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Frequency, characteristics and impact of multiple consecutive nosocomial infections in patients with decompensated liver cirrhosis and ascites

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Abstract

Background: Nosocomial infections are a particular threat for patients with liver cirrhosis. It is not uncommon that individuals develop even several consecutive infections during a single hospital stay. We aimed to investigate the impact and characteristics of multiple, consecutive nosocomial infections.

Methods: A total of 514 consecutive patients with liver cirrhosis and ascites were included and followed up for 28 days for nosocomial infection, death or liver transplantation (LTx). Laboratory values were assessed at the time of hospitalization as well as at the onset of each new infectious episode.

Results: 58% ($n = 298$) of the patients developed at least one nosocomial infection and in 23% ($n = 119$) even multiple infections were documented during a single hospital stay. Consecutive infections usually occurred shortly after the previous episode. Spontaneous bacterial peritonitis (SBP) was the most common infection. However, the proportion of SBP declined from 43% at the first to only 31% at the third nosocomial infection ($p = 0.096$). In contrast, the likelihood for other, less common types of infection such as blood stream infections increased. Third nosocomial infections were also more likely to be linked to the detection of fungal pathogens (21% vs. 52%; $p = 0.001$). Each additional infectious episode had a dramatic detrimental impact on LTx-free survival that was independent from the stage of liver disease (adjusted-HR: 6.76, $p = 0.002$ for first nosocomial infection; adjusted-HR: 14.69, $p < 0.001$ for second nosocomial infection; adjusted-HR: 24.95, $p < 0.001$ for third nosocomial infection).

Conclusion: In patients with decompensated liver cirrhosis LTx-free survival significantly decreases with every consecutive infectious episode. Development of prevention strategies is urgently required.

Keywords

Liver cirrhosis, multiple infections, nosocomial, fungal, bacterial

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Introduction

Bacterial infections are a common and severe complication in patients with liver cirrhosis.[1] Mortality is increased four times, and up to 30% of patients die within 1 month.[2] Infections are particularly dangerous if acquired during hospitalization, which may partly be explained by the higher risk for multidrug-resistant organisms (MDRO).[1,3]

Liver cirrhosis is frequently accompanied by a complex and so far not completely understood immune

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dysfunction (cirrhosis-associated immune dysfunction, CAID). Patients have a status of chronic systemic inflammation and may show a hyperinflammatory response in the case of bacterial infection, but at the same time also suffer from an impairment of immune defence, which predisposes for bacterial infections.[4,5] On the one hand, structure of reticuloendothelial system is altered. This leads to restricted elimination of pathogens and reduced phagocytosis in the liver.[4,6–9] On the other hand, the synthesis capacity of the liver is limited. Thus, proteins of innate immunity are not sufficiently produced. Furthermore, there is an altered function and frequency of circulating immune cells.[4,6–9] Moreover, intestinal permeability is heightened, especially in patients with portal hypertension and ascites, facilitating bacterial translocation. One reason for this is reduced gut motility. In addition, shunts of portal blood exist, which further predisposes for bacteremia.[10] Overall, the risk for the development of bacterial infections is four to five times higher compared with non-cirrhotic individuals.[5,11]

Hospital treatment further increases the likelihood for infections, as invasive procedures are frequently required in patients with progressive liver disease.[1] Given the particularly high susceptibility for bacterial infections in those with cirrhosis it is not unusual that an individual patient develops even multiple consecutive infections during a single hospital stay.[12,13] While several recent studies put a focus on different aspects of nosocomial infections in patients with cirrhosis, the relevance of multiple consecutive infections has been poorly investigated so far.[14–17] Currently, there are quite limited data available concerning whether a second nosocomial or even third nosocomial infectious episode during the same hospital stay is any different to a first nosocomial episode. It is not well studied whether consecutive nosocomial infections differ in the most frequent site of infection and clinical outcome and may therefore even require a different clinical management strategy.

In this study we aimed to investigate the incidence and clinical characteristics of consecutive nosocomial infectious episodes as well as their impact on survival in patients with decompensated liver cirrhosis. Moreover, we intended to identify risk factors for multiple nosocomial infections to characterize patients who might be at particular need for a close monitoring during hospitalization.

Patients and methods

Patient cohort

All consecutive hospitalized patients in whom a paracentesis was performed between January 2012 and April 2018 at Hannover Medical School were considered for this study. In a first step, patients were identified automatically using the Enterprise Clinical Research Data Warehouse (ECRDW) of Hannover Medical School.[18] Afterwards the following exclusion criteria were applied through a careful manual check of patients' medical records: no sufficient evidence of cirrhosis, malignant tumour other than hepatocellular carcinoma within MILAN criteria, HIV infection, congenital immune dysfunction, history of organ transplantation, secondary intra-abdominal infection, presence of acute viral or community-acquired infection (onset previous to or <48 h after hospital admission), proof of more than one infection at the same day and no sufficient written informed consent.

