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Pyogenic spinal infections in patients with chronic liver disease: illustrative case and systematic review

Gaston Camino-Willhuber, MD,[1,2] Ryan S. Beyer, BS,[3] Matthew J. Hatter, BA,[3] Austin J. Franklin, BA,[3] Nolan J. Brown, BS,[3] Sohaib Hashmi, MD,[2] Michael Oh, MD,[4] Nitin Bhatia, MD,[2] and Yu-po Lee, MD[2]

[1]Orthopaedic and Traumatology Department, Institute of Orthopedics "Carlos E. Ottolenghi," Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; Departments of [2]Orthopaedics and [4]Neurosurgery, University of California, Irvine, Orange, California; and [3]School of Medicine, University of California, Irvine, Orange, California

BACKGROUND Pyogenic spinal infections (PSIs) are a group of uncommon but serious infectious diseases that are characterized by inflammation of the endplate–disc unit. PSIs are considered more prevalent and aggressive among patients with chronic immunocompromised states. Association between PSIs and liver disease has not been systematically analyzed. The authors performed a systematic review to study baseline characteristics, clinical presentation, and mortality of patients with PSI in the setting of chronic liver disease.

OBSERVATIONS The authors presented the case of a 72-year-old female patient with chronic liver disease who presented with severe low back pain and bilateral lower weakness. Imaging studies showed T10–11 spondylodiscitis. The patient received decompression and fusion surgery with partial neurological improvement. The authors performed a systematic literature search of spondylodiscitis and liver disease, and eight published articles met the studies inclusion and exclusion criteria. These studies featured a total of 144 patients, of whom 129 met inclusion criteria (mean age, 60.5 years, range 40 to 83 years; 62% males). Lumbar infection was the most common report (67%), with *Staphylococcus aureus* (48%) as the main causative microorganism. Neurological compromise was present in 69% of patients. Surgical intervention occurred in 70.5% of patients, and the average duration of antibiotic treatment was 69.4 days. Postoperative complication rate was 28.5%, with a 30- and 90-day mortality of 17.2% and 24.8%, respectively.

LESSONS Pyogenic spondylodiscitis in patients with liver disease was associated with a high rate of neurological compromise, postoperative complications, and mortality.

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KEYWORDS vertebral osteomyelitis; spondylodiscitis; liver disease; cirrhosis; pyogenic spinal infection

Pyogenic spinal infections (PSIs) are a group of uncommon but serious infectious diseases that are characterized by inflammation of the disc–vertebral unit. With an estimated prevalence of 5.4 per 100,000 in Western societies,[1] PSIs encompass a range of clinical conditions, including spondylitis, discitis, spondylodiscitis, vertebral osteomyelitis (VO), epidural abscess, and paravertebral abscess. These conditions have been shown to be more prevalent among patients above 65 years with chronic debilitating conditions (uncontrolled diabetes mellitus and immunocompromised states), intravenous drug users, and persons with alcoholism, sickle cell anemia, HIV infection, malignancy, renal failure, liver cirrhosis, rheumatologic diseases, and history of previous spinal surgery.[2] Despite the historical scarcity of PSI, its incidence appears to be on the rise. This observation is likely secondary to the increasing prevalence of immunocompromised persons, increasing numbers of invasive spinal procedures, intravenous drug abuse, increasing life expectancy for patients with chronic debilitating diseases, emergence of drug-resistant microorganisms, and development of complex comorbidities. Additionally, it is likely that higher diagnostic awareness and yield have played a role in the increased incidence of PSI.[3–6] This is important because PSI has historically been diagnosed late in the disease course as a result of its association with nonspecific symptoms such as generalized back pain. This clinical characteristic paves the way for infectious spread with neurological complications and even death.[7]

ABBREVIATIONS CRP = C-reactive protein; PSI = pyogenic spinal infection; VO = vertebral osteomyelitis.

