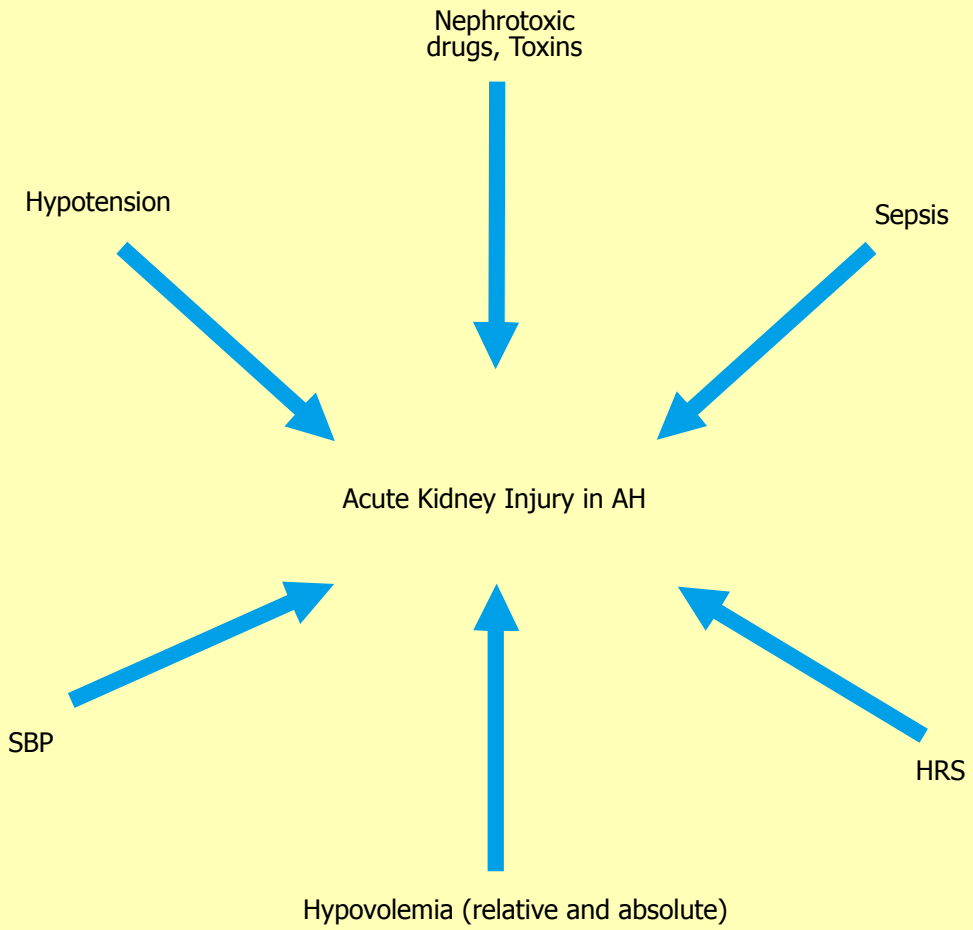
ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2011 May 27; 3(5): 99-136



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WJH World Journal of Hepatology

A peer-reviewed, online, open-access journal of hepatology

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World Journal of Hepatology

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Monthly Volume 3 Number 5 May 27, 2011

World Journal of Hepatology
Volume 3 Number 5 May 27, 2011

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NAME OF JOURNAL
World Journal of Hepatology

LAUNCH DATE
October 31, 2009

SPONSOR
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
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http://www.wjgnet.com

PUBLISHING
Baishideng Publishing Group Co., Limited,
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
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http://www.wjgnet.com

PUBLICATION DATE
May 27, 2011

ISSN
ISSN 1948-5182 (online)

EDITORIAL OFFICE
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ONLINE SUBMISSION
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World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v3.i5.99

World J Hepatol 2011 May 27; 3(5): 99-107
ISSN 1948-5182 (online)

EDITORIAL

Insulin resistance and chronic liver disease

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Author contributions: Kawaguchi T, Taniguch E, Itou M, Sakata M and Sumie S drafted the manuscript; Kawaguchi T and Sata M organized and revised the manuscript.
Supported by the Grant-in-Aid for Young Scientists (B)(No. 22790874 to T.K.) and a Grant-in-Aid for Scientific Research (C) (No. 21590865 to M.S.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and by Health and Labour Sciences Research Grants for Research on Hepatitis from the Ministry of Health, Labour and Welfare of Japan
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Received: November 18, 2010 Revised: March 26, 2011
Accepted: April 2, 2011
Published online: May 27, 2011

Abstract

Increased insulin resistance is frequently associated with chronic liver disease and is a pathophysiological feature of hepatogenous diabetes. Distinctive factors including hepatic parenchymal cell damage, portal-systemic shunting and hepatitis C virus are responsible for the development of hepatogenous insulin resistance/diabetes. Although it remains unclear whether insulin secretion from pancreatic beta cells is impaired as it is in type 2 diabetes, retinopathic and cardiovascular risk is low and major causes of death in cirrhotic patients with diabetes are liver failure, hepatocellular carcinoma and gastrointestinal hemorrhage. Hemoglobin A1c is an inaccurate marker for the assessment and management of hepatogenous diabetes. Moreover, exogenous insulin or sulfonylureas may be harmful because these agents may promote hepatocarcinogenesis. Thus, pathogenesis, cause of death, assessment and therapeutic strategy for hepatogenous insulin resistance/diabetes differ from those for lifestyle-related type 2 diabetes. In this article, we review features of insulin resistance in relationship to chronic liver disease. We also discuss the impact of anti-diabetic agents on interferon treatment and hepatocarcinogenesis.

