

# World Journal of *Hepatology*

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### AIM AND SCOPE

*World Journal of Hepatology* (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

*WJH* covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Prospective Study

# Bacterial infections post-living-donor liver transplantation in Egyptian hepatitis C virus-cirrhotic patients: A single-center study

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## Abstract

### AIM

To determine risk factors, causative organisms and



antimicrobial resistance of bacterial infections following living-donor liver transplantation (LDLT) in cirrhotic patients.

## METHODS

This prospective study included 45 patients with hepatitis C virus-related end-stage liver disease who underwent LDLT at Ain Shams Center for Organ Transplant, Cairo, Egypt from January 2014 to November 2015. Patients were followed-up for the first 3 mo after LDLT for detection of bacterial infections. All patients were examined for the possible risk factors suggestive of acquiring infection pre-, intra- and post-operatively. Positive cultures based on clinical suspicion and patterns of antimicrobial resistance were identified.

## RESULTS

Thirty-three patients (73.3%) suffered from bacterial infections; 21 of them had a single infection episode, and 12 had repeated infection episodes. Bile was the most common site for both single and repeated episodes of infection (28.6% and 27.8%, respectively). The most common isolated organisms were gram-negative bacteria. *Acinetobacter baumannii* was the most common organism isolated from both single and repeated infection episodes (19% and 33.3%, respectively), followed by *Escherichia coli* for repeated infections (11.1%), and *Pseudomonas aeruginosa* for single infections (19%). Levofloxacin showed high sensitivity against repeated infection episodes ( $P = 0.03$ ). *Klebsiella*, *Acinetobacter* and *Pseudomonas* were multi-drug resistant (MDR). Pre-transplant hepatocellular carcinoma (HCC) and duration of drain insertion (in days) were independent risk factors for the occurrence of repeated infection episodes ( $P = 0.024$ ).

## CONCLUSION

MDR gram-negative bacterial infections are common post-LDLT. Pre-transplant HCC and duration of drain insertion were independent risk factors for the occurrence of repeated infection episodes.

**Key words:** Living-donor liver transplantation; Bacterial infection; Multi-drug resistance; Hepatitis C virus; Liver cirrhosis

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**Core tip:** We evaluated 45 patients with hepatitis C virus-related end-stage liver disease for the occurrence of bacterial infections during the first 3 mo post-living-donor liver transplantation. Thirty-three patients (73.3%) suffered from bacterial infections; 21 of them had a single infection episode, and 12 had repeated infection episodes. Bile was the most common site for both single and repeated episodes of infection (28.6% and 27.8%, respectively). Multi-drug resistant gram-negative bacteria, especially *Klebsiella*, *Acinetobacter* and *Pseudomonas*, were the most commonly isolated bacteria. Pre-transplant hepatocellular carcinoma

and duration of drain insertion were independent risk factors for occurrence of repeated infection episodes.

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## INTRODUCTION

Infection following living-donor liver transplantation (LDLT) is a serious problem with a high mortality rate reaching 50%. Many factors were associated with high risks of acquiring infection following LDLT, including the difficulty of surgery, the poor patient's condition, and the immunosuppressive drugs<sup>[1]</sup>.

Nearly 80% of recipients develop one infection episode during the first year, predominantly during the first three months post-transplant. Bacterial infections account for 50%-75% of infections post-LDLT and commonly occur in the first month post-transplant<sup>[2]</sup>.

Patients may become infected with antimicrobial-resistant bacteria, especially methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecalis*, *Clostridium difficile*, and gram-negative bacteria<sup>[3]</sup>. Currently, multidrug-resistant (MDR) organisms are the most common cause of nosocomial infections in liver transplant recipients<sup>[1]</sup>.

Multiple organism infection is common as well as concurrent infections caused by different infectious agents<sup>[4]</sup>. Infections are usually difficult to diagnose because the usual manifestations of infection, such as fever and leukocytosis, may be absent and because of the need to exclude an acute rejection episode<sup>[5]</sup>.

The aim of the present study was to determine risk factors, causative organisms and antimicrobial resistance patterns of bacterial infections following LDLT in Egyptian cirrhotic patients.

