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Arthroplasty in patients with rare conditions

Total joint arthroplasty in patients with chronic infectious liver disease

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ABSTRACT

The opportunity for total joint arthroplasty (TJA) in patients with chronic infectious liver disease is rapidly expanding. This is the product of both superior survival of chronic hepatitis patients, evolving implant technologies, and improvement of techniques in TJA. Unfortunately, treating this group of patients is not without significant challenges that can stem from both intrahepatic and extrahepatic clinical manifestations. Moreover, many subclinical changes occur in this cohort that can alter hemostasis, wound healing, and infection risk even in the asymptomatic patient. In this review, we discuss the various clinical presentations of chronic infectious liver disease and summarize the relevant literature involving total joint arthroplasty for this population. Hopefully, through appropriate patient selection and perioperative optimization, treating surgeons should see continued improvement in outcomes for patients with chronic infectious liver disease.
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Introduction

Medical advances in recent years have improved the morbidity and mortality of many chronic conditions. Chronic infectious liver conditions are now associated with superior survival outcomes, and as such, garner increased attention from care providers as challenges associated with increased longevity are encountered [1,2].

Technological advances in techniques and materials of total joint arthroplasty (TJA) have allowed for longer implant survival and the ability to treat younger patients [3—5]. This convergence has generated an overlap between chronic infectious liver disease patients and TJA that mandates the attention of orthopedic surgeons and collaborating providers caring for this challenging population.

Case history

A 57 year-old male patient was referred for evaluation. He was status post bilateral TKA. The left TKA was performed 3 years and 11 months previously, and the right TKA was performed 3 years and 6 months previously. The patient had been experiencing worsening pain in the left knee, now rated 10/10, and was unable to weight bear on the knee for the past 6 weeks, requiring a power scooter for general mobility. Images at initial presentation are shown in Fig. 1.

Examination at that time demonstrated an obtunded patient with a BMI of 35.9. He had well healed incisions, with a symmetric range of motion from 20 to 100°. There was a mild effusion and tenderness at the femur and tibial aspects of the left knee, with inability to bear weight on the limb. Lab values included WBC 4.2k, CRP 1.3, Hgb 9.3, and a platelet count of 76. Two recent knee aspirations performed at our center demonstrated no evidence of bacteria on the gram stains or final cultures. Synovial WBC count was initially 720 with 60% neutrophils, and the second aspirate performed four months later revealed 1980 WBC with 83% neutrophils.

During the initial examination, the patient was frankly disoriented and incoherent and was spoken for by his wife, who advocated for him to seek surgical intervention for his knee pain. He had a well-established history of viral hepatitis with cirrhosis, and had been admitted for hepatic encephalopathy 4 to 5 times over the past 2 years at various local hospitals. After a brief orthopedic exam, the patient was removed from the office by emergency rescue and admitted to the hospital directly, where he was treated once again for encephalopathy and ultimately released.
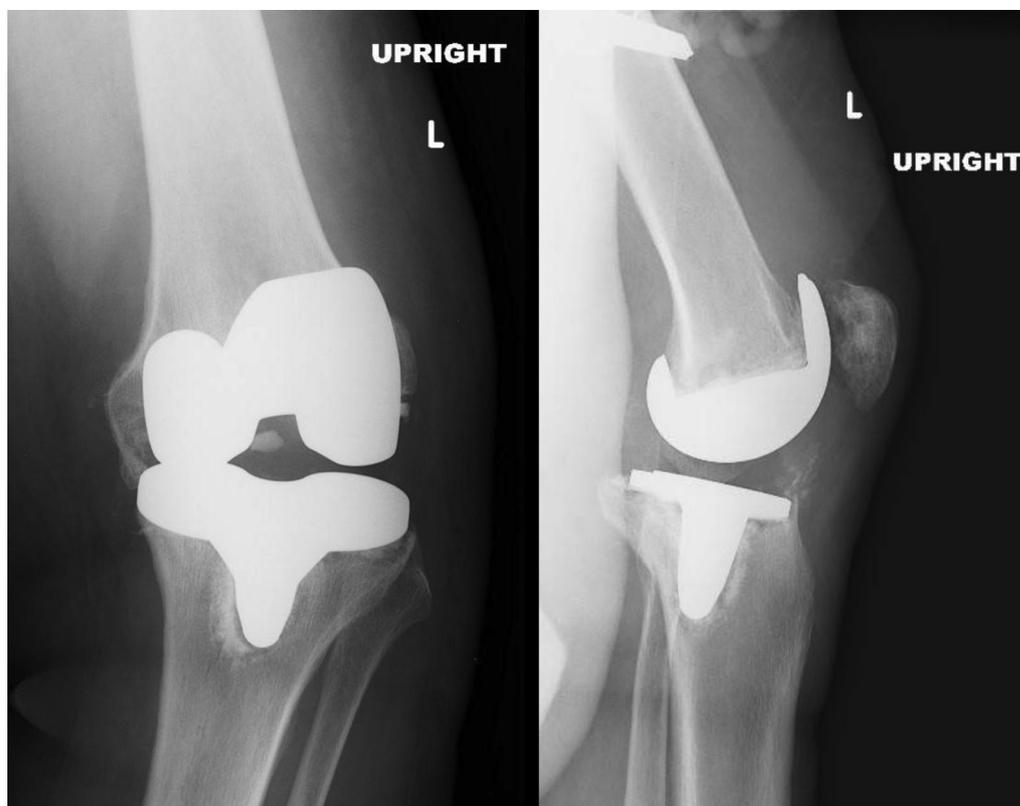
Figure 1. Pre-operative radiographs at initial presentation demonstrating prior left TKA.