Data assessment

Laboratory values and medication were automatically extracted from the clinical information systems using the ECRDW-Technology without any media break. All other data were collected by a cautious manual review of the patients' medical records. Liver cirrhosis was diagnosed by ultrasound, FibroScan (≥14.5 kPa), biochemical results and/or liver biopsy. Infection was diagnosed based on clinical symptoms and the following diagnostic criteria and/or the judgement of the treating physician: urinary tract infection (UTI): leukocyturia and/or positive urine cultures (bacteriuria) and/or significant germination number. Pneumonia: evidence of pulmonary infiltrates in X-ray. Spontaneous bacterial peritonitis (SBP): ≥500 nucleus-containing cells/mm^3 ascites fluid. Blood stream infection: positive blood cultures. *Clostridium difficile*-associated colitis: detection of *Clostridium difficile* in stool samples. Infection without identifiable source: start of antibiotic treatment for a suspected bacterial infection. Acute kidney injury (AKI) was diagnosed by an increase in serum creatinine by ≥0.3 mg/dl within 48 h or ≥1.5-fold from baseline within 7 days.[19] Acute-on-chronic liver failure (ACLF) was defined according to the current recommendations of the European Association for the Study of the Liver.[20–22] MDRO were defined as Methicillin-resistant *Staphylococcus aureus*, Vancomycin-resistant Enterococcus and multi-resistant Gram-negative bacteria (3/4MRGN) according to KRINKO (Commission on Hospital Hygiene and Infection Protection at the Robert Koch Institute).[23]

Study design

Differences in the outcome between a first nosocomial, a second nosocomial and a third nosocomial infectious episode. Primary endpoint of the analysis was liver transplantation (LTx) or death (LTx-free survival).

Patients were followed up for 28 days after hospital admission for liver transplantation, death or infection (group one). If the patient developed a nosocomial infection during hospitalization, the patient was censored in group one at that time point and allocated to group two. A new 28-day follow-up was initiated to document the outcome of infection. The same procedure was used for the second nosocomial (group three) and third nosocomial infection (group four). To avoid time biases because of different observation time periods we adjusted the univariate and multivariate analysis to the outcome starting at each individual infectious episode. All laboratory values were newly assessed at the time of each new infection, which was considered as new baseline. Besides the number of the respective nosocomial infection several potential confounders (length of hospital stay, MELD score, albumin, CRP, leukocytes, sodium and platelets at the onset of the respective infection) were integrated into the univariate and multivariate model.

Identifying risk factors for developing a consecutive nosocomial infection. A competing risk analysis was performed using the development of a second nosocomial and third nosocomial infection, respectively, as primary endpoint and handling the event of liver transplantation or death as competing risk. Several potential predictors were included in the multivariate model:

- Laboratory values (assessed at the time of the previous infectious episode): MELD score, CRP, platelets, leukocytes, sodium
- Complications of cirrhosis/infection: AKI and ACLF within 72 h after the onset of the previous infection
- Placement of a catheter: central venous, urinary tract or abdominal
- Selected patient characteristics: sex, age and diabetes mellitus.

Statistics

All analyses except the competing risk analysis were performed using SPSS (IBM SPSS Statistics 25) and Microsoft Excel. Continuous variables are presented as means with standard deviation. Categorical variables are displayed as proportions and Fisher's Exact Test was calculated. Kaplan–Meier curves, univariate and multivariate Cox-Regression (backward stepwise regression) were executed to assess LTx-free survival. All parameters with $p < 0.1$ in univariate analysis were included in multivariate analysis. The 'in-criterion' was 0.05 and the 'out-criterion' was 0.1. Competing risk analysis was implemented for predictors of consecutive infections. This was done in R (crrstep-package).[24–26] Here also backward direction was selected. Further, Akaike's information criterion was chosen as criterion for model selection. To transform the data into hazard ratios and *p*-values crrstep.output was applied.[27]

Ethics

The study was approved by the local ethic committee of Hannover Medical School on 22 June 2018 and executed according to Declaration of Helsinki. All analysed patients provided written consent for the scientific use of their clinical data at the time of hospital admission.