## MATERIALS AND METHODS

Forty-five adult patients with hepatitis C virus (HCV)-related end-stage liver disease (ESLD) who were eligible for and underwent LDLT at Ain Shams Center for Organ Transplant, Cairo, Egypt, during the period from January 2014 to November 2015, were included in the current prospective study. They were followed-up for the first 3 mo post-LDLT for detection of bacterial infections.

Patients with other etiologies for ESLD (hepatitis B virus, primary biliary cirrhosis, and others) and patients with pre-operative infections, infections within 48 h after transplantation or early post-operative death

were excluded.

Each patient provided an informed written consent prior to enrollment. The study protocol was accepted by the Research Ethical Committee of the Faculty of Medicine-Ain Shams University. This was in accordance to the ethical guidelines of the 1975 Declaration of Helsinki.

### **Immunosuppressive drugs**

Immediately following liver transplantation (LT), we used triple-therapy of immunosuppressive drugs which was comprised of a steroid, a calcineurin inhibitor: Cyclosporine or tacrolimus, and mycophenolate mofetil. In patients with renal dysfunction, immunosuppression with monoclonal antibodies to T-cells was used. In patients with hepatocellular carcinoma (HCC), tacrolimus monotherapy was used to decrease the incidence of HCC recurrence.

### **Antimicrobial prophylaxis**

Piperacillin/tazobactam 4.5 mg/d was used post-operatively for 5 d. A polymerase chain reaction (PCR) assay for cytomegalovirus (CMV) was done every two weeks until patient's discharge. Ganciclovir for prevention of CMV disease was used if the PCR assay was positive.

### **Checked parameters**

All patients were checked for the following parameters: (1) pre-operatively: Demographic data, other co-morbidities, presence of HCC, any bridging techniques, Child and MELD scores, CBC with differential cell count, liver profile, C-reactive protein, serum ferritin, documented or suspected SBP and third generation cephalosporin administration, renal impairment, and positive cultures; (2) intra-operatively: Total operative period, cold and warm ischemia time, amount of transfused blood or blood products and type of biliary anastomosis; and (3) post-operatively: Intensive care unit stay, ventilator duration, duration of central venous line and catheter insertion, duration of abdominal drain placement, dialysis post-transplant and immunosuppressive drugs.

### **Case identification**

Post-operative infection was defined as any positive culture, based on clinical suspicion, within 3 mo following LDLT, according to the Centers for Disease Control and Prevention's definition of a nosocomial infection and as described in liver transplant recipients<sup>[6,7]</sup>. The diagnosis of wound infection was established by the presence of redness/induration and the presence of pus on exploration and/or positive wound culture. The diagnosis of urinary tract infection was based upon the following criteria: The patient has at least one of the following symptoms or signs with no other identified cause: fever ( $> 38^{\circ}\text{C}$ ), dysuria, frequency, urgency, suprapubic or costovertebral angle pain or tenderness, as well

as a positive urine culture, that is,  $\geq 10^5$  CFU/mL of urine with no more than 2 species of microorganisms. The diagnosis of pneumonia was based upon the presence of pulmonary infiltrates together with clinical symptoms indicating lower respiratory tract infection, the identification of a relevant etiologic microorganism, and the absence of another possible diagnosis during the follow-up. Bloodstream infection was diagnosed when microorganisms were isolated from one blood culture. Ascitic fluid cultures were performed for all patients with manifestations of bacterial peritonitis or who were suspected of having bacterial peritonitis. Samples were collected before the start of any antimicrobial treatment. Bile samples were withdrawn for those suspected of having a biliary tract infection. In cases of suspected sepsis-induced cholestasis, cultures from blood, the biliary tube, abdominal drains, urine, and sputum were collected, and culture based-treatment was started accordingly.

The term multidrug-resistant (MDR) was used to refer to pathogens resistant to three or more classes of the following antibiotics: extended-spectrum penicillins, 3<sup>rd</sup> generation cephalosporins, quinolones, carbapenems, and aminoglycosides<sup>[8]</sup>.

Recruited patients were divided into two groups. Group 1 included patients who had a single episode of post-operative bacterial infection, and Group 2 included those patients who had more than one episode of a bacterial infection.

