

World Journal of *Hepatology*

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AIMS AND SCOPE

The primary aim of *World Journal of Hepatology (WJH, World J Hepatol)* is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (ESCI), Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJH* as 2.4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yi-Xuan Cai, Production Department Director: Xiang Li, Cover Editor: Xiang Li.

NAME OF JOURNAL

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

LAUNCH DATE

October 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

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<https://www.wjgnet.com/1948-5182/editorialboard.htm>

PUBLICATION DATE

March 27, 2024

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PUBLISHING PARTNER

Department of Infectious Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

POLICY OF CO-AUTHORS

<https://www.wjgnet.com/bpg/GerInfo/310>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

PUBLISHING PARTNER'S OFFICIAL WEBSITE

http://2yuan.xjtu.edu.cn/Html/Departments/Main/Index_21148.html

Retrospective Study

Retrospective study of the incidence, risk factors, treatment outcomes of bacterial infections at uncommon sites in cirrhotic patients

Sophie Schneitler, Christina Schneider, Markus Casper, Frank Lammert, Marcin Krawczyk, Sören L Becker, Matthias Christian Reichert

Specialty type: Infectious diseases

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Wan X, China

Received: December 6, 2023

Peer-review started: December 6, 2023

First decision: December 19, 2023

Revised: January 2, 2024

Accepted: February 8, 2024

Article in press: February 8, 2024

Published online: March 27, 2024



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Abstract**BACKGROUND**

Bacterial infections (BI) negatively affect the natural course of cirrhosis. The most frequent BI are urinary tract infections (UTI), pneumonia, and spontaneous-bacterial peritonitis (SBP).

AIM

To assess the relevance of bacterial infections beyond the commonly recognized types in patients with cirrhosis and to investigate their relationship with other clinical variables.

METHODS

We retrospectively analyzed patients with cirrhosis and BI treated between 2015 and 2018 at our tertiary care center. BIs were classified as typical and atypical, and clinical as well as laboratory parameters were compared between the two groups.

RESULTS

In a cohort of 488 patients with cirrhosis, we identified 225 typical BI (95 UTI, 73

SBP, 72 pulmonary infections) and 74 atypical BIs, predominantly cholangitis and soft tissue infections (21 each), followed by intra-abdominal BIs ($n = 9$), cholecystitis ($n = 6$), head/throat BIs ($n = 6$), osteoarticular BIs ($n = 5$), and endocarditis ($n = 3$). We did not observe differences concerning age, sex, or etiology of cirrhosis in patients with typical *vs* atypical BI. Atypical BIs were more common in patients with more advanced cirrhosis, as evidenced by Model of End Stage Liver Disease (15.1 ± 7.4 *vs* 12.9 ± 5.1 ; $P = 0.005$) and Child-Pugh scores (8.6 ± 2.5 *vs* 8.0 ± 2 ; $P = 0.05$).

CONCLUSION

Atypical BIs in cirrhosis patients exhibit a distinct spectrum and are associated with more advanced stages of the disease. Hence, the work-up of cirrhosis patients with suspected BI requires detailed work-up to elucidate whether typical BI can be identified.

Key Words: Bacterial infection; Empirical antibiotic therapy; End-stage liver disease; Escherichia coli; Multi-resistant pathogens

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Core Tip: Bacterial infections (BI) affect the natural course of liver cirrhosis and can trigger decompensation or death. The most frequent BI in cirrhosis (urinary tract infections, pneumonia or spontaneous-bacterial peritonitis) were retrospectively compared to infections at other body sites, which are thought to be less frequently affected (so-called “atypical BI”). When comparing typical/atypical BI, no differences in age, sex, or etiology of cirrhosis were found. Notably, for atypical BI, the stage of cirrhosis was less advanced, as expressed by laboratory parameters and clinical scores (*e.g.* Model of End Stage Liver Disease - and Child-Pugh-Score).