Key words: Viral hepatitis; Hyperinsulinemia; Hypoglycemic drug; Hepatoma

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Kawaguchi T, Taniguchi E, Itou M, Sakata M, Sumie S, Sata M. Insulin resistance and chronic liver disease. *World J Hepatol* 2011; 3(5): 99-107 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i5/99.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i5.99

INTRODUCTION

An association between diabetes mellitus (DM) and liver cirrhosis was first described by Bohan[1] and named as hepatogenous diabetes by Megyesi *et al*, in which 57% of cirrhotic patients showed increased insulin resistance[2]. Various pathogenetic factors are involved in development of the insulin resistance[3-7]. Serum insulin levels are higher in diabetic patients with chronic liver disease than those in patients with lifestyle-related DM[8], suggesting that besides over-eating, obesity and physical inactivity, distinctive factors may underlie the pathophysiology of hyperinsulinemia in patients with chronic liver disease.

Since blood glucose is delivered to the liver through the portal vein, hyperinsulinemia in patients with liver cir-

rhosis may be secondary to either hepatic parenchymal cell damage or to portal-systemic shunting[9-12]. The rate at which insulin is degraded in the liver is reduced in patients with liver cirrhosis[11,12]. Moreover, despite peripheral hyperinsulinemia, insulin levels in the portal and hepatic veins are decreased in cirrhotic patients with portal systemic shunting[9,10]. However, hyperinsulinemia is also seen in patients with chronic hepatitis C virus (HCV) infection who do not show both severe hepatic parenchymal cell damage and portal-systemic shunting[6,8,13-16], indicating that increased hepatic insulin resistance is another factor related to hyperinsulinemia in patients with liver disease, particularly in HCV-related chronic liver disease[8,13,17-21].

PATHOGENESIS OF INSULIN RESISTANCE IN PATIENTS WITH CHRONIC HEPATITIS C

Insulin resistance parallels the liver fibrosis stage[22-26] and is associated with a reduced level of sustained virological response (SVR) to pegylated interferon and ribavirin[27-30]. Thus, insulin resistance is involved in the disease progression and success of treatment and it is important to understand the pathogenesis of insulin resistance in patients with chronic hepatitis C.

Changes in serum levels of leptin, adiponectin, tumor necrosis factor-alpha and interleukin-6 are known to be associated with the development of insulin resistance[31-36]. However, in patients with chronic hepatitis C, changes in these cytokines are not always correlated with insulin resistance[37-39]. On the other hand, insulin resistance is increased in the HCV core cDNA-transfected hepatoma cell lines and mice[8,40] and serum levels of HCV core protein are associated with the development of insulin resistance in patients with chronic hepatitis C[14,41]. Furthermore, insulin resistance is correlated with HCV viral kinetics[42,43] and is improved by clearance of HCV by interferon therapy[44-47]. These findings suggest that HCV *per se* is an important factor for the development of insulin resistance.

Recently, the relationship between HCV genotype and insulin resistance has been revealed. HCV genotypes 1, 3 and 4 associated with more severe insulin resistance[24,42,48]. In human hepatoma cell lines, HCV genotype 1 up-regulates suppressor of cytokine signaling (SOCS) 3 and causes ubiquitination of insulin receptor substrate (IRS)1/2, which subsequently suppresses insulin-induced phosphorylation of the p85 subunit of phosphatidylinositol 3-kinase and Akt and reduces glucose uptake (Figure 1)[8]. These changes are not seen in hepatoma cell lines infected with HCV genotype 2, suggesting that IRS1/2 degradation through up-regulation of SOCS3 is a genotype-specific mechanism[49]. In agreement with these results of basic research, hepatic expression of SOCS3 is higher in patients with HCV genotype 1 than in those with genotype 2 and increased hepatic expression of SOCS3 is correlated with poor response to antiviral treatment[50,51]. Two further mechanisms are reported in HCV genotype 1: activation of

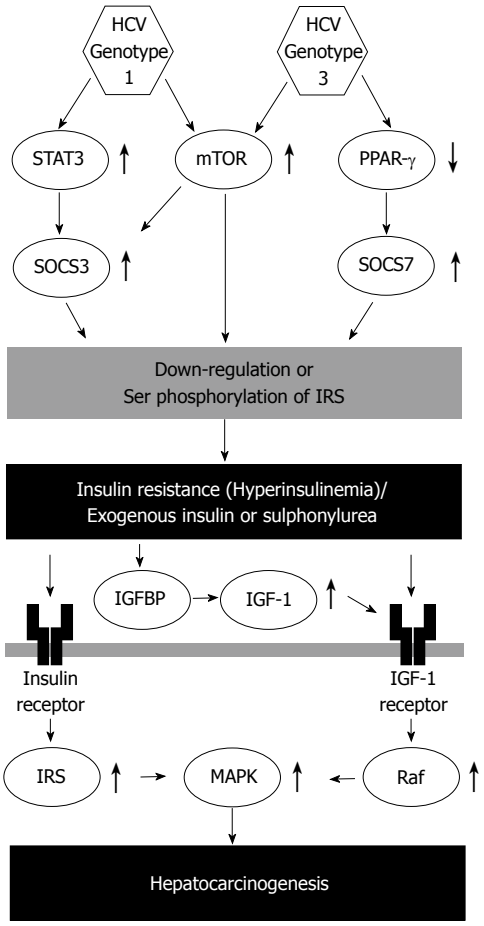

Figure 1 Scheme for HCV genotype difference in the molecular pathogenesis of insulin resistance and hepatocarcinogenesis. HCV: Hepatitis C virus; STAT: Signal transducer and activator of transcription; SOCS: Suppressor of cytokine signaling; mTOR: Mammalian target of rapamycin; PPAR: Peroxisome proliferator-activated receptor; IGFBP: Insulin-like growth factor binding protein; IGF: Insulin-like growth factor; IRS: Insulin receptor substrate; MAPK: Mitogen-activated protein kinase.

the mammalian target of rapamycin[52] and up-regulation of serine phosphorylation of IRS1(Figure 1)[43]. In addition, amino acid substitutions in the core region of HCV genotype 1b [Gln70 (His70) and/or Met91] have recently been reported as significant predictors of severe insulin resistance[53,54]. Although the underlying molecular mechanisms remain unclear, these findings indicate a unique molecular pathogenesis for insulin resistance in HCV genotype 1.