Further information was then obtained from the patient's internist and gastroenterologist. Records revealed a diagnosis of Hepatitis C, Type 2b. Known co-morbidities included neutropenia, anemia, thrombocytopenia, and cirrhosis with established portal hypertension. A prior transjugular intrahepatic portosystemic shunt (TIPS) procedure had already been performed to help stabilize his cirrhosis.

RNA Viral load three years prior to his presentation above was 196552 IU/mL (reference 0–615 IU/mL) and both Hepatitis A and B testing were non-reactive. His MELD score at that time was 10. Albumin was 2.8 G/dL (Ref Range: 3.5–5.5 G/dL) and total protein was 7.4 G/dL (Ref Range: 6–8.3 G/dL). Within a year of presentation, records revealed his MELD score had climbed to 15, with an RNA viral load of 560431 IU/mL. Three months prior to presentation, his ammonia level was 108 ug/mL (reference 17–80 ug/mL), and the albumin had improved to 3.1 G/dL.

After the patient's encephalopathy was clinically stabilized he expressed a clear desire to seek treatment for his left knee, and then underwent further preoperative testing with the support of his medical physicians. It was felt that he was optimized to the best degree achievable at that time, and that the potential benefit of revision TKA for this patient outweighed the risks for complications.

Scintigraphic testing with a 3-phase bone scan was conducted (Fig. 2), revealing increased activity at the left knee on all three phases. Delayed images showed diffuse, marked uptake on both sides of the left knee joint suspicious for a prosthesis infection. A radio labeled Indium WBC scan (Fig. 3) demonstrated an area of focal uptake on the medial left knee without concordant uptake on the bone marrow scan, therefore suspicious for infection. Preoperative labs revealed an ESR of 52, and INR of 1.5, and a CBC showed a WBC of 2.8, hemoglobin 8.8, and platelets of 96k.

Intraoperative findings revealed diffuse thickening of the synovium with no purulence, and gross loosening of the femur and

tibial components of the TKA. The failed rotating-platform TKA was then revised in a single-stage fashion. Cemented stems with metal component augmentation was used with retention of the well-fixed patellar resurfacing button, and a constrained implant design (Triathalon TS, Stryker Corporation, Kalamazoo, MI, USA) was selected given his significant intra-operative periarticular tissue laxity (Fig. 4) Intraoperative frozen sections revealed an average of 2 neutrophils per high power field. Cultures of joint fluid, and two tissue cultures showed no bacteria on any gram stains or final cultures, and both fungal and AFB stains and cultures were also negative.

Postoperatively, the patient was given a compressive dressing with a knee immobilizer for two weeks while being allowed to weight bear as tolerated on the left lower extremity. DVT prophylaxis with Lovenox 40 mg SC Daily was initiated and maintained for 4 weeks, and his Aspirin 81 mg daily dose was continued throughout. The patient healed uneventfully in the early phase of recovery. At the time of this report, he is now 2 years and 6 months postop. He has regained the ability to walk and continues to use a cane for balance. ROM of the left knee is from 0 to 120 with stable collateral exam and smooth patellar tracking. He reports intermittent fatigue and is intermittently somnolent, but is able to complete all ADL's and continues to be independent at baseline. No further viral load testing is available at this time.

Discussion

Epidemiology

Chronic infectious liver conditions span a diverse set of patients stemming from multi-faceted modes of transmission. Such modes result in new infections across all age groups. Since the broad adaptation of the hepatitis B vaccine into medical practice, the

Figure 2. Tc-99m MDP three-phase bone scan. Study demonstrated mildly increased flow to the left knee. On the tissue phase, there was increased activity surrounding both sides of the left knee joint, more prominent on the femoral side. On delayed imaging, there was diffuse, marked increased uptake on both sides of the left knee joint suggestive of prosthesis infection.

incidence of hepatitis B has been steadily decreasing across all age groups [6]. However, a significant population still exists with chronic HBV infections, amounting to ~800,000 people in the United States [7]. Most infections take place via sexual transmission and blood borne routes.

For hepatitis C, the Center for Disease Control (CDC) recently reported that the highest incidence of new infections occurred in patients between 20 and 29 years of age in 2012 (2 reported per 100,000 population). Patients aged 50 to 59 were found to have an increasing incidence between 2010 and 2013 from 0.2 per 100,000 to 0.35 per 100,000 [6]. This population segment is coincident with the patient group now most commonly seeking total joint arthroplasty in the United States, prompting the need for surgeon awareness of this topic. Furthermore, 60% of hepatitis transmissions took place in the setting of intravenous drug use, 10% secondary to transfusions, 15% were sexually transmitted, and 5% of infections were seen in hemodialysis and healthcare workers secondary to needle sticks [8]. A total of approximately 4 million persons in the United States are now living with chronic hepatitis C virus, representing 1.5% of the 320.7 million people currently living in the US [9].

