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Risk factors for *Enterobacteriaceae* bacteremia after liver transplantation

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Summary

Enterobacteriaceae are now the predominant pathogens isolated in bloodstream infections complicating orthotopic liver transplantation (OLT). We conducted a retrospective cohort study of patients who underwent OLT in a University hospital between 01/01/1997 and 31/03/2003 to investigate the risk factors of *Enterobacteriaceae* bacteremia (EB) after OLT. EB was defined as the isolation of an *Enterobacteriaceae* species from at least one blood culture within 3 months following OLT. Pre-, per- and postoperative variables were collected from the medical records and analyzed in relation to EB. Forty (12.5%) of the 320 patients developed EB. The origin of EB was abdominal in 32% of the patients, urinary in 18%, pulmonary in 10%, and primary in the remaining 40% of the patients. Two-thirds of EB occurred within 1 month following OLT. The main pathogens were *Escherichia coli* (42%), *Enterobacter cloacae* (17%) and *Klebsiella pneumoniae* (17%). Susceptibility rates varied from 82.5% for ciprofloxacin to 95% for amikacin. Fourteen patients (35%) with EB died. Variables significantly associated with EB after multivariate analysis were a MELD score >20 (OR: 2.79 [1.24–6.30], $P = 0.013$), transplantation for post-hepatitic B (OR: 4.47 [1.67–11.98], $P = 0.03$) or posthepatitic C (OR: 3.79 [1.59–9.01], $P = 0.03$) cirrhosis, a positive bile culture (OR: 3.47 [1.19–10.13], $P = 0.023$) and return to surgery (including retransplantation) (OR: 2.72 [1.32–5.58], $P = 0.006$). EB is a frequent and severe complication following OLT. Patients grafted for a posthepatitic cirrhosis, with a severe pretransplantation status, with a positive bile culture and those undergoing reoperation have a high risk of developing EB.

Introduction

Bacterial infections are extremely frequent after orthotopic liver transplantation (OLT), occurring in approximately 35–70% of the patients, and are associated with a significant morbidity and mortality [1–4]. Bacteremia represents 30–59% of bacterial infections following OLT [2–8]. In cohorts with a follow-up of 6 months or more, 50–55% of the episodes of bacteremia occurred in the first 3 months after OLT [2,8]. In the 1980s–1990s, Gram-positive pathogens were the leading cause of bacteremia. Nevertheless, as selective digestive decontamination has been abandoned by most transplantation teams, Gram-negative pathogens have emerged as a leading cause

of bacterial infections and especially bacteremia after OLT. In particular, *Enterobacteriaceae,* which are natural inhabitants of the digestive commensal flora in human, are now the predominant pathogens isolated in bloodstream infections complicating OLT [9]. Gram-negative bacteremia is well-described in the general population. It is associated with a high mortality, exceeding 50% in the case of severe sepsis or septic shock. In contrast, there are, to our knowledge, few data concerning *Enterobacteriaceae* bacteremia (EB) and its risk factors in liver transplant recipients. The identification of specific risk factors for EB after OLT has potential implications for the prevention of infection in these patients. Therefore, we undertook the present study in order to describe the characteristics of EB occurring after OLT and to identify independent risk factors of EB during the 3 months following surgery in liver transplant recipients. For this purpose, we conducted a retrospective cohort study including all consecutive liver transplant recipients at Beaujon Hospital (Clichy, France) over a 75-month period.

Patients and methods

Study population

This study was conducted between 1 January 1997 and 31 March 2003 in Beaujon hospital, a 500-bed tertiary-care hospital. During this period, 363 adult patients underwent OLT.

We studied the occurrence of EB and their follow-up within 90 days of transplantation. EB was defined as the isolation of an *Enterobacteriaceae* species in at least one set of blood cultures within 90 days after transplantation. It was considered as primary bacteremia if it was of unknown origin or related to an intravascular catheter, and as secondary bacteremia if the source of the bacteremia was identified, i.e. when the blood isolate was cultured from another infected site (urine; intra-abdominal abscess, bile, or peritoneal fluid; broncho-alveolar fluid or bronchial aspirate). If one patient experienced several episodes of bacteremia, only the first episode was considered. Because we studied the risk factors for developing EB during the 90-day post-OLT period, the 43 patients who died during this period without EB were excluded from the study as one cannot predict whether they would have subsequently developed EB or not. The 320 remaining patients, including those who developed EB within 90 days of OLT and those who survived throughout this period without developing EB, constituted the study population. Patients who developed bacteremia on account of species other than *Enterobacteriaceae* were not excluded from the study population for several reasons: (i) the aim of the study was to investigate specific risk factors for EB compared to no bacteremia or to bacteremia on account of another micro-organism; (ii) this would have introduced a bias towards a lower severity of the non EB group; and (iii) the risk factors would have been nonspecific to EB but to occurrence of a bacteremia.