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Diagnosing PSIs is a multidisciplinary effort requiring input from radiology, spine surgery, nuclear medicine, and infectious disease specialists. When paired with the nonspecificity of symptoms, what begins as low-grade inflammation can progress into debilitating infection if not diagnosed and treated within a reasonable time frame.[8] This is especially true in immunocompromised patients with comorbidities such as end-stage renal disease and liver disease and patients receiving organ transplants. For example, patients with chronic liver disease may have increased morbidity and mortality due to variceal bleeding, ascites, and hepatic carcinoma, each of which can complicate a diagnosis of PSI.[9,10] Regarding the association between PSI and chronic liver disease, some studies have suggested a higher rate of neurological compromise, epidural abscess, and mortality in this group of patients.[11,12]

We report an illustrative case an aggressive pyogenic spondylodiscitis in a patient with chronic liver disease. To our knowledge, no systematic review concerning the overall incidence, characteristics, prognosis, and estimated mortality in patients with PSI secondary to liver disease has been performed. Therefore, the objective of this study is to analyze, through a systematic literature review, the baseline characteristics, clinical presentation, and mortality of patients with PSI in the setting of chronic liver disease.

Illustrative Case

A 72-year-old woman presented to the outpatient clinic with severe low back pain that had started approximately 25 days earlier. She reported no traumas or falls, and she had referred progressive bilateral leg weakness over the last 7 days.

On physical examination, tenderness to palpation was confirmed at the thoracolumbar region. Bilateral lower extremity strength was 3/5 for quadriceps and soleus muscles groups and 5/5 for the other muscle groups. Patellar reflexes were 3+ bilaterally, and positive clonus was detected.

Imaging studies revealed an aggressive spondylodiscitis at T10–11 levels (Fig. 1). Patient past medical history revealed chronic liver disease due to nonalcoholic steatohepatitis and smoking as positive background.

Preoperative C-reactive protein (CRP) and sedimentation rate were 102 and 95 mg/L, respectively, white blood cell count was 13,500, and blood culture was positive for *Staphylococcus aureus*.

Surgery was performed through posterior approach, a T9–L1 posterior instrumentation with T10–11 laminectomy, and interbody debridement mesh cell (Fig. 2). The operative time was 180 minutes, with estimated blood loss of 400 mL. The patient experienced partial improvement of motor strength and was able to ambulate with use of a walker. She completed an 8-week course of antibiotics and showed improvement of laboratory parameters.

Discussion

Observations

Primary spinal infections in patients with chronic liver disease may behave differently in terms of epidemiology, clinical presentation, and outcomes compared with patients without liver disease. A systematic literature search was performed in PubMed, Web of Science, and Google Scholar in November 2021 to identify studies reporting the outcome of pyogenic spinal infection in patients with either liver cirrhosis or chronic liver failure. The search strategy was developed by one author (G.C.W.) by consulting the Peer Review of Electronic Search Strategies (PRESS) criteria.[13] The search strategy for PubMed, Web of Science, and Google Scholar is displayed in Table 1. We performed the literature search with records filtered from January 2000 to November 2021. We included retrospective case series and individual case reports. Study selection was performed by three authors (N.B., R.B., and M.H.), and data extraction was performed by one author (N.B.). Full articles were retrieved when authors found titles and abstracts potentially relevant

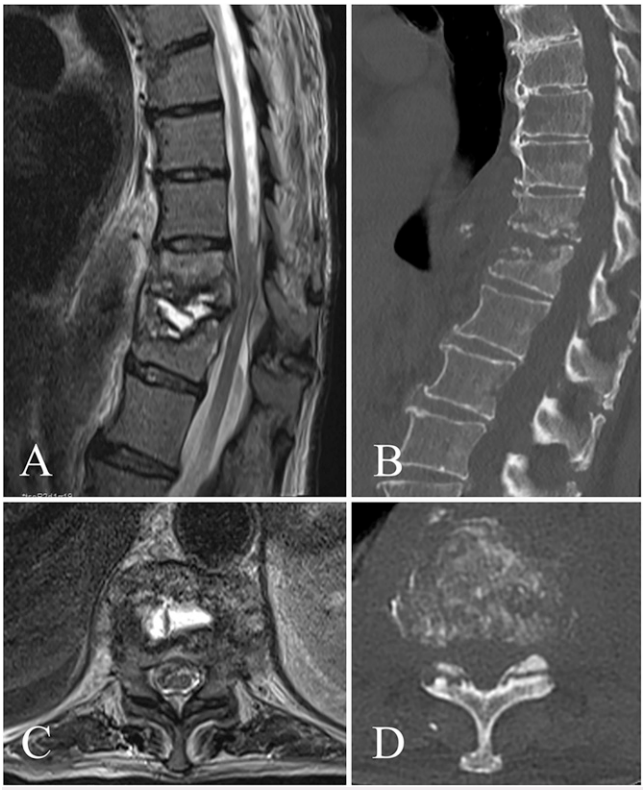

FIG. 1. Magnetic resonance imaging and computed tomography scans showing aggressive T10–11 spondylodiscitis.