Citation: Schneitler S, Schneider C, Casper M, Lammert F, Krawczyk M, Becker SL, Reichert MC. Retrospective study of the incidence, risk factors, treatment outcomes of bacterial infections at uncommon sites in cirrhotic patients. *World J Hepatol* 2024; 16(3): 418-427

URL: <https://www.wjgnet.com/1948-5182/full/v16/i3/418.htm>

DOI: <https://dx.doi.org/10.4254/wjh.v16.i3.418>

INTRODUCTION

Bacterial infections (BI) significantly affect the natural history of cirrhosis and may lead to a dramatic increase in mortality of infected patients[1-3]. Furthermore, BI are the most common event causing hepatic decompensation[4]. The more severe course of BI is attributed to the acquired immunodeficiency of patients with cirrhosis, the increased bacterial translocation from the intestinal tract, and the consequences of portal hypertension. The most common BI in cirrhosis include urinary tract infection (UTI), pneumonia, and spontaneous-bacterial peritonitis (SBP)[3]. Whereas infections at other body sites also occur relatively frequently in patients with cirrhosis (herein further called “atypical BI”), these have been investigated far less in-depth, in particular due to the lack of sufficiently large cohorts of patients with these specific BI in the setting of cirrhosis.

Accurate microbiological diagnostics are essential for targeted antibiotic therapy. This is often challenging in patients with cirrhosis, as invasive collecting of samples (*e.g.* ascites, or sputum) is not always feasible. Commonly, empirical antibiotic therapy is insufficient. Indeed, Lameirão Gomes *et al*[5] showed in a retrospective analysis that in only 60% of cases, empirical therapy was adequate against the infection-causing pathogens.

Here, we aimed to specifically compare the clinical and microbiological characteristics of patients with cirrhosis and typical BI (pneumonia, UTI and SBP) as compared to atypical BI, by exploiting a large database[6] (INCA database) of patients with BI and cirrhosis.

MATERIALS AND METHODS

Study population

This analysis was carried out as sub-study of the INCA trial, the study protocol of which has been published[6]. The study analyzed data from inpatients with cirrhosis and BI who received treatment at Saarland University Medical Center in Homburg, Southwest Germany, between January 1, 2015, and December 31, 2018. All hospitalized patients with cirrhosis were considered for inclusion. Patients with severe comorbidities such as end-stage heart failure, HIV infection and non-resectable cancer (except hepatocellular carcinoma Barcelona Liver Clinic Classification stages A-C), as well as patients in whom a BI could not be confirmed were excluded. Cirrhosis was defined by (1) biopsy; (2) a combination of clinical, laboratory, ultrasound and endoscopic findings; or (3) transient elastography > 13.0 kPa[7]. In patients with

transient elastography < 19.7 kPa, diagnosis of cirrhosis was additionally confirmed by (1) or (2). Results pertaining to different disease aspects of this cohort have been reported previously [7]. Overall, 488 patients with cirrhosis and BI requiring antibiotic therapy were finally included. BI were categorized applying stringent criteria (Supplementary Table 1). The electronic medical records were reviewed for clinical data, and further information regarding medication use (such as antibiotic therapy, beta-blocker, lactulose, statins) and laboratory parameters at the time of inclusion were recorded. The use of long-term antibiotics (prescribed for prophylaxis of SBP or for recurrent hepatic encephalopathy) was also documented.

Bacterial infections and antibiotic therapy

All atypical BI cases were analyzed using the microbiological databases HyBASE® (epiNET AG, Germany) and M/Lab (Dorner, Germany) at Saarland University Medical Center. The diagnostics carried out during the event period, the main detected pathogens, and the related antibiotic therapy were recorded. Of note, all microbiological diagnostic procedures such as Gram staining, culture techniques and identification methods were performed using standard operating procedures. Species identification of culture-grown bacterial colonies was carried out using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS, Bruker, Germany). Subsequently, the pathogens were grouped into Gram-positive and Gram-negative pathogens. In addition, the available antibiograms were interpreted with respect to resistance behavior using the multi-drug resistance (MDR) classification by Magiorakos *et al* [8]. The antibiotic therapy was categorized into the following antibiotic classes: Penicillins, cephalosporins, carbapenems, quinolones, macrolides, glycopeptides, linezolid, metronidazole, and others. In addition, the assessment included the administration of monotherapy and combination therapies, the length of therapy given, and the effectiveness of empirical therapy.