HCV genotype 3 also causes down-regulation of IRS1; however, the molecular pathogenesis differs from that of HCV genotype 1. HCV genotype 3 promotes down-regulation of IRS1 by up-regulating SOCS7 but not SOCS3 (Figure 1)[52]. SOCS-7 mRNA expression is independent of signal transducer and activator of transcription 3 and is modulated by peroxisome proliferator-activated receptor gamma activity (Figure 1)[52,55]. HCV genotype 4 is the most common variant in the Middle East and Africa and is increasing in prevalence in Western countries[56]. Infection with HCV genotype 4 is associated with a high prevalence of hepatic steatosis and obesity; however, the impact of

adiponectin on insulin resistance remains controversial[57,58] and specific mechanisms of insulin resistance in HCV genotype 4 infection also remain unclear.

Besides direct association of HCV with intracellular insulin signaling, hepatic steatosis is associated with increased BMI and insulin resistance and HOMA index is reported to be a predictor of SVR in patients with HCV non 3 genotypes[27,59-62]. In patients with HCV genotype 3, hepatic steatosis directly correlates with circulating and hepatic viral load, which is mediated by an impaired very-low-density lipoprotein assembly and secretion and by an up-regulation of the sterol depending protein signaling pathway, which regulates de novo lipogenesis and inhibits mitochondrial fatty acid b-oxidation[63,64].

CHANGES IN PANCREATIC BETA CELLS IN PATIENTS WITH LIVER DISEASE

A decrease in islet mass and/or beta-cell dysfunction is a pathogenesis for type 2 DM[65,66]. In patients with chronic liver disease, impairment of insulin secretion is also reported[11,67]; however, insulin resistance/hyperinsulinemia is also characteristic in such patients[8,13,17-21] and it therefore remains unclear whether the pathogenesis of hepatogenous DM is same as that of type 2 DM.

Pancreatic islet hypertrophy is reported in surgical biopsy tissue of patients with liver cirrhosis[68]. Islet hypertrophy and hyperplasia are also reported in thioacetamide-treated rats[69] and in HCV-core transgenic mice[40]. Moreover, Takei *et al* reported that islets in patients with cirrhosis show higher proliferation and lower apoptosis compare to those in patients with no chronic liver disease[70]. These findings suggest that hyperinsulinemia in cirrhotic patients may be caused by an adaptive response of the pancreatic beta cells to increased insulin resistance.

Although cross-talk between the pancreas and liver is an important issue in the development of insulin resistance, little is known about this relationship. Further studies regarding morphological and pathological changes of pancreatic alpha-or beta cells are required to characterize the pathogenesis of insulin resistance in patients with liver disease.

CAUSES OF DEATH IN DIABETIC PATIENTS WITH LIVER DISEASE

The prevalence of DM in patients with chronic liver disease is reportedly 18%-71%[18,20,71-73]. DM leads to several complications including cardiovascular disease. Generally, the therapeutic strategy in DM is to reduce the incidence of cardiovascular disease and to prevent a subsequent decrease in quality of life and improve prognosis. However, hepatogenous DM is less often associated with a positive family history, retinopathy and cardiovascular diseases[18,74-76]. In fact, major causes of death in cirrhotic patients with DM relate to liver disease or its complications, such as chronic liver failure, hepatocellular carcinoma (HCC) and gastrointestinal hemorrhage[18,19,77-79]. Therefore, the management of DM in patients with liver cirrhosis should aim to reduce such hepatic complications and to improve prognosis. Because the incidence of HCC has been well demonstrated to relate to DM[80], a major target in the management of DM should be to reduce the incidence of HCC in patients with liver cirrhosis.

ASSESSMENT OF DM IN PATIENTS WITH LIVER DISEASE

Plasma glucose and hemoglobin A1c (HbA1c) are generally used for routine assessment and management of patients with type 2 DM, whereas there is less information regarding the association between these markers and HCC incidence or prognosis in patients with liver cirrhosis. HbA1c level in patients with HCC is higher than in patients with liver cirrhosis or in control subjects[81]. In patients with liver cirrhosis, however, HbA1c does not properly represent glycemic control status in cirrhotic patients because of the short lifespan of erythrocytes caused by hypersplenism[82-86]. These data indicate that assessment and management of hepatogenous DM using HbA1c is inaccurate, although poor glucose control is associated with HCC incidence.

Strict control of blood glucose levels may improve survival in HCV patients. In patients with HCV-related liver cirrhosis, the prognosis for patients with hyperglycemia (fasting plasma glucose $\geqslant$ 7.0 mmol/L; 126 mg/dL) was worse than for those with normoglycemia[19]. Therefore, fasting plasma glucose < 7.0 mmol/L (126 mg/dL) appears to be meaningful in hepatogenous DM.

Fasting serum insulin and homeostasis model assessment of insulin resistance (HOMA-IR) are also used as markers of glucose tolerance. In patients with HCV infection, HCC development is associated with increased fasting serum insulin level and by HOMA-IR[87]. Moreover, HCC recurrence has also been demonstrated to be related to HOMA-IR[88,89]. In addition, prognosis is worse in HCC patients with increased fasting serum insulin level or HOMA-IR[90]. These data suggest that the assessment of insulin is also meaningful in patients with liver cirrhosis. Taken together, fasting plasma glucose and either serum insulin or HOMA-IR are candidate markers for the assessment of hepatogenous insulin resistance/DM. However, further studies are required to clarify the utility of these markers and their target values in terms of complications induced by liver cirrhosis including HCC or prognosis.