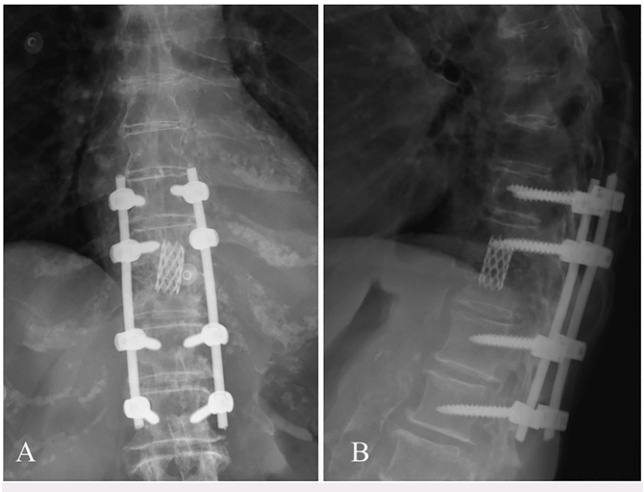

FIG. 2. Postoperative radiographs showing T9–L1 instrumented fusion and T10–11 mesh cell.

TABLE 1. Search strategy

PubMed	("spondylodiscitis" OR "pyogenic spondylodiscitis" OR "infectious spondylodiscitis" OR "discitis") OR ("spondylitis" OR "tuberculosis") AND ("liver disease" OR "liver cirrhosis" OR "liver failure" OR "chronic liver disease" OR "liver insufficiency")
Web of Science	(discitis OR spondylodiscitis OR "epidural abscess" OR "pyogenic discitis" OR "pyogenic spondylodiscitis") AND (spine OR vertebra OR spinal OR vertebral OR vertebrae OR disc OR disk) AND (cirrhosis OR "liver disease" OR "hepatic disease" OR "liver cirrhosis" OR "viral hepatitis" OR "alcoholic liver disease" OR "nonalcoholic steatohepatitis" OR "hepatocellular carcinoma" OR "nonalcoholic fatty liver cirrhosis")
Google Scholar	liver disease cirrhosis spinal infections discitis spondylodiscitis osteomyelitis cirrhosis OR liver OR disease "systematic review"

based on the inclusion criteria (i.e., included VO/spondylodiscitis patients with infections secondary to liver cirrhosis). A mismatch of one article was resolved by a fourth author (G.C.W.) with regard to the exclusion criteria. The data from each study was then extracted and analyzed with respect to age, sex, years of diagnosis of liver disease, time from onset of back pain to diagnosis, region of spine infection (cervical, thoracic, lumbar), causative organisms, steroid treatment, inflammatory markers, comorbidities, neurological deficit outcome, duration of antibiotic treatment, surgical outcome morbidity, and mortality. If a study did not explicitly mention the presence of a clinical characteristic, it was assumed the characteristic was not present in that patient set.

Records identified through the searches were added to a database, and duplicates were removed. Titles and abstracts from PubMed were screened by one author (G.C.W.), from Web of Science by one author (R.B.), and from Google Scholar by one author (M.H.). The articles were limited to human studies published in English. Editorials, reviews, and letters to the editor were excluded. We collected the following data from the included studies: author, publication year, study design, number of patients, patient characteristics, treatment, antibiotic duration, and length of follow-up.

We provide a descriptive and analytical review of the studies included in this review along with a narrative and tabular summary of the data collected. We analyzed similarities and differences within and in between studies to identify patterns and offer an explanation for the findings. Furthermore, we developed an evidence map illustrating the baseline characteristics, clinical presentations, and outcomes for patients with chronic liver disease diagnosed with PSI. This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[14]

Figure 3 shows the study selection process. The literature search initially identified 161 studies (111 from Google Scholar, 26 from PubMed, and 24 from Web of Science). In total, 8 articles published between 2003 and 2020 were selected based on the inclusion and exclusion criteria for the present systematic review,[15–22] including 5 case series and 3 case reports (Table 2).