### **Statistical analysis**

Statistical analyses were performed using IBM® SPSS® Statistics version 22 (IBM® Corp., Armonk, NY, United States). Continuous numerical variables were shown as the mean and standard deviation, and differences between groups were compared using the unpaired *t* test. Discrete numerical variables were shown as the median and interquartile range, and the Mann-Whitney test was used to compare intergroup differences. Categorical data were shown as ratios or as the number and percentage, and differences between groups were compared using Pearson's  $\chi^2$  test or Fisher's exact test. Variables shown to be significantly associated with the occurrence of repeated infection episodes by univariate analysis were entered in multivariate binary logistic regression analysis to identify independent predictors of this outcome. Time-to-event analysis was done using the Kaplan-Meier method, and the log-rank test was used to compare individual Kaplan-Meier curves. A *P*-value  $< 0.05$  was considered significant.

The statistical methods for this study were performed by Sameh M. Hakim, Diploma of Medical Biostatistics, Faculty of Medicine of Ain Shams University, Cairo, Egypt.

## **RESULTS**

The present study enrolled forty-five adult patients

**Table 1** Comparison between patients who developed post-living-donor liver transplantation single episode and those who developed repeated episodes of infection regarding pre-operative parameters *n* (%)

	Single episode of infection ( <i>n</i> = 21)	Repeated episodes of infection ( <i>n</i> = 12)	<i>P</i> value
Recipient's age (yr, mean ± SD)	51.2 ± 8.3	52.08 ± 8.7	0.767
Donor's age (yr, mean ± SD)	26.9 ± 6.3	32.3 ± 6.1	0.021
Recipient's gender (male/female)	19/2	12/0	0.523
Donor's gender (male/female)	19/2	10/2	0.610
Hepatocellular carcinoma	6 (28.6)	8 (66.7)	0.033
History of bridging procedures <sup>1</sup>	4 (19.0)	6 (50.0)	0.114
History of SBP	10 (47.6)	1 (8.3)	0.052
History of paracentesis	11 (52.4)	4 (33.3)	0.290
Diabetes mellitus	8 (38.1)	5 (41.7)	1.000
Child-Pugh class (B/C)	10/11	5/7	0.741
MELD score (median, interquartile range)	14 (12-16)	16 (15-18)	0.136
Thrombocytopenia <sup>2</sup>	20 (95.2)	12 (100.0)	1.000
Leucopenia <sup>3</sup>	9 (42.9)	5 (41.7)	0.947
Renal impairment	2 (9.5)	1 (8.3)	1.000
High serum ferritin <sup>4</sup>	13 (61.9)	5 (41.7)	0.261
High C-reactive protein <sup>5</sup>	14 (66.7)	11 (91.7)	0.206

<sup>1</sup>Bridging procedures included: Radiofrequency ablation, trans-arterial chemo-embolization and micro-wave ablation; <sup>2</sup>Thrombocytopenia: Platelets less than 150000/mm<sup>3</sup>; <sup>3</sup>Leucopenia: WBCs less than 4000/mm<sup>3</sup>; <sup>4</sup>High serum ferritin: More than 333 ng; <sup>5</sup>High C-reactive protein: More than 0.5 mg/L. SBP: Spontaneous bacterial peritonitis.

with HCV-related ESLD, and each patient was followed-up for 3 mo post-LDLT for the occurrence of bacterial infections. Thirty-three patients (73.3%) suffered from bacterial infections post-transplant and fulfilled the inclusion criteria. They were further subdivided into two groups. Group 1 included 21 patients who developed a single episode of infection (19 males and 2 females), and Group 2 included 12 patients (all of them were males) who developed recurrent episodes of infection (total number of attacks = 36) throughout the follow-up period.

Table 1 shows the comparison between patients who developed a single episode of infection post-LDLT and those who developed repeated episodes of infection regarding pre-operative parameters. The presence of pre-transplant hepatocellular carcinoma (HCC) showed a statistically significant increased risk of developing repeated episodes of infection post-LDLT (*P* = 0.033).

There was no significant difference between patients who developed a single episode and those who developed repeated episodes of infection regarding the operative details (*P* > 0.05) (Table 2).

