Improving efficacy and reducing adverse effects of immunosuppression after liver transplantation

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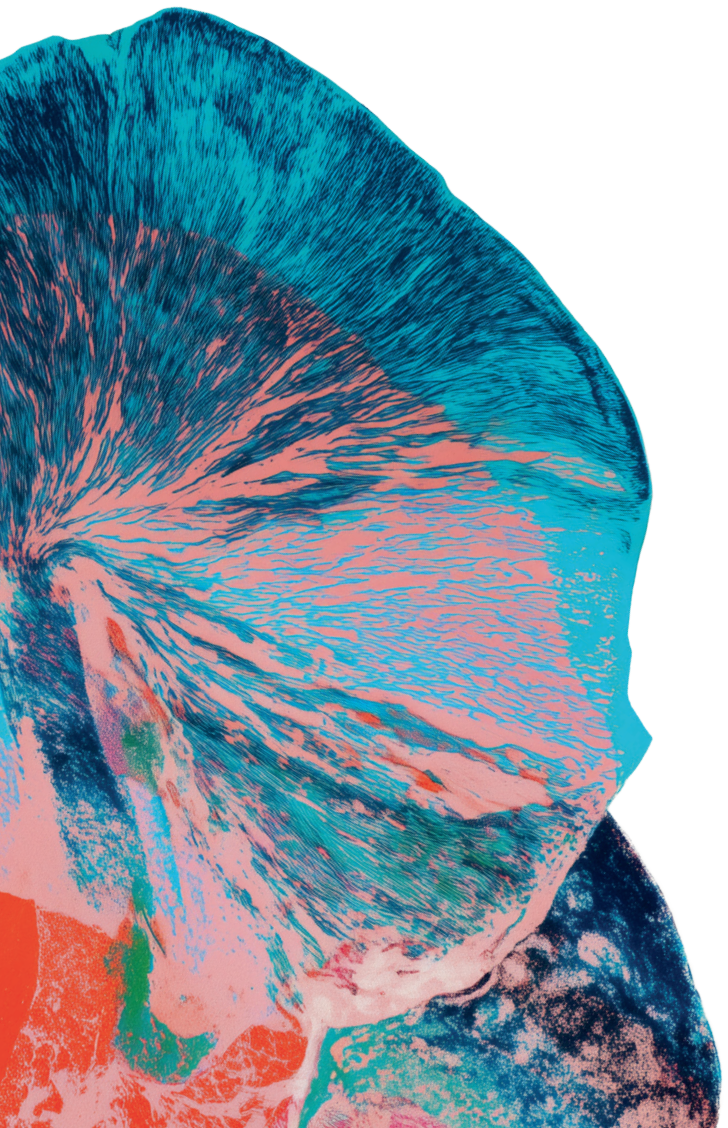
CHAPTER 7



BACTERIAL INFECTIONS AFTER LIVER TRANSPLANTATION AND THE ROLE OF ORAL SELECTIVE DIGESTIVE DECONTAMINATION. A RETROSPECTIVE COHORT STUDY

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Transplant Proc. 2024;56(2):427-433

Abstract

Background
Bacterial infections are common after liver transplantation (LT) and cause serious morbidity and mortality. In our center, prolonged selective digestive decontamination (SDD) is standard of care, which may lead to a reduced number and severity of bacterial infections. The aim of the current study was to investigate bacterial infection rates, the causative pathogens, localization and the possible influence of SDD within the first year after LT.

Methods
A retrospective single-center cohort study was performed. Patients within their first year after LT between 2012 – 2017 were included. Patients received SDD for 3 weeks immediately after LT. The type of infection, bacterial subtype, CSI-classification, severity and potential interventions were recorded.

Results
186 patients were included in the study. 78 patients (41.9%) had a bacterial infection within the first year after LT. The most common types of infection were cholangitis (25.8%) and secondary infected abdominal fluid collections (25.3%). The most common bacteria were Gram-positive enterococcal- (36.5%) and Gram-negative enterobacterial species (34.2%). 35.5% of the infections occurred within the first month after LT, mainly caused by Gram-positive bacteria (76.7%).

Conclusion
Cholangitis and infected abdominal fluid are the most common types of infection within one year after LT, mainly caused by enterococcal- and enterobacterial species. Within the first month after LT, infections were mostly caused by Gram-positive bacteria, which could be a consequence of protocol use of SDD. The results can be used for the choice of empirical antibiotic therapy, based upon the most common types of bacteria and time frame after LT.