Results

Patient characteristics and frequency of infections

Overall, 1314 consecutive patients were identified automatically and further screened. After applying the predefined exclusion criteria a total of 514 individuals were considered for the final analysis (Figure 1). A minority of the included patients was female (36%), and mean age was 56 years. In most individuals the aetiology of liver cirrhosis was considered to be alcohol-related (46%). Oesophageal varices were present in the majority of patients (76%). A total of 267 patients developed an ACLF and 182 circulation failure during follow-up. Overall, 42% of individuals had no proof of infection and 35% experienced only a single nosocomial infectious episode during the observation period. Of note, 119 out of 514 patients (23%) developed multiple nosocomial infections within the same hospital stay. Evidence of a second nosocomial infection was present in 14% ($n = 74$) of patients, and in 9% ($n = 45$) of the individuals even a third nosocomial infection was documented (Table 1, Supplementary Table 1).

Time interval between consecutive nosocomial infections

Median time to first nosocomial infection after admission to our hospital was 4 days (interquartile range $(IQR)_{25–75}$: 0–8). In 31% of the patients who were initially treated at a different hospital, infection was diagnosed on the arrival day at our centre. Of note, consecutive nosocomial infections usually followed shortly after the previous episode. The second nosocomial infection was diagnosed within a median of 7 days ($IQR_{25–75}$: 3–13) after the first nosocomial infection. Median time interval between the second nosocomial and the third nosocomial infection was 9 days ($IQR_{25–75}$: 4–18) (Supplementary Figure 1).

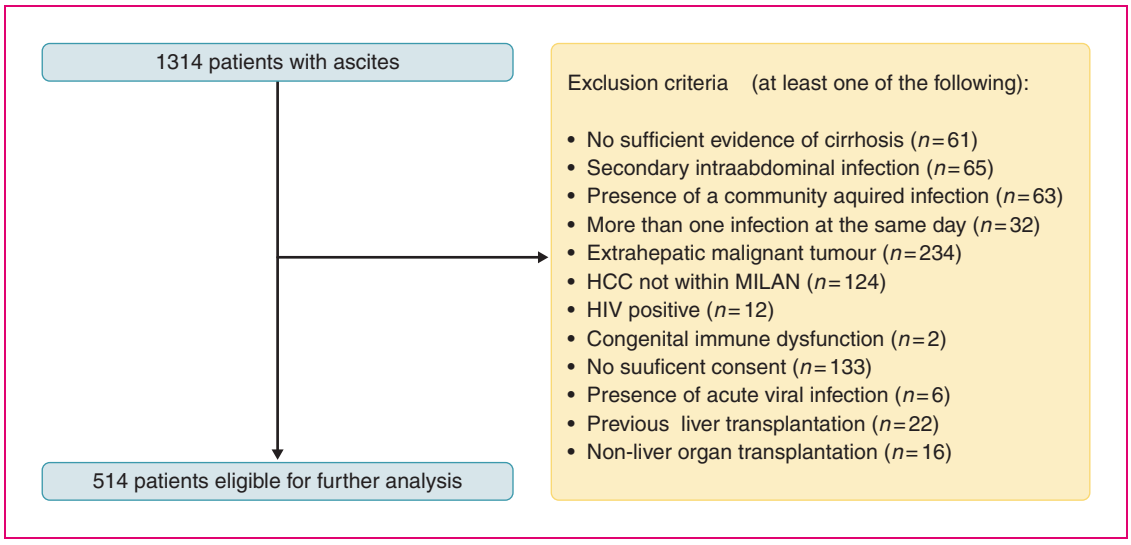

Figure 1. Flowchart of patient recruitment.
HCC: hepatocellular carcinoma; HIV: human immunodeficiency virus.

Differences in the sites of infection between the first nosocomial, second nosocomial and third nosocomial infectious episode

The most prevalent sites of the first nosocomial infection were SBP (43%) and UTI (19%). The third most common type of infection was pneumonia (8%), while in 15% the source of infection could not be clearly identified. At consecutive episodes distribution of infections changed towards other, less common types for cirrhotic patients (e.g. *Clostridium difficile*-associated colitis and skin infection): the frequency of SBP decreased from 43% at the first nosocomial infection to only 31% among the third nosocomial infections ($p = 0.096$). Similarly, 'other' sites of infection than SBP, UTI or pneumonia were detected in only 11% at the first nosocomial but in 27% at the third nosocomial infection ($p = 0.008$) (Supplementary Table 2). Of note, there was a particular increase in the proportion of patients with blood stream infection (4% and 13% of first nosocomial and third nosocomial infections, respectively, $p = 0.020$) (Figure 2).