Table 3 shows that the duration of drain insertion revealed a statistically significant increased risk for the development of repeated episodes of infection (*P* = 0.002).

Table 4 shows that bile was found to be the most common site for both single and repeated episodes of infection (28.6% and 27.8%, respectively), followed by the bloodstream for repeated infection episodes (22.2%) and drains for a single infection episode (23.8%).

The most common isolated organisms were gram-negative bacteria for both single and repeated episodes of infections. *Acinetobacter baumannii* was found

solely to be the most common organism isolated from both single and repeated infection episodes (19% and 33.3%, respectively), followed by *Escherichia coli* (*E. coli*) for repeated infections (11.1%), and *Pseudomonas aeruginosa* for a single infection (19%). Additionally, *Acinetobacter baumannii* was found in combination with other organisms in three cultures.

Table 5 shows the antimicrobial sensitivity pattern in patients who suffered from single vs repeated episodes of infection. The sensitivity of levofloxacin was found to be statistically significant against repeated episodes of infection (*P* = 0.03). Repeated episodes of infection showed 100% resistance to penicillins. Single episodes of infection were 100% resistant to ciprofloxacin and co-trimoxazole. Both single and repeated episodes of infections were 100% resistant to cefotaxime and aztreonam.

Regarding the pattern of resistance of isolated organisms to the major antibiotic groups, most of the isolated gram-negative organisms were found to be resistant to several groups of antibiotics; especially *Klebsiella* species, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, all of which were proven to be MDR.

The detailed antibiotic-resistance pattern was as follows: For *Klebsiella* species, 100% of the isolates showed resistance to each of the quinolones and aminoglycosides, 87.5% showed resistance to cephalosporins, 80% to carbapenems, and 25% showed resistance to piperacillin-tazobactam. For *Acinetobacter baumannii*, 100% of the isolates showed resistance to aminoglycosides, 60% to carbapenems, 46.5% to quinolones, 42% to cephalosporins, and 33.3% showed resistance to piperacillin-tazobactam. For *Pseudomonas aeruginosa*, 100% of the isolates showed resistance to quinolones, and 83.3% showed

**Table 2** Comparison between patients who developed single episode and those who developed repeated episodes of infection regarding operative details

	Single episode of infection ( <i>n</i> = 21)	Repeated episodes of infection ( <i>n</i> = 12)	<i>P</i> value
CIT (min), mean ± SD	43.6 ± 17.3	50.8 ± 17.7	0.259
WIT (min), mean ± SD	45.7 ± 13.4	50.8 ± 12.4	0.288
Recipient's operative time (h), mean ± SD	10.3 ± 1.1	10.5 ± 1.5	0.704
Packed red cell transfusion (U), (median, interquartile range)	2 (2-4)	3 (2-6)	0.493

CIT: Cold ischemia time; WIT: Warm ischemia time.

**Table 3** Length of intensive care unit stay, length of exposure to invasive procedures, and time to occurrence of infection in patients who suffered from single *vs* repeated episodes of infection

	Single episode of infection ( <i>n</i> = 21)	Repeated episodes of infection ( <i>n</i> = 12)	<i>P</i> value
Length of ICU stay (d)	6 (5-7)	7 (5-7)	0.969
Days on mechanical ventilator	1 (1-1)	1 (1-1)	0.176
Days with CVC	6 (5-7)	6 (5-7)	0.770
Days with urinary catheter	6 (5-7)	7 (6-8)	0.467
Days with drains	17 (15-20)	25 (21-30)	0.002
Time-to-infection (d)	14 (12-17)	9 (6-19)	0.189

Data are presented as median (interquartile range). ICU: Intensive care unit; CVC: Central venous catheter.