Background

Liver transplantation (LT) can be a lifesaving treatment for patients with end-stage liver disease with a one- and five year survival rate of 90% and 80%, respectively[1]. One of the challenges after LT is the handling of infections. A previous study estimates that 80% of the patients will suffer from at least one infection within the first year after LT[2]. These infections lead to significant morbidity and mortality[3]. Risk-factors for post-transplant infections are well-defined, but often multifactorial and difficult to manage[4].

Up to 70% of post-transplant infections are caused by bacteria, and of these bacterial infections, 40% have an onset within the first month after LT[5-7]. Half of these early infections are from abdominal origin (hepatic abscesses, cholangitis, infected fluid collections or peritonitis), followed by septicemia (34%), pulmonary infections (31%) and wound problems (10%)[3,6,7]. Intra-abdominal infections are associated with transplant failure and re-transplantation[5,8].

Infections in LT patients can be less symptomatic due to the use of immunosuppression, which can cause a diagnostic delay, potentially leading to a more serious course of the infection[4,7].

During and on the first day after LT, the use of prophylactic antibiotics is considered as standard of care in most centers[10,11]. Earlier studies suggested that the use of oral selective digestive decontamination (SDD) directly after LT may be beneficial; this was based on the finding that up to 67% of early post-transplant bacterial infections are caused by Gram-negative bacteria[3,9]. On the other hand, SDD may lead to antibiotic resistance in Gram-positive bacteria[4,9]. In the overall intensive care unit (ICU) population, Gram-negative bacterial infections and mortality can be reduced by the use of SDD[12]. However, previous systematic reviews are inconclusive regarding the beneficial effect of protocol SDD usage after LT[13,31].

In our transplant center, prophylaxis with SDD for a period of three weeks immediately after LT has been standard of care since 1994. This retrospective study investigated infections and bacterial species within the first year after LT in a single center using protocol SDD.

Methods

Patients and study design
We performed a single center, retrospective cohort study. All adult patients who underwent a first orthotopic LT between 2012 and 2017 at the Leiden University

Medical Center were included. Patients with previous or concomitant organ transplantation were excluded.

Immunosuppressive therapy was initiated according to protocol, with basiliximab induction and post-operative treatment with calcineurin-inhibitors (CNI's, mostly tacrolimus) and prednisolone, in some cases combined with mycophenolate mofetil (MMF), sirolimus or everolimus.

The standard antibiotic prophylaxis for LT consisted of intravenous cefazolin, penicillin, metronidazole and gentamicin from start of operation until 24 hours post-operatively. The prophylaxis could be adapted in case of allergies, or in case of colonization with known bacteria with resistance to certain antibiotics.

All patients received SDD during a period of 3 weeks after transplantation, with the first dose given immediately before LT. SDD consisted of a combination of oral norfloxacin, amphotericin B and polymyxin/neomycin. In addition, intubated patients received orabase (2% gentamicin/ colistin/vancomycin) and intravenous cefotaxime for a period of four days.

Because of the retrospective nature of the study with existing data and the consent of patients to use the data, the institutional review board waived the need for further consent. This study complied with the latest version of the Declaration of Helsinki. The data will be made available on request.

Evaluations and definitions
Patient characteristics like age, sex, LT indication, MELD-score, type of donor organ, ischemia-times, operation duration and hospitalization time and microbiological results for all proven bacterial infections within the first year after LT were extracted from electronic patient records and the transplant database.

The criteria for Clinically significant bacterial infections (CSI), according to the Centers for Disease Control and Prevention, were used to define clinically significant bacterial infections[14]. All infections with a positive culture and who met the CSI criteria were included. The associated bacterial species was recorded, along with the type of infection, antibiotic treatment, potential intervention and clinical outcome. Clinical suspicion of an infection without a positive culture were not included.

Regarding the type of infection, a distinction was made between an infected abdominal collection and infected ascites. Ascites was considered as diffuse abdominal fluid, whereas an abdominal collection had to be clearly localized. Biliary peritonitis was defined by any abdominal fluid collection with proven

high bilirubin levels. A positive blood culture without any overt localized infection was called bacteremia. Any complications related to the infection were scored according to the Clavien-Dindo classification[15].

Endpoints
The primary endpoint of the study was infection type and bacterial species.

Secondary endpoints were intervention type, infection related complications, re-transplantation, one-year mortality and the incidence of infection related to time after LT. Four different time periods were defined: LT < 1 month, 1-3 months after LT, 4-6 months after LT, 7-12 months after LT.

Statistical analysis
Categorical data were reported as frequency (percentage), and continuous data were reported as mean with standard deviation (SD). All of the data was collected and analyzed by SPSS Statistics 25 (IBM, Chicago IL, USA).