Differences in the detected pathogens between the first nosocomial, second nosocomial and third nosocomial infection

Overall, a pathogen could be detected in 40% of the infections (in 36% of first nosocomial, in 41% of second nosocomial and in 60% of third nosocomial infections). The most prevalent organisms detected during the first nosocomial infection were Gram-positive bacteria, affecting 73% of the cases. This rate decreased to 67% and 63% for the second nosocomial and third nosocomial infectious episode, respectively. In contrast, there was a significant increase in the detection of fungal organisms from the first nosocomial (21%) to the third nosocomial infectious episode (52%) ($p = 0.001$) (Figure 3, Supplementary Table 3, 4). In a considerable number of patients (33%) multiple different organisms were detected at the same time. Of note, rates of MDRO were rather low and remained relatively stable towards consecutive infectious episode (2.8%, 6.1%, and 3.7%).

Differences in LTx-free survival between the first nosocomial, second nosocomial and third nosocomial infection

LTx-free survival decreased dramatically with each consecutive infection (Figure 4). In the univariate analysis the number of infection (no, first nosocomial, second nosocomial and third nosocomial, respectively) as well as MELD score, CRP, leukocytes and platelets (at time of admission and time of infection, respectively) were associated with LTx-free survival. However, only MELD score (HR: 1.13; $p<0.001$) and the number of infection remained independent predictors of LTx-free survival in the multivariate model (Table 2). A first nosocomial infectious episode was already associated with a more than six-fold increase in mortality (HR: 6.76; $p = 0.002$). For the second nosocomial infection a HR of 14.69 ($p<0.001$) and for the third nosocomial infection a HR of 24.95 ($p<0.001$) were calculated. Likewise, the adjusted risk for LTx or death after a second nosocomial infection was two times higher compared with the first nosocomial episode (HR: 2.12; $p = 0.010$). A similar increase was

Table 1. Baseline characteristics.

Variable	All patients
Total number of patients	514
Sex	
• Female (*n*, %)	187 (36.4%)
• Male (*n*, %)	327 (63.6%)
Age (years)	56.3 (±11.09)
Aetiology of liver cirrhosis	
• Alcohol-related (*n*, %)	235 (45.7%)
• Cryptogenic (*n*, %)	64 (12.5%)
• Viral (*n*, %)	56 (10.9%)
• NASH (*n*, %)	25 (4.9%)
• Cholestatic (*n*, %)	24 (4.7%)
• Other (*n*, %)	58 (11.3%)
• Mixed (*n*, %)	52 (10.1%)
Laboratory values (at admission)	
• MELD score	18.9 (±7.4)
• Albumin (g/l)	27.1 (±6.0)
• Bilirubin (µmol/l)	103.8 (±151.0)
• CRP (mg/l)	31.9 (±36.7)
• INR (Ratio)	1.53 (±0.46)
• Creatinine (µmol/l)	142.1 (±105.2)
• Leukocytes (10^3/µl)	9.2 (±6.6)
• Sodium (mmol/l)	133.9 (±5.6)
• Platelets (10^3/µl)	145.9 (±99.2)
Oesophageal varices (*n*, %)	393 (76.5%)
Diabetes mellitus (*n*, %)	126 (24.5%)
Beta-blockers (*n*, %)	228 (44.5%*,[a])
Proton pump inhibitors (*n*, %)	428 (84.4%*,[b])
Maximal number of infections	
• No infection (*n*, %)	216 (42.0%)
• One nosocomial infection (*n*, %)	179 (34.8%)
• Two nosocomial infections (*n*, %)	74 (14.4%)
• Three nosocomial infections (*n*, %)	45 (8.8%)

Values are expressed as percentage (categorical variables) and mean (continuous variables) and standard deviation; [a]In two patients information on β-blocker intake was missing; [b]In seven patients information on Proton Pump Inhibitor intake was missing.
NASH: Nonalcoholic steatohepatitis; MELD score: Model for End-Stage Liver Disease; CRP: c-reactive protein, INR: international normalized ratio.

calculated for the third nosocomial compared with the second nosocomial infection (HR 1.72; $p = 0.076$). However, this difference closely failed to reach statistical significance after adjusting to other potential confounders in the multivariate analysis (Table 3).

Predictors for development of a consecutive infection

Given the increasing and tremendous hazard of each consecutive infection, we aimed to identify risk factors for the development of a second nosocomial and third nosocomial infectious episode, respectively. Among all considered parameters only female sex (HR: 1.53; $p = 0.023$), MELD score ($p = 0.076$) and CRP ($p = 0.008$) (at the time of the first nosocomial infection) were identified as possible predictors for the onset of a second nosocomial infection in the multivariate competing risk analyses (Table 4). However, the MELD score did not reach statistical significance. Of note, placement of a catheter (central venous, urinary tract or abdominal) had no statistical significant impact.