*Natural history of chronic infectious liver disease*

Hepatitis C

Prior to 1990, before routine screening of donated blood for HCV, patients at highest risk for acquiring acute hepatitis C included those who received blood transfusions, blood products or anti-D immunoglobulin in pregnancy, intravenous drug users, tattoo or body piercing recipients under unsterile conditions, heath care workers, dialysis patients, and those partaking in "high risk" sexual activities [1]. After the introduction of routine screening of blood products, the demographic profile of newly infected patients changed to predominantly those who use intravenous drugs and homosexual men [10]. For those who are infected, the acute phase is often unrecognized, as patients are typically asymptomatic or have mild, viral flu-like complaints. The rate of clearance of the hepatitis C virus in the acute phase is reported to be roughly 15–40% [1,11].

The evolution of liver cirrhosis secondary to chronic HCV infection has been reported to be 10–20% over the course of 20–30 years [12,13]. Co-infection with hepatitis B and HIV, given the shared route of transmission for these diseases is common and puts the patient at a higher risk for progression to liver cirrhosis and the associated development of hepatocellular carcinoma (HCC) [14,15]. Treatment of patients with anti-viral medications (such as interferon-alpha, sofosbuvir, and simeprevir) has demonstrated significant improvements in necro-inflammation and fibrosis scores that correlate with improved surgical outcomes [16,17].

Hepatitis B

Infection by the hepatitis B virus shares a similar etiology as hepatitis C; however, the majority of the infected hepatitis B
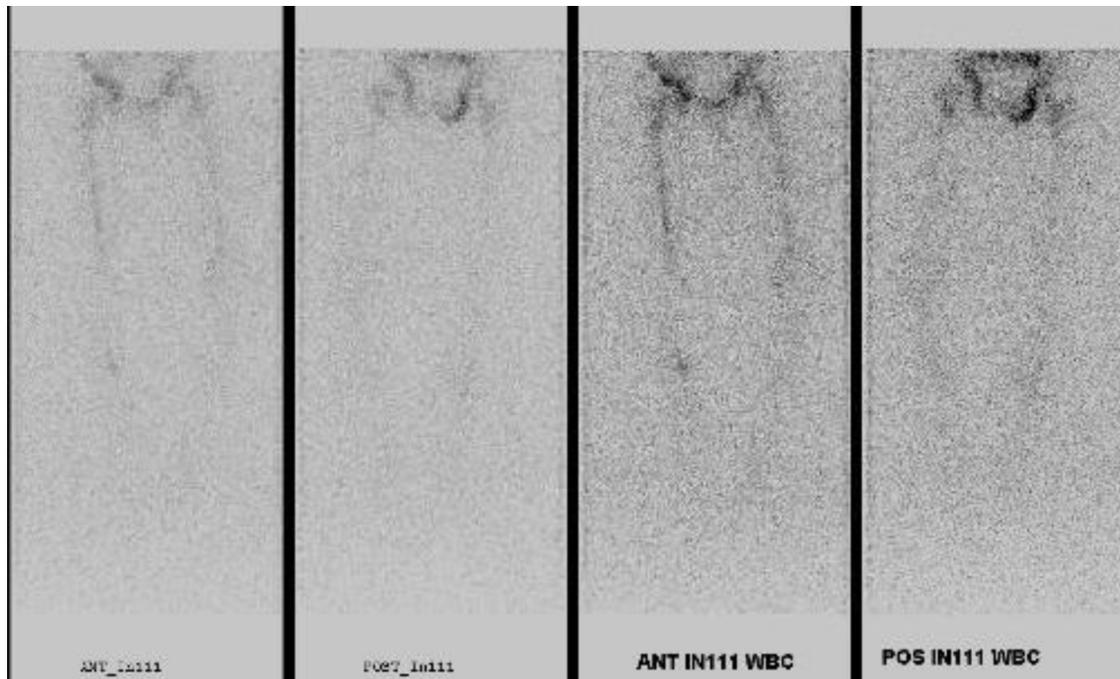
Figure 3. Indium WBC scan. Study demonstrated focus of mild increased white blood cell uptake located at the medial femoral component of the left total knee arthroplasty without concordant uptake on the bone marrow scan. This was found to correspond with the site of the most prominent increased uptake on the 3-phase bone scan consistent for prosthesis infection.

population is able to clear the virus, such that fewer than 5–10% of the patients go on to have persistent infection [18–20]. Of the cohort that continues on to develop chronic HBV infection, roughly 20% eventually develop liver cirrhosis. Factors such as HIV and HCV co-infection and chronic alcohol intake have been linked to the incidence of liver cirrhosis [20]. Similar trends were seen when evaluating the development of HCC in patients with hepatitis B with the annual incidence of HCC estimated be at 2–3% in patients with chronic hepatitis B [21].

Anti-viral therapies aimed at reducing viral loads have shown to significantly reduce necroinflammation and fibrosis leading to cirrhosis. This has resulted in a significantly higher portion of patients who do not progress onto cirrhosis or developing HCC [22,23].