Results

Patients
Between 2012 and 2017, 205 patients underwent LT in our center. Nineteen patients were excluded based on the defined criteria: 12 patients with a combined kidney-liver transplantation, 4 auxiliary liver transplantations, 2 living related liver transplantations and 1 patient with a previous stem cell transplantation.

All other 186 patients were included in this study. Patient characteristics are shown in Table 1. The majority of patients were male (71.5%), with a median age of 57 years. 171 patients (92%) underwent their first LT, 15 patients (8%) were re-transplanted due to graft failure. The most common underlying liver disease was hepatocellular carcinoma (HCC) (37.4%), followed by cholangiopathies (22.5%) and alcoholic liver disease (15.1%). The two different donor types, donation after brain death (DBD) and donation after circulatory death (DCD) were relatively even distributed: 52.2% versus 47.8% respectively.

Endpoints

Primary endpoints
Within the first year of LT, 78 patients (41.9%) developed 186 bacterial infections. The most common type of infection was cholangitis (n = 48; 25.8%), followed by infected abdominal collections (n = 47; 25.3%) and urinary tract infections (n = 23; 12.4%). The majority of these infections were caused by Gram-positive Enterococcus species

(*Enterococcus faecium* 25.3%, *Enterococcus faecalis* 11.2%) and Gram-negative enterobacterial species (*Escherichia coli* 11.2%, *Klebsiella pneumoniae* 7.6%).

The most common type of intervention was percutaneous drainage of abdominal fluid collections (23%), followed by biliary drainage (17%) via endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous biliary drainage (PTCD).

Most of the complications were graded as grade 2 (44%) or 3A (40%), according to the Clavien-Dindo classification. All primary endpoints are presented in Table 2.

Table 1. Baseline-characteristics

	Total patients (n = 186)
Male, n (%)	133 (71.5%)
Age, median (spread)	57 (19-72)
DBD (Donation after Brain Death), n (%)	97 (52.2%)
DCD (Donation after Circulatory Death), n (%)	89 (47.8%)
MELD-score (Matched MELD), median (spread)	24 (6-40)
MELD-score (Lab MELD), median (spread)	13 (6-40)
Underlying liver disease	5 (2.6%)
Viral hepatitis (HBV[1], HCV[2]), n (%)	69 (37.4%)
Hepatocellular carcinoma, n (%)	42 (22.5%)
Cholangiopathies (PSC[3], PBC[4], ITBL[5], CCA[6]), n (%)	7 (3.7%)
Auto-immune hepatitis, n (%)	28 (15.1%)
Post-alcoholic liver disease, n (%)	11 (5.9%)
Metabolic disorders (NASH[7], Wilson, A1ATD[8]), n (%)	6 (3.2%)
Vascular liver disease (Budd-Chiari, HAT[9]), n (%)	9 (4.9%)
Acute liver failure or ACLF, n (%)	8 (4.2%)
Others, n (%)	
Ischemia times	
Donor warm ischemia time in minutes, median (range)	14 (6-174)
Cold ischemia time in minutes, median (range)	527 (270-1089)
Warm ischemia time in minutes, median (range)	35 (18-102)
Operation duration in minutes, median (range)	315 (153-590)
Hospitalization duration in days, median (range)	14 (6-174)

[1] Hepatitis B virus, [2] Hepatitis C virus, [3] Primary sclerosing cholangitis, [4] Primary biliary cholangitis, [5] Ischemic type biliary lesions, [6] Cholangiocarcinoma, [7] Non-alcoholic steatohepatitis, [8] Alfa-1 antitrypsin deficiency, [9] Hepatic artery thrombosis

Table 2. Bacterial infections within the first year of LT (n = 186)

Characteristics	**Total**
Number of patients with an infection	78 (41.9%)
DBD recipients with an infection	42 (53.8%)
DCD recipients with an infection	36 (46.2%)
One-year overall mortality	16 (8.6%)
Number of retransplantation within 1 year	11 (5.9%)
Infection type	48 (25.8%)
Cholangitis	
Infected abdominal fluid collection	47 (25.3%)
Urinary tract infection	23 (12.4%)
Infected ascites	17 (9.1%)
Pneumonia	14 (7.5%)
Biliary peritonitis	14 (7.5%)
Wound infection	10 (5.4%)
Bacteremia	4 (2.2%)
Gastro-enteritis	4 (2.2%)
Central line associated infection	3 (1.6%)
Pancreatitis	2 (1.1 %)
Bacterial species	
Enterococcus species	36.5%
Enterococcus faecium	*77 (25.3%)*
Enterococcus faecalis	*34 (11.2%)*
Enterobacterial species	34.2%
Escherichia coli	*34 (11.2%)*
Klebsiella pneumoniae	*23 (7.6%)*
Others	(29.3%)

Data are expressed as n (%)

Secondary endpoints
The one-year survival rate of this group was 91.4%. Eleven patients (5.9%) were re-transplanted within the first year after LT. 35.5% of infections occurred within the first month of LT (period 1), 25.8% between the first and third month (period 2), 24.7% between the fourth and six month (period 3) and 14% between seven and 12 months after LT (period 4).