No clinically valuable predictor for third nosocomial infection was identified in the multivariate model. However, age (HR: 0.97; $p = 0.027$), CRP (HR: 1.00; $p = 0.043$) and platelets (HR: 1.00; $p = 0.024$) were significantly linked to the development of a third nosocomial infection (Table 5).

Discussion

Nosocomial infections represent a particular risk in patients with decompensated liver cirrhosis, as they further complicate hospital treatment and are associated with a high mortality. Given the increased susceptibility for infections in cirrhotic patients it is not uncommon that even multiple infectious episodes occur during a single hospital stay. In this large cohort of patients with decompensated cirrhosis we demonstrated that consecutive infections are in many ways different from the first nosocomial infectious episode. Different sites of infections as well as different microorganisms have to be expected and mortality dramatically increases.

However, the first important result of our study might be that the frequency of multiple nosocomial infections was indeed considerably high. Almost one out of four patients developed at least two different infections during the same hospital stay. Our results are well in line with previous studies by Bajaj et al. and Piano et al. reporting an incidence for a second infection during hospitalization of 24% and 21%, respectively.[12,13] Together these data demonstrate the high clinical relevance of consecutive infections in patients with cirrhosis, although this topic has rarely been investigated so far.

Even more importantly, we were able to demonstrate that each consecutive nosocomial infectious episode is associated with dramatically worse prognosis than the previous one. Of note, the negative impact on survival of each infectious episode was independent from the stage of liver disease as indicated by the MELD score. In a previous well-performed study, Bajaj et al. documented a higher mortality in cirrhotic patients who develop two infections compared with those with only one infection during hospital treatment.[12] However, in the study of Bajaj et al. a significant proportion of the first infectious episodes were attributable to community-acquired infections. In contrast, all second infections were nosocomial acquired.

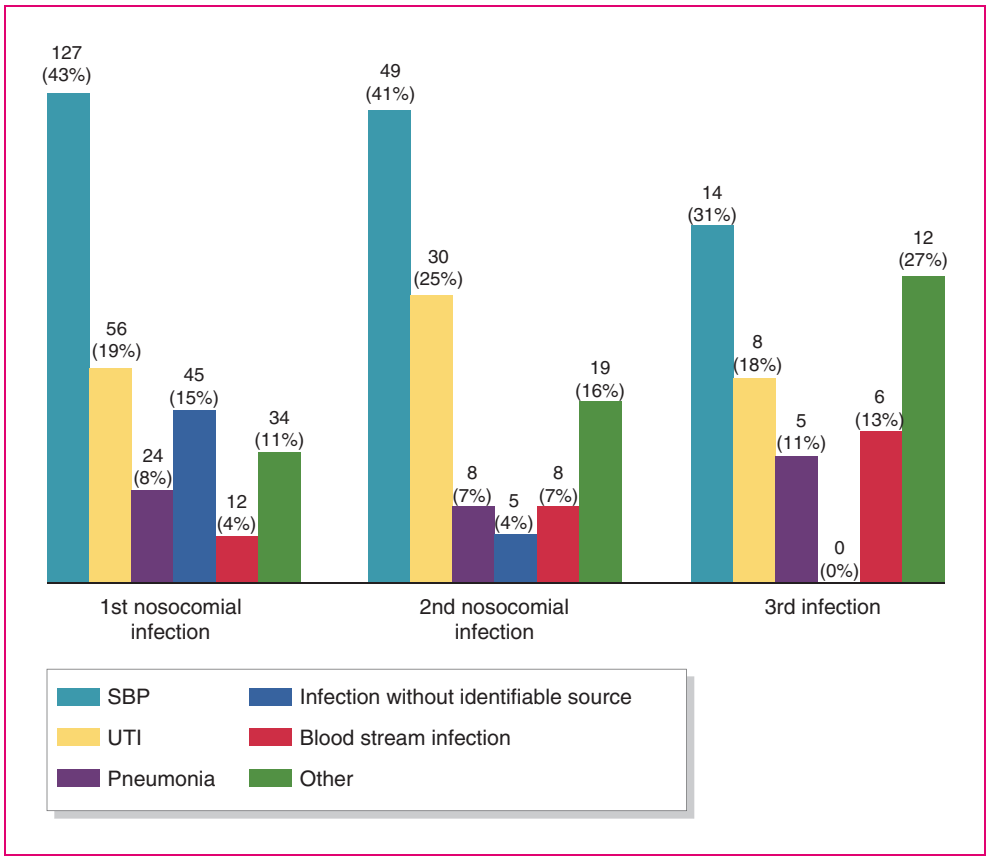

Figure 2. Differences in the sites of infection between the first nosocomial, second nosocomial and third nosocomial infectious episode.