Extrahepatic manifestation of chronic infectious liver disease

In addition to intrahepatic manifestations, numerous extrahepatic presentations can manifest in chronic liver disease patients [24,25]. Manifestations can affect numerous organ systems, including hematologic, dermatologic, renal, endocrine, ocular, vascular, neuromuscular, and neuropsychiatric [26]. A significant portion of these findings are immune related. Mixed cryoglobulinemia vasculitis is a small vessel vasculitis that presents with damage to multiple end organs. The skin is affected most frequently in the form of palpable purpura and chronic cutaneous ulcers. Neuropathies are often encountered, as well as, membranoproliferative glomerulonephritis related nephropathy [26]. Some studies have noted the conversion of the relatively benign vasculitis to a more malignant lymphoproliferative state, particularly, B-cell non-Hodgkin lymphoma [27]. Cardiovascular disease in the form of coronary atherosclerosis and carotid plaques have been implicated with chronic hepatitis [24,28]. Though the etiology is unclear, an increased association of insulin-resistant diabetes mellitus has been

reported. Cacaoub et al., reported that 38% of the patients included in their analysis manifested at least 1 extrahepatic finding, with a preponderance of rheumatic (19%) in the form of arthralgia, myalgia and Sicca syndrome and cutaneous symptoms (17%) [24,26,29].

Effects of subclinical hepatitis

Observable clinical symptoms do not always portray the true extent of disease in chronic infectious liver disease patients. Studies have shown that numerous subclinical changes occur leading to important changes in physiology even in the asymptomatic patient (Table 1). Pour et al. investigated patients with non-cirrhotic hepatitis C ($n = 71$) undergoing TJA [30]. All of the patients underwent either total knee arthroplasty (TKA) or total hip arthroplasty (THA) and had no signs of active infection, defined as normal liver enzymes and no signs of cirrhosis. Compared to the control group ($n = 150$) increased surgical complications were noted in seropositive asymptomatic patients including longer hospital stays (5.2 days vs. 3.5 days, $p = .006$), and higher reoperation rates (15% vs. 4.2%, $p = .004$).

Similar findings were found in a recent article across a national database for increased medical complications in asymptomatic hepatitis C seropositive patients undergoing a TJA [31]. Compared to a control group, patients with hepatitis C were twice as likely to suffer a medical complication including the need for a blood transfusion, post-transfusion anemia, acute renal failure, cardiac-related complication, and pneumonia. A multivariable regression analysis showed that the odds ratio for the occurrence of a medical complication in a patient with hepatitis C (OR 2.102) undergoing a total hip or knee arthroplasty was higher than a similar patient with atrial fibrillation (OR 1.844), diabetes mellitus (OR 0.937) or an old myocardial infarction (OR 0.877), and was comparable to having congestive heart failure (OR 2.108). Also, when matched to the seronegative controls, the asymptomatic hepatitis C cohort without cirrhosis had nearly 4 times the odds of developing a pulmonary
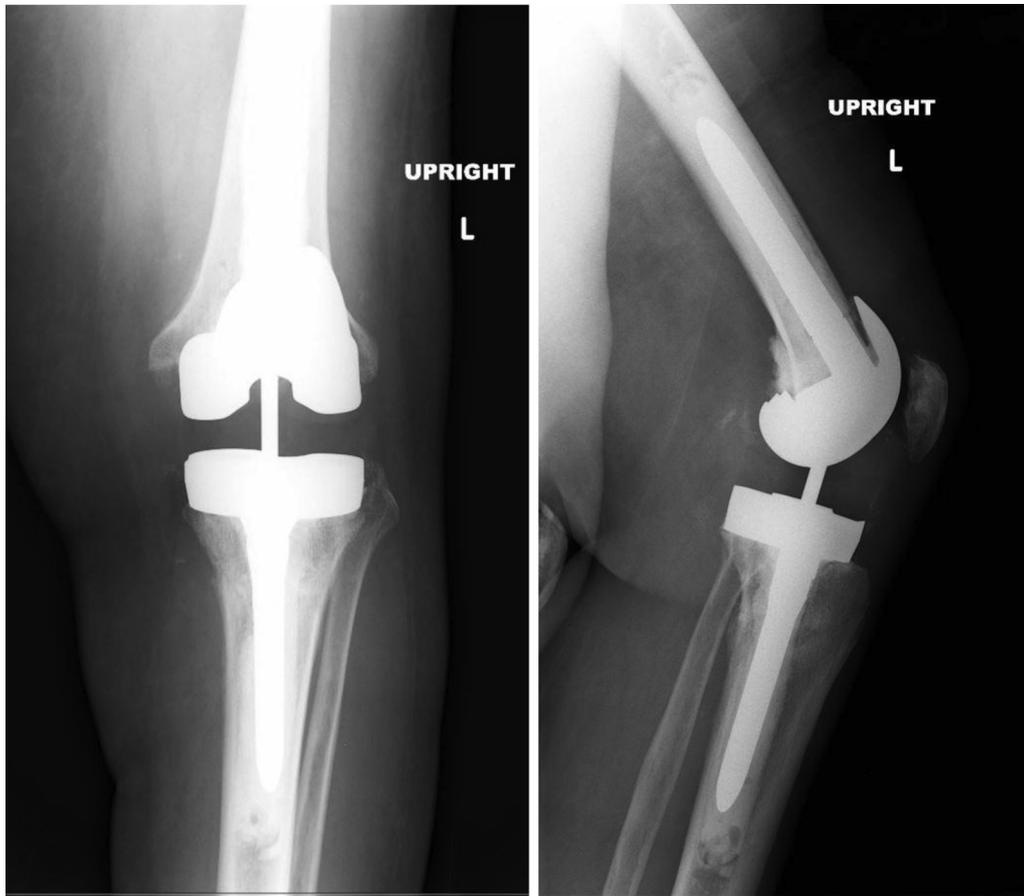
Figure 4. Post-operative left TKA revision radiographs.