**Table 4** Site of infection and implicated organisms in patients who suffered from single *vs* repeated episodes of infection *n* (%)

	Single episode ( <i>n</i> = 21)	Repeated episodes ( <i>n</i> = 36) <sup>1</sup>	<i>P</i> value
Site of organism isolation			0.896
Bile	6 (28.6)	10 (27.8)	
Wound	1 (4.8)	2 (5.6)	
Sputum	3 (14.3)	7 (19.4)	
Drains	5 (23.8)	7 (19.4)	
Blood	3 (14.3)	8 (22.2)	
Urine	2 (9.5)	2 (5.6)	
Ascitic fluid	1 (4.8)	0 (0.0)	
Organism isolated			0.456
<i>Coagulase (-) Staph. aureus</i>	3 (14.3)	1 (2.8)	
<i>Staph. aureus</i>	0 (0.0)	1 (2.8)	
MRSA	3 (14.3)	1 (2.8)	
<i>E. coli</i>	2 (9.5)	4 (11.1)	
<i>Klebsiella species</i>	2 (9.5)	3 (8.3)	
<i>Pseudomonas aeruginosa</i>	4 (19.0)	3 (8.3)	
<i>Acinetobacter baumannii</i>	4 (19.0)	12 (33.3)	
<i>Proteus</i>	0 (0.0)	2 (5.6)	
<i>Enterobacteriaceae</i>	1 (4.8)	1 (2.8)	
<i>Enterococci</i>	1 (4.8)	2 (5.6)	
<i>Bacillus species</i>	0 (0.0)	2 (5.6)	
<i>Pseudomonas + Acinetobacter</i>	1 (4.8)	0 (0.0)	
<i>Pseudomonas + Klebsiella</i>	0 (0.0)	2 (5.6)	
<i>Acinetobacter + Klebsiella</i>	0 (0.0)	1 (2.8)	
<i>Acinetobacter + coagulase (-) Staph. aureus</i>	0 (0.0)	1 (2.8)	

<sup>1</sup>Represents the total number of attacks occurred among the 12 patients who developed repeated episodes of infections. MRSA: Methicillin-resistant *Staphylococcus aureus*.

resistance to cephalosporins. Meanwhile, 100% of them were sensitive to aminoglycosides, piperacillin-tazobactam and carbapenems. For *E. coli*, 70% of the isolates showed resistance to cephalosporins,

50% to quinolones, and 25% showed resistance to aminoglycosides. Moreover, 100% of them were sensitive to piperacillin-tazobactam and carbapenems.

Table 6 and Figure 1 show that the two variables identified by multivariate analysis as independent risk factors for the occurrence of repeated episodes of infection were HCC and the duration of drain insertion (in days) (*P* = 0.024 and odds ratio = 25.44 and 1.38, respectively).

The median time-to-infection was 14 d in the single infection episode group and 8.5 d in the repeated infection episodes group, with no significant difference observed between groups (*P* = 0.647) (Table 7 and Figure 2).

## DISCUSSION

Infectious complications have become the most common sources of mortality and morbidity following LT. Multiple organism infection is common. The occurrence of infection following LT is due to the dysfunction of the patient's defensive mechanisms, as a result of liver cirrhosis and the use of immunosuppressant drugs<sup>[4]</sup>.

The current study included 45 patients with HCV-related ESLD who were eligible for and underwent LDLT at Ain Shams Center for Organ Transplant, Cairo, Egypt during the period from January 2014 to November 2015. They were followed-up for the first 3 mo post-LDLT for the detection of bacterial infections.

In the current study, 73.3% of included patients developed a nosocomial bacterial infection in the first 3 mo post-LDLT. This finding is in agreement with previous reports, which denoted a high incidence of bacterial infections post-LDLT ranging from 50% to 75%<sup>[1,2]</sup>.