Infected abdominal fluid collections (24.2%) and ascites (22.7%) were the most common type of infection during period 1. The majority of infections during this time frame were caused by Gram-positive bacteria (76.7%), especially enterococcus species (49%). Infected abdominal fluid collections were also frequently seen (17.4 - 33.3%) during the second, third and fourth period, along with cholangitis (33.3 - 46.2%). Most of the infections during this time frame were caused by Gram-positive (enterococcus) species (22-9 - 37.2%) and Gram-negative (enterobacterial) species (35.2 - 52.1 %). Overall, Gram-positive bacterial infections were frequently seen shortly after LT, whereas most of the later infections within the first year of LT were caused by Gram-negative bacteria. All types of infection, intervention types and severity score per time frame are presented in Table 3a. The associated bacterial species are presented in Table 3b. An overview of all bacterial species, specified for different types of infection can be found in Table 4.

Table 3a. Bacterial infections per time frame

Characteristics	**Period 1** ***< 1 month***	**Period 2** ***1-3 months***	**Period 3** ***4-6 months***	**Period 4** ***7-12 months***
Number of patients with infection	45	31	28	17
Infections per period, n (%)	66 (35.5 %)	48 (25.8%)	46 (24.7 %)	26 (14%)
1 infection	32	19	19	11
2 infections	8	7	4	3
3 infections	3	5	2	3
4 infections	1	0	2	0
5 infections	1	0	1	0
Infection type				
Cholangitis, n (%)	3 (4.5%)	16 (33.3 %)	17 (37 %)	12 (46.2 %)
Infected abdominal fluid collection, n (%)	16 (24.2%)	16 (33.3 %)	8 (17.4%)	7 (27%)
Urinary tract infection, n (%)	5 (7.6%)	8 (16.7%)	8 (17.4%)	2 (7.7%)
Infected ascites, n (%)	15 (22.7%)	1 (2.1%)	0 (0%)	1 (3.8%)
Pneumonia, n (%)	8 (12.1%)	1 (2.1%)	4 (8.7%)	1 (3.8%)
Wound infection, n (%)	6 (9.1%)	1 (2.1%)	3 (6.5%)	0 (0%)
Biliary peritonitis, n (%)	8 (12.1 %)	5 (10.4%)	0 (0%)	1 (3.8%)
Bacteremia, n (%)	3 (4.5%)	0 (0%)	1 (2.2 %)	0 (0%)
Central line infection, n (%)	1 (1.5%)	0 (0%)	1 (2.2%)	1 (3.8%)
Pancreatitis, n (%)	1 (1.5 %)	0 (0%)	1 (2.2%)	0 (0%)
Gastro-enteritis, n (%)	0 (0%)	0 (0%)	3 (6.5%)	1 (3.8%)
Antibiotic treatment, n (%)	62 (34.3%)	47 (26%)	46 (25.4%)	26 (14.4%)
Intervention				
ERCP, n (%)	2 (5.1%)	6 (18.8%)	5 (19.2%)	3 (20%)
Drainage, n (%)	17 (43.6%)	14 (43.8%)	5 (19.2%)	7 (46.7%)
Surgery, n (%)	12 (30.8%)	3 (9.4%)	0 (0%)	0 (0%)
ICU-admission, n (%)	1 (2.6%)	4 (12.5%)	4 (15.4%)	0 (0%)
PTCD, n (%)	0 (0%)	3 (9.4%)	9 (34.6%)	4 (26.7%)
Wound revision, n (%)	6 (15.4%)	1 (3.1%)	2 (7.7%)	0 (0%)
Bronchoalveolar lavage, n (%)	1 (2.6%)	1 (3.1%)	1 (3.8%)	1 (6.7%)
Severity				
Clavien-Dindo score I, n (%)	4 (6.1%)	1 (2.1%)	0 (0%)	0 (0%)
Clavien-Dindo score II, n (%)	31 (47%)	17 (35.4%)	22 (47.8%)	11 (42.3%)
Clavien-Dindo score IIIA, n (%)	18 (27.3%)	23 (48%)	19 (41.3%)	14 (53.8%)
Clavien-Dindo score IIIB, n (%)	13 (19.7%)	2 (4.2%)	0 (0%)	0 (0%)
Clavien-Dindo score IV, n (%)	0 (0%)	5 (10.4%)	4 (8.7%)	0 (0%)
Clavien-Dindo score V, n (%)	0 (0%)	0 (0%)	1 (2.2%)	1 (3.8%)