Statistical analyses

All variables are described as proportions, means with standard deviations, or medians with interquartile ranges (IQR). The univariate analysis was performed with chi²-square test, *t*-test, or Mann-Whitney *U* test, according to the distribution of the test variable. The statistical analyses were performed with SPSS 22.0 (SPSS, Munich, Germany). Two-sided *P* values < 0.05 were regarded as significant.

RESULTS

Overall, the retrospective search of the electronic data records of hospitalized patients with cirrhosis yielded 1128 patients with cirrhosis. Among them, 488 (43.3%) patients were treated with antibiotics due to BI. Figure 1 illustrates the workflow for the inclusion of patients into the study cohort. Tables 1 and 2 summarize the detailed baseline and specific characteristics of these patients.

The patients were predominantly men (*n* = 322, 66.1%). The median age was 61 [Range 26-92, (IQR 54-68)], and the predominant etiology of cirrhosis was alcohol-associated (*n* = 259, 53.1%). Most patients were in Child-Pugh stage (CPS) B. Figure 1 shows the distribution of the BI. In general, patients with BI were in an advanced stage of cirrhosis, as reflected by lower serum sodium and albumin concentrations as well as hemoglobin levels and higher creatinine, bilirubin and international normalized ratio, as compared to patients with cirrhosis and no BI. No differences were found concerning the presence of age, sex, or diabetes.

Concerning the common BI, 95 urinary tract infections, 73 SBP, 72 pulmonary infections, and 11 *Clostridioides difficile* infections were recorded. The most frequently atypical BI were soft-tissue infections (*n* = 21), bacterial cholangitis (*n* = 21), and intra-abdominal BI (*n* = 9) (Figure 1). Regardless of Gram classification, cholangitis (*n* = 21, 28.4% each) and soft tissue infections (*n* = 21, 28.4%) were the most common atypical BI presentations. These were followed by intra-abdominal infections, including cholecystitis (*n* = 15, 19%). Among neck and head infections, peritonsillar abscesses and parotitis were equally common (2 each).

The most frequent bacterial detections for atypical BI were detected in the Gram negative (*n* = 20; most frequently *Escherichia coli* (*E. coli*), *Pseudomonas* spp.) spectrum, *e.g.* being responsible for 8 out of 20 cholangitis cases and 6 out of 20 soft tissue infections. Most MDR detections were Gram-negative (8/20), and *Escherichia coli* (*E. coli*) (6/8) was the most frequently detected pathogen (Table 3).

A total of 70 cases (94.6%) were treated with empirical antibiotic therapy, with penicillin predominating (Table 4), followed equally by cephalosporins and metronidazole (19.2% each). Metronidazole was always used as a combination partner, with cephalosporin being the most frequently used combination (11.0%). The administered antibiotic therapy was most common targeted against Gram-positive pathogens (35.6%) and frequently administered over a period of up to two weeks (38.4%). Looking at the efficiency of empirical antibiotic therapy in terms of microbiological detection, the most common problem was that sufficient microbiological tests were not performed, and hence no microbiological analysis was performed (32.9%) (Table 4).

When comparing patients with common *vs* atypical BI, the stage of cirrhosis in patients with atypical BI was less advanced, as reflected by lower creatinine levels (1.14 ± 0.60 *vs* 1.38 ± 1.17 ; *P* = 0.018) as well as CPS (7.99 ± 2.15 *vs* 8.61 ± 2.50 ; *P* = 0.05) and Model of End Stage Liver Disease (MELD) scores (12.9 ± 5.1 *vs* 15.1 ± 7.44 ; *P* = 0.005). No differences were found with respect to sex or diabetes. Long-term antibiotics (*P* = 0.002), lactulose (*P* = 0.03) and proton pump inhibitors (*P* = 0.013) were prescribed more frequently for patients with common BI.

