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**Case Report**

# Hepatotoxicity after Sevoflurane Exposure in a Patient with Chronic Hepatitis C

**Abstract**

Sevoflurane is considered a safe inhaled anesthetic of choice in patients with liver disease. Compared to other halogenated inhaled anesthetics, Sevoflurane is reported to lessen the severity of decreased hepatic blood flow and undergoes a different mechanism of hepatic metabolism. In patients with preexisting liver disease, there is potential for low-flow Sevoflurane to induce acute liver damage through other mechanisms. Limited data exists to guide clinical decision-making when quantifying the severity of cirrhosis in patients with hepatitis C and its relationship to anesthesia choice. Previous studies have found that exposure to general anesthesia during abdominal surgery may increase the risk of hepatorenal failure. This study has raised a concern that anesthetics may interfere with various hepatic functions secondary to viral infection. The generation of abnormal liver enzymes and hypercoagulation has provided further exploration for such toxicity.

## Introduction

Previous studies have found that exposure to general anesthesia during abdominal surgery may increase the risk of hepatorenal failure. This study has raised a concern that anesthetics may interfere with various hepatic functions secondary to viral infection. The generation of abnormal liver enzymes and hypercoagulation has provided further exploration for such toxicity. Sevoflurane is considered a safe inhaled anesthetic of choice in patients with liver disease. Compared to other halogenated inhaled anesthetics, Sevoflurane is reported to lessen the severity of decreased hepatic blood flow and undergoes a different mechanism of hepatic metabolism. In patients with preexisting liver disease, there is potential for low-flow Sevoflurane to induce acute liver damage through other mechanisms. Limited data exists to guide clinical decision-making when quantifying the severity of cirrhosis in patients with hepatitis C and its relationship to anesthesia choice.

## Case Description

A 53-year-old male with a history of hypertension and Hepatitis C underwent elective hernia repair. He was referred to the surgical clinic for intermittent abdominal discomfort secondary to a 10x8cm ventral hernia. During the clinic visit, patient reported that he had history of Hepatitis C, but was otherwise asymptomatic and no physical stigmata of cirrhosis were evident. Patient stated that the ventral hernia was the result of abdominal trauma in 1983 requiring laparotomy, and has been progressively enlarging. Aside from occasional discomfort while lying flat, the remainder of review of systems was negative. He had no other surgery besides the posttraumatic laparotomy, any allergies or organ dysfunction. Hypertension was controlled with Furosemide and Spironolactone. He was never symptomatic or treated for Hepatitis C. After discussing the risks, benefits and alternatives of a hernia repair, he was scheduled for operative repair. Preoperative testing and laboratory were ordered according to best practice guidelines. Given this patient history of Hepatitis C, Complete metabolic panel and coagulation panel were ordered (Table 1). On admission, the patient had decreased platelet count (98 x 109/L) and hematocrit (35.7%). Liver aminotransferases and alkaline phosphatase were elevated as well as slightly elevated PT/INR (Table 1). Serum electrolytes and kidney function tests were within normal ranges. Preoperative sedation with Midazolam 2mg was administered. The operation happened as planned. Initially it took about 30 minutes of lysis of adhesions due to his prior hernia. Attention was focused on the hernia repair, therefore no effort was made to lyse adhesions that did not interfere with the procedure, or to explore the rest of the abdomen. However, a portion of the liver, which was readily visible, revealed a hard and nodular appearance, consistent with cirrhosis. During the separation of components, the cutaneous flaps were not excessive, and the external oblique release provided enough length to achieve