**Table 5** Antimicrobial sensitivity in patients who suffered from single *vs* repeated episodes of infection *n* (%)

Antimicrobial		All episodes of infection ( <i>n</i> = 57)	Single episode of infection ( <i>n</i> = 21)	Repeated episodes of infection ( <i>n</i> = 36)	<i>P</i> value
Levofloxacin	S	11 (52.4)	2 (22.2)	9 (75.0)	0.030
	R	10 (47.6)	7 (77.8)	3 (25.0)	
Ciprofloxacin	S	5 (38.5)	0 (0.0)	5 (45.5)	0.487
	R	8 (61.5)	2 (100.0)	6 (54.5)	
Co-trimoxazole	S	1 (7.1)	0 (0.0)	1 (10.0)	1.000
	R	13 (92.9)	4 (100.0)	9 (90.0)	
Penicillin	S	1 (11.1)	1 (14.3)	0 (0.0)	1.000
	R	8 (88.9)	6 (85.7)	2 (100.0)	
Doxycycline	S	14 (77.8)	5 (100.0)	9 (69.2)	0.278
	R	4 (22.2)	0 (0.0)	4 (30.8)	
Vancomycin	S	8 (88.9)	4 (100.0)	4 (80.0)	1.000
	R	1 (11.1)	0 (0.0)	1 (20.0)	
Piperacillin-tazobactam	S	8 (72.7)	3 (75.0)	5 (71.4)	1.000
	R	3 (27.3)	1 (25.0)	2 (28.6)	
Aminoglycosides	S	9 (75.0)	1 (50.0)	8 (80.0)	0.455
	R	3 (25.0)	1 (50.0)	2 (20.0)	
Imipenem	S	20 (69.0)	8 (88.9)	12 (60.0)	0.201
	R	9 (31.0)	1 (11.1)	8 (40.0)	
Ceftriaxone	S	7 (38.9)	1 (16.7)	6 (50.0)	0.316
	R	11 (61.1)	5 (83.3)	6 (50.0)	
Cefotaxime	R	8 (100.0)	7 (100.0)	1 (100.0)	-
Aztreonam	R	6 (100.0)	1 (100.0)	5 (100.0)	-

S: Sensitive; R: Resistant.

**Table 6** Multivariate binary logistic regression model for prediction of the occurrence of repeated episodes of infection

	Regression coefficient	SE	Odds ratio	95%CI	<i>P</i> value
Donor's age (yr)	0.05	0.08	1.05	0.90-1.23	0.552
Hepatocellular carcinoma (HCC = 1, no HCC = 0)	3.24	1.43	25.44	1.53-422.21	0.024
Duration of drain insertion (d)	0.32	0.14	1.38	1.04-1.83	0.024
Constant	-10.28				
Model diagnostics					
-2 Log Likelihood test			<i>P</i> value, < 0.001		
Hosmer and Lemeshow test			<i>P</i> value, 0.369		
Correct classification rate			87.88%		
ROC curve analysis					
AUC		0.935 (95%CI: 0.791-0.991; <i>P</i> value < 0.0001)			
Sensitivity, %		91.7 (95%CI: 61.5-99.8)			
Specificity, %		81.0 (95%CI: 58.1-94.6)			
PPV, %		73.3 (95%CI: 43.8-92.7)			
NPV, %		94.4 (95%CI: 72.7-99.9)			

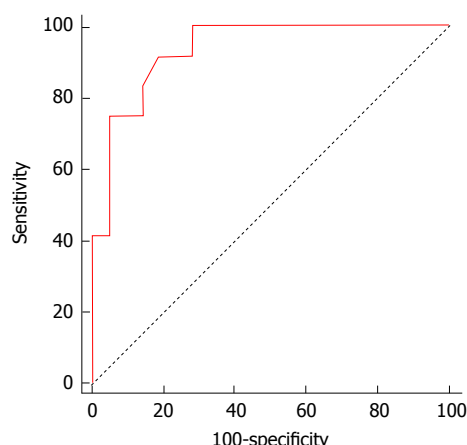
HCC: Hepatocellular carcinoma; AUC: Area under ROC curve; ROC: Receiver-operating characteristic; PPV: Positive predictive value; NPV: Negative predictive value.

In the current study, the presence of pre-transplant HCC was an independent risk factor for the occurrence of repeated episodes of bacterial infection in the recipients during the early post-transplant period. HCC patients are more susceptible to infection due to poor long-term nutrition, poor physical condition and weak immune system<sup>[1]</sup>.