IMPACT OF ANTI-DIABETIC AGENTS IN PATIENTS WITH LIVER DISEASE

Exogenous insulin and sulphonylureas

Despite the recognition of this potential link between insulin resistance and life-threatening complications including HCC, there is no common therapeutic strategy for

Table 1 Effects of anti-diabetic agents in patients with chronic liver disease

Anti-diabetic agent	Subjects	Outcome	Reference
Exogenous insulin or sulphonylurea	Patients with liver cirrhosis or HCC	Increased HCC risk	[100]
Exogenous insulin or sulphonylurea	Patients with chronic hepatitis C	Increased HCC risk	[101]
Exogenous insulin	Chronic viral hepatitis patients who had undergone curative resection for HCC	Increased risk of HCC recurrence	[102]
Metformin	Treatment-naïve female patients with HCV genotype 1-related chronic hepatitis and insulin resistance	Increased SVR rate	[16]
Metformin	Patients diabetes mellitus and liver cirrhosis or HCC	Decreased HCC risk	[101]
Metformin	Patients with liver cirrhosis or HCC	Decreased HCC risk	[112]
Pioglitazone	Chronic hepatitis C patients who had previously failed to respond to antiviral therapy	No increase in EVR rate	[115]
Pioglitazone	Treatment-naïve chronic hepatitis C patients with insulin resistance	Increased SVR rate	[116]

HCC; hepatocellular carcinoma, EVR; early virological response, SVR; sustained virological response.

insulin resistance in patients with chronic liver disease. Since insulin is a growth-promoting hormone with mitogenic effects[91], exogenous insulin and sulphonylureas, which increase serum insulin levels, are considered to enhance carcinogenesis. In fact, a large-scale cohort study has reported that exogenous insulin increases the risk of malignancies in patients with DM[92,93]. Exogenous insulin and sulphonylureas are known to promote breast cancer[94], colorectal cancer[95,96] and pancreatic cancer[95,97] in patients with DM. Recently, a possible link between anti-diabetic agents and the risk of cancer is noted in the consensus statement from the American Diabetes Association and the American Cancer Society[98].

An association between anti-diabetic agents and hepatocellular carcinoma (HCC) was first described in 1986 by Lawson *et al*[99]. In addition, we, along with others, have recently shown that use of exogenous insulin or sulphonylurea increases the development and recurrence of HCC in patients with chronic hepatitis C (Table 1)[80,100-102]. Exogenous insulin or second-generation sulphonylurea increases serum insulin levels. Since insulin has mitogenic and cell proliferative effects, these anti-diabetic agents could be a carcinogenic factor. Insulin binds to insulin receptors and activates the mitogenactivated protein kinase pathway[91,103]. Insulin also cross-reacts with insulin like growth factor (IGF)-1 receptor and activates the Raf cascade, leading to mitosis and cell proliferation[104]. Moreover, excess insulin binds to IGF-binding proteins, resulting in increased levels of free serum IGF-1 (Figure 1)[87,105-107]. Thus, hyperinsulinemia induced by use of exogenous insulin or sulphonylurea may enhance hepatocarcinogenesis through multiple pathways.

The association of exogenous insulin or second-generation sulphonylurea with HCC was more evident in females than in males[101]. Sex affects the development of HCC and females are less prone to HCC than males[108,109]; therefore, we assume that use of exogenous insulin or a 2nd-generation sulfonylurea may accelerate development of HCC mainly in patients who have negative factor for the development of HCC.

Metformin

Metformin is an oral biguanide with insulin-sensitizing effects. However, biguanides are reported to predispose patients with liver cirrhosis to lactic acidosis and are considered as a contraindication in this situation[110]. Recently, Romero-Gomez *et al* first reported that adding metformin to peginterferon and ribavirin is safe and improved insulin sensitivity in treatment-naïve patients with HCV genotype 1 infection and DM[16]. In an intent-to-treat analysis, no beneficial effects of metformin on SVR were seen; however, in female patients with insulin resistance, adding metformin to antiviral treatment doubled the SVR rate (58% *vs* 29%)[16]. Although the reason for this sex difference is still unclear, elevated estradiol-to-testosterone ratio is known to be associated with better response to metformin treatment[111], suggesting a possible association between sex hormones and metformin-induced high SVR rate. Donadon *et al* and our research group have reported that metformin reduced risk of HCC in patients with DM and chronic liver disease[101,112]. Metformin is also known to attenuate the response of cancer cells to insulin *in vitro*[113,114]. Thus, metformin has potential benefits as an insulin sensitizer for patients receiving antiviral treatment or those with liver cirrhosis(Table 1).

Pioglitazone

Pioglitazone is a thiazolidinedione with insulin-sensitizing effects. Recently, Overbeck *et al* reported that adding pioglitazone to pegylated interferon-alpha and ribavirin improves insulin resistance; however, none of the patients achieved a satisfactory virological response after 12 wk of treatment (Table 1)[115]. On the other hand, Khattab *et al* reported that pioglitazone improves sustained virological response to antiviral therapy in hepatitis C patients with insulin resistance (Table 1)[116]. The effect of pioglitazone on SVR therefore remains controversial; however, a difference in enrolled subjects may account for this discrepancy. The study by Overbeck *et al* enrolled patients with chronic hepatitis C who previously failed to respond to peginterferon plus ribavirin therapy[115], whereas the

study by Khattab *et al* enrolled naïve chronic hepatitis C patients with insulin resistance[116]. Thus, pioglitazone may not enhance the effect of antiviral therapy in intractable chronic hepatitis C. However, insulin resistance is reduced in both studies and pioglitazone may therefore be able to improve insulin resistance-related complications in patients with HCV infection. Further study will need to focus on the effects of pioglitazone, not only on antiviral treatment but also on the development of hepatic fibrosis, hepatocarcinogenesis and patient prognosis.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase (DPP)-4 inactivates incretin hormones including glucagon-like peptide-1 (GLP-1)[117,118], which enhances insulin secretion and reduces body weight[119,120]. DPP-4 inhibitors are therefore used as anti-diabetic agents[117,118]. DPP-4 is also known as CD26, an immune-regulation molecule expressed on T-cells[121], and transfection of a HCV non-structural genome region is reported to increase DPP-4 expression in a hepatoma cell line[122]. Treatment of HCV-infected patients with interferon decreases serum DPP-4 activity, which is related to interferon-induced immune activation[123]. Although changes in DPP-4 activity after interferon treatment may just represent indirect evidence, one would think that changes in DPP-4 activity could be involved in the pathogenesis of HCV-related insulin resistance.