The sample size across all studies was 144 patients, with 129 remaining after application of inclusion and exclusion criteria. This cohort of 129 patients ranged in age from 40 to 83 years. The mean age was 60.5 years. There were 80 men (62%) and 49 women (38%). Etiologies for liver disease were reported for all 129 patients and included alcohol (n = 54; 41.9%), virus (n = 53; 41.1%), nonalcoholic steatohepatitis (n = 9; 6.9%), cystic liver disease (n = 2; 1.5%), liver cancer (n = 1; 0.7%), and other (n = 10; 7.7%). Child-Turcotte-Pugh score was reported for 122 patients, of whom 10.6% (n = 13) had class A, 36.1% (n = 44) had class B, and 53.3% (n = 65) had class C.

Local pain and fever were reported for 44 patients, of whom 97.7% (n = 43) presented with local pain and 45.4% (n = 20) presented with fever. Neurological deficit was present in 89 patients (69%). Septic manifestation was present in 67 patients (51.9%). Individual leukocyte levels were reported for 44 patients, of whom 36.3% (n = 16) presented with elevated white blood cell count. Individual CRP levels were reported for 41 patients, of whom 100% (n = 41) presented with elevated levels. Level of spinal infection was reported for 100 patients, of whom 13% (n = 13) presented with cervical infection, 31% (n = 31) presented with thoracic infection, and 67% (n = 67) presented with lumbar infection. Epidural abscess was reported for all 129 patients, of whom 79.8% (n = 103) presented with epidural abscess. Psoas abscess was reported for 44 patients, of whom 29.5% (n = 13) presented with psoas abscess.

The main causative organism of spinal infection was reported for all 129 patients. *Staphylococcus aureus* was reported as the main causative organism in 48% (n = 62) of patients, of whom 40.3% (n = 25) were methicillin resistant. Gram-negative microorganisms infected 17.8% (n = 23) of patients. Other causative organisms included *Enterococcus* (3.1%; n = 4), other *Staphylococcus* species (4.7%; n = 6), *Streptococcus* (0.7%; n = 1), *Escherichia coli* (0.7%; n = 1), and *Pasteurella multocida* (0.7%; n = 1). In 19.4% of cases (n = 25), causative microorganisms were not specified and reported as "other." No microorganism growth was reported in 7.7% (n = 10) of patients. Time between onset of symptoms and diagnosis was reported for 36 patients, with an average of 44.2 days. Antibiotic duration was reported for 98 patients, with an average of 69.4 days.

The type of treatment (conservative versus surgery) was reported for all 129 patients, of whom 76.7% (n = 99) underwent surgery. The combined anterior and posterior approach was performed in 77.8% (n = 28) of patients and the minimally invasive approach in 83.3% (n = 30) in Abdelrahman et al.[15] These approaches were followed by posterior only 13.9% (n = 5) and anterior only in 2.8% (n = 1). Notably, Kim et al.[16] made the designation of "early surgery," defined as a surgical treatment performed under general anesthesia within 30 days after pyogenic vertebral osteomyelitis diagnosis (n = 34 patients), of whom 26.5% (n = 9) underwent spinal instrumentation. One patient from Cross and Howell[19] received uneventful L4–5 laminectomy and drainage of an L4–5 abscess, and one patient from Webster et al.[20] received urgent neurosurgical evacuation of a T9–12 epidural abscess. In one patient reported by Sakaguchi et al.,[21] open drainage operation was performed to control infection upon diagnosis of a retropharyngeal abscess. Lastly, in Lin et al.,[22] 2 patients out of 14 who met our inclusion criteria received successful full endoscopic debridement and drainage. All fourteen patients reported immediate relief from pain (especially back pain) after this procedure.