During the study period, standard perioperative antibiotic prophylaxis consisted of cefoxitin, as previously described [10]. Patients allergic to penicillin received clindamycin and gentamicin. Selective digestive decontamination was not used. Most patients received tacrolimus and corticosteroids as primary immunosuppressive therapy. Doses of tacrolimus were adjusted to achieve plasma levels of 10–15 ng/ml. Corticosteroid therapy consisted of an i.v. methylprednisolone taper from 5 to 0.3 mg/kg/day on postoperative days 1–8 followed by oral prednisone (20 mg/day). From January 1997 to July 1998, cyclosporine was used as alternative to tacrolimus. During the period 1997–2000, patients received azathioprine (2 mg/kg/day) in addition to tacrolimus and corticosteroids. Patients with renal failure at the time of surgery received anti-lymphocyte serum as primary immunosuppression. Blood cultures were performed by the BioArgos automated system (BioRad, Marnes-la-Coquette, France). *Enterobacteriaceae* isolates were identified by the API20E system (bioMérieux, Marcy l'Etoile, France). Susceptibility to antibiotics was tested by the agar disk diffusion test.

Data collection

The following recipient variables were collected from the medical records. Pretransplantation variables were: gender, age, underlying liver disease leading to liver failure, presence of hepatocellular carcinoma, any history of ascites, spontaneous bacterial peritonitis, hepatic encephalopathy or bleeding on account of oesophageal varices, previous major abdominal surgery, mean waiting time on the waiting list, *Staphylococcus aureus* nasal carriage, the following laboratory data at the time of enrolment on the waiting list: serum levels of creatinine, bilirubin and albumin, prothrombin ratio and MELD score. Perioperative variables were: duration of the transplantation procedure, type of graft (whole or reduced-size organ), type of donor (deceased or living-related), number of organs transplanted (liver only or multiple organ transplantation) and requirement for blood (number of units of packed red blood cells transfused). Postoperative variables were: cytomegalovirus (CMV) infection, return to surgery and/or retransplantation, positive bile culture, urinary tract infection.

The following data were recorded for each episode of EB: organism, antimicrobial susceptibility, source of bacteremia, temperature, severity of sepsis, treatment and outcome.

Statistical analysis

Statistical analysis was performed using the SAS version 8.2 program (SAS Institute, Carry, NC, USA). The mean (and its standard error) graft survival in patients having EB was estimated using the Kaplan–Meier approach; death was considered as an event, and patients without graft rejection nor death were censored. Univariate analysis was used to identify associations between each of the pretransplantation, perioperative or postoperative variables described above and occurrence of EB. The chi-squared test and, for small numbers, the Fisher's exact test were used for comparison of categorical data. Continuous variables were compared using the Student's *t*-test. A P-value < 0.05 was considered statistically significant. No adjustment for multiple tests was done because the univariate analysis was a preliminary step for a multivariate analysis. For the multivariate analysis, only variables that demonstrated a P-value < 0.2 in the univariate analysis were tested. A stepwise logistic regression analysis was performed and only variables with a P-value < 0.05 were kept in the final model.

Results

Patients with *Enterobacteriaceae* bacteremia

Enterobacteriaceae bacteremia occurred in 40 (12.5%) of the 320 patients. The clinical characteristics of the patients with EB are shown in Table 1. Bacteremia was diagnosed with a median time of 16 days after transplantation and two thirds (65%) of these episodes occurred within the first month following transplantation.

Sixteen (40%) of EB episodes were primary, including two catheter-related episodes and 14 episodes of unknown origin. For 12 of these 14 episodes, all the microbiological samples (except blood cultures) were

Table 1. Demographic and clinical characteristics of the patients with *Enterobacteriaceae* bacteremia ($N = 40$).