Although changes in GLP-1 and DPP-4 remain unclear in hepatogenous insulin resistance, we previously investigated changes of these molecules in patients with HCV infection[124]. The serum level of the active GLP-1 in HCV-infected patients is significantly lower than that in hepatitis B virus-infected patients and healthy subjects. On the other hand, DPP-4 is up-regulated in the serum, ileum and liver of HCV-infected patients more than that of hepatitis B-infected patients and healthy subjects. Taken together, it seems that inactivation of GLP-1 through up-regulation of DPP-4 is a possible pathogenetic mechanism for HCV-related insulin resistance.

DPP-4 inhibitors are now available in the clinical setting and decrease plasma glucose levels as well as HbA1c levels with a low incidence of hypoglycemia in patients with type 2 diabetes mellitus[125,126]. Unlike other anti-diabetic agents, DPP-4 inhibitors are metabolized in the kidney and rarely cause hepatic dysfunction[127,128]. Moreover, GLP-1 analogs improve insulin sensitivity in insulin-resistant obese fa/fa Zucker rats[129] and DPP-4 inhibitors increase hepatic glucose uptake[130]. Thus, further study will be focus on the effects of DPP-4 inhibitors on HCV-related insulin resistance.

COFFEE CONSUMPTION

In various studies including a large prospective study, patients with HCV-related liver disease with a regular coffee consumption show a lower rate of disease progression such as hepatic fibrosis[131-133] and HCC[134-138]. Recently, it was also reported that more than 3 cups per day coffee drinkers are three times more likely to have a virological response to peginterferon plus ribavirin treatment than non-drinkers[139]. Since coffee consumption increases insulin sensitivity[140] and inhibits the development of non-alcoholic fatty liver disease in healthy subjects[141], coffee intake may be protective by mechanisms modulating insulin sensitivity and resulting in a reduced extent of liver steatosis in patients with HCV infection.

CONCLUSION

In this paper, we summarize the features of insulin resistance in relationship to chronic liver disease. Pathogenesis, assessment and cause of death in insulin resistance related to liver disease differ from those of lifestyle-related insulin resistance. Furthermore, exogenous insulin or sulfonylureas may be harmful because these agents may promote hepatocarcinogenesis. There is, therefore, a need for a unique therapeutic strategy for hepatogenous insulin resistance.

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S- Editor Zhang HN **L- Editor** Roemmele A **E- Editor** Zhang L

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v3.i5.108

World J Hepatol 2011 May 27; 3(5): 108-113
ISSN 1948-5182 (online)

TOPIC HIGHLIGHT

Ashwani K Singal, MD, *Series Editor*

Definition, epidemiology and magnitude of alcoholic hepatitis

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Received: October 28, 2010 Revised: March 6, 2011
Accepted: March 13, 2011
Published online: May 27, 2011

Abstract

Alcoholic liver disease (ALD) is a major cause of alcohol-related morbidity and mortality. Its presentation ranges from fatty liver to alcoholic hepatitis (AH), cirrhosis, and hepatocellular carcinoma. Although the amount and pattern of alcohol consumption is a well recognized predisposing factor for the development of serious liver pathology, environmental factors and the host's genetic make-up may also play significant roles that have not yet been entirely explored. Continuing alcohol consumption is a major factor that influences the survival of patients with AH. The presence of cirrhosis at presentation or its development on follow up is a major factor determining the outcome in the long run. This chapter deals with the epidemiology and magnitude of ALD in general and AH in particular.

Key words: Alcoholic hepatitis; Acute alcoholic hepatitis; Alcoholic liver disease; Epidemiology; Magnitude; Disease burden

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Basra S, Anand BS. Definition, epidemiology and magnitude of alcoholic hepatitis. *World J Hepatol* 2011; 3(5): 108-113 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i5/108.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i5.108

DEFINITION

Alcoholic liver disease (ALD) describes a spectrum of conditions ranging from reversible fatty liver to alcoholic hepatitis (AH), cirrhosis, and hepatocellular carcinoma (HCC). AH is a distinct clinical syndrome caused by chronic alcohol abuse and carries a particularly poor prognosis with a 28-day mortality ranging from 30% to 50%[1]. Although AH is an acute condition, nearly 50% of patients with AH have established cirrhosis at the time of clinical presentation[2].

AH typically occurs in an individual with long-standing history of alcohol intake although abstinence for several weeks prior to admission is not uncommon. However, clinical presentation after abstinence of more than 3 mo should raise suspicion of advanced underlying alcoholic cirrhosis or chronic liver disease.

Several pro-inflammatory cytokines have been detected in AH patients. In uncomplicated cases, histology of AH is characterized by neutrophilic infiltration (a marker of alcohol-induced hepatitis), ballooning degeneration of hepatocytes, spotty necrosis and fibrosis in the perivenular and perisinusoidal space of Disse ("chicken wire" fibrosis), and Mallory hyaline inclusions[3].

EPIDEMIOLOGY

Amount of alcohol intake

The amount of alcohol consumption that places an individual at risk of developing AH is not known. However, in practice, most patients with AH drink more than 100 g/d[4] (which corresponds to 6-7 drinks per day where one drink contains 13-15 g of alcohol), with 150-200 g per day being common[5]. The typical patient has consumed alcohol heavily for two or more decades[5], although in an occasional patient alcohol abuse may be for less than 10 years. However, clinicians should consider anyone drinking more than 30-50 g/d for more than 5-10 years at risk of developing ALD[6].