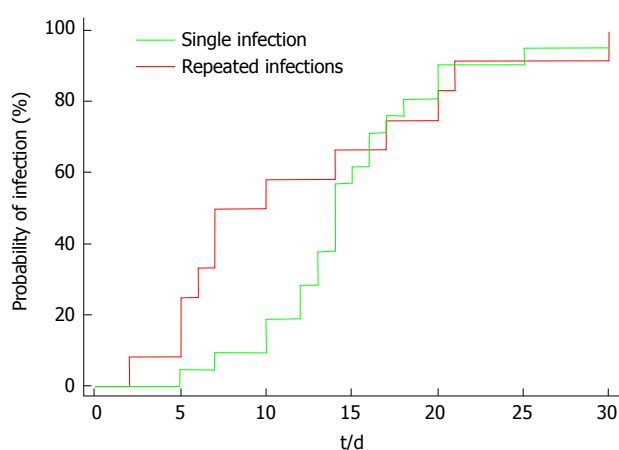
In the present study, the duration of time for abdominal drain placement was considered an independent risk factor for the development of repeated episodes of bacterial infection as confirmed by the multivariate binary logistic regression model. Patients with prolonged drain insertion time had an increased risk of developing recurrent episodes of infection compared to

patients who had less drain insertion time.

Results in our study revealed that the major sites of bacterial infections in patients who experienced a single infection episode were as follows: Bile (28.6%), followed by the drains (23.8%), sputum (14.3%), bloodstream infections (14.3%), urine (9.5%) and lastly wound and ascitic fluid infection (4.8% each). These results were in accordance with another Egyptian multicenter study performed by Mukhtar *et al*<sup>[11]</sup>. In contrast, Kim *et al*<sup>[9]</sup> and Iida *et al*<sup>[10]</sup> revealed that the most dominant bacterial infection was bacteremia, which was catheter-related. El-Araby *et al*<sup>[11]</sup> showed that the main sites of infection were the chest (24.4%), followed by the bile duct or cholangitis (17.1%), and



**Figure 1** Receiver-operating characteristic curve derived from the multivariate binary logistic regression model for prediction of the occurrence of repeated episodes of infection. AUC = 0.935 (95%CI: 79.1%-99.1%;  $P < 0.0001$ ); sensitivity: 91.7% (95%CI: 61.5%-99.8%); specificity: 81.0% (95%CI: 58.1%-94.6%); PPV: 73.3% (95%CI: 43.8%-92.7%); NPV: 94.4% (95%CI: 72.7%-99.9%). AUC: Area under ROC curve; PPV: Positive predictive value; NPV: Negative predictive value.



**Figure 2** Kaplan-Meier curves for the time-to-infection in patients who suffered from single and repeated episodes of infection. HR = 1.16 (95%CI: 56%-92.4%;  $P = 0.647$ ).

lastly the bloodstream (12.2%). However, Kawecki *et al.*<sup>[12]</sup> revealed that the urinary tract was the main site of infection after LDLT. The discrepancies between the major sites of post-transplant infection between the different centers are most likely related to the variability of the hygienic measures, infection control programs, as well as the peri-, intra- and post-operative disparities.

In the current study, the most common isolated organisms were the gram-negative bacteria for both single and repeated episodes of infections, and these results were consistent with El-Araby *et al.*<sup>[11]</sup> and Linares *et al.*<sup>[13]</sup>. Shi *et al.*<sup>[14]</sup> reported the same results and explained that the prevalence of gram-negative bacteria may be because these bacteria are inhabitants of the digestive tract. In the current study, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were found to be the most common organisms in the

**Table 7** Results of the Kaplan-Meier analysis for time to infection in patients who suffered from single and repeated infection episodes

	Single infection episode ( $n = 21$ )	Repeated infection episodes ( $n = 12$ )
Median time to infection (d)	14 (95%CI: 13-16)	8.5 (95%CI: 6-17)
Hazard ratio	1.16 (95%CI: 56-2.40)	
Log-rank test	$P$ value = 0.647	

single infection episode group (19% each), followed by methicillin resistant *Staphylococcus aureus* (MRSA) and coagulase-negative *Staphylococcus aureus* (14.3% each), and *Klebsiella* species and *E. coli* (9.5% each). These results were in accordance with Zhong *et al.*<sup>[15]</sup>. However, Sganga *et al.*<sup>[5]</sup> and Iida *et al.*<sup>[10]</sup> concluded that *Pseudomonas aeruginosa* was the most common isolated organism.