**Table 1:** Coagulation and Liver Function Characteristics.

| | Post-Operative Day 3 | Post-Operative Day 2 | Pre-Operative |
|---|---|---|---|
| Biochemistry | | | |
| PT (seconds) | 19 | 18.9 | 13.9 |
| INR | 1.9 | 2 | 1.4 |
| Partial Thromboplastin Time (seconds) | 34.25 | 32.7 | 29 |
| Alk-Phos (units/L) | 188 | 91.7 | 120 |
| ALT (units/L) | 3810 | 1504.7 | 148 |
| AST (units/L) | 14598.5 | 3544.25 | 169 |
| Total Bilirubin (mg/dL) | 5.85 | 3.27 | 1.1 |
| Albumin (gm/dL) | 3.25 | 2.36 | 2.7 |
| BUN (mg/dL) | 12.75 | 26.8 | 12 |
| Cr (mg/dL) | 2.375 | 3 | 0.9 |

Key: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; Alk-Phos: Alkaline Phosphatase; BUN: Blood Urea Nitrogen; Cr: Creatinine; PT: Prothrombin Time; INR: International Normalized Ratio; IV: Intravenous.

a tension free fascia approximation. A light weight polypropylene mesh was placed in the retrorectus space and fixated with transfascial absorbable sutures. The patient tolerated the procedure without any immediate complications.

Low doses of IV Fentanyl 150 mcg, Propofol (Diprivan) 200 mg, Rocuronium (Zemuron) 50 mg, and Ketamine (Ketalar) 20 mg anesthesia was maintained with sevoflurane in end-tidal concentrations of 1.6% volume with oxygen and air (fresh gas flow 2L/min) induced general anesthesia. Anesthesia lasted 4 hours. Throughout the procedure, heart rate, blood pressure, and temperature remained within normal limits. Oxygen saturation stayed above 98%. Estimated blood loss was 700 mL, due to exploration with lysis of adhesions, and reduction of the hernia. Postoperatively, the patient was extubated and he regained consciousness. After recovery in the PACU, the patient was transferred to the general floor. Pain was controlled with Dilaudid. Two days after surgery, the patient became tachycardic, tachypneic, and hypotensive. His abdominal wound was intact but his abdomen was distended and dressings were saturated with blood. After stat labs (Table 1), and imaging, the patient was transferred to the ICU due to impending shock. Labs showed metabolic acidosis with increased anion gap due to lactic acidosis. Despite hemodynamic support, he had a cardiac arrest required CPR. Once return of spontaneous circulation was achieved after 20 minutes, emergent hemodialysis was required for metabolic derangements.

Post-op day three, the patient continued to be hemodynamically unstable was in hypovolemic shock. Acute blood loss despite blood products suggestive of disseminated intravascular coagulation (DIC) and low urine output suggestive of acute renal failure. Increased abdominal distention and high bladder pressure were concerning for abdominal compartment syndrome which lead to emergent decompressive laparotomy. Intraoperatively, there was no major source of bleeding, the liver was cirrhotic but without injury, and there was no evidence of ischemic bowel. Patient was taken to the ICU for further care where he required continued multiple pressor support, hemodialysis, and blood products. Despite all efforts and aggressive measures, the patient became hemodynamically unstable due to multi-organ failure and suffered from cardiac arrest twice. After failure to resuscitate the patient, the decision was made to withdraw all lifesaving measures and the patient expired. With pending autopsy findings, the patient's cause of death is multi-system organ failure in the setting of hepatic dysfunction and DIC.

Autopsy was performed at the patient's family request. Findings, as per medical examiners, revealed no direct anatomical cause of death; however, the patient was noted to have severe macronodular (nodules noted > 3 mm) cirrhosis with dilated venous collaterals, diffuse pulmonary edema, and cardiomyopathy.

## Discussion

Hepatitis C virus, a member of the *Flaviviridae* family with six known genotypes [1], causes a major public health problem and leading cause of decompensated chronic liver disease at a rate of 5% per year [2]. Hepatic decompensation is characterized by ascites secondary to hepatorenal syndrome, hepatic hydrothorax, spontaneous bacterial peritonitis, encephalopathy, bleeding varices, and coagulopathy [2].