Estimates of the amount of alcohol consumed may not be accurate since it is based on interviewing the patient and/or family members[7]. The patient's history reveals the type of alcohol intake and the amount consumed in volume or number of drinks. One drink is typically defined as 12 ounces (355 mL, 4%-5% weight by volume or w/v) of beer, 5 ounces (125 mL, 10%-12% w/v) of wine or 1.5 ounces (45 mL, 40%-50% w/v) of spirits.

Patterns of alcohol intake around the world are constantly evolving and have a strong bearing on the prevalence and incidence of ALD. In one study reporting data for adult per capita consumption of alcohol in the year 2000, spirits dominated the type of alcohol consumed in most regions of the world. The highest amount of alcohol per adult was reported in Europe, especially in Russia and surrounding countries, and the least was in the mostly Islamic regions of the Eastern Mediterranean and in the less developed region of Southeast Asia, predominantly India[8]. The annual per capita change in alcohol consumption in various countries has a direct correlation to cirrhosis mortality rates. A Canadian study confirmed that per capita alcohol consumption is closely related to mortality rates from alcoholic cirrhosis in both men and women[9]. In another analysis of 22 European countries, the relationship between an increase in liver disease and increase in per capita alcohol intake was shown for both men and women[10].

Population-based surveys indicate that 68% of adult Americans drink at least one alcoholic beverage per month. Traditionally, drinking is considered harmful if alcohol use impacts the daily functioning and/or social life of the individual such as loss of job, accident, loss of family member, or death[11]. About 10% of the population consumes more than two drinks per day, which is a commonly used definition of "heavy drinking"[12]. However, substantial differences exist in the prevalence of heavy drinking among population subgroups. For example, 18% of men but only 3% of women are classified as heavy drinkers. Further, heavy drinking is reported to be more common in Whites than in African Americans or Hispanics. Heavy alcohol consumption is generally more common in people with low educational level and income, the unemployed, and in those with occupations that are characterized by job alienation, job stress, and low job satisfaction[13].

Environmental and host factors

A dose-dependent relationship has been observed between self-reported alcohol intake and the risk of developing ALD[6]. Although physicians should consider anyone drinking $\geqslant$ 30-50 g/d for more than 5-10 years at risk for developing ALD, the disease does not develop in everyone with this amount of alcohol consumption. About 90% to 100% of heavy drinkers have steatosis, 10% to 35% have AH, and 8% to 20% have alcoholic cirrhosis[14]. The point prevalence of cirrhosis is 1% in persons drinking 30 to 60 g of alcohol a day and up to 5.7% in those consuming 120 g daily[15]. Clearly, other factors related to environment or the host predispose an individual to the development of liver disease[16]. These factors are:

Age: The typical age at presentation of AH is between 40 and 50 years, with the majority occurring before the age of 60 years[17,18].

Gender: The risk of developing alcohol-induced liver disease increases significantly from 7 to 13 beverages per week for women and from 14 to 27 beverages per week for men; the relative risk increases more steeply for women than for men with increasing alcohol intake[6]. This gender difference is due to several factors such as differences in gastric alcohol, dehydrogenase (ADH) levels, and a higher proportion of body fat in women[19]. Although women are at an increased risk of developing liver disease with alcohol intake[16], the majority of patients with AH are males because men are twice as likely to abuse alcohol compared to women[11].

Race and ethnicity: The rates of development of cirrhosis and mortality are higher in African Americans and Hispanics compared to Caucasians[20]. This was reflected in an analysis of changes in national drinking patterns between 1984 and 1992, which showed longer and heavier drinking patterns in blacks and Hispanics compared to whites[21].

Obesity: The presence of long-standing obesity is an independent risk factor for liver disease and cirrhosis in alcoholics[22]. Given the burgeoning problem of obesity in the developed world, it is likely that alcohol-related injury will increase[23]. Obesity potentiates the severity of ALD in all its stages, including fatty liver, AH, and cirrhosis[24].

Protein Calorie Malnutrition: Most patients with AH are malnourished[25], and the risk of death is closely correlated with the degree of malnutrition[26]. Mortality increases in direct proportion to the extent of malnutrition, approaching 80% in patients with severe malnutrition (i.e., less than 50% of normal nutritional intake)[27]. Micronutrient abnormalities, such as hepatic vitamin A depletion or depressed vitamin E levels, may also potentially aggravate liver disease[28]. Parenteral and enteral feeding improves nutritional status but does not improve short-term survival[29].

Drinking patterns and type: The type of alcoholic beverage and the pattern of drinking also affect the development of liver disease. In one study from Denmark, the chances of getting liver disease were higher from drinking beer and spirits as compared to drinking wine[30]. Drinking outside of meal times increases the risk of developing liver disease. Binge drinking defined as intake of $\geqslant$ 5 drinks at a time, another risk factor for AH, is reported in about 28% of adults with a history of alcohol abuse[31-33].

Hepatitis C virus: Concomitant alcohol abuse and hepatitis C virus (HCV) for various reasons, occur in about 14% of individuals with chronic liver disease[34]. Alcohol and HCV act synergistically to increase the incidence of cirrhosis and HCC, more rapid progression to fibrosis and cirrhosis, and reduced survival compared to when either of these factors is present alone[34]. Drinking more than 50 g/day of alcohol increases the relative risk of liver fibrosis in HCV patients 1.3-fold compared to HCV-infected non-drinkers and is associated with higher viremia[35]. Worse clinical course with a higher mortality is also observed with AH in the presence of hepatitis C[36]. A similar interaction has been postulated between chronic hepatitis B infection and alcohol[37], but the evidence is unclear.

Genetic factors: There is higher occurrence of alcoholism in adopted children of alcoholic parents and in monozygotic twins compared to dizygotic twins[38,39]. Polymorphisms of genes encoding for ADH and cytochrome P-450enzymes have been associated with higher occurrence of liver disease[40,41].