Data/origin of *Enterobacteriaceae* bacteremia	All $N = 40$	Primary* $N = 16$ (40%)	Abdominal $N = 13$ (32%)	Pulmonary $N = 4$ (18%)	Urinary $N = 7$ (10%)
Male, *n* (%)	30 (75)	13 (81.2)	9 (56)	4 (100)	4 (57)
Mean age [range]	45	46.7 [27–59]	40.4 [18–64]	46.5 [44–48]	48.6 [30–68]
Underlying disease, *n* (%)					
Alcohol-induced cirrhosis	4 (10)	1 (6.2)	1 (7.7)	0	2 (28.5)
Posthepatitic cirrhosis	24 (60)	10 (62.5)	6 (46.2)	4 (100)	4 (57.2)
PBC, PSC	4 (10)	2 (12.5)	2 (15.3)	0	0
Fulminant hepatitis	4 (10)	2 (12.5)	1 (7.7)	0	1 (14.3)
Other	4 (10)	1 (6.2)	3 (23)	0	0
Hepatocellular carcinoma, *n* (%)	13 (32)	7 (43.7)	3 (23)	1 (25)	2 (28.5)
Comorbidities, *n* (%)					
Diabetes mellitus	3 (7.5)				
Haemodialysis	3 (7.5)				
Peritoneal dialysis	1 (2.5)				
History of OLT	1 (2.5)				
History of renal tranplantation	3 (7.5)				
Previous major abdominal surgery, *n* (%)	11 (27.5)	4 (25)	6 (46)	0	1 (16)
Mean MELD score [range]	18.4 [3.7–44.2]	19.4 [5.9–44.2]	16.9 [3.7–29.4]	10.9 [7.4–13.8]	22.9 [5.6–34.2]
Mean donor age (years) [range]	44 [10–72]				
Median time between OLT and EB (days) [range]	16 [1–85]	12.5 [1–53]	23 [3–85]	9.5 [4–52]	55 [5–85]
Pathogen, *n* (%)					
Escherichia coli	17 (42.5)	5 (31.2)	6 (46.2)	1 (25)	5 (71.5)
Enterobacter sp.	8 (20)	3 (18.8)	4 (30.8)	1 (25)	0
Klebsiella sp.	11 (27.5)	7 (43.8)	1 (7.7)	1 (25)	2 (28.5)
Other (*Morganella morganii*, *Serratia marcescens*)	4 (10)	1 (6.2)	2 (15.3)	1 (25)	0
Fever, *n* (%)	32 (80)	12 (75)	10 (77)	3 (75)	7 (100)
Septic shock, *n* (%)	16 (40)	5 (45)†	9 (64)	1 (25)	1 (16)
Death, *n* (%)	14 (35)	7 (43.8)	6 (46.2)	0	1 (16)
Median time between EB and death (days) [range]	13 [0–75]	25 [1–75]	2 [0–72]	–	65
Direct link between EB and death, *n* (%)	5/14 (35.7)	1/7 (14.3)	4/6 (66.7)	–	0/1

PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; OLT, orthotopic liver transplantation.
*Including two catheter-related episodes and 14 episodes of unknown origin.
†Data available for only 11/16 patients.

Table 2. Therapeutic options for the 40 patients with *Enterobacteriaceae* bacteremia.