The major risk factors for acquisition of hepatitis C is associated with intravenous drugs, transfusion of blood products, tattoos, sexual transmission or occupation risk [3,4]. This knowledge has allowed researchers to identify variables and various treatment options.

HCV elicits a weak T cell response in chronic infection. There is a progressive loss in the strength of reaction towards HCV antigens during chronic infection. Impaired CD8 responses are the consequence of dysfunctional T cell rather than persistent infection [6,7]. CD-8 induced liver damage or autoimmune phenomena occur. Viral persistence includes the suppressive effect of HCV antigens on the innate and adaptive immune systems [1]. Progression to persistent infection and immunologic mechanisms of liver injury are a consequence of complex interactions among the virus and host [1].

Significantly higher rate of liver complications include age (>50 years), blood transfusion, HCV genotypes 1 and 4, fibrosis and cirrhosis [8]. In addition, abnormalities in bilirubin (>40μmol/L), albumin, prothrombin time, thrombocytopenia (<50,000 cells/dL) and detection of AFP (>20 μg/L) [8]. Patients are at a higher risk of developing liver complications from chronic hepatitis C with advanced hepatic fibrosis or cirrhosis. Infected individuals are predominantly asymptomatic, but can progress to end stage liver disease, liver cirrhosis, portal hypertension, hepatocellular carcinoma and premature death. The rate of fibrotic progression in chronic hepatitis C is highly variable and natural history extends over decades [9]. Factors that influence the rate of progression include age at diagnosis, male gender, HCV genotype, and a weak association towards alcohol consumption [10,11]. Personal, viral and disease related factors that influence the development remains poorly documented [9].

Approximately 80% of those who become infected fail to clear the virus and progress to chronic infection, with poorly defined outcomes [1]. Some people recover, remain viremic without overt liver damage, remain static with elevated AST without symptoms, progressive with fibrosis and cirrhosis, or develop liver failure or hepatocellular carcinoma [19]. The course of the disease spans 20 to 40 years before the outcome is reached. Reduced life expectancy with transfusions, drug use, and other exposures exacerbates HCV mortality [12].

Fibrotic scar tissue within the liver causes blood to back up within the splanchnic circulation resulting in adverse complications. Clinical symptoms were identified in approximately 10% of patients [10]. These include [20], ascites (abdominal distention, shifting dullness, and confirmed fluid by paracentesis or abdominal imaging), variceal bleeding (endoscopic evaluation with upper gastrointestinal hemorrhage, 35-85% with cirrhosis; bleeding 25-40%; 30-50% 3 month survival), spontaneous bacterial peritonitis (>500 white blood cells/mL, >250 polymorphonuclear cells/mL, positive culture), hepatic hydrothorax (right sided pleural effusion), and hepatic encephalopathy (asterixis flapping tremor). Management requires aggressive diuresis, pleural taps, and immediate consideration for

liver transplantation based on the MELD (Model for End Stage Liver Disease) [21].

Therapy for hepatitis C is indicated for patients 18 to 60 years with persistently abnormal alanine aminotransferase levels, HCV RNA in serum, liver biopsy showing chronic hepatitis with fibrosis or inflammation [32]. The goal is to prevent complications and death from HCV infection. Short-term outcomes are measured by normalization of serum ALT, undetected HCVR RNA by sensitive PCR analysis, and non-detectable fibrosis on histology [12]. The most important labeled treatment is considered by sustained virological response, defined as the absence of HCV RNA from serum by sensitive PCR assay 24 weeks after cessation of therapy [1]. Rapid virological response [12,33], is defined as undetectable HCV RNA at 4 weeks of treatment with a lower limit of detection of 50 IU/mL, with a higher likelihood for achievement. Early virological response [12,33], defined as absence of serum HCV RNA at 12 weeks, is the most accurate predictor of not achieving sustained viral response.