MAGNITUDE

Incidence and prevalence

The precise incidence of AH is unknown, although a prevalence of approximately 20% was noted in a cohort of 1604 patients with alcoholism who underwent liver biopsy[4]. The true prevalence of AH is difficult to assess because AH may be completely asymptomatic and often remains undiagnosed[32]. The prevalence of AH may be estimated from the prevalence of alcoholism, which affects 8% of general population in the United States or about 16 million people. In Italy the estimated number of alcoholics is 1 500 000, with 3 500 000 at-risk drinkers[42]. About 10 to 35% of all alcoholics have changes consistent with AH[43]. Since up to 35% of alcoholics are estimated to have AH, the number of AH patients in the United States may be nearly 5 million and in Italy about 500 000.

Global and economic burden

Heavy drinking and its consequences have a significant impact on public health. Five percent of the deaths occurring annually in the United States (approximately 100 000 per year) are either directly or indirectly attributable to alcohol abuse[12]. In 1994, approximately 7.4% of adult Americans met the DSM-IV criteria for the diagnosis of alcohol abuse and/or alcohol dependence[44]. More recent data suggest that 4.6% meet criteria for alcohol abuse and 3.8% for alcohol dependence[45].

In 1990, alcohol accounted for 3.5% of the global burden of disease, whereas tobacco accounted for 2.6%[8]. In industrialized countries, between 5% and 66% of all chronic liver disease is related to alcohol use. The costs to society from alcohol abuse cannot be overemphasized. The estimated overall cost in the United States in 1998 was $184.6 billion, with healthcare costs accounting for $26.5 billion of that total. Approximately $600 million to $1.8 billion was spent on hospital-related costs. As per the Centers for Disease Control (CDC), the incidence of chronic liver disease between December 1998 and November 1999 was 72.3 per 100 000. Of these cases, 24% were due to alcohol and 57% were due to HCV[46].

ALD is the second most common indication for orthotopic liver transplantation (OLT) for chronic liver disease in the Western world[47]. According to the United Network for Organ Sharing (UNOS) database, 41 734 liver transplants using organs from dead donors (cadaveric transplants) were performed in the United States between 1992 and 2001[48]. Of those, 12.5% were performed on patients with ALD, and 5.8% on patients with ALD and concurrent HCV infection (Figure 1). This makes ALD the second most frequent indication (after hepatitis C) for OLT. Whereas alcoholic cirrhosis is a widely accepted indication for OLT, there is only limited experience of transplantation in patients with AH. Since the current consensus is that at least 6 mo of abstinence is required prior to OLT, most patients with AH do not qualify for OLT[47].

Mortality data

Excessive alcohol consumption is the third leading preventable cause of death in the United States[49,50]. Globally alcohol consumption accounts for an estimated 3.8% mortality[8]. Although there are varoius causes of death among alcoholics, liver disease stands out as a significant cause of mortality. In 2003, 44% of all deaths from liver disease were attributed to alcohol[51], while approximately 10%-15% of U.S. alcoholics eventually developed ALD[52]. Since alcoholism is high among young people, approximately 30 years of life are lost per alcohol-associated death with about 2.3 million years of potential life lost in 2001 in the U.S.[49].

Trends in mortality from ALD: Age- and sex adjusted incidence rates of ALD-related deaths decreased from 6.9/100 000 persons in 1980 to 4.4/100 000 persons in 2003. The age- and sex-adjusted ALD-related mortality (per 100 000 persons) decreased from 6.3 to 4.5 in Caucasians, 11.6 to 4.1 in African Americans, and 8.0 to 3.7 in the "other" race groups[53]. Hence, as of 2003, ALD-related mortality affected the three race categories similarly. The rates of deaths related to AH did not increase over the 24-year period[54]. However, this may provide an incomplete picture as AH is often misdiagnosed by physicians and by coding specialists and the true burden of AH related deaths may be underestimated[32].

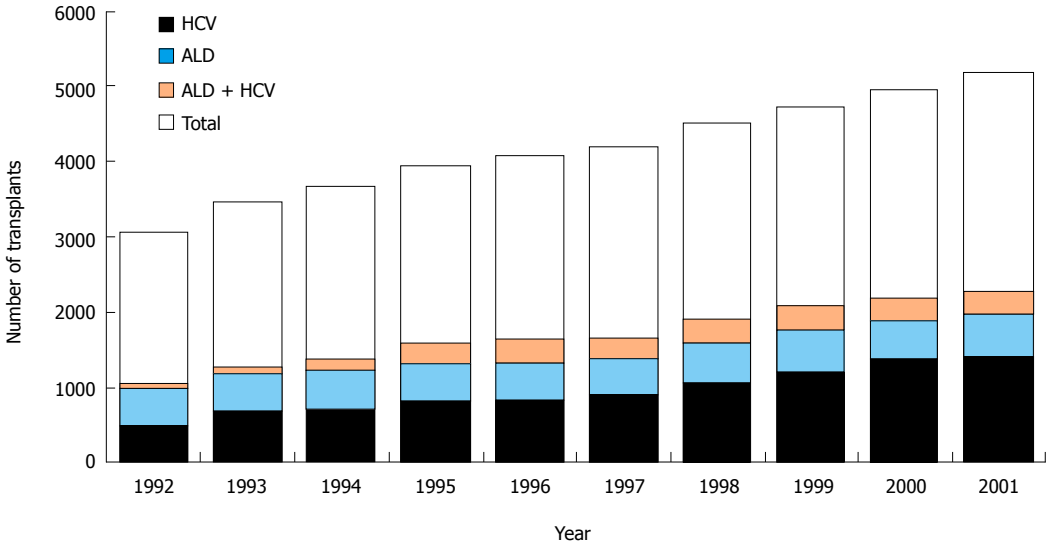

Figure 1 Liver transplantation for alcoholic liver disease and hepatitis C, 1992-2001. Source: United network for organ sharing (UNOS) registry, 1988-2001. Public data from UNOS/OPTN scientific registry (http://www.unos.org). Accessed on December 2002.ALD: Alcoholic liver disease; HCV: Hepatitis C virus infection.