Patient	Micro-organism	Resistance to 3rd generation cephalosporin	Source of bacteremia	Administered antibiotics	Surgery (S)/percutaneous drainage (PD)
24	*Serratia marcescens*	No	Abdominal (hepatic abscess/biliary ischemia/HA stenosis)	Cefpirom + Oflox.	Yes (PD)
63	*Klebsiella pneumoniae*	No	Abdominal (multiples hepatic abscesses/HA thrombosis)	Cefotaxim	No
288	*Morganella morganii*	No	Abdominal (hepatic abscess)	Pip.–Tazo. + Amik.	Yes (PD)
341	*Enterobacter cloacae*	No	Abdominal (infected hematoma + gen. peritonitis + w. abscess)	Imipenem + Ciproflox.	Yes (S)
175	*Enterobacter cloacae*	No	Abdominal (infected hepatic necrosis + gen. peritonitis)	NA	NA
128	*Escherichia coli*	No	Abdominal (gen. peritonitis + w. abscess)	Pip.–Tazo. + Amik.	Yes (S)
207	*Escherichia coli*	Yes (ESBL)	Abdominal (gen. peritonitis)	Imipenem + Amik.	No
168	*Escherichia coli*	No	Abdominal (infected ascitis)	Cefotaxim	No
195	*Escherichia coli*	No	Abdominal (biliary peritonitis)	Pip.–Tazo.	Yes (S)
267	*Enterobacter cloacae* (+MSSA)	No	Abdominal (biliary peritonitis/biliary leak)	Pip.–Tazo. + Ciproflox.	Yes (S)
271	*Escherichia coli*	No	Abdominal (biliary peritonitis/biliary leak + w. abscess)	Pip.–Tazo. + Amik.	No
297	*Escherichia coli*	No	Abdominal (biliary leak + hepatic abscess)	Cefotaxim + Oflox.	No
28	*Enterobacter cloacae*	Yes (ESBL)	Abdominal (bilio-digestive fistula + loc. peritonitis + w. abscess)	Ceftazidime then Imipenem + Amik.	Yes (S)
21	*Escherichia coli*	No	Unknown	Ciproflox.	No
29	*Enterobacter cloacae*	No	Unknown	Ceftazidime + Amik. + Oflox. then Cefepime + Oflox.	No
59	*Escherichia coli*	No	Unknown	Cefotaxim	No
71	*Klebsiella oxytoca* (+MRSA)	No	Unknown	Piperacillin + Ciproflox.	No
108	*Enterobacter aerogenes*	No	Unknown	NA	NA
123	*Klebsiella pneumoniae*	No	Unknown	Pefloxacin	No
163	*Escherichia coli*	No	Unknown	Cefotaxim + Gentamicin	No
166	*Klebsiella pneumoniae*	No	Unknown	Cefotaxim	No
181	*Serratia marcescens*	No	Unknown	NA	NA
193	*Enterobacter cloacae*	No	Unknown	NA	NA
240	*Escherichia coli*	No	Unknown	Piperacillin + Ciproflox. then Cefepim + Amik.	No
260	*Klebsiella pneumoniae*	Yes (*amp C*)	Unknown	NA	NA

Table 2. continued

Patient	Micro-organism	Resistance to 3rd generation cephalosporin	Source of bacteremia	Administered antibiotics	Surgery (S)/percutaneous drainage (PD)
263	*Klebsiella pneumoniae*	No	Unknown	Pip.–Tazo. + Ciproflox.	No
308	*Escherichia coli*	No	Unknown	Pip.–Tazo. + Ciproflox.	No
60	*Klebsiella pneumoniae*	Yes (ESBL)	Urinary	Cefotetan + Amik.	No
176	*Escherichia coli*	No	Urinary	Cefotaxim + Oflox.	No
187	*Escherichia coli*	No	Urinary	Pip.–Tazo. + Gentamicin	No
254	*Escherichia coli*	No	Urinary	Cefotaxim + Ciproflox.	No
276	*Klebsiella oxytoca*	No	Urinary	Pip.–Tazo. + Gentamicin	No
337	*Escherichia coli*	No	Urinary	Amox.–Clav. + Oflox.	No
343	*Escherichia coli*	No	Urinary	Amox.–Clav. + Ciproflox.	No
158	*Serratia marcescens*	No	Pulmonary	Cefotaxim	No
172	*Escherichia coli*	No	Pulmonary	Pip.–Tazo. + Amik.	No
257	*Klebsiella* sp.	No	Pulmonary	Ceftazidime + Amik.	No
259	*Enterobacter cloacae*	Yes (*amp C*)	Pulmonary	Cefepime + Ciproflox.	No
261	*Klebsiella oxytoca*	No	Primary (catheter)	Pip.–Tazo. + Amik.	No
334	*Klebsiella pneumoniae* (+*Candida glabrata*)	No	Primary (catheter)	Piperacillin + Ciproflox.	No

Amik., amikacin; Amox.–Clav., amoxicillin–clavulanate; Amp C, cephalosporinase hyperproducing strain; Ciproflox., ciprofloxacin; ESBL, extended-spectrum β-lactamase enterobacteria; NA, nonavailable data; Oflox., ofloxacin; Pip.–Tazo., piperacillin–tazobactam.