Despite management, HCV RNA levels do not change, and relapses occur soon after cessation of treatment. The therapeutic regimen includes interferon-α given subcutaneously in a dose of 3 million units three times weekly for 12 months [2]. Modifications include a combination therapy with interferon-α and ribavirin [34-36]. Patients receiving interferon-α alone or in combination, had low to non-detectable HCV RNA 6 months after therapy (indicating sustained virology response) [12,34-36]. Residual viral indices maintain persistent humoral and cellular immunologic responses once the therapy reduces viral load [5,37]. An additional option is a long-term continuous interferon or ribavirin therapy in patients with extrahepatic manifestations, those with marked fibrosis on liver biopsy or those at high risk for hepatocellular carcinoma [1].

Chronic HCV infection is the leading indication for liver transplantation in the U.S. population [40]. Criteria for liver transplant includes [1,2,12], signs of hepatic decompensation, encephalopathy, variceal bleed, MELD score [21], >10 (indicated by bilirubin, creatinine, and INR). Immunocompromised patients have a higher recurrence and lower survival rate, which advocates the use of interferon-based antiviral therapy. Other studies have suggested that patients with mild histological disease respond better compared to those with more advanced liver diseases [2,12]. This allows for closer monitoring of post-transplant patients using liver biopsy to monitor progressive fibrosis and initiate treatment [12,41-44]. Graft re-infection is universal with 25% to 30% graft loss from recurrent HCV with progressive fibrosis [41-44]. Profound graft dysfunction may occur after viral clearance, which necessitates immediate management [45]. Efforts to define criteria for diagnosis, therapy, optimal timing, duration to treat recurrence, are important. Once cirrhosis develops, hepatic decompensation is common with poor results of re-transplantation [12].

Preoperatively, it is important to evaluate patients for liver disease since it has been associated with increased postoperative complications and mortality [52]. With the patient's history of hepatitis C, the next step was to assess the severity of liver dysfunction. Our patient had confirmatory HCV testing with a high viral load using quantitative HCV RNA by PCR (1,678,859 Intl Unit/mL). Additionally, he was never treated for HCV with pegylated interferon or ribavirin which aims to slow the progression of fibrosis and prevent the development of cirrhosis [53]. Preoperative lab evaluation Table 1 showed platelets <140,000 and AST/ALT ratio ≥ 1 which are highly suggestive of cirrhosis in patients with chronic HCV [54]. Using noninvasive methods, the Child-Turcotte-Pugh (CTP) and the Model for End Stage Liver Disease (MELD) scoring systems can be used to quantify the severity of hepatic dysfunction. The CTP score predicts severity of liver dysfunction and postoperative morbidity and mortality risk. Preoperative, this patient fell into CTP class B, associated with a 10% surgical mortality rate. The MELD score can be used to predict 30 day mortality postoperatively in patients with cirrhosis by estimating the severity of liver disease. We have found that this patient had a MELD score of 11 that predicts a 10.3% 30- day mortality rate [55,56].

Although no specific guidelines have been widely established, there are several considerations that have been suggested by the American College of Gastroenterology, which include, contraindication to elective surgery in patients with CTP class C, high MELD score, ASA class V, acute hepatitis, severe coagulopathy, or severe extrahepatic manifestations of liver disease [57]. Management of ascites, coagulopathy and encephalopathy are required before proceeding with surgery. In general, for asymptomatic patients with mildly elevated aminotransferase levels, and a normal total bilirubin, cancellation of surgery is rarely needed [58].

We suggest that sevoflurane may have attributed to this patient's demise through several mechanisms of injury. Since its introduction in 1990, sevoflurane has been established into clinical practice, and considered safer than other halogenated anesthetics. Yet hepatic injuries have been reported over the years [64]. While many factors contribute to our patient's hepatic injury, such as chronic hepatitis, he was hemodynamically stable preoperatively and intraoperatively. However over time, this patient suffered hypercoagulability unresponsive to supportive therapy, and eventually expired. Postoperatively, liver enzymes were dramatically elevated (Table 1) and it became clear to investigate further into sevoflurane toxicity with underlying viral illnesses such as hepatitis C.