Short-term mortality of AH: In the short term, the mortality of AH is closely related to the severity of illness on presentation. Overall, there is 15% mortality at 30 d and 39% at 1 year[55]. Mortality varies with the disease severity with about 20% in mild forms, and between 30% and 60% in severe AH[56]. In a British study, 30-day mortality rates of less than 20% were observed in patients with mild to moderate disease but exceeded 40% in individuals with severe liver injury[57]. Survival in this study was poorer among women[57].

Long-term follow up and progression to cirrhosis of AH: In a study on a cohort of patients with AH followed for over 4 years, survival was about 58% in uncomplicated AH, but 35% in AH with cirrhosis[58]. The probability of developing cirrhosis in patients with AH is approximately 10% to 20% per year, and approximately 70% of patients with AH will ultimately develop cirrhosis[59]. In one study, approximately 40% of patients with AH were found to have cirrhosis on repeat biopsy 5 years later[60]. Outcome depends largely on abstinence from alcohol. In individuals with complete cessation of alcohol intake, complete recovery of liver function and reversion to normal liver histology has been described in about 10% of the cases[61]. In this same study, progression of AH to cirrhosis despite abstinence occurred in a higher proportion of women compared to men indicating that women are at a greater risk of progression of ALD[62].

In summary, AH, a frequent cause of alcohol related morbidity and mortality in patients with chronic alcohol abuse is a common and distinct clinical syndrome. Alcohol abstinence is the dominant factor determining outcome in the short-term as well as on long-term follow-up.

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S- Editor Zhang HN **L- Editor** Hughes D **E- Editor** Zhang L

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v3.i5.114

World J Hepatol 2011 May 27; 3(5): 114-117
ISSN 1948-5182 (online)

TOPIC HIGHLIGHT

Ashwani K Singal, MD, *Series Editor*

Pathogenesis of alcoholic hepatitis: Role of inflammatory signaling and oxidative stress

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Received: November 26, 2010 Revised: March 7, 2011
Accepted: March 14, 2011
Published online: May 27, 2011

Abstract

Inflammatory signaling and oxidative stress are two major components in the pathogenesis of alcoholic hepatitis. Alcohol consumption results in translocation of gut bacteria into the portal system along with lipopolysaccharides that interact with toll-like receptors and results in the production of inflammatory and immunogenic mediators such as tumor necrosis factor-alpha (TNF-α) and interferons. Chronic consumption of alcohol causes priming of this process in which there is enhanced production of cytokines, interferon, interleukins, and TNF-α. Oxidative stress, genetic predisposition, and the unfolded protein response are other contributory mechanisms. Novel therapies aimed at these pathways may prevent, decrease, or delay the complications of alcoholic hepatitis.

Key words: Alcoholic hepatitis; Lipopolysaccharide; Toll like receptors; Oxidative stress; Endotoxin

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Jampana SC, Khan R. Pathogenesis of alcoholic hepatitis: Role of inflammatory signaling and oxidative stress. *World J Hepatol* 2011; 3(5): 114-117 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i5/114.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i5.114

INTRODUCTION

It is important to understand the pathogenesis of acute alcoholic hepatitis (AH) in order to develop new treatment strategies for management of this potentially fatal condition.

MECHANISMS OF ALCOHOL INDUCED STEATOSIS

Macrovesicular steatosis occurs in all drinkers within a few weeks of drinking and is completely reversible on abstinence. A combination of increased lipogenesis and impaired fatty acid breakdown results in steatosis which worsens as the ALD progresses. Mechanisms of ethanol-induced steatosis are: (1) increase in fatty acid synthesis through transcription factor sterol regulatory-element-binding protein (SREBP-1) which codes for lipogenic enzymes; (2) ethanol promotes lipid metabolism through inhibition of peroxisome-proliferator–activated receptor α (PPAR-α) and AMP kinase and stimulation of sterol regulatory element-binding protein 1. This in turn, increases fatty acid oxidation and leads to lipid storage remodeling; (3) lowering of circulating adiponectin levels which further decreases AMPK; (4) increase in insulin resistance in adipocytes that disrupts insulin signaling to phosphoinositide 3-kinase

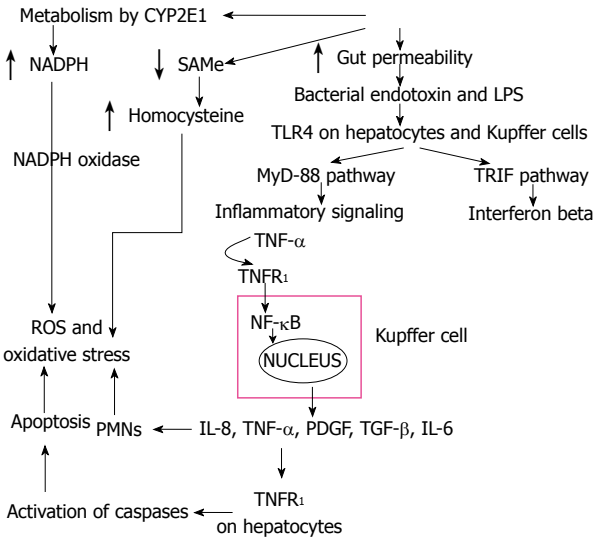

Figure 1 Overview of the pathway of alcoholic injury resulting in the direct production of oxidative stress and the LPS-TLR pathway that culminates in production of cytokines and other inflammatory processes that result in hepatitis of the liver.

(PI3K)13; and (5) interference with fatty acid beta oxidation in mitochondria and peroxisomes through increase in NADH/NAD ratio[1].

LIVER INJURY DUE TO ALCOHOL METABOLITES

Hepatocytes convert ethanol to acetaldehyde through three mechanisms