negative, and no infectious focus was identified; for the two remaining episodes, there were multiple positive microbiological samples from different origins, and we thus could not determine if there was a unique source for the bacteremia. The identified portals of entry in the 24 secondary episodes were as follows: abdominal: 13 (32%), urinary tract: 7 (18%), pulmonary: 4 (10%). Among the 13 episodes of abdominal origin, there were eight generalized peritonitis (three of a biliary origin, two following intra-abdominal collections and three of a non identified origin), one localized peritonitis associated with a bilio-digestive fistula, and four liver abscesses (two associated with an obstruction of the hepatic artery). All primary episodes of EB occurred within the first 5 weeks following transplantation, whereas 70% of the episodes of urinary origin occurred after the sixth week. The episodes with an abdominal portal of entry had a homogeneous distribution over the 3-month period.

Eighty per cent of the patients had fever (body temperature > 38 °C) at the time of onset of bacteremia; one patient (2.5%) had hypothermia (temperature < 36 °C), and the remaining patients (17.5%) were afebrile. More than one third of patients (37.5%) developed a septic shock within hours following EB; most of them had EB of abdominal origin.

The predominant pathogen was *Escherichia coli* which accounted for 42% of isolates, followed by *Klebsiella* and *Enterobacter* species (Table 1). Blood cultures were plurimicrobial in four patients (10%) (1 patient: *Enterobacter cloacae* + methicillin-susceptible *S. aureus*, 1: *Klebsiella oxytoca* + methicillin-resistant *S. aureus*, 1: two different strains of *E. cloacae*, 1: *Klebsiella pneumoniae* + *Candida glabrata*).

The susceptibility rates of the 40 isolated strains were as follows: piperacillin–tazobactam: 82.5%, cefotaxime: 87.5%, cefepime: 92.5%, imipenem: 100%, gentamicin: 87.5%, amikacin: 95% and ciprofloxacin: 82.5%. Five (12.5%) isolates were resistant to third-generation cephalosporin, including three isolates with extended-spectrum β-lactamase production and two isolates with cephalosporinase hyperproduction.

All the patients received an appropriate parenteral antibiotherapy, associated if necessary to the removal of infected catheters. Three quarters of the patients received two or more associated antibiotics, for a mean treatment time ranging from 10 to 14 days, depending on the source of the bacteremia. Return to surgery and percutaneous drainage of an abdominal abscess were necessary in five and two patients, respectively. The therapeutic options are detailed in Table 2.

Fourteen patients (35%) with EB had died 90 days after OLT. For these 14 patients who died, the median

Table 3. Clinical data for the 14 patients with *Enterobacteriaceae* bacteremia (EB) after orthotopic liver transplantation (OLT) who died.

Patient	Time between OLT and death (days)	Time between EB and death (days)	Cause of the death	Direct link between EB and death
28	59	56	Haemorrhagic and septic shock	No
29	18	15	Septic shock (candidemia)	No
60	149	65	Multiorgan failure (candidemia)	No
108	3	3	Cerebral death (OLT for fulminant hepatitis)	No
128	4	1	Septic shock	Yes
175	34	0	Septic shock, liver infarcts	Yes
181	19	11	Septic shock	Yes
193	46	34	Septic shock, massive digestive haemorrhage	No
195	6	1	Septic shock	Yes
240	88	75	Septic shock (pneumonia)	No
260	3	1	Cerebral death (OLT for fulminant hepatitis)	No
263	36	33	Haemorrhagic shock and multi organ failure	No
288	37	3	Septic shock and multi organ failure	Yes
341	159	72	Septic shock (pneumonia)	No

time between bacteremia and death was 13 days (range 0–75 days) and death was attributed to EB itself in five of 14 patients (Table 3). The mean graft survival estimated from all the 40 patients with EB was 258 days (SE = 31).

Risk factors analysis

The characteristics of the patients both with and without occurrence of EB were compared in Table 4. Variables significantly associated with EB compared to no or other bacteremia in the univariate analysis were a return to surgery and/or retransplantation ($P = 0.004$) and a positive bile culture ($P = 0.034$).