Data are expressed as n (%)

Table 3b. Bacterial species per time frame

Characteristics	Period 1 *< 1 month*	Period 2 *1-3 months*	Period 3 *4-6 months*	Period 4 *7-12 months*
Gram-positive species				
Enterococcus species	**46 (49%)**	**35 (37.3%)**	**19 (27.9%)**	**11 (22.9%)**
Enterococcus faecalis	13 (13.9%)	12 (12.8%)	3 (4.4%)	6 (12.5%)
Enterococcus faecium	33 (35.1%)	23 (24.5%)	16 (23.5%)	5 (10.4%)
Staphylococcus species	**17 (18.1%)**	**5 (5.4%)**	**1 (1.5%)**	**5 (10.5%)**
Staph. haemolyticus	6 (6.4%)	1 (1.1%)	0 (0%)	3 (6.3%)
Staph. epidermidis	9 (9.6%)	3 (3.2%)	1 (1.5%)	2 (4.2%)
Staph. hominis	2 (2.1%)	0 (0%)	0 (0%)	0 (0%)
Staph. aureus	0 (0%)	1 (1.1%)	0 (0%)	0 (0%)
MRSA	1 (1.1%)	0 (0%)	1 (1.5%)	0 (0%)
Streptococcus species	**4 (4.3%)**	**3 (3.2%)**	**2 (2.9%)**	**2 (4.2%)**
Streptococcus gordoni	2 (2.1%)	2 (2.1%)	0 (0%)	0 (0%)
Streptococcus mitis	1 (1.1%)	1 (1.1%)	2 (2.9%)	2 (4.2%)
Streptococcus oralis	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)
Lactobacillus species	**4 (4.2%)**	**4 (4.2%)**	**3 (4.4 %)**	**0 (0%)**
Lactobacillus paracasei	2 (2.1%)	2 (2.1%)	1 (1.5%)	0 (0%)
Lactobacillus gasseri	2 (2.1%)	2 (2.1%)	2 (2.9%)	0 (0%)
Clostridioides difficile	0 (0%)	0 (0%)	2 (2.9%)	1 (2.1%)
Gram-negative species				
Enterobacter species	**15 (16%)**	**33 (35.2%)**	**31 (45.6%)**	**25 (52.1%)**
Klebsiella pneumoniae	2 (2.1%)	6 (6.4%)	10 (14.7%)	5 (10.4%)
Klebsiella oxytoca	1 (1.1%)	4 (4.3%)	2 (2.9%)	3 (6.3%)
Escherichia coli	6 (6.4%)	12 (12.8%)	9 (13.2%)	7 (14.6%)
Enterobacter cloacae	2 (2.1%)	6 (6.4%)	3 (4.4%)	4 (8.3%)
Citrobacter spp	0 (0%)	0 (0%)	3 (4.4%)	4 (8.3%)
Morganelli morgani	0 (0%)	1 (1.1%)	0 (0%)	0 (0%)
Serratia marcescens	3 (3.2%)	2 (2.1%)	1 (1.5%)	1 (2.1%)
Hafnia alvei	0 (0%)	2 (2.1%)	1 (1.5%)	1 (2.1%)
Proteus mirabilis	1 (1.1%)	0 (0%)	1 (1.5%)	0 (0%)
Campylobacter jejuni	0 (0%)	0 (0%)	1 (1.5%)	0 (0%)
Bacteroidales species	**0 0%)**	**3 (3.2%)**	**0 (0%)**	**0 (0%)**
Prevotella species	0 (0%)	1 (1.1%)	0 (0%)	0 (0%)
Bacteroides fragilis	0 (0%)	2 (2.1%)	0 (0%)	0 (0%)
Mycobacterium tuberculosis	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)
Stenotrophomonas maltophilia	1 (1.1%)	3 (3.2%)	5 (7.4%)	1 (2.1%)
Pseudomonas aeruginosa	6 (6.4%)	7 (7.4%)	2 (2.9%)	1 (2.1%)
Haemophiles influenza	0 (0%)	1 (1.1%)	2 (2.9%)	1 (2.1%)

Data are expressed as n (%)