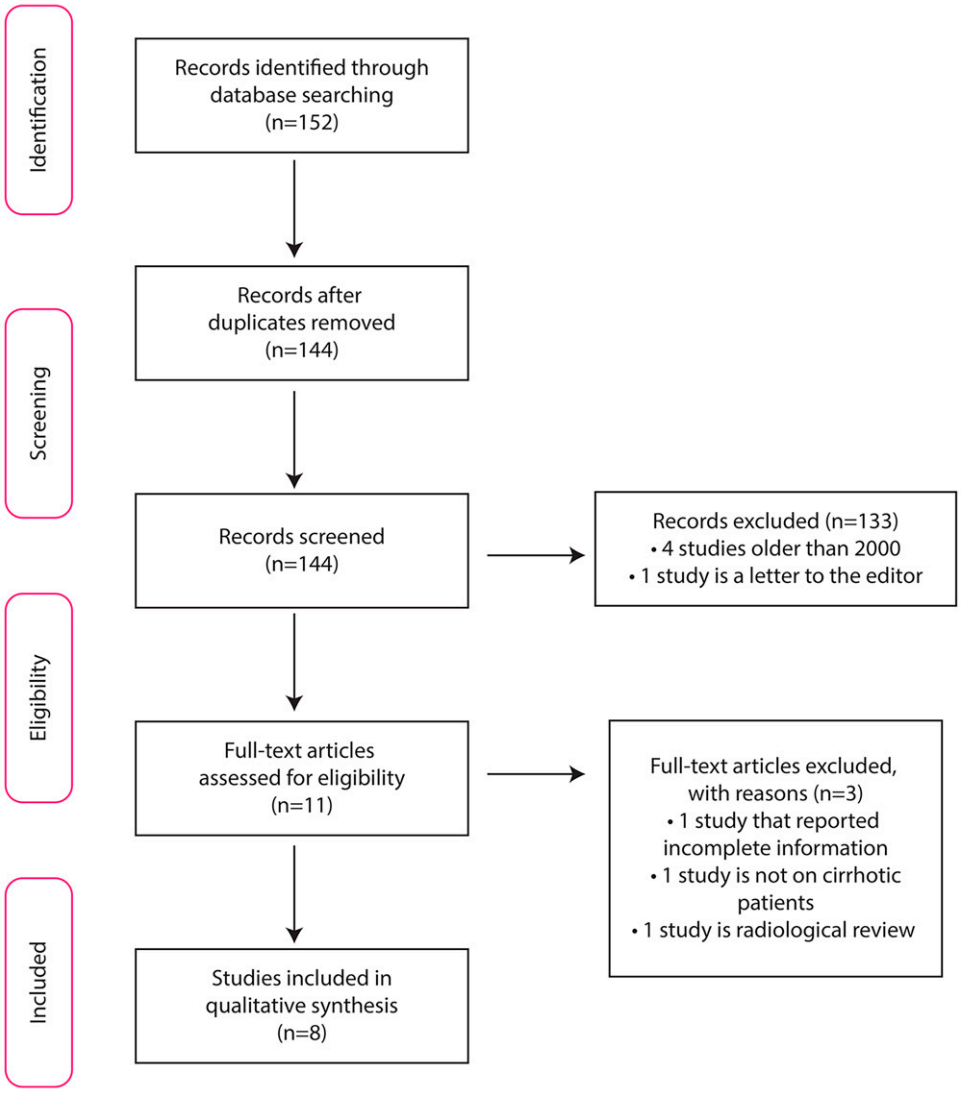

FIG. 3. PRISMA study selection flow diagram.

Postoperative complications occurred in 30.7% (n = 28) of cases; 46.4% (n = 13) of postoperative complications involved a recurrence of infection, 28.5% (n = 8) involved a surgical site infection, and 25% (n = 7) involved surgical instrument failure. Mean follow-up time was reported for 42 patients, with an average of 677 days (range, 21–772).

One-year mortality rates were reported for all 129 patients, of whom 28.9% (n = 37) had died after 1 year; 90-day mortality rates were reported for 93 patients, of whom 24.8% (n = 32) had died after 90 days; and 30-day mortality rates were reported for 93 patients, of whom 17.2% (n = 16) had died after 30 days.

Limitations

Our study has some limitations that should be discussed. First, the articles included in our review were categorized as level IV evidence, including retrospective cases series and case reports with inherent limitations of a retrospective nature study. However, considering that both pyogenic infections and liver disease are relatively uncommon, the authors believe this is the expected evidence provided by the literature and should not be underestimated. This could also be considered a bias in the results presented in this study. On the other hand, we provided the evidence reported by the authors, and in this regard, this is the first study that systematically summarized and reported the association between spinal infections and liver disease.

Lessons

We performed a systematic review of patients with primary PSI and chronic liver disease and found that the main etiology of liver disease was alcohol-related, the most common clinical presentation was neurological deficit, 70.5% of patients required surgical treatment, with postoperative complication rates of 30.8%; and 30-day, 90-day, and 1-year mortality rate were 17.2%, 24.8%, and 28.9%, respectively.