The 11 variables with a P-value < 0.2 in the univariate analysis were tested in the multivariate analysis. For the variable 'underlying liver disease', which was divided in six classes, we first performed a univariate stepwise logistic regression analysis, which showed that the only items that differed from others were posthepatitic B and posthepatitic C cirrhosis. Thus, underlying liver disease was defined as a variable with three classes in the multivariate analysis: transplantation for posthepatitic B cirrhosis, transplantation for posthepatitic C cirrhosis and others (taken as the reference class). In the final model, a MELD score > 20, transplantation for posthepatitic B or C cirrhosis, return to surgery and/or retransplantation, and a positive bile culture were found as independent predictors of EB (Table 5).

Discussion

In this cohort, we identified a high incidence (12.5%) of EB in the 3 months following liver transplantation. The three predominant pathogens were *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. In a large American surveillance program in 1997 [11], which studied 4076 community- and healthcare-associated Gram-negative bacteremia, the predominant pathogens were *E. coli* [accounting for 41% of Gram-negative bacteria (GNB) and 54% of *Enterobacteriaceae*], *Klebsiella* spp. (17.9% of GNB and 23% of *Enterobacteriaceae*), *Pseudomonas aeruginosa* (10.6% of GNB) and *Enterobacter* spp. (9.4% of GNB and 12% of *Enterobacteriaceae*). A similar frequency was reported in the vast majority of the studies collected in 1993 in a large review on Gram-negative sepsis [12], and in more recent publications [13–15]. We deliberately restricted our study to *Enterobacteriaceae*, and excluded nonfermentative bacteria, on account of the great differences in their infection pathophysiology.

The source of bacteremia was predominantly either unknown or of abdominal origin. In the studies on Gram-negative bacteremia in the general population, the most frequent portal of entry was invariably the urinary tract [15–18]. This confirms our hypothesis that the pathophysiology of EB differs between the general population and liver-transplant patients. After liver transplantation, early EB appears to be essentially on account of bacterial translocation from the digestive tract, to bacterial colonization of a normally sterile site such as the biliary tract by the intestinal flora, or to intra-abdominal infection secondary to surgery.

A multiple logistic regression model was used to identify risk factors associated with EB. The results show that a MELD score > 20, transplantation for posthepatitic B or C cirrhosis, a return to surgery and/or a retransplantation, and a positive postoperative bile culture were independently associated with an increased risk of EB within the 3 months following liver transplantation.

In the literature, we found no data showing a link between transplantation for posthepatitic cirrhosis and an

Table 4. Comparison of patients with or without occurrence of *Enterobacteriaceae* bacteremia.

Variable	Without *Enterobacteriaceae* bacteremia (*N* = 280)	With *Enterobacteriaceae* bacteremia (*N* = 40)	*P*-value
Male gender, *n* (%)	183 (65.3)	30 (75)	0.23
Mean age (years)	47.4	45	0.18
Underlying liver disease, *n* (%)			0.07
Alcohol-induced cirrhosis	62 (22.1)	4 (10)	
Posthepatitic B cirrhosis	32 (11.4)	9 (22.5)	
Posthepatitic C cirrhosis	71 (25.4)	15 (37.5)	
Primary biliary cirrhosis, primary sclerosing cholangitis	28 (10)	4 (10)	
Fulminant hepatitis	28 (10)	4 (10)	
Other	59 (21.1)	4 (10)	
Hepatocellular carcinoma, *n* (%)	85 (30.3)	14 (35)	0.55
Ascites, *n* (%)	140 (51.2)*	21 (52.5)	0.89
Spontaneous bacterial peritonitis, *n* (%)	34 (12.4)*	5 (12.5)	1.00
Hepatic encephalopathy, *n* (%)	77 (28.2)*	15 (37.5)	0.23
Oesophageal varices bleeding, *n* (%)	56 (20.5)*	11 (27.5)	0.31
Previous major abdominal surgery, *n* (%)	82 (29.6)†	12 (30)	0.96
Mean serum creatinine level (μmol/l)	102.5	141.2	0.09
Mean serum bilirubin level (μmol/l)	94.2	121.4	0.49
Mean serum albumin level (g/l)	35.1	35.7	0.61
Mean prothrombin rate (%)	57.7	56.1	0.72
Mean MELD score	15.8†	18.4	0.10
MELD score > 20, *n* (%)	68 (24.6)	15 (37.5)	0.09
MSSA nasal carriage, *n* (%)	53 (18.9)	9 (23.1)§	0.62
MRSA nasal carriage, *n* (%)	18 (6.4)	0 (0)§	0.14
Mean time on the waiting list (days)	141.8	109.5	0.38
Other transplanted organ, *n* (%)	13 (4.6)	5 (12.5)	0.06
Reduced-sized graft, *n* (%)	14 (5)	2 (5)	1.00
Living-related donor, *n* (%)	33 (11.8)	8 (20)	0.15
Median duration of surgery (hours)	10	10	0.52
Number of packed red blood cells transfused	3.7	4.2	0.16
CMV infection, *n* (%)	19 (5.9)	5 (12.5)	0.20
Return to surgery and/or retransplantation, *n* (%)	70 (25.4)¶	19 (47.5)	0.004
Enterobacteriaceae positive bile culture, *n* (%)	15 (5.4)	6 (15)	0.034
Enterobacteriaceae urinary tract infection, *n* (%)	86 (30.7)	14 (35)	0.58