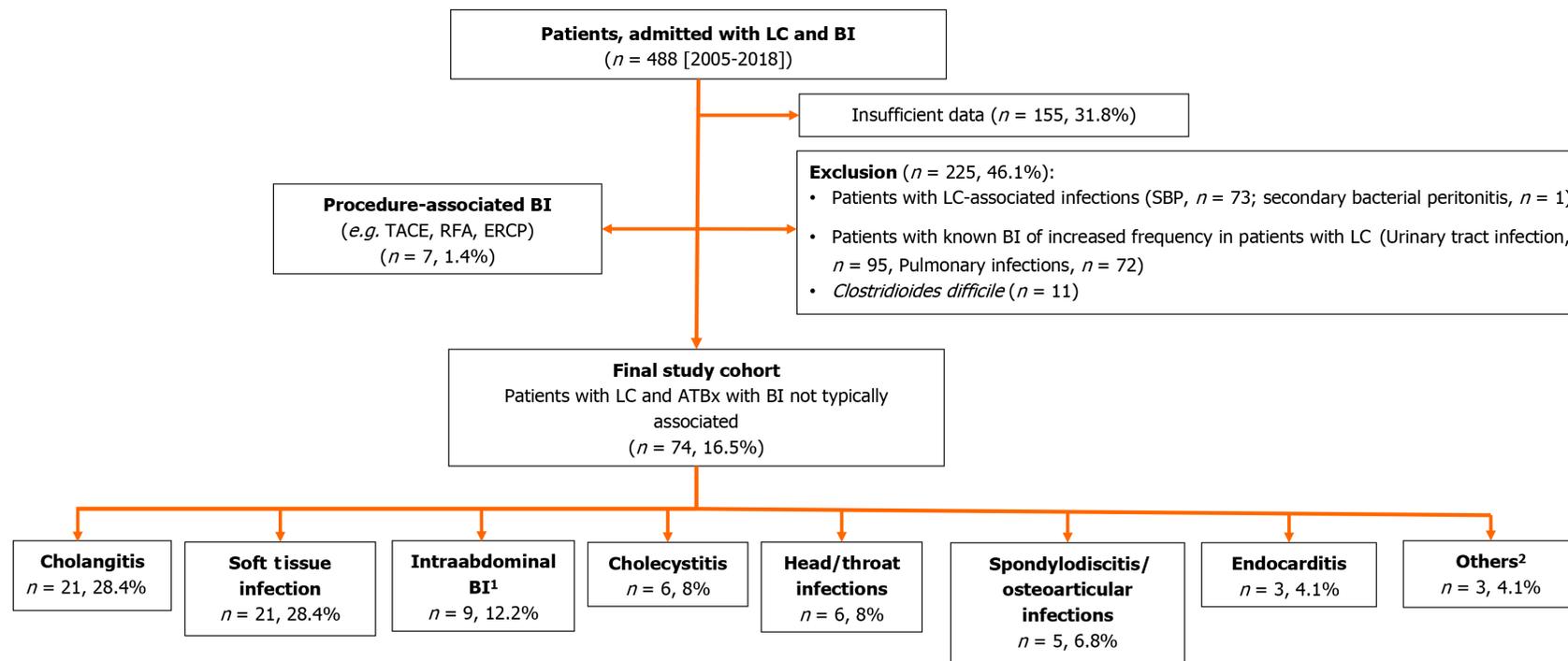


Figure 1 illustrates the workflow for the inclusion of patients into the study cohort. ¹6× enteritis, 1× liver abscess, 1× appendicitis with peritonitis, 1× diverticulitis. ²1× Epididymitis, 1× SBP equivalent of pleura, 1× vascular catheter associated infection; ATBx: Antibiotic therapy; BI: Bacterial infection; LC: Liver cirrhosis; TACE: Transarterial Chemoembolisation; RFA: Radiofrequency ablation; ERCP: Endoscopic retrograde cholangiopancreatography; SBP: Spontaneous bacterial Infection.