Table 4: Bacterial species per infection type

	T1[1]	T2[2]	T3[3]	T4[4]	T5[5]	T6[6]	T7[7]	T8[8]	T9[9]	T10[10]	T11[11]
Gram-positive species											
Enterococcus species	**26 (28.9%)**	**42 (50%)**	**10 (33.3%)**	**6 (30%)**	**2 (11.8%)**	**8 (50%)**	**12 (52.2%)**	**2 (25%)**	**2 (40%)**	**1 (100%)**	**0 (0%)**
Enterococcus faecalis	7 (7.9%)	13 (15.5%)	3 (10%)	0 (0%)	1 (5.9%)	3 (18.8%)	5 (21.7%)	1 (12.5%)	1 (20%)	0 (0%)	0 (0%)
Enterococcus faecium	19 (21.1%)	29 (34.5%)	7 (23.3%)	6 (30%)	1 (5.9%)	5 (31.3%)	7 (30.4%)	1 (12.5%)	1 (20%)	1 (100 %)	0 (0%)
Staphylococcus species	**0 (0%)**	**3 (3.6%)**	**0 (0%)**	**3 (15%)**	**1 (5.9%)**	**1 (6.3%)**	**1 (4.3%)**	**1 (12.5%)**	**1 (20%)**	**0 (0%)**	**0 (0%)**
Staph. haemolyticus	0 (0%)	3 (3.6)%	0 (0%)	2 (6.7%)	1 (5.9%)	0 (0%)	1 (4.3%)	1 (12.5%)	1 (20%)	0 (0%)	0 (0%)
Staph. hominis	0 (0%)	0 (0%)	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Staph. aureus	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
MRSA	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)
Streptococcus species	**3 (3.3%)**	**5 (6%)**	**0 (0%)**	**1 (3.3%)**	**0 (0%)**	**1 (6.3%)**	**1 (4.3%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Streptococcus gordoni	1 (1.1%)	4 (4.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Streptococcus mitis	2 (2.2%)	1 (1.2%)	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	1 (4.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Streptococcus oralis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 4: *Continued.*

	T1[1]	T2[2]	T3[3]	T4[4]	T5[5]	T6[6]	T7[7]	T8[8]	T9[9]	T10[10]	T11[11]
Lactobacillus species	**0 (0%)**	**6 (7.1%)**	**0 (0%)**	**2 (6.7%)**	**1 (5.9%)**	**0 (0%)**	**1 (4.3%)**	**0 (0%)**	**1 (20%)**	**0 (0%)**	**0 (0%)**
Lactobacilles paracasei	0 (0%)	2 (2.4%)	0 (0%)	1 (3.3%)	1 (5.9%)	0 (0%)	1 (4.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lactobacilles gasseri	0 (0%)	4 (4.8%)	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)
Clostridioides defficile	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (75%)
Gram-negative species											
Enterobacterial species	**49 (54.4%)**	**21 (25%)**	**16 (53.3%)**	**4 (20%)**	**3 (17.6%)**	**5 (31.3%)**	**5 (21.7%)**	**4 (80%)**	**0 (0%)**	**0 (0%)**	**1 (25%)**
Klebsiella pneumonia	12 (13.3%)	3 (3.6%)	6 (20%)	0 (0%)	0 (0%)	1 (6.3%)	1 (4.3%)	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)
Klebsiella oxytoca	3 (3.3%)	3 (3.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (8.7%)	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)
Escherichia coli	14 (15.6%)	8 (9.5%)	6 (20%)	2 (10%)	0 (0%)	3 (18.8%)	0 (0%)	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)
Enterobacter cloacae	10 (11.1%)	3 (3.6%)	2 (6.7%)	2 (10%)	0 (0%)	0 (0%)	1 (4.3%)	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)
Citobacter spp	6 (6.7%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Morganelli morgani	0 (0%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Serratia marcescens	0 (0%)	2 (2.4%)	1 (3.3%)	0 (0%)	3 (17.6%)	1 (6.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 4: *Continued.*

	T1[1]	T2[2]	T3[3]	T4[4]	T5[5]	T6[6]	T7[7]	T8[8]	T9[9]	T10[10]	T11[11]
Hafnia alvei	3 (3.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Proteus mirabilis	1 (1.1%)	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Campylo bacter jejuni	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)
Bacteroidales species	**1 (1.1%)**	**1 (1.2%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Prevotella species	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bacteroides fragillis	0 (0%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mycobacterium tuberculosis	0 (0%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stenotrophomonas maltophilia	5 (5.6%)	3 (3.6%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)
Pseudomonas aeuroginosa	1 (1.1%)	2 (2.4%)	4 (13.3%)	1 (5%)	7 (41.2%)	1 (6.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Haemophilus influenza	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	2 (8.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Data are expressed as n (%)
[1] Cholangitis, [2] Abdominal abscess, [3] Urinary tract infection, [4] Infected fluid collection, [5] Pneumonia, [6] Wound infection, [7] Biliary peritonitis, [8] Bacteremia, [9] Catheter-related bloodstream infection, [10] Pancreatitis, [11] Gastroenteritis

Discussion

In this retrospective study, we evaluated bacterial infections within the first year of LT, localization, the associated bacterial species and the possible influence of prolonged SDD prophylaxis.