Clinicians are warned to avoid sevoflurane with unexplained liver injury following any exposure to fluoridated inhaled anesthetic. Sevoflurane is metabolized to hexafluoroisopropanol inorganic fluoride, and formaldehyde [65], which are eliminated in urine. Sevoflurane defluorination is metabolized by human P450 2E1 and is responsible for anesthetic toxicity, predominantly in the liver. Heme oxygenase has also been postulated to react with sevoflurane, because it may be stimulated by Kupffer cells to prevent reperfusion injury, in the pericentral region. Free radical release can also be expected through tissue interaction with sevoflurane, with the induction of P450 E1 metabolism [69].

Total intravenous anesthesias with sevoflurane and propofol (Diprivan) have proven to show variable results based on patients with renal and liver functions. In a study in 2009 and 2013, [66,67], hepatic and renal function tests were conducted during preoperative and postoperative days 1 and 3. AST and alkaline phosphatase were also shown to increase. Coagulopathy and hyperbilirubinemia are also

known to increase with drug induced sevoflurane hepatic necrosis. Additionally with an underlying HCV infection and the exposure to sevoflurane there is a risk of hepatic necrosis with life threatening consequences [68]. It is important to note that at a low concentration of sevoflurane, compound a toxicity would not affect this patient either through beta lyase pathway or N-acetylation. Even though this patient was at a low flow rate of 2L/min, anesthesia providers should be aware of the accumulation of compound A and its association with sevoflurane in the setting of renal and hepatic toxicity [70].

## References

1. Liang TJ, Rehermann B, Seef LB, Hoofnagle JH (2000) Pathogenesis, natural History, treatment, and prevention of hepatitis C. Ann Intern Med 132: 296-305.

2. Sherman KE (2011) Advanced Liver Disease: What every hepatitis C virus treater should know. Top Antiviral Med 19: 121-125.

3. Tong MJ, El-Farra NS, Reikes AR, Ruth L (1995) Clinical outcome after transfusion associated hepatitis C N Engl J Med 332: 1463-1466.

4. Gordon SC, Bayati N, Silverman A (1998) Clinical outcome of hepatitis C as a function of mode of transmission. Hepatology 23: 487-496.

5. Rehermann B, Chang KM, McHutchison JG, Kokka R, Houghton M, et al. (1996) Quantitative analysis of the peripheral blood cytotoxic T lymphocyte response in patients with chronic hepatitis C virus infection. J Clin Invest 98: 1432-1440.

6. Cox AL, Mosbruger T, Lauer GM, Pardoll D, Thomas DL, et al. (2005) Comprehensive analysis of CD8+ T cell responses during longitudinal study of acute human hepatitis C. Hepathology 42: 104-112.

7. Cabrera R, Tu Z, Xu Y, Firpi RJ, Rosen HR, et al. (20004 An immune-modulatory rule for CD4(+)CD25(+) regulatory T lymphocytes in hepatitis C virus infection. Hepatology 40: 1062-1071.

8. Spangenberg HC, Viazov S, Kersting N, Neumann-Haefelin C, McKinney D, et al. (2005) Intrahepatic CD8+ T-cell failure duing chronic hepatitis C virus infection. Hepatology 42: 828-837.

9. Khan MH, Farrell GC, Byth K, Lin R, Weltman M, et al. (2000) Which Patients with Hepatitis C Develop Liver Complications? Hepatology 31: 513-520.

10. Poynard T, Bedossa P, Opolon P (1997) Natural History of liver fiborosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 349: 825-832.

11. Harris DR, Gonin R, Alter HJ, Wright EC, Buskell ZJ, et al. (2001) The relationship of acute transfusion-associated hepatitis to the development of cirrhosis in the presenece of alcohol abuse. Ann Intern Med 134: 120-124.

