin, CD-Clindamycin, VAN-Vancomycin, LZ-Linezolid, LEV-Levofloxacin, Teicoplanin; R-Resistant, S-Sensitive.

Among the 30 recipients, 2 patients were found to have an UTI caused by Candida albicans and the other 2 patients had SSI caused by Aspergillus species. Epstein-Barr virus, a common virus associated with post-transplant lymphoproliferative disease (PTLD) was diagnosed in 2 patients by Real time Polymerase Chain Reaction (RT-PCR) with a symptom of fever, malaise and lower respiratory tract infection, 4 months after surgery. Blood investigations showed a raised ESR, leucopoenia, thrombocytopenia, and anaemia. CT scan of thorax showed multiple Mediastinal lymphadenopathy. The patient was treated with monoclonal antibody (Rituximab) and chemotherapy. Acute rejection was observed in 6 patients, and they were treated with high dose of corticosteroids (intravenous Methyl prednisolone) for 3 days in-order to reduce inflammation and it is gradually tapered to oral prednisolone. Tacrolimus assay was performed in 22 patients and cyclosporin assay was performed in 8 patients in-order to maintain its level within a narrow therapeutic range of tacrolimus (5.0 to 15.0 ng/mL) and cyclosporin (100-400 ng/mL) in whole blood.

DISCUSSION

Liver transplant is the typical treatment option for end-stage liver disease. The risk of infection after liver transplant is still a major cause of limiting the survival rate. Screening the donor and recipients for infectious complication may reduce the risk of infection after transplantation. Although, an unexpected infection derived from donor during transplantation remains a major concern. Several studies stated that, the incidence of infection transmitted from donor to recipient is very low. According to the study conducted by Chan et al., 2019 and Outerelo et al., 2013, the risk of infection is limited even when the organ is transplanted from the infected donor[12,13]. However, the scarcity of donor is the limiting factor in the field of transplantation. Therefore, it is suggested that the donors with bacterial infection should not be excluded; instead administering prophylactic antibiotics may reduce the complications. In our study, the donor did not show significant microbial growth in various samples and no evidence of transmission of infection from donor to recipient. Also, the recipients were not found to have significant preoperative infection upon screening various samples for culture.

Majority of infection are nosocomial that arise during the first month (early period) of post transplantation, despite of advances in surgical techniques.[5] Among which bacterial infection is the most common followed by fungal and viral infection. In this study, bacteria (n=24, 80% of total organisms identified) were the most common causative agent of infection among the recipients after LT followed by fungi (n=4, 13%) and virus (n=2, 7%). This rate is comparable with the previous report as bacteria (90.9%), fungi (7.5%) and virus (2%).[14] Among the pathogenic bacteria identified, Klebsiella pneumoniae (41.6%) and Staphylococcus aureus (33.3%) were the leading pathogen followed by E.coli (16.6%) and Enterococcus species (8.3%). These organisms showed increased rate of resistance against several antibiotics; gram negative bacteria like Klebsiella pneumoniae and E.coli were ESBL producers and 3 of the Klebsiella pneumoniae and one of E.coli were carbapenemase producer. Amongst them, 60% Klebsiella pneumoniae and 50% E.coli identified were ISMR (Imipenem Susceptible but Meropenem Resistant). This is an emerging nosocomial pathogen which is a misdiagnosis of Carbapenemase producing Enterobacteriaceae (CPE), has been identified throughout Japan.[15,16] Among the gram-positive bacteria, methicillin-resistant Staphylococcus aureus (MRSA) is the major cause of UTI and pulmonary infection. High prevalence of MRSA after LT was documented by previous studies, stating that 6.7% - 22% of recipients acquire MRSA colonization after LT.[6,17]

In addition, Invasive Fungal Infection(s) (IFIs) is the second major cause of morbidity and mortality which requires invasive procedure for diagnosis. Among various fungal species Candida species and Aspergillus species are the far most common species[6,8,9,18] In our study, among 15 LT recipients, IFIs developed in 4 (13%) patients, caused by Candida albicans and Aspergillus species. Similarly, a retrospective study reported 4.8% of LT recipients developed IFIs among 3 tertiary care hospital of Korea.[19] .