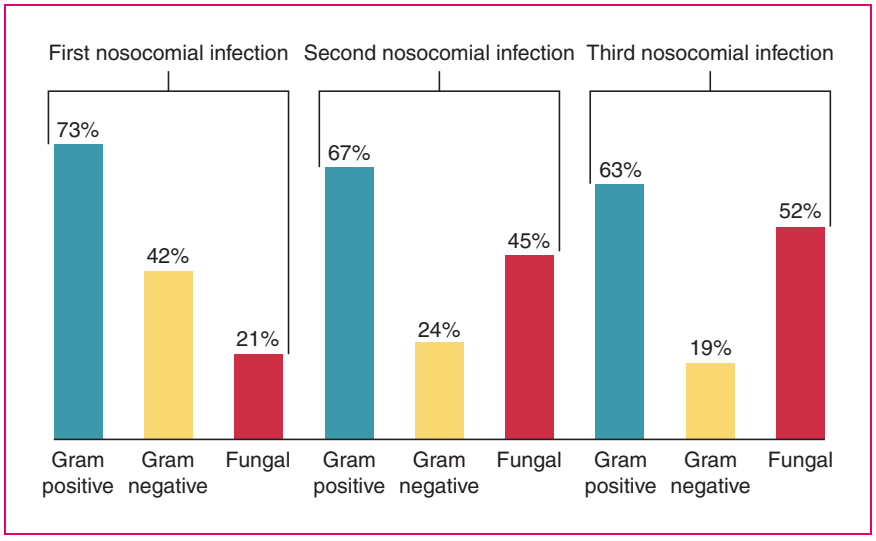

Figure 3. Differences in the detected pathogens between the first nosocomial, second nosocomial and third nosocomial infection. More than 100% possible as several pathogens were detected in some patients.

Thus the higher mortality after the second infection episode could at least partly be explained by the higher frequency of nosocomial infections, which are well known to be more complicated. This potential bias can be excluded for our results, as only nosocomial infections were considered. Further limitations of the study by Bajaj et al. include a longer observation period in those with a second infection, as the outcome

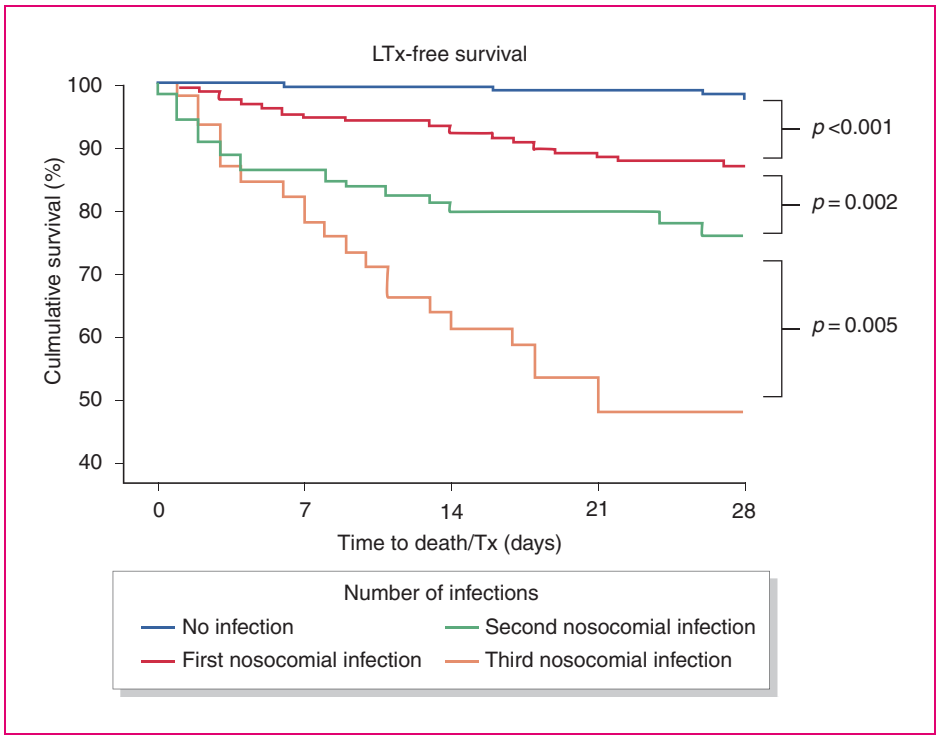

Figure 4. LTx-free survival after onset of nosocomial infection/hospital admission.
LTx: liver transplantation.