12. Ghaney MG, Strader DB, Thomas DL, Seeff LB (2009) Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 49: 1335-1374.

13. Simmonds P, Bukh J, Combet C, Deleage G, Enomoto N, et al (2005) Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology 42: 962-973.

14. Nainan OV, Alter MJ, Kruszon-Moran D, Gao FX, Xia G, et al (2006) Hepatitis C virus genotypes and virla concentrations in participants of a general population survey in the United States. Gastroenterology 131: 478-484.

15. Zekri AR, Bahnassy AA, Shaarawy SM, Mansour OA, Maduar MA, et al. (2000) Hepatitis C virus genotyping in relation to neu-oncoprotein overexpression and the development of hepatocellular carcinoma. J Med Microbiol 49: 89-85.

16. Colin C, Lanoir D, Touzet S, Meyaud-Kraemer L, Bailly F, et al. (2001) Sensitivity and specificity of third generation hepatitis C virus antibody detection assays: an analysis of the literature. J viral Hepat 8: 87-95.

17. Saldanha J, Lelie N, Heath A (1999) Establishment of the first international standard for nucleic acid amplification technology (NAT) assays for HCV RNA. WHO Collaborative Study Group. Vox Sang 76: 149-158.

18. Pawlotsky JM, Bouvier-Alias M, Hezode C, Darthuy F, Remire J, et al. (2000) Standardization of hepatitis C virus RNA amplification. Hepatology 32: 654-659.

19. Armstrong GL, Wasley A, Simard EP, McQUillan GM, Kuhnert WL, et al. (2006) The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 144: 705-714.

20. Afdhal NH (2004) The natural history of hepatitis C. Semin Liver Dis 24: 3-8.

21. Murillas J, Rimola A, Laguno M, de Lazzari E, Rascón J, et al. (2009) The model for end-stage liver disease score is the best prognostic factor in Human Immunodeficiency Virus 1-infected patients with end stage liver disease: A prospective cohort study. Liver Transpl 15: 1133-1141.

22. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, et al. (1999) Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 341: 403-409.

23. Rolachon A, Cordier L, Bacq Y, Nousbaum JB, Franza A, et al. (1995) Ciprofloxacin and long term prevention of spontaneous bacterial peritonitis: results of a prospective controlled trial. Hepatology 22: 1171-1174.

24. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, et al. (2010) Rifaxmin treatment in hepatic encephalopathy. N Engl J Med 362: 1071-1081.

25. D'AMico G (1998) Renal involvement in hepatitis C infection: cryoglobulinemic glomerulonephritis. Kidney Int 54: 650-671.

26. Sabry AA, Sobh MA, Irving WL, Grabowska A, Wagner BE, et al. (2002) A comprehensive study of the association between hepatitis C virus and glomerulopathy. Nephrol Dial Transplant 17: 239-245.

27. Dore MP, Fattovich G, Sepulveda AR, Realdi G (2007) Cryoglobulinemia releated to hepatitis C virus infection. Dig Dis Sci 52: 897-907.

28. Roccatello D, Fornasieri A, Giachino O, Rossi D, Beltrame A, et al. (2007) Multicenter study on hepatitis C virus-related cryoglobulinemic glomerulonephritis. Am J Kidney Dis 49: 69-82.

29. Agnello V, Chung RT, Kaplan LM (1992) A role for hepatitis C virus infection in type II cryoglobulinemia. N Engl J Med 327: 1490-1495.

30. Markowitz GS, Cheng JT, Colvin RB, Trebbin WM, D'Agati VD (1998) Hepatitis C viral infection is associated with fibrillary glomerulonephritis and immunotactoid glomerulopathy. J Am Soc Nephrol 9: 2244-2252.

31. Tang S, Lai KN (2005) Chronic viral hepatitis in hemodialysis patients. Hemodial Int 9: 169-179.

32. (1997) National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C: Hepatology 26: 25-105.