embolism and almost 3 times the odds of developing a DVT following total joint arthroplasty.

A recent study of the NIS database further supported such findings across a general population of patients infected with hepatitis C. First, the study acknowledged that the percentage of patients infected with hepatitis C receiving TKAs increased from 0.18% to 0.5% between 1998 and 2010. Expectedly, hepatitis C infected patients ($n = 23,338$) were found to be younger (67 vs. 58 yrs) and had a higher rate of surgical indication related to osteonecrosis (0.7 vs. 1.6%, $p < .0001$). Hepatitis C infection in the context of TKA carried a 1.34 higher odds ratio of perioperative complications including pulmonary embolism, implant infection, deep venous thrombosis and wound related complications. Following the trend of TJA in general, both groups, however, had shorter length of stays at the end of the studied period, but was lower in the hepatitis population (4 vs. 3.75 days) [32].

Studies have shown that although the asymptomatic, seropositive patient may have normal liver enzymes, the presence of autoantibodies, cryoglobulins and impaired lymphoproliferation may explain the observed differences in this patient population. These changes may also play an indirect role in wound healing, hemodynamics, infection rates and medical stability [25,33].

Table 1
Important subclinical changes in the chronic infectious liver disease patient.

Autoantibodies
Cryoglobulins
Lymphoproliferation
Thrombocytopenia
Impaired platelet function

Additionally, it is well known that even in the absence of cirrhosis, patients may have impaired platelet function and thrombocytopenia [34,35]. Pour et al. recognized the possible contribution of impaired platelet function when noting increased wound drainage following total hip arthroplasty, but not following TKA in patients with asymptomatic hepatitis C compared to the control group [30]. This difference seen between the hip and knee patients was postulated to be secondary to the use of a tourniquet in the total knee population leading to extrinsic small arterial and capillary hemostasis.

Effects of cirrhotic hepatitis

Historically, chronic liver disease has been associated with higher rates of surgical morbidity and mortality. Numerous studies have reported perioperative mortality rates as high as 25% in non-orthopedic procedures [36,37]. In addition to high mortality rates, complications are not limited to increased bleeding, higher infection rates, renal insufficiency, encephalopathy, as well as multisystem organ failure [38].

Shih et al., were one of first groups to look at cirrhotic patients undergoing total joint arthroplasty. They followed 51 patients following TKA over an average of 42 months and compared how they did to a matched cohort without liver cirrhosis [39]. Etiology of cirrhosis in their group included hepatitis B, hepatitis C, and secondary to alcohol use. However, etiology specifically was not found to be a contributing factor when evaluating outcomes. Cirrhotic patients had statistically significant higher rates of overall complications (22/51 vs. 3/51, $p < .001$), higher mortality rates (15/42 vs.

2/42, $p < .001$), lower functional scores (76 vs. 88, $p < .001$) and longer operative times (128 min vs. 102 min, $p < .001$). Observed risk factors for increased complications included a history of hepatic decompensation or variceal bleeding, attributing to a relative risk increase of 3.3 compared to the control. Factors for infection, the most common complication, included the above along with increased age, and history of thrombocytopenia. Yet, despite the higher complication rates, Child-Turcotte-Pugh (CTP) class-A (Table 2) cirrhotic patients achieved good functional results in 71% of cases [40]. In light of the clinical improvement, the authors felt that in selected patients, TKA was a safe and beneficial intervention.

Another recent investigation suggests that from 2000 to 2009 in the United States there was a national volume increase of 182% and 304% for primary THA and TKA performed in patients also diagnosed with cirrhosis within the National Inpatient Sample. This study may be the largest to date, and evaluated a total of 2.082 million THA and 4.475 million TKA patients and showed increased risks for patients with cirrhosis following lower extremity arthroplasty, including longer LOS, increased cost, thrombocytopenia, infection, acute renal failure, hemorrhage, stroke, and postoperative blood transfusion. Patients with alcoholic cirrhosis had the highest adjusted risk for thrombocytopenia (OR THA 14.54, TKA 19.45) compared with viral hepatitis (OR THA 3.99, TKA 3.76); overall adjusted risk of all complications for patients with alcoholic hepatitis was also higher (OR THA 2.23, TKA 2.58) than seen in patients with viral hepatitis (OR THA 1.35, TKA 1.33) [41].