DISCUSSION

Bacterial Infections remain a major contributor to morbidity in patients with liver cirrhosis, but data on less frequently occurring infections are scarce. In this retrospective analysis we compared less frequent BI (termed “atypical BI”), such as soft tissue infections, and found them to be present in a relevant proportion of BI in patients with cirrhosis. Our cohort of patients resembled a typical cohort of patients with cirrhosis in Western countries with respect to age, etiology of cirrhosis (predominantly alcoholic), and sex (predominantly male patients). Notably, the stage of cirrhosis in patients with atypical BI was less advanced. The typical BI frequently observed in cirrhosis were associated with liver function. We also confirmed previous observations that BI occurred more commonly in patients with advanced stage of cirrhosis, as expressed by higher MELD score and CPS[9,10].

Of note, the definition of atypical BI is not consistent in the literature. Even though pneumonia, UTI and SBP are consistently reported as common BI, discrepancies exist for other infections, in particular cellulitis. For example, in their recent analysis, Fricker *et al*[11] subsumed cellulitis as atypical BI. Other study groups *e.g.* Jalan *et al*[12] included cellulitis among the more frequent BI. Additionally, the localization of skin- and soft tissue BI is usually not further specified.

Table 1 Comparing common and non-common bacterial infections

	Atypical BI (n = 74)	Common BI (n = 225)	No BI (n = 640)	P value ¹	P value ²	P value ³
Sex (female)	20 (27.0)	80 (35.6)	218 (34.1)	0.20	0.243	0.88
Age (yr)	61.14 ± 12.61	61.34 ± 11.95	60.45 ± 10.76	0.901	0.61	
Diabetes (yes)	28 (37.8)	69 (30.7)	199 (31.1)	0.26	0.238	0.706
Etiology of cirrhosis						
Alcoholic	35 (47.3)	147 (65.3)	317 (49.5)			
Hepatitis C	2 (2.7)	29 (12.9)	101 (15.8)			
Hepatitis B	1 (1.4)	3 (1.3)	21 (3.3)			
NASH	5 (6.8)	7 (3.1)	60 (9.4)			
Cryptogenic	6 (8.1)	19 (8.4)	72 (11.3)			
PSC	7 (9.5)	2 (0.9)	6 (0.9)			
Others	11 (14.9)	10 (4.4)	48 (7.5)			
Hemochromatosis	3 (4.1)	1 (0.4)	10 (1.6)			
PBC	4 (5.4)	2 (0.9)	5 (0.8)			
Medication						
Beta blocker	33 (45.8)	115 (51.8)	297 (47.1)	0.42	0.901	0.359
Long term ATBx	13 (18.1)	74 (33.1)	73 (11.6)	0.017	0.128	< 0.001
Lactulose	24 (33.3)	108 (48.6)	196 (31.1)	0.029	0.689	< 0.001
PPI	49 (68.1)	183 (82.4)	419 (66.3)	0.013	0.794	< 0.001
Laboratory parameters						
Serum sodium (mmol/L)	137.62 ± 4.04	136.56 ± 5.03	138.10 ± 4.61	0.10	0.346	< 0.001
Creatinine (mg/dL)	1.14 ± 0.60	1.38 ± 1.17	1.029 ± 0.52	0.018	0.106	< 0.001
Total bilirubin (mg/dL)	2.83 ± 4.00	3.73 ± 5.88	2.21 ± 3.96	0.14	0.205	< 0.001
Albumin (g/dL)	33.24 ± 6.73	32.95 ± 6.91	36.64 ± 7.14	0.75	< 0.001	< 0.001
Hemoglobin (g/dL)	11.98 ± 2.21	11.19 ± 2.34	12.66 ± 2.48	0.009	0.025	< 0.001
INR	1.27 ± 0.34	1.37 ± 0.58	1.25 ± 0.32	0.15	0.639	0.001
ASAT	108.69 ± 257.76	80.55 ± 104.89	84.75 ± 185.15	0.31	0.475	0.930
ALAT	71.46 ± 219.92	53.63 ± 121.43	69.08 ± 164.11	0.39	0.911	0.327
Platelets	164.93 ± 110.00	150.74 ± 88.46	150.27 ± 79.27	0.26	0.151	0.527
MELD	12.86 ± 5.13	15.10 ± 7.44	11.60 ± 5.13	0.005	0.049	< 0.001
CPS	7.99 ± 2.15	8.61 ± 2.50	7.19 ± 5.44	0.05	0.003	< 0.001
Fibroscan (kPa)	41.96 ± 21.94	46 ± 21.90	37.06 ± 21.44	0.22	0.106	< 0.001