The presence of liver disease is understood to be a risk factor for pyogenic infections for various reasons such as higher rate of bacteremia, abnormal intestinal permeability with subsequent bacterial translocation, increased number of invasive procedures, and decrease in neutrophil,

TABLE 2. Summary of studies included

Authors & Year	Study Design	No. of Pts	Age (yrs), Sex	Etiology (n)	Segments Affected (n)	Microorganism (n)	Neurological Deficit (n)	Op (n)	Time Btwn Sxs & Op (days)	Antibiotic Tx Duration (days)	Mean FU (days)
Abdelrahman et al., 2020[15]	Case series	36	Mean, 60.7 (range, 41–80), 26 M (72.2%), 10 F (27.8%)	Alcohol (22); nonalcoholic steatohepatitis (9); viral hepatitis (3); cystic liver disease (2)	Cervical (8); thoracic (16); lumbar (23)	*Staphylococcus aureus* (17); MRSA (4); *S. epidermidis* (5); *Enterococcus* (4); gram-negative (2); *Streptococcus* (1)	24	32	Mean, 33.5 (± 25.1)	56	772
Kim et al., 2019[16]	Case series	85	Mean, 60.5 (± 8.7), 50 M (58.9%), 35 F	Viral (47); alcoholic (29); other (9)	Cervical (4); thoracic (13); lumbar (39)	*S. aureus* (42); MRSA (21); other gram-positive (15); gram-negative Enterobacteriaceae (18); other (10)	60	62	W/in 7 (9), btwn 7 & 28 (25)	Mean, 77.1 (± 28.3)	NA
Malek et al., 2019[17]	Case report	1	60, M	Viral (hepatitis C) (1)	Lumbar (1)	Gram-negative *Pasteurella multocida* (1)	NA	NA	183 (from Sxs to Dx)	63	63
Stanescu et al., 2018[18]	Case report	1	53, F	Alcohol (1)	Lumbar (1)	Gram-negative *Enterobacter* spp. (1)	1	NA	14 (from Sxs to Dx)	3	NA
Cross & Howell, 2003[19]	Case report	2	47, F 54, F	Alcohol (1); viral (1)	Lumbar (2)	*S. aureus* (2)	1	1	NA	21; 122	84; 21
Webster et al., 2007[20]	Case series	4	40, M	Viral/IVDU (1)	Thoracic (1)	*S. aureus* (1)	1	1	2	56	56
Sakaguchi et al., 2017[21]	Case report	1	67, M	Alcohol (1)	Cervical (1)	Gram-negative *Escherichia coli* (1)	NA	1	2	46	NA
Lin et al., 2019[22]	Case series	14	83, M; 72, F	Liver cancer (1); other (1)	Thoracic (1); lumbar (1)	*Staphylococcus* (1)	2	2	426; 92	77; 49	365

Dx = diagnosis; FU = follow-up; IVDU = intravenous drug use; NA = not applicable; Op = surgery; Sxs = symptoms; Tx = treatment.

reticuloendothelial, and immunoglobulin function.[23–25] Those factors, combined with poor nutritional status in this population, may affect protective immune mechanisms, making the rate and aggressiveness of infections more relevant.[26]

PSIs predominantly involve vertebrae and the intervertebral disc and commonly arise from hematogenous spread of bacteria, with *S. aureus* and *Streptococcus* species frequently isolated as causative agents of PSIs.[6,27] Notably, infections with *S. aureus* in the patients with VO are associated with a higher rate of complications and a trend toward higher mortality.[28] VO can originate exogenously, such as direct infection after injury to a wound and bone, or endogenously, in which infection spreads from other areas of the body, such as in endocarditis.[29] Patients with liver cirrhosis have frequent bacteremias brought about physiologically by increased intestinal permeability, immune dysfunction, and the need for frequent invasive procedures. Liver cirrhosis–associated immune dysfunction involves changes to both innate and acquired immunity via increased systemic inflammation and immunodeficiency. Persistent stimulation of immune cells leads to the production of proinflammatory cytokines. An exaggerated inflammatory response in cirrhosis caused by increased intestinal translocation of bacteria increases the occurrence of systemic bacterial infections.[30,31]

Interestingly, our study showed a relatively high rate of neurological compromise. Neurological status was reported in all 129 patients, with neurological deficit occurring in 89 (69%), a higher value compared with other studies. In 207 patients with spondylodiscitis, Pola et al.[32] found a 23% rate of neurological deficit at the time of diagnosis. Madhavan et al.,[33] in a systematic review of 212 patients with spondylodiscitis and end-stage renal disease, found a rate of 46% of neurological compromise. Similar to our findings, Pojskić et al.,[34] in a review of 237 patients, reported 72% preoperative neurological compromise. Of note, 146 patients (61.6%) had epidural abscess at the time of diagnosis in their series. In our study, epidural abscess was found in 103 patients (79.8%).