Expanding on earlier work, Orozco et al. focused more specifically on the surgical impact of thrombocytopenia and fibrosis in patients with hepatitis C [42]. The retrospective study of 72 patients found no significant differences between patients with hepatitis C and a control group in regards to length of stay, blood loss, or hemoglobin drop following both THA and TKA. When a subset of patients with clinical thrombocytopenia (<150,000/μL) was examined, no statistically significant differences were observed across many outcomes including infection rate, reoperation rate, requirement for irrigation and debridement, and hemoglobin drop. Though not significant, the results did show a trend toward increased infection rate in the thrombocytopenic group (25% vs. 9%, $p = .23$), increased cellulitis or hematoma related admissions (12% vs. 4%, $p = .40$) and an increase in any adverse event (37% vs. 13%, $p = .13$). Unfortunately, as the authors attest, the study was simply underpowered to reach any significant conclusions regarding these findings. The authors did find significant differences when isolating patients with fibrosis and comparing them to the group of hepatitis C patients without fibrosis. Statistically significant increases in rates of infection and admission for cellulitis and hematoma, as well as greater hemoglobin drops were observed in the group with fibrosis. These findings supported the viewpoint that fibrosis is associated with higher complication rates but failed to address the impact of clinically significant thrombocytopenia in patients with hepatitis C undergoing TJA [37,42].

Table 2
Child-Turcotte-Pugh (CTP) classification system [42].

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Grade 1–2	Grade 3–4
Bilirubin (mg/dL)	<2	2–3	3>
Prothrombin (INR)	<1.7	1.7–2.3	>2.3
CPT classification:			
Child A: score 5–6 (well compensated)			
Child B: score 7–9 (significant functional compromise)			
Child C: score 10–15 (decompensated)			

Table 3
Positive predictive factors for reduced complication rates in patients undergoing TJA with chronic infectious liver disease.

Young patients
Child class-A cirrhosis
MELD < 10
No history of hepatic decompensation
No history of variceal bleeding
Elective circumstances

As shown by Cohen et al., surgical outcomes may also vary between patients undergoing elective and emergent TJA [43]. The authors showed that in general, all cirrhotic patients when matched to an equal control group, had longer operative times (138 min vs. 93 min; $p = .0004$), longer hospital stays (8.3 days vs. 5.1 days, $p = .0007$) and an increased number of major perioperative complications (6 vs. 3, $p = .006$). However, when the elective cases were separated from the emergent cases, substantial differences emerged. With the exception of hospital length of stay, (8.7 days vs. 4.7 days, $p = .0005$) no significant differences existed for elective total hip arthroplasty in patients with cirrhosis and the control group. In contrast, those undergoing emergent total hip arthroplasty with a concurrent diagnosis of cirrhosis had statistically significant higher rates of blood loss, operative time, hospital days, major complications, liver decompensation and death compared to the elective cases. These findings further support the claim that recognition of risk factors and subsequent perioperative optimization plays an important role in risk reduction for cirrhotic patients undergoing TJA.

Current controversies and future considerations

Currently, no formal guidelines exist for the treatment of patients with infectious chronic liver disease undergoing TJA. Despite this, recommendations can be made to decrease the likelihood of perioperative complications and optimize overall outcomes. First, all patients should be screened for preoperative anemia and thrombocytopenia. Second, all patients should be interviewed to determine the etiology of the cirrhosis (if present), as alcoholic liver disease may have a higher risk profile than viral hepatitis cases undergoing arthroplasty. Any known history of GI varices or acute bleeding events, hepatocellular carcinoma, or hepatic encephalopathy should be identified and considered as definite indicators of more advanced liver disease.

In all cases, a complete and thorough discussion must be had with the patient to emphasize the increased speculative risk

$$MELD = 3.78 \times \log_e \text{ serum bilirubin (mg/dL)} +$$
$$11.20 \times \log_e \text{ INR} +$$
$$9.57 \times \log_e \text{ serum creatinine (mg/dL)} +$$
$$6.43 \text{ (constant for liver disease etiology)}$$
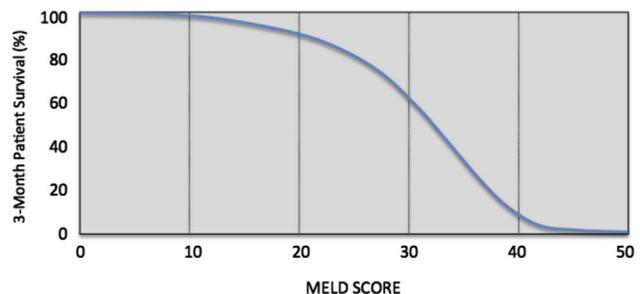
Figure 5. Model for End Stage Liver Disease (MELD) score [43].

associated with an elective procedure, even in cases of an asymptomatic patient with subclinical hepatitis. These risks may be magnified in patients undergoing THA as compared with TKA, but caution is to be emphasized in all cases. A multi-disciplinary approach is warranted, including preoperative consultations with both an internist and hepatologist; consultation with a hematologist may be indicated when preparing for surgery to better address the complex hemostasis issues that are unique to liver disease patients. Given equivocal data regarding thrombocytopenia, functional platelet testing may also be reasonable.