In 41.9% of the patients at least one infection developed within the first year after LT. The majority of these infections (33.5%) occurred within the first month after LT and most of these were infected abdominal collections (24.2%) or infected ascites (22.7%). This finding is in line with previous studies and is related to the recent major surgery and strong immunosuppression directly after LT[6,7]. The majority of infections occurring between four and twelve month after LT were caused by cholangitis. This can be explained by the frequent occurrence of post-transplant cholangiopathy with occurrence of ischemic-type biliary lesions (ITBL) -usually with non-anastomotic biliary strictures-, which become clinically manifest typically during this time frame and which is more frequent in a liver from donation after cardiac death -making up 46% of our population-[5].

Gram-positive enterococcus species and Gram-negative enterobacterial species were responsible for the majority of infections within the first year of LT. Notably, 76.7% of the early infections (within the first month of LT) were caused by Gram-positive bacteria versus 23.3% Gram-negative bacteria. This is probably the result of standard post-operative SDD prophylaxis and differs from an earlier report, which demonstrated a higher (67%) cumulative incidence of Gram-negative infections in the early phase after LT[3]. An important finding was that the majority of the enterococcal infections were caused by *E. faecium*, which is usually resistant to amoxicillin. This has consequences for the empirical treatment of infections.

Infections with Gram-negative bacteria are associated with a higher inflammatory response and more severe sepsis than with Gram-positive bacteria[22], even in immunocompetent patients. Despite this, the use of early post-operative SDD after LT is still under debate. SDD has been proven to reduce Gram-negative bacterial infections and mortality in the overall intensive care unit (ICU) population[12]. Despite this, two systematic reviews were unable to demonstrate an overall beneficial effect of standard SDD use in LT patients in terms of mortality or re-transplantation[13,21]. There is a great heterogeneity between (small) randomized controlled trials[16-20], which all use different definitions of infection, SDD regimen and primary outcome, thus making an overall judgement regarding benefits of SDD difficult.

A shift towards more Gram-positive cultures with SDD administration after LT has been described elsewhere[9,16,19]. The duration of SDD treatment varies throughout the different studies, with starting times ranging from admission on the LT waiting

list until postoperative discharge from the ICU. Duration of SDD also differs between studies. In our center, we use a prolonged prophylaxis of three weeks, starting on the day of surgery. A beneficial effect of this prolonged prophylaxis remains unclear and needs further investigation, although there seems to be a trend to less severe infections during the first month of LT compared to after the first month in our study. Extension of prophylaxis with Gram-positive coverage could reduce early overall infections, but could lead to antibiotic resistance or bacterial overgrowth (including *C. difficile*), which is already a concern in LT patients[5,7,9]. Another interesting finding of our study was the absence of occurrence of *Pneumocystis jirovecii* infections, despite the use of double, and even triple, immunosuppressants.

This study was limited by its retrospective design and lack of randomization for demonstrating a beneficial effect of standard SDD use in LT patients. Possible other limitations of this study were the inclusion of multiple bacterial species in the same positive culture, thereby potentially analyzing non-pathogenic bacteria. Furthermore, patients with clinical signs of infection, but without positive cultures, have been excluded; this could have led to an underestimation of infections.

Nevertheless, this study gives an overview of bacterial infection types and their associated pathogens during the first year after LT, in the context of prolonged post-operative administration of SDD prophylaxis. The follow-up time is significantly longer than in previous studies[16-20], thereby giving a more detailed insight into the course of post-LT infections. The results can be a guidance for the design of future studies with SDD, and may help in daily practice in LT patients. An example could be the use of a more broad Gram-positive empirical treatment for infections in the early phase after LT in a center using SDD.