Table 2. Univariate and multivariate Cox-Regression of LTx-free survival.

	univariate		Multivariate	
Variable	*p*-value	HR	*p*-value	Adjusted-HR (95% confidence interval)
MELD score	<0.001*	1.165	<0.001*	1.134 (1.009; 1.169)
Albumin (g/l)	0.723	1.009		
CRP (mg/l)	<0.001*	1.008		
Leukocytes (10^3/µl)	<0.001*	1.032		
Sodium (mmol/l)	0.425	1.017		
Platelets (10^3/µl)	0.001*	0.994		
Duration of hospital stay	0.606	1.004		
Number of infections				
• First nosocomial infection	<0.001*	9.407[a]	0.002*	6.760 (2.026; 22.557)[a]
• Second nosocomial infection	<0.001*	22.150[a]	<0.001*	14.692 (4.369; 49.401)[a]
• Third nosocomial infection	<0.001*	49.774[a]	<0.001*	24.952 (7.326; 84.990)[a]

[a]Compared with no infection. MELD score: Model for End-Stage Liver Disease; CRP: c-reactive protein; LTx: liver transplantation.

analysis was focused on the prognosis of the individual patient starting at the time of hospital admission. In contrast, we decided to focus on the individual infectious episode by restarting a new predefined follow-up and reassessing all relevant laboratory values including the MELD score at the onset of each new infection. Finally, the number of patients with a second infection was quite small ($n = 50$) in the study by Bajaj et al. and further infectious episodes were not documented. In this study we were able to observe 119 patients with a second nosocomial infection, and importantly also demonstrated for the first time that a further, third nosocomial infection even leads to an additional impairment of LTx-free survival.

Although all included infections were nosocomial acquired, there were still remarkable differences when comparing the first nosocomial, second nosocomial and third nosocomial episodes that may help to explain the lower survival after consecutive infections. First of all, we documented a shift in the most common sites of

Table 3. Multivariate Cox-regression of LTx-free survival between each infectious episode.

	1st nosocomial infection (vs. no infection)		2nd nosocomial infection (vs. 1st infection)		3rd nosocomial infection (vs. 2nd infection)	
Variable	*p*-value	Adjusted-HR (95% confidence interval)	*p*-value	Adjusted-HR (95% confidence interval)	*p*-value	Adjusted-HR (95% confidence interval)
MELD score	<0.001*	1.154 (1.100; 1.210)	<0.001*	1.145 (1.104; 1.188)	<0.001*	1.092 (1.043; 1.144)
Infection	0.003*	6.156 (1.828; 20.733)	0.010*	2.118 (1.199; 3.741)	0.076	1.717 (0.945; 3.120)
Leukocytes (10^3/µl)					0.049*	1.038 (1.000; 1.078)
Platelets (10^3/µl)					0.141	0.996 (0.991; 1.001)

MELD score: Model for End-Stage Liver Disease; LTx: liver transplantation.

Table 4. Backward multivariate competing risk model for development of a second nosocomial infection.

Variable	*p*-value	Adjusted-HR (95% confidence interval)
Female sex	0.023*	1.531 (1.061; 2.209)
MELD score[a]	0.076	1.019 (0.998; 1.041)
CRP[a] (mg/l)	0.008*	1.003 (1.001; 1.005)

[a]At time of first nosocomial infection; Included parameters: sex, age, diabetes, AKI, ACLF, catheter, MELD, CRP, leukocytes, sodium, platelets. MELD score: Model for End-Stage Liver Disease; CRP: c-reactive protein; AKI: acute kidney injury; ACLF: acute-on-chronic liver failure.

Table 5. Backward multivariate competing risk model for development of a third nosocomial infection.

Variable	*p*-value	Adjusted Hazard Ratio (95% confidence interval)
Age (years)	0.027*	0.972 (0.949; 0.997)
CRP[a]	0.043*	1.005 (1.000; 1.009)
Platelets[a]	0.024*	1.003 (1.001; 1.006)

[a]At time of second nosocomial infection; Included parameters: sex, age, diabetes, AKI, ACLF, catheter, MELD, CRP, leukocytes, sodium, platelets. MELD score: Model for End-Stage Liver Disease; CRP: c-reactive protein; AKI: acute kidney injury; ACLF: acute-on-chronic liver failure.