¹Uncommon bacterial infections (BI) versus common BI.

²Uncommon BI versus no BI.

³Any BI versus no BI.

Data is presented as frequency and percentage or median and standard deviation. Significant *P* values are marked in bold. ALAT: Alanine aminotransferase; ASAT: Aspartate aminotransferase; ATBx: Antibiotic therapy; BI: Bacterial infection; CPS: Child-Pugh-Score; CRP: C-reactive-protein; INR: International normalized ratio; MELD: Model of End Stage Liver Disease; WBC: White blood cells; UTI: Urinary tract infections; SBP: Spontaneous-bacterial peritonitis. Long term ATBx = minimum 28 d, in the case of hepatic encephalopathy or prophylaxis of SBP.

Compared to typical BI, cellulitis is often a purely clinical diagnosis without a confirmatory laboratory method, making it much more difficult to classify and this may be one of the reasons why the definition and classification in the literature varies. Due to the clinically frequent presence of peripheral edema with dysfunction of the skin barrier, skin and soft tissue infections of the lower limb are more likely to occur in cirrhotics and should therefore be given more attention as a potential typical focus of infection.

Table 2 Characteristics of patients with atypical bacterial infection (at the time of bacterial infection diagnosis)

	Atypical BI (n = 74)
Outcome	
Dead within 30 d	7 (9.5)
Sepsis	9 (12.7)
Laboratory parameters (at BI)	
Serum sodium (mmol/L)	137 ± 5.5
Creatinine (mg/dL)	1.13 ± 13.5
Total bilirubin (mg/dL)	1.9 ± 6.67
Albumin (g/dL)	30.0 ± 6.25
Hemoglobin (g/dL)	11.8 ± 3.00
INR	1.20 ± 0.48
ASAT (U/l)	67.0 ± 42.47
ALAT (U/l)	44 ± 30.92
Platelets	154 ± 103
MELD	14.5 ± 6.23
CPS	8 ± 1.86
WBC (×10 ⁹)	8.2 ± 5.05
CRP (mg/dL)	43.1 ± 61.77

Data are presented as frequency and percentage or median and standard deviation. Significant *P* values are marked in bold. ALAT: Alanine aminotransferase; ASAT: Aspartate aminotransferase; BI: Bacterial infection; CPS: Child-Pugh-Score; CRP: C-reactive-protein; INR: International normalized ratio; MELD: Model of End Stage Liver Disease; WBC: White blood cells.