Patient selection is also an important component for improved outcomes (Table 3). Potential risk factors including prior history of hepatic decompensation, variceal bleeding, and cirrhosis, all of which have been found to negatively impact outcomes, mandates both a further discussion with the patient regarding expected outcomes as well as adequate perioperative optimization. Stratifications such as Child-Turcotte-Pugh scores and MELD scores (Fig. 5) may provide objective data in which to educate the patient and co-management teams [44,45]. For example, Tiberi et al., found that MELD scores less than 10 were predictive of better outcomes in patients undergoing TJA with liver cirrhosis. Especially, in cases of elective surgical intervention, medical optimization such as viral treatment to lower the overall burden of disease may improve the long-term outcome. Unfortunately, newer therapies such as Sofosbuvir may not be cost-effective. Moreover, the short-term or long-term outcomes that accompany decreased viral loads has not been vigorously tested [17]. A study on HIV patients undergoing TJA found that a significant drop in CD4 counts accompanied the development of deep implant infections, but lower values did not lead to increased rates [46]. This study suggests that change in viral load and disease progression may be more important than absolute viral load.

Summary

Fortunately for the many patients who suffer from mild to moderate infectious chronic liver disease and degenerative joint disease, the literature supports performing TJA for this population despite an elevated potential for perioperative risk, especially under elective conditions in younger patients without a history of hepatic decompensation, variceal bleeding, or fibrosis associated with liver cirrhosis. For patients with more severe liver disease, including documented cirrhosis and varices, more significant caution is urged before considering TJA. This higher risk population should be comprehensively evaluated by a multidisciplinary team of specialists preoperatively, as complication rates following TJA can rise dramatically and may negatively affect outcomes.

KEY POINTS

- TJA can be performed safely in patients with chronic infectious liver disease when properly screened and medically optimized.

- Subclinical changes in patients with chronic infectious liver disease can lead to devastating complications.

- Risk factors for increased complications include older patients, MELD score >10, history of hepatic decompensation and/or variceal bleeding, as well as emergent timing.

- MELD score should be considered in patients during initial screening.

References

[1] Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol 2014;61(1S):S58.
[2] Fung J, Lai CL, Yuen MF. Management of chronic hepatitis B in severe liver disease. World J Gastroenterol 2014;20(43):16053.
[3] Ravi B, Croxford R, Reichmann WM, et al. The changing demographics of total joint arthroplasty recipients in the United States and Ontario from 2001 to 2007. Best Pract Res Clin Rheumatol 2012;26(5):637.
[4] Pivec R, Johnson AJ, Mears SC, Mont MA. Hip arthroplasty. Lancet 2012;380(9855):1768.
[5] Kamath AF, Prieto H, Lewallen DG. Alternative bearings in total hip arthroplasty in the young patient. Orthop Clin North Am 2013;44(4):451.
[6] CDC. Viral Hepatitis Surveillance. 2012.
[7] Wasley A, Kruszon-Moran D, Kuhnert W, et al. The prevalence of hepatitis B virus infection in the United States in the era of vaccination. J Infect Dis 2010;202(2):192. Accessed 15.12.14.
[8] Rosen HR. Chronic hepatitis C infection. N Engl J Med 2011;364(25):2429.
[9] Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology 2010;138(2):513. Accessed 20.12.14.
[10] Van de Laar TJW, Matthews GV, Prins M, Danta M. Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection. AIDS 2010;24(12):1799. Accessed 25.12.14.
[11] Wang CC, Krantz E, Klarquist J, et al. Acute hepatitis C in a contemporary US cohort: modes of acquisition and factors influencing viral clearance. J Infect Dis 2007;196(10):1474. Accessed 25.12.14.
[12] Yano M, Kumada H, Kage M, et al. The long-term pathological evolution of chronic hepatitis C. Hepatology 1996;23(6):1334. Accessed 25.12.14.
[13] Seeff LB. Natural history of chronic hepatitis C. Hepatology 2002;36(5 Suppl. 1):S35. Accessed 08.12.14.
[14] Cho LY, Yang JJ, Ko K-P, et al. Coinfection of hepatitis B and C viruses and risk of hepatocellular carcinoma: systematic review and meta-analysis. Int J Cancer 2011;128(1):176. Accessed 25.12.14.
[15] Thein H-H, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. AIDS 2008;22(15):1979. Accessed 25.12.14.
[16] Marcellin P, Boyer N, Gervais A, et al. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. Ann Intern Med 1997;127(10):875. Accessed 09.12.14.
[17] Hagan LM, Sulkowski MS, Schinazi RF. Cost analysis of sofosbuvir/ribavirin versus sofosbuvir/simeprevir for genotype 1 hepatitis C virus in interferon-ineligible/intolerant individuals. Hepatology 2014;60(1):37.
[18] Ganem D, Prince AM. Hepatitis B virus infection—natural history and clinical consequences. N Engl J Med 2004;350(11):1118. Accessed 27.11.14.
[19] Wright TL, Lau JY. Clinical aspects of hepatitis B virus infection. Lancet 1993;342(8883):1340. Accessed 14.12.14.
[20] Yim HJ, Lok AS-F. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology 2006;43(2 Suppl. 1):S173. Accessed 08.12.14.
[21] McMahon BJ, Holck P, Bulkow L, Snowball M. Serologic and clinical outcomes of 1536 Alaska Natives chronically infected with hepatitis B virus. Ann Intern Med 2001;135(9):759. Accessed 25.12.14.
[22] Lin SM, Sheen IS, Chien RN, Chu CM, Liaw YF. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. Hepatology 1999;29(3):971. Accessed 25.12.14.
[23] Dienstag JL, Goldin RD, Heathcote EJ, et al. Histological outcome during long-term lamivudine therapy. Gastroenterology 2003;124(1):105. Accessed 08.12.14.
[24] Cacoub P, Gragnani L, Comarmond C, Zignego AL. Extrahepatic manifestations of chronic hepatitis C virus infection. Dig Liver Dis 2014;46(S5):S165.
[25] Mayo MJ. Extrahepatic manifestations of hepatitis C infection. Am J Med Sci 2003;325(3):135.
[26] Sène D, Limal N, Cacoub P. Hepatitis C virus-associated extrahepatic manifestations: a review. Metab Brain Dis 2004;19(3–4):357. Accessed 20.12.14.
[27] Ferri C. Non-Hodgkin's lymphoma: possible role of hepatitis C virus. J Am Med Assoc 1994;272(5):355.
[28] Aslam F, Alam M, Lakkis NM. Hepatitis C and carotid atherosclerosis: a retrospective analysis. Atherosclerosis 2010;209(2):340. Accessed 26.01.15.
[29] Cacoub P, Poynard T, Ghillani P, et al. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment virus C. Arthritis Rheum 1999;42(10):2204. Accessed 20.12.14.
[30] Pour AE, Matar WY, Jafari SM, et al. Total joint arthroplasty in patients with hepatitis C. J Bone Joint Surg Am 2011;93(15):1448.
[31] Best MJ, Buller LT, Klika AK, Barsoum WK. Increase in perioperative complications following primary total hip and knee arthroplasty in patients with hepatitis C without cirrhosis. J Arthroplasty 2014.
[32] Issa K, Naziri Q, Boylan MR, Perfetti DC, Mont MA. Total knee arthroplasty in hepatitis-C patients: evaluation of 23,338 patients in nationwide inpatient database. In: American Academy of Orthopaedic Surgeons Annual Meeting, Paper No. 896; 2015. Accessed 09.04.15.