33. Yu JW, Wang GQ, Sun LJ, Li XG, Li SC (2007) Predictive value of rapid virological response and early virological response on sustained virological response in HCV patients treated with pegylated interferon alpha-2a and ribavirin. J gasroenterol Hepatol 22: 832-836.

34. Yu ML, Dai CY, Lee LP, Hou NJ, Hsieh MY, et al. (2006) A 24 week course of high dose interferon-alpha plus ribavirin for Taiwanese chronic hepatitis C patients with persistently normal or near-normal alanine aminotransferase levels. Liver Int 26: 1187-1195.

35. Jacobson IM, Ahmed F, Russo MW, Lebovics E, Dieterich DT, et al. (2004) Interferon alfa-2b [correction of alpha-2b] and ribavirin for patients with chronic hepatitis C and normal ALT. Am J Gastroenterol 99: 1700-1705.

36. Zeuzem S, Diago M, Gane E, Reddy KR, Pockros P, et al. (2004) Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. Gastroenterology 127: 1724-1732.

37. Chen M, Sällberg M, Sönnerborg A, Weiland O, Mattsson L, et al. (1999) Limited humoral immunity in hepatitis C virus infection. Gastroenterology 116: 135-143.

38. Prince AM, Brotman B, Huima T, Pascual D, Jaffery M, et al. (1992) Immunity in hepatitis C infection. Limited humoral immunity in hepatitis C infection. J Infect Dis 165: 438-443.

39. Mizorogi F, Hiramoto J, Nozato A, Takekuma Y, Nagayama K, et al. (2000) Hepatitis C virus infection in patients with B cell non-Hodgkin's Lymphoma. Intern Med 39: 112-117.

40. Alter H (2006) Viral Hepatitis. Hepatology 43: S230-234.

41. Ghobrial RM, Steadman R, Gornberg J, Lassman C, Holt CD, et al. (2001) A 10year experience of liver transplantation for hepatitis C: analysis of factors determining outcome in over 500 patients. Ann Surg 234: 384-393.

42. Neumann UP, Berg T, Bahra M, Puhl G, Guckelberger O, et al. (2004) Long term outcome of liver transplants for chronic hepatitis C: A 10 year follow up. Transplantation 77: 226-231.

43. Neumann UP, Berg T, Bahra M, Seehofer D, Langrehr JM, et al. (2004) Fibrosis progression after liver transplantation in patients with recurrent hepatitis C. J Hepatol 41: 830-836.

44. Yilmaz N, Shiffman ML, Stravitz RT, Sterling RK, Luketic VA, et al. (2007) A prospective evaluation of fibrosis progression in patients with recurrent hepatitis C virus following liver transplantation. Liver Transpl 13: 975-983.

45. Rowe IA, Webb K, Gunson BK, Mehta N, Haque S, et al. (2008) The impact of disease recurrence on graft survival following liver transplantation: a single centre experience. Transpl Int 21: 459-465.

46. Koziel MJ, Liang TJ (1994) Vaccination against hepatitis C virus infection: miles to go before we sleep [editorial]. Hepatology 20: 758-760.

47. Koziel M, Liang TJ (1997) DNA vaccines and viral hepatitis: are we going around in circles? Gastroenterology 112: 1410-1414.

48. Varnavski AN, Khromykh AA (1999) Noncytopathic flavivirus replicon RNA based system for expression and delivery of heterologous genes. Virology 255: 366-375.

49. Thomas DL, Seeff LB (2005) Natural History of hepatitis C. Clin Liver Dis 9: 383-398.

50. Strader DB, Seeff LB (1996) The natural history of chronic hepatitis C infection. Eur J Gastroenterol Hepatol 8: 324-328.