infection towards more unusual sites like skin infection or *Clostridium difficile*-associated colitis increased during later episodes. Similar data were recently published by Piano et al. for a second infection.[13] It is tempting to speculate that this might increase the risk for a delay in diagnosis, which has been shown to have significant detrimental effects on the prognosis in cirrhotic patients.[28] However, we were unable to provide any evidence for this with our retrospective data set. Of note, consecutive infections were more frequently blood stream infections, which have previously been associated with a particular severe course in patients with cirrhosis.[29,30] Finally, we documented a considerable shift in the detectable pathogens. There was a significant increase in the frequency of the detection of fungal organisms, which have previously been linked to a higher mortality as well as a delayed diagnosis and treatment in patients with cirrhosis.[31–33] It has to be considered that the detection of a fungal pathogen does not necessarily mean that it is also the causing agent. Some of the respective infections might be triggered by undetectable bacteria or viruses. The clinical relevance of the detection of fungal species often remains a matter of debate depending on the detected pathogen and specimen (e.g. Candida species in urine samples), and differentiation between infection and colonization is especially difficult due to the partially altered clinical course of fungal infections. To date, except for histological proven fungal infection, no clear diagnostic criteria demonstrate a reliable proof of invasive fungal infection. However, while they may not always directly cause an infection, any detection of fungal species, for example in urine, might still indicate a more complicated clinical and infectiological course as it has been associated with an overall impaired outcome, for example among critically ill patients.[33–35] Interestingly, there are overall some significant differences regarding the most frequent pathogens detected in our study when comparing with previous studies by Piano et al. and Fernandez et al. In our study we found far more Gram-positive bacteria.[3,13] However, this might be explained by slightly different patient cohorts, regional differences and, importantly, by the fact that only nosocomial infections were considered in our study.

Besides a timely and fitting antibiotic or (maybe) antifungal therapy, it is essential to identify patients at high risk for developing following nosocomial infectious episodes and develop strategies for early diagnosis or, even better, a suitable prophylaxis. For this purpose, a deeper understanding of the pathomechanisms will be needed. Severe infections such as sepsis are associated with a hyperinflammatory response, which also leads to activation of anti-inflammatory signalling. At some stage the anti-inflammatory cascade may overtake, leading to a

status of immunosuppression. Until the level of immune activation returns to a balanced status, patients may be particularly vulnerable for another infectious episode.[36] In patients with cirrhosis this imbalance may be further complicated by the often underlying CAID.[4] Similar effects may occur after ACLF, which is also characterized by hyperinflammatory status and is often triggered by an infection.[22,37,38] As a second nosocomial or third nosocomial infection in our study often occurred shortly after the previous episode, it seems entirely possible that many infections indeed occurred in such an immunosuppressive status, which may further explain the poor outcome. Antibiotic prophylaxis could be discussed and further studied in the future to prevent consecutive infections in vulnerable patients. However, wide use of antibiotics may certainly lead to a further increase in MDRO, which is already a tremendous and emerging problem in these patients.[3,13] Thus, a careful and individualized approach would be necessary. Unfortunately, no markers have been established so far that reliably reflect the immune status of cirrhotic patients before or after an infection or ACLF. Interestingly, our data suggest a higher risk for second nosocomial infection in female patients, which is in line with other reports suggesting a higher risk for death in females in the case of advanced liver dysfunction.[39] However, our results also demonstrate that relying exclusively on clinical parameters might be insufficient to accurately select patients for such a strategy. Thus, identification of new valid biomarkers will be an important need for the future.

The main limitation of our study is the retrospective single-centre design. Therefore, our data might not necessarily reflect the situation in other treatment centres, in particular with regard to the most prevalent bacteria, as considerable regional differences have previously been reported.[3] Due to the retrospective design some information is incomplete, and diagnosis of infections as well as the selected therapy may have varied between treating physicians. It seems entirely possible that not all infections were diagnosed according to international recommendations. Furthermore, as a polymorphonuclear cell count was not available at that time in our as well as several other centres, SBP might have been misclassified in a few patients. Moreover, a delay in infection diagnosis may have led to misclassification of healthcare-associated as nosocomial infections in some cases. Finally, the manual validation of the automatically identified patients may have introduced a selection bias. However, we still think that our data provide some valuable implications for clinical care and future research needs.

In summary, we demonstrated that consecutive infections in patients with decompensated liver cirrhosis significantly differ from previous nosocomial episodes. There is an almost two-fold decrease in LTx-free survival after each additional infection. A careful monitoring of cirrhotic patients is required particularly in the timeframe shortly after an infection. Moreover, physicians need to consider more unusual types as well as fungal infections at later episodes and adjust diagnostic and therapeutic procedures. Further studies focusing on predictive biomarkers and suitable strategies to prevent multiple infections in decompensated liver cirrhosis are urgently needed.

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Conflict of interest

The authors have no conflicts of interest to declare.

Ethics approval

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Informed consent

All analysed patients provided written consent for the scientific use of their clinical data at the time of hospital admission.

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Supplemental material

Supplemental material for this article is available online.

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