Multidrug resistance is an increasingly important issue[13]. The range here is wide, from 29% Extended Spectrum Beta Lactamase-producing Enterobacterales in Korea to rather Gram-positive problems, with 9% vancomycin-resistant enterococci in the United States[14,15]. Fricker *et al*[11] reported an antibiotic resistance in 38% of cases, but did not specify how resistance was defined and which antibiotic classes were considered. Jalan *et al*[12] also discuss that depending on the geographical region, multidrug-resistant bacterial infections have become more frequent. In our analysis, we were able to show that when a pathogen was detected, resistance tended to occur in the Gram-negative range and one major pathogen was *E. coli*. In our study, not many multi-resistant pathogens were detected. However, it must be considered that only the cases with microbiological pathogen identification were considered. Internationally, gram-negative pathogens predominate in infections of liver cirrhotic patients, whereby no distinction is made between typical and atypical infections. Our data showed an empirically more frequent antibiotic coverage in the gram-positive spectrum with, however, more frequent detection of a gram-negative infection. Hillert *et al*[16] found, that a gram-positive pathogen was detected in 54% of cases, with the most common single pathogen detection being *E. coli*. Hillert *et al*[16] inclusion criterion was the presence of ascites.

Our data indicate that the general recommendations for antibiotic therapy can also be followed for atypical BI in cirrhotics and that empirical antibiotic therapy should be based on the localization of the clinical infection focus. Despite immunosuppression and multiple contacts in the health care system, broader antibiotic coverage is not empirically necessary, especially not for multidrug-resistant pathogens. In addition to the clinical localization, the presence of a long-term antibiotic therapy must also be included in the consideration of antibiotics therapy in cirrhotics and need further studies.

To our knowledge, there is no study evaluating how microbiological diagnostics and long-term use of antibiotics in liver cirrhosis patients influence infections and whether previous long-term antibiotics should be included in empirical treatment decisions.

A limiting factor in this data collection is the retrospective method, which makes it difficult to objectively assess appropriate microbiological diagnostics and the resulting decisions. Furthermore, the inclusion of many centers to collect sufficient case numbers and other experiences would certainly be useful to avoid monocentric aspects.

CONCLUSION

Cirrhosis is expected to further increase worldwide in the coming years, e.g. due to the increase in non-alcoholic steato-

Table 3 Microbiological characteristics of selected infections

Pathogen	Organs frequently affected (n)	% MDR ¹
Gram positive (n = 17)		
<i>Staphylococcus aureus</i> (n = 10)	Soft tissue infection[3], abscess[3], discitis/osteomyelitis[2], endocarditis[2]	1/10
<i>Streptococcus</i> spp. (n = 4)	Cholangitis/cholecystitis[1], endocarditis[1], meningitis[1], epididymitis[1]	NU
<i>Enterococcus faecium</i> (n = 3)	Cholangitis/cholecystitis[3]	NA
Gram negative (n = 20)		
<i>Escherichia coli</i> (n = 7)	Cholangitis[5], soft tissue infection[2]	6/7
<i>Klebsiella</i> spp. (n = 3)	Cholangitis[1], soft tissue infection[1], appendicitis[1]	1/3
<i>Enterobacter</i> spp. (n = 2)	Cholangitis[1], periprothetic infection of hip joint[1]	1/2
<i>Pseudomonas</i> spp. (n = 4)	Soft tissue infection[2], cholangitis[1], abscess[1]	0/4
<i>Campylobacter</i> spp. (n = 3)	Colitis[3]	0/3
<i>Acinetobacter baumannii</i> (n = 1)	Soft tissue infection[1]	0/1

¹Multi-drug classification used by[8]. NU: No MDR classification; NA: Not available.

Table 4 Characteristics of antibiotic therapy

Variable	Number (n = 73) ¹
Empirical antibiotic treatment	
Monotherapy	40 (54.8)
Combination therapy with > 2 antibiotics (n)	24 (32.9)
Combination therapy with > 3 antibiotics (n)	6 (8.2)
Unspecific antibiotic information	3 (4.1)
Antibiotic classes¹	
Penicillins	25 (34.2)
Cephalosporins	14 (19.2)
Metronidazole	14 (19.2)
Carbapenems	13 (17.8)
Other	13 (17.8)
Quinolones	11 (15.1)
Glycopeptides	6 (8.2)
Not assessable	4 (5.5)
Most frequent antibiotic combinations	
Cephalosporins with Metronidazole	8 (11)
Carbapenems with others	4 (5.5)
Quinolones with Metronidazole	3 (4.1)
Coverage	
Gram positive	26 (35.6)
Gram negative	17 (23.3)
Gram positive and negative	12 (16.4)
Gram negative and anaerobic	12 (16.4)
Non-rankable/gram positive. Negative and anaerobic	6 (8.2)