51. Seeff LB (2002) Natural history of chronic hepatitis C. Hepatology 36: S35-S46.

52. Nicoll A (2012) Surgical risk in patients with cirrhosis. Journal of Gastroenterology and Hepatology 27: 1569–1575.

53. Wilkins T, Malcolm J, Raina D, Schade R (2010) Hepatitis C: Diagnosis and Treatment. American Family Physician 81: 1351-1357.

54. Iacobellis A, Mangia A, Leandro G, Clemente R, Festa V, et al. (2005) External validation of biochemical indices for noninvasive evaluation of liver fibrosis in HCV chronic hepatitis. American J Gastroenterol 100: 868-873.

55. Hanje AJ, Patel T (2007) Preoperative evaluation of patients with liver disease. Nature Reviews Gastroenterology & Hepatology 4: 266-276.

56. Teh SH, Nagorney DM, Stevens SR, Offord KP, Therneau TM,, et al. (2007) Risk factors for mortality after surgery in patients with cirrhosis. Gastroenterology 132: 1261-1269.

57. Keegan MT, Plevak DJ (2005) Preoperative Assessment of the Patient with Liver Disease. The American Journal of Gastroenterology 100: 2116- 2127.

58. Hanje AJ, Patel T (2007) Preoperative evaluation of patients with liver disease. Nature Clinical Practice Gastroenterology & Hepatology 4: 266-276.

59. Chelala E, Gaede F, Douillez V, Dessihy M, Alle JL (2003) The suturing concept for laparoscopic mesh fixation in ventral and incisional hernias: preliminary results. Hernia 7: 191–196.

60. Ramirez OM, Ruas E, Dellon AL (1990) "Components separation" method for closure of abdominal-wall defects: an anatomic and clinical study. Plast Reconstr Surg 86: 519–526.

61. Heniford BT, Park A, Ramshaw BJ, Voeller G (2003) Laparoscopic Repair of Ventral Hernias: Nine Years' Experience With 850 Consecutive Hernias. Ann Surg 238: 399–400.

62. Rives J, Lardennois B, Pire JC, Hibon J (1973) Les grandes eventrations:importance du 'volet abdominal' et des troubles respiratoires qui lui sont sécondaires. Chirurgie 99: 547– 563.

63. Kingsnorth A (2006) The Management of Incisional Hernia. Ann R Coll Surg Engl 88: 252–260.

64. Alotaibi WM (2009) Severe Hepatic Dysfunction After Sevoflurane Exposure. Saudi Medical Journal 29: 1344-1346.

65. Martin JL (2005) Volatile Anesthetics and Liver Injury: a Clinical Update or What Every Anesthesiologist Should Know. Canadian Journal of Anesthesia 52: 125-129.

66. Kim JW, Kim JD, Yu SB, Ryu SJ (2013) Comparison of Hepatic and Renal Function Between Anesthesia and Sevoflurane and Remifentanil and Total Intravenous Anesthesia with Propofol and Remifentanil for Thyroidectomy. Korean Journal Anesthesiology 112-116.

67. Obata R, Bito H, Ohmura M, Moriwaki G, Ikeuchi Y, et al. (1993) The effects of prolonged low-flow sevoflurane anesthesia on renal and hepatic function. Anesthesiology 79: 795-807.

68. Singhal S, Gray T, Guzman G, Verma A, Anand K (2010) Sevoflurane Hepatotoxicity: a case report of sevoflurane Hepatic necrosis and review of the literature. American Journal of Therapeutics 17: 219-222.

69. Hoetzel A, Leitz D, Schmidt R, Tritschler E, Bauer I, et al. (2006) Mechanism of Hepatic Heme Oxygenase-1 Induction by Isoflurane. Anesthesiology 104: 101-109.

70. Liu SJ, Li Y, Sun B, Wang Cs, Gong YL, et al. (2012) Sofnolime with Different Water Content Causes Different Effects in Two Sevoflurane Inhalational Induction Techniques with Respect to the Output of Compound-A. Int J Med Sci 9: 435-440.