Secondary epidural abscesses in patients with PSIs are considered a more aggressive form of spondylodiscitis.[32,35] In this regard, the same factors that predispose patients with chronic liver disease to higher risk of PSI could also explain more aggressive infections. In their study consisting of 55 patients with spondylodiscitis, Urrutia et al.[11] found that chronic liver failure was significantly associated with the presence of neurological compromise secondary to epidural abscess. Similar to Urrutia et al., our findings indicate that chronic liver disease could increase the risk of epidural abscess and neurological compromise because liver disease is a general risk factor for infections.[23,36] These patients have increased permeability at the gastrointestinal barrier system due to changes in the intestinal flora. Moreover, the compromised neutrophil and reticuloendothelial systems and higher rate of skin and mucous membrane disruption due to invasive procedures (central and urinary catheter, endotracheal intubation) can put these patients at a higher risk of bacteremia and, consequently, risk of infection.[23,24,37,38]

That spondylodiscitis in this population appears to be more aggressive may explain higher indications for surgery; our study showed that surgery was performed in 91 patients (70.5%). Similar results were reported by Pojskić et al.;[34] the authors treated 221 of 237 patients (93%) surgically. Similar to our findings, the authors reported a high rate of neurological compromise. On the other hand, in 250 patients with spondylodiscitis with 2 years of follow-up, Pola et al.[32] performed surgery in 101 (44%). The main indications for surgery in their study were neurological compromise and segmental instability. Our study also showed a high rate of postoperative complications (n = 28; 30%) compared with other series such as Pojskić et al. (21%) and Pola et al. (3.6%).

Regarding mortality, our study showed a 1-year mortality rate of 28.9%. This value is considered higher compared with the rates reported in the literature by most of the studies (1.8%–24%).[33,34,39–42] In a cohort of 298 patients with spondylodiscitis, Kehrer et al.[43] found a 1-year mortality rate of 20%, and among factors associated with increased mortality, the authors mentioned abscess formation and neurological deficit as well as alcohol dependence and immunocompromised status as predictors of mortality. Madhavan et al.,[33] in a systematic review of 212 patients with spondylodiscitis and end-stage renal disease, found a mortality rate of 24%. Both liver and renal disease are well-known factors associated with increased mortality in patients without spondylodiscitis.[44–45] In our study, we believe that the same factors that explain the higher aggressiveness of spondylodiscitis in patients with chronic liver disease could contribute to the higher mortality found in this population.

Our study showed that patients with spondylodiscitis and chronic liver disease had higher rates of epidural abscess and neurological compromise and, therefore, indication for surgery. Moreover, postoperative complications and mortality were also higher compared with patients without liver disease. In this regard, our findings suggest that spondylodiscitis appears to be more aggressive in this population. This observation should be considered at the time of treating this severe combination, with efforts aimed at improving patient condition and decreasing the rate of postoperative complications and mortality.

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Author Contributions

Conception and design: Camino-Willhuber, Hatter, Brown, Oh, Bhatia, Lee. Acquisition of data: Camino-Willhuber, Beyer, Hatter, Bhatia, Lee. Analysis and interpretation of data: Camino-Willhuber, Beyer, Hatter, Brown, Bhatia, Lee. Drafting the article: Camino-Willhuber, Beyer, Hatter, Franklin, Brown, Bhatia. Critically revising the article: Camino-Willhuber, Beyer, Hatter, Franklin, Brown, Oh, Bhatia, Lee. Reviewed submitted version of manuscript: Camino-Willhuber, Beyer, Franklin, Brown, Hashmi, Oh, Bhatia. Approved the final version of the manuscript on behalf of all authors: Camino-Willhuber. Statistical analysis: Bhatia. Administrative/technical/material support: Hashmi, Bhatia. Study supervision: Brown, Hashmi, Oh, Bhatia.

Correspondence

Gaston Camino-Willhuber: University of California, Irvine, Orange, CA. gcaminow@hs.uci.edu.