*Data available for only 273 patients without *Enterobacteriaceae* bacteremia.
†Data available for only 277 patients without *Enterobacteriaceae* bacteremia.
§Data available for only 39 patients with *Enterobacteriaceae* bacteremia.
¶Data available for only 276 patients without *Enterobacteriaceae* bacteremia.

increased risk of infection. We have no clear explanation for this association.

There are several reports evaluating the utility of the pretransplant MELD score in predicting the outcome after OLT, whose results are discordant [19–25, review in 26]. Nevertheless, none of them specifically studied the value of the MELD score in predicting infections after OLT. Thus, this is the first report demonstrating an independent link between a high pretransplantation MELD score (>20) and an increased infectious risk (here: EB).

Two previous reports showed that a return to surgery after OLT was a risk factor of infection in general [1], and of bacteremia in particular [27]. Moreover, in

Table 5. Variables associated with the occurrence of *Enterobacteriaceae* bacteremia in the multivariate analysis.

Variable	OR (95% confidence interval)	*P*-value
MELD score > 20	2.79 (1.24–6.30)	0.013
Underlying liver disease		
Posthepatitic B cirrhosis	4.47 (1.67–11.98)	0.003
Posthepatitic C cirrhosis	3.79 (1.59–9.01)	0.003
Return to surgery and/or retransplantation	2.72 (1.32–5.58)	0.006
Enterobacteriaceae positive bile culture	3.47 (1.19–10.13)	0.023

another study, regrafting was identified as the unique risk factor of a major infection after OLT [28]. This is in agreement with our hypothesis of bacterial translocation from the gut flora, or a surgical complication being the predominant mechanisms of EB after OLT.

We identified a link between a positive bile culture growing an *Enterobacteriaceae* species and the risk of bacteremia. Bile samples were taken via a drainage tube (T-tube in patients having one, or abdominal drainage tube when there was a bile leak), or during surgery when necessary. Therefore, as all the patients did not have a biliary drainage, we could not estimate the rate of bacterial colonization and adequately compare the incidence of bacteremia in patients with or without a positive bile culture. In our cohort, an *Enterobacteriaceae* positive bile culture concerned a small number of patients ($n = 21$); however, among those, nearly one-third (6/21) developed EB. Thus, a positive bile culture could reflect the presence of a T-tube (which has been previously identified as a risk factor of bacteremia of abdominal origin after OLT [29]), or of postoperative biliary complications such as a bile leak.

These results are concordant with a previous report studying the significance of aerobic Gram-negative bacilli in clinical specimens after OLT [30]. Among 284 patients undergoing OLT, only nine (3%) demonstrated a positive bile culture growing an *Enterobacteriaceae* species. Among those, three patients (33%) experienced a biliary tract infection (but the presence of a potential secondary bacteremia was not specified). Despite the rarity of these complications, their severity and their consequences on the graft and patient survival are well described. We thus suggest a systematic appropriate antibiotherapy in case of a positive bile culture, though a significant association between a positive bile culture and EB needs further prospective data to be confirmed.

Authorship

CB: collected the clinical data and wrote the paper. FB: collected bacteriological data. FD: charge of the patients. SR: performed the statistical analysis. JB: operated the patients. FM: designed and supervised the statistical analysis. BF: designed the study and wrote the paper.

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