[33] Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001;345(1): 41.

[34] Cines DB, Liebman H, Stasi R. Pathobiology of secondary immune thrombocytopenia. Semin Hematol 2009;46(1 Suppl. 2):S2.

[35] Panzer S, Seel E, Brunner M, et al. Platelet autoantibodies are common in hepatitis C infection, irrespective of the presence of thrombocytopenia. Eur J Haematol 2006;77(6):513.

[36] Rice HE, O'Keefe GE, Helton WS, Johansen K. Morbid prognostic features in patients with chronic liver failure undergoing nonhepatic surgery. Arch Surg 1997;132(8):880.

[37] Friedman LS. The risk of surgery in patients with liver disease. Hepatology 1999;29(6):1617.

[38] Ziser A, Plevak DJ, Wiesner RH, et al. Morbidity and mortality in cirrhotic patients undergoing anesthesia and surgery. Anesthesiology 1999;90(1):42.

[39] Shih LY, Cheng CY, Chang CH, et al. Total knee arthroplasty in patients with liver cirrhosis. J Bone Joint Surg Am 2004;86-A(2):335.

[40] Cholongitas E, Papatheodoridis GV, Vangeli M, et al. Systematic review: the model for end-stage liver disease—should it replace Child-Pugh's classification

for assessing prognosis in cirrhosis? Aliment Pharmacol Ther 2005;22(11—12):1079.

[41] Mudd CD, Schiltz NK, Pillai AC, et al. Impact of cirrhosis on hospital length of stay, costs, and complications after total hip and knee arthroplasty. In: American Academy of Orthopaedic Surgeons Annual Meeting, Poster No. 084; 2015.

[42] Orozco F, Post ZD, Baxi O, Miller A, Ong A. Fibrosis in hepatitis C patients predicts complications after elective total joint arthroplasty. J Arthroplasty 2014;29(1):7.

[43] Cohen SM, Te HS, Levitsky J. Operative risk of total hip and knee arthroplasty in cirrhotic patients. J Arthroplasty 2005;20(4):460.

[44] Tiberi 3rd JV, Hansen V, El-Abbadi N, Bedair H. Increased complication rates after hip and knee arthroplasty in patients with cirrhosis of the liver. Clin Orthop Relat Res 2014;472(9):2774.

[45] Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124(1):91. Accessed 27.01.15.

[46] Lin CA, Takemoto S, Kandemir U, Kuo AC. Mid-term outcomes in HIV-positive patients after primary total hip or knee arthroplasty. J Arthroplasty 2014;29(2):277.