Duration of therapy	
One week	18 (24.7)
Up to two weeks	28 (38.4)
More than two weeks	10 (13.7)
No data	18 (24.7)
Efficacy of empirical antibiotic therapy	
No sufficient data	17 (23.3)
No resistance to antibiotics being used	19 (26)
Change in multi-resistant germ under antibiotic therapy	2 (2.7)
Antibiotic therapy not adequate	7 (9.6)
No germ detection with adequate diagnostics. Effectiveness of antibiotic therapy cannot be assessed	5 (6.8)
No germ detection in the absence of microbiological diagnostics	24 (32.9)

¹n = 73 because of one patient without specific treatment.

hepatitis[17,18]. BI remain a major cause of morbidity and mortality in these patients. The relevance of a correct adequately chosen antibiotic in face of an increasing antimicrobial resistance rate worldwide is paramount[19]. Our data shows that atypical BI in patients with cirrhosis have different characteristics. With an increasing degree of liver failure, the severity and the spectrum of BI change. Prospective multicentric studies are needed to improve our understanding of an optimal diagnostic and therapeutic management of these disease entities in patients with liver cirrhosis. Further research is also warranted to identify whether infections at atypical body sites and more common sites differ depending on the causative bacterial species.

ARTICLE HIGHLIGHTS

Research background

Typical infections in patients with liver cirrhosis have standardized diagnostic algorithms and are therefore recognized and treated quickly. Clinically, however, unusual infections are also more frequent in patients with cirrhosis. These are not included in guidelines and are therefore often not adequately addressed in diagnostic and therapeutic algorithms.

Research motivation

The study aimed to analyze a cirrhosis cohort for typical and atypical infections. The aim is to derive improved diagnostic and therapeutic algorithms from these analyses in the future.

Research objectives

The main aim is to identify the most common pathogens for atypical infections and their resistance patterns in relation to the stage of liver cirrhosis. Algorithms for the improved detection of infections, including atypical situations, can then be developed.

Research methods

For the analysis, data were analyzed in relation to the research question in a cirrhosis cohort.

Research results

The cohort showed that atypical infections are not so rare overall and should be clinically investigated more frequently in order to initiate the correct diagnosis and treatment. It was also shown that the pathogen spectrum recorded did not always correspond correctly with the empirical therapy, and that microbiological diagnostics are therefore particularly relevant in this patient population.

Research conclusions

We were able to show that the stage of cirrhosis is associated with a change in infections and that this needs to be taken into account. The relevance of these findings must be considered in the light of the increasing role of liver disease and its sequelae in the global burden of disease.

Research perspectives

Confirmation of these results in larger multicenter studies and development of corresponding algorithms.

ACKNOWLEDGEMENTS

We would like to thank all patients who participated in the study.

FOOTNOTES

Author contributions: Reichert MC, Schneitler S, Lammert F, and Becker SL designed the study; Reichert MC, Casper M, Schneider C, and Schneitler S participated in the acquisition of clinical data, drafted the manuscript, and together with Krawczyk M and Becker SL, analyzed the data and finalized the manuscript, which was then revised by all authors; the final draft of the manuscript was approved by all authors.

Institutional review board statement: The study was conducted according to the Declaration of Helsinki and Good Clinical Practice (European guidelines). Institutional review board approval was obtained by the *Ethikkommission der Ärztekammer des Saarlandes* (approval 71/11).

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All authors declare that they do not have anything to disclose regarding conflicts of interest with respect to this manuscript.

Data sharing statement: No additional data are available.

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S-Editor: Liu JH

L-Editor: A

P-Editor: Guo X

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