References

1. Rana A, Ackah RL, Webb GJ, Halazun KJ, Vierling JM, et al. No Gains in Long-term Survival After Liver Transplantation Over the Past Three Decades. Annals of Surgery 2019;269(1):20-27.
2. Kawecki D, Pacholczyk M, Lagiewska B, Sawicka-Grzelak A, Durlik M, Mlynarczyk G, et al. Bacterial and fungal infections in the early post-transplantation period after liver transplantation: etiologic agents and their susceptibility. Transplant Proc. 2014;46(8):2777-81.
3. Vera A, Contreras F, Guevara F. Incidence and risk factors for infections after liver transplant: single-center experience at the University Hospital Fundación Santa Fe de Bogotá, Colombia. Transpl Infect Dis. 2011;13(6):608-15.
4. van Hoek B, de Rooij BJ, Verspaget HW. Risk factors for infection after liver transplantation. Best Pract Res Clin Gastroenterol. 2012;26(1):61-72.
5. Kim SI. Bacterial infection after liver transplantation. World J Gastroenterol. 2014;28(20):6211-20.
6. Blair JE, Kusne S. Bacterial, mycobacterial, and protozoal infections after liver transplantation--part I. Liver Transpl. 2005;11(12):1452-9.
7. Righi E. Management of bacterial and fungal infections in end stage liver disease and liver transplantation: Current options and future directions. World J Gastroenterol. 2018;24(38):4311-4329.
8. Razonable, R. (2015). Infections in transplant recipients. In D. Schlossberg (Ed.), Clinical Infectious Disease (pp. 573-584)
9. Resino E, San-Juan R, Aguado JM. Selective intestinal decontamination for the prevention of early bacterial infections after liver transplantation. World J Gastroenterol. 2016;(26):5950-7.
10. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013;70(3):195-283.
11. Fagiuoli S, Colli A, Bruno R, Craxì A, Gaeta GB, Grossi P, et al. Management of infections pre- and post-liver transplantation: report of an AISF consensus conference. J Hepatol. 2014;60(5):1075-89.
12. Oostdijk EAN, Kesecioglu J, Schultz MJ, Visser CE, de Jonge E, van Essen EHR, et al. Effects of decontamination of the oropharynx and intestinal tract on antibiotic resistance in ICUs: a randomized clinical trial. JAMA. 2014;312(14):1429-1437.
13. Gurusamy KS, Nagendran M, Davidson BR. Methods of preventing bacterial sepsis and wound complications after liver transplantation. Cochrane Database Syst Rev. 2014;(3):CD006660.
14. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988;16(3):128-40.

15. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187-96.
16. Zwaveling JH, Maring JK, Klompmaker IJ, Haagsma EB, Bottema JT, Laseur M, et al. Selective decontamination of the digestive tract to prevent postoperative infection: a randomized placebo-controlled trial in liver transplant patients. Crit Care Med. 2002;30(6):1204-9.
17. Hellinger WC, Yao JD, Alvarez S, Blair JE, Cawley JJ, Paya CV, et al. A randomized, prospective, double-blinded evaluation of selective bowel decontamination in liver transplantation. Transplantation. 2002;73(12):1904-9.
18. Smith SD, Jackson RJ, Hannakan CJ, Wadowsky RM, Tzakis AG, Rowe MI. Selective decontamination in pediatric liver transplants. A randomized prospective study. Transplantation. 1993;55(6):1306-9.
19. Bion JF, Badger I, Crosby HA, Hutchings P, Kong KL, Baker J, et al. Selective decontamination of the digestive tract reduces gram-negative pulmonary colonization but not systemic endotoxemia in patients undergoing elective liver transplantation. Crit Care Med. 1994;22(1):40-9.
20. Arnow PM, Carandang GC, Zabner R, Irwin ME. Randomized controlled trial of selective bowel decontamination for prevention of infections following liver transplantation. Clin Infect Dis. 1996 ;22(6):997-1003.
21. Safdar N, Said A, Lucey MR. The role of selective digestive decontamination for reducing infection in patients undergoing liver transplantation: a systematic review and meta-analysis. Liver Transpl. 2004;10(7):817-27.
22. Abe R, Oda S, Sadahiro T, Nakamura M, Hirayama Y, Tateishi Y, et al. Gram-negative bacteremia induces greater magnitude of inflammatory response than Gram-positive bacteremia. Crit Care. 2010;14(2):R27

Abbreviations

CNI	Calcineurin-inhibitor
CSI	Clinically Significant Bacterial Infections
DBD	Donation after Brain Death
DCD	Donation after Circulatory Death
ERCP	Endoscopic retrograde cholangiopancreatography
HCC	Hepatocellular carcinoma
ICU	Intensive Care Unit
ITBL	Ischemic Type Biliary Lesion
LT	Liver transplantation
MMF	Mycophenolate mofetil
PTCD	Percutaneous biliary drainage
SDD	Selective digestive decontamination