Acute rejection in LT is a major complication with an incidence ranging from 15-25% of liver transplants even on tacrolimus based immunosuppressive agents.[20] Generally acute rejection occurs within 5 to 15 days after transplantation which is clinically suspected by elevation in serum aminotransferase and alkaline phosphatase. In our study, acute rejection was observed in 20% of LT recipients (6 patients) and they were treated with 500 – 1000 mg of Methylprednisolone.

However, this acute rejection can be treated by using corticosteroids (3-5 days of 500-1000mg of Methylprednisolone).[21] The use of immunosuppressive agents such as CNIs and mTOR inhibitors may eventually reduce the rate of rejection in LT. However, the net state of immunosuppression contributes to the risk of infections, hence monitoring or measuring the trough level of drug will avoid the toxicity of drug, organ rejection and post transplantation infection infections.[4,22]

CONCLUSION

Infections after LT are the major cause of morbidity and mortality in the liver transplant recipients. Bacterial infections are the most common in the early postoperative period. Later, fungal and viral infections also occur due to the usage of immunosuppressants. The inappropriate use of antibiotics may lead to multi-drug resistant organisms. Hence monitoring of infections continuously and initiation of appropriate therapy plays a vital role in the outcome of liver transplant recipients.

Authors' contribution

MM, SRu, JS, RV, SRa - conceptualization and designing of the study; MM, PS, KG - collection and analysis of data, interpretation of results; PS, KG - manuscript preparation; SRu, JS, RV, SRa - manuscript renewal and final approval.

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Declaration of competing interest

There is no conflict of interest about the authors or the article.

