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Retrospective Study

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

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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

Data about BI at other body sites (atypical BI) are scarce.

METHODS

Retrospectively we analysed patients with cirrhosis and BI between 2015 and 2018 at our tertiary care centre. Typical and atypical BI were categorised, and clinical and laboratory parameters were compared among both groups.

RESULTS

Among 488 cirrhosis patients, we identified 225 typical BI (95 UTI, 73 SBP, 72 pulmonary infections) and 74 atypical BI, mainly cholangitis and soft tissue infections (21 each), followed by intra-abdominal BI (n = 9), cholecystitis (n = 6), head/throat BI (n

= 6), osteoarticular BI (n = 5), and endocarditis (n = 3). We did not observe differences concerning age, sex, or aetiology of cirrhosis in patients with typical *versus* atypical BI. Atypical BI occurred more frequently in patients with more advanced cirrhosis, as evidenced by MELD (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 show a different spectrum and there is an association between cirrhosis stage and atypical BI. Hence, the work-up of cirrhosis patients with suspected BI requires detailed work-up if no typical BI can be identified.

INTRODUCTION

Bacterial infections (BI) significantly affect the natural history of cirrhosis and may lead to a dramatic increase in mortality of infected patients (1,2,4) Furthermore, BI are the most common event causing hepatic decompensation (3). 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) (4). 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. showed in a retrospective analysis that in

only 60% of cases, empirical therapy was adequate against the infection-causing pathogens (5).

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

Patients and Methods

Study Population

This analysis was carried out as sub-study of the INCA trial, the study protocol of which has been published [Casper *et al*]. The study analysed 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 hospitalised 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 (HCC) Barcelona Lever Clinic Classification (BCLC) stages A-C), as well as patients in whom a BI could not be confirmed were excluded. Cirrhosis was defined by (A) biopsy, (B) a combination of clinical, laboratory, ultrasound and endoscopic findings, or (C) transient elastography > 13.0 kPa (7). In patients with transient elastography < 19.7 kPa (21), diagnosis of cirrhosis was additionally confirmed by (A) or (B). 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 categorised applying stringent criteria (supplementary). 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

spontaneous bacterial peritonitis (SBP) or for recurrent hepatic encephalopathy) was also documented.

Bacterial Infections and Antibiotic Therapy

All atypical BI cases were analysed 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 (SOPs). Species identification of culture-grown bacterial colonies was carried out using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). Subsequently, the pathogens were grouped into Gram-positive and Gram-negative pathogens. In addition, the available antibiograms were interpreted with respect to resistance behaviour using the multi-drug resistance (MDR) classification by Magiorakos *et al* (8). The antibiotic therapy was categorised 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 (SD), or medians with interquartile ranges (IQR). The univariate analysis was performed with chi^2-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 hospitalised 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. **Table 1 and 2** summarizes 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 aetiology 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 haemoglobin levels and higher creatinine, bilirubin and INR, 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 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.

DISCUSSION

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, aetiology 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 and consistently reported as common BI, discrepancy exist for in particular cellulitis. For example, in their recent analysis, Fricker Z *et al* (2021)

subsumed cellulitis as atypical BI (11). Other study groups *e.g.* Jalan R. *et al* (2014) included cellulitis among the more frequent BI (12). Additionally, the localisation of skin- and soft tissue BI is usually not further specified. 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 oedema 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.

Multidrug resistance is an increasingly important issue (13). The range here is wide with 29% Extended Spectrum Beta Lactamase producing Enterobacterales in Korea to rather Gram-positive problems, with 9% vancomycin-resistant enterococci (VRE) in the USA (14,15). Fricker Z *et al* reported an antibiotic resistance in 38% of cases, but did not specify how resistance was defined and which antibiotic classes were considered (11). Jalan R. *et al* also discuss that depending on the geographical region, multidrug-resistant bacterial infections have become more frequent (12). 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, it must be added though, that only the cases with germ identification can be 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* found, that a gram-positive pathogen was detected in 54% of cases, with the most common single pathogen detection being *E. coli* (16). Hillert *et al* inclusion criterion was the presence of ascites (16).

Our data indicates, that the general recommendations for antibiotic therapy can also be followed for atypical BI in cirrhotics and that empirical antibiotic therapy is sufficient in relation to the clinical localisation. 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 localisation, the presence of a long-term ATBx therapy must also be included in the consideration of antibiotics therapy in cirrhotics and need further studys.

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 this 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 centres 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, among other reasons because of the increase in non-alcoholic steatohepatitis (17,18). BI remain a major cause of morbidity and mortality in these patients. The relevance of a correct antibiotic administration in face of an increasing antimicrobial resistance rate worldwide is paramount (19). Out data shows that atypical BI in patients with cirrhosis have different characteristics. As the degree of liver failure increases the severity, but also spectrum of BI changes. 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.

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