At present, MDR organisms are the most common causes of nosocomial infections in post-LDLT patients. Zhong *et al.*<sup>[15]</sup> found that MDR gram-negative bacilli were isolated in 56% of patients with gram-negative infection, which was in accordance with Shi *et al.*<sup>[14]</sup>, who stated that the three most common pathogens of MDR gram-negative bacilli were *Acinetobacter baumannii*, *E. coli* and *Klebsiella* species. This finding is not fully consistent with a previous report by Pappas *et al.*<sup>[16]</sup> who found that the four most common MDR gram-negative bacilli were *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The difference in the findings between the studies was related to differences in patients' underlying diseases and nosocomial infections.

Our results are consistent to some extent with that of Mukhtar *et al.*<sup>[1]</sup> in their retrospective multicenter Egyptian study on bacterial infections post-LDLT. The authors reported that *Pseudomonas aeruginosa* was the most commonly isolated species (26%), followed by *Klebsiella* (19%), *E. coli* (16%), *Acinetobacter baumannii* (8%), and MRSA (7.7%). In their study, 75% of the gram-negative bacteria were MDR, including 90% of *Acinetobacter baumannii* isolates, 76% of *Pseudomonas aeruginosa* isolates, 57% of *Klebsiella* species isolates, and 53% of *E. coli* isolates.

Our study revealed that most of the gram-negative organisms were found to be resistant to several groups of antibiotics, especially *Klebsiella* species, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, which proved to be MDR. In the study of Zhong *et al.*<sup>[15]</sup>, *Acinetobacter baumannii* displayed resistance to all antibiotic groups, including  $\beta$ -lactams, quinolones, and aminoglycosides and even showed high resistance to carbapenems, including 100% resistance to meropenem and imipenem. *E. coli* was found to be sensitive to aminoglycosides, carbapenems and piperacillin-tazobactam but showed a pattern of resistance to cephalosporins. Among all the antibiotics used in the current cohort, levofloxacin was found to be of

statistical significance regarding its sensitivity in the treatment of repeated episodes of infection.

It is worth mentioning that all infection episodes in our study occurred in the first month post-operative and by applying Kaplan-Meier analysis for time-to-infection. The median time-to-infection was 14 d in the single infection episode group and 8.5 d in the repeated infection episodes group. Similarly, previous studies have reported that the majority of bacterial infections occurred during the first month following LT<sup>[1,17]</sup>.

In conclusion, MDR gram-negative bacterial infections are common post-LDLT. Pre-transplant HCC and duration of drain insertion are independent risk factors for the occurrence of repeated infection episodes.

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## COMMENTS

### Background

Bacterial infections are common following living-donor liver transplantation (LDLT), especially multiple-organism infections. The occurrence of infection following liver transplantation is due to the dysfunction of the patient's defensive mechanisms, as a result of liver cirrhosis and the use of immunosuppressant drugs.

### Research frontiers

The authors assessed 45 patients with hepatitis C virus-related end-stage liver disease for the occurrence of bacterial infections during the first 3 mo post-LDLT. Thirty-three patients (73.3%) suffered from bacterial infections; 21 patients experienced a single episode of infection, and 12 patients experienced repeated episodes of infection. Bile was the most common site for both single and repeated episodes of infection (28.6% and 27.8%, respectively). Multi-drug resistant (MDR) gram-negative bacteria, especially *Klebsiella*, *Acinetobacter* and *Pseudomonas*, were the most commonly isolated bacteria. Pre-transplant hepatocellular carcinoma and duration of drain insertion were independent risk factors for the occurrence of repeated infection episodes.

### Innovations and breakthroughs

This study is a single-center Egyptian study that addresses risk factors, causative organisms and antimicrobial resistance of bacterial infections following LDLT in cirrhotic patients.

### Applications

The findings in this study may help in determining the proper antimicrobial prophylaxis for cirrhotic patients pre-LDLT.

### Terminology

MDR was used to refer to pathogens resistant to three or more classes of the following antibiotics: Extended-spectrum penicillins, 3<sup>rd</sup> generation cephalosporins, quinolones, carbapenems, and aminoglycosides.

### Peer-review

Acceptance of this manuscript for publication is recommended.

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