REFERENCES

1. WHO|GHO data repository. http://apps.who.int/gho/data/ view.main.53420
2. Mansard, M., Siddachari, R., Kumar, G., Subramanian, N. and Olithselvan, A. (2020). Liver Transplantation Program in India: The Core-Satellites Model. Tropical Gastroenterology, 41(2), 54-59.
3. Tasdogan, B.E., Ma, M., Simsek, C., Saberi, B. and Gurakar, A. (2019). Update on Immunosuppression in Liver Transplantation. Euroasian J Hepatogastroenterol, 9(2), 96-101. doi: 10.5005/jp-journals-10018-1301.
4. Choudhary, N.S., Saigal, S., Shukla, R., Kotecha, H., Saraf, N. and Soin, A.S. (2013) Current status of immunosuppression in liver transplantation. J Clin Exp Hepatol, 3(2), 150-8. doi: 10.1016/j.jceh.2013.04.005.
5. Ayvazoglu Soy, E.H., Akdur, A., Yildirim, S., Arslan, H. and Haberal, M. (2018). Early Postoperative Infections After Liver Transplant. Exp Clin Transplant, 16, 145-148. doi: 10.6002/ect.TOND-TDTD2017.
6. Hernandez Mdel, P., Martin, P. and Simkins, J. (2015). Infectious Complications After Liver Transplantation. Gastroenterol Hepatol (N Y), 11(11), 741-53.
7. Kim, S.I. (2014). Bacterial infection after liver transplantation. World J Gastroenterol, 20(20), 6211-20. doi: 10.3748/wjg.v20.i20.6211.
8. Pedersen, M. and Seetharam, A. (2014). Infections after orthotopic liver transplantation. J Clin Exp Hepatol, 4(4), 347-60. doi: 10.1016/j.jceh.2014.07.004.
9. Romero, F.A. and Razonable, R.R. (2011). Infections in liver transplant recipients. World J Hepatol, 3(4), 83-92. doi: 10.4254/wjh.v3.i4.83.
10. Van Hoek, B., de Rooij, B.J. and Verspaget, H.W. (2012). Risk factors for infection after liver transplantation. Best Pract Res Clin Gastroenterol, 26(1), 61-72. doi: 10.1016/j.bpg.2012.01.004.
11. Fishman, J.A. (2007). Infection in solid-organ transplant recipients. N Engl J Med, 357(25), 2601-14. doi: 10.1056/NEJMra064928.
12. Chan, K-M., Cheng, C-H., Wu, T-H., et al. (2019). Impact of donor with evidence of bacterial infections on deceased donor liver transplantation: a retrospective observational cohort study in Taiwan. BMJ Open, 9, e023908. doi:10.1136/ bmjopen-2018-023908
13. Outerelo, C., Gouveia, R., Mateus, A., Cruz, P., Oliveira, C. and Ramos, A. (2013). Infected donors in renal transplantation: expanding the donor pool. Transplant Proc, 45(3), 1054-6. doi: 10.1016/j.transproceed.2013.02.014.
14. Lim, S., Kim, E.J., Lee, T.B., Choi, B.H., Park, Y.M., Yang, K. et al. (2018). Predictors of postoperative infectious complications in liver transplant recipients: experience of 185 consecutive cases. Korean J Intern Med, 33(4), 798-806. doi: 10.3904/kjim.2017.230.
15. Kayama, S., Koba, Y., Shigemoto, N., Kuwahara, R., Kakuhama, T., Kimura, K., et al. (2015). Imipenem-susceptible, meropenem-resistant Klebsiella pneumoniae producing OXA-181 in Japan. Antimicrob Agents Chemother, 59(2), 1379-80. doi: 10.1128/AAC.04330-14.
16. Shigemoto, N., Kuwahara, R., Kayama, S., Shimizu, W., Onodera, M., Yokozaki, M., et al. (2012). Emergence in Japan of an imipenem-susceptible, meropenem-resistant Klebsiella pneumoniae carrying blaIMP-6. Diagn Microbiol Infect Dis, 72(1), 109-12. doi: 10.1016/j.diagmicrobio.2011.09.019.
17. Santoro-Lopes, G. and de Gouvêa, E.F. (2014). Multidrug-resistant bacterial infections after liver transplantation: an ever-growing challenge. World J Gastroenterol, 20(20), 6201-10. doi: 10.3748/wjg.v20.i20.6201.
18. Ferrarese, A., Cattelan, A., Cillo, U., Gringeri, E., Russo, F.P., Germani, G. et al. (2020). Invasive fungal infection before and after liver transplantation. World J Gastroenterol, 26(47), 7485-7496. doi: 10.3748/wjg.v26.i47.7485.
19. Kim, Y.J., Kim, S.I., Choi, J.Y., Yoon, S.K., Na, G.H., You, Y.K. et al (2019). Invasive fungal infection in liver transplant recipients in a prophylactic era: A multicenter retrospective cohort study in Korea. Medicine (Baltimore), 98(26), e16179. doi: 10.1097/MD.0000000000016179.
20. Choudhary, N.S., Saigal, S., Bansal, R.K., Saraf, N., Gautam, D. and Soin, A.S. (2017). Acute and Chronic Rejection After Liver Transplantation: What A Clinician Needs to Know. J Clin Exp Hepatol, 7(4), 358-366. doi:10.1016/j.jceh.2017.10.003
21. Dogan, N., Hüsing-Kabar, A., Schmidt, H.H., Cicinnati, V.R., Beckebaum, S. and Kabar, I. (2018). Acute allograft rejection in liver transplant recipients: Incidence, risk factors, treatment success, and impact on graft failure. J Int Med Res, 46(9), 3979-3990. doi:10.1177/0300060518785543
22. Roberts, M.B. and Fishman, J.A. (2020). Immunosuppressive Agents and Infectious Risk in Transplantation: Managing the "Net State of Immunosuppression". Clin Infect Dis, 17, ciaa1189. doi: 10.1093/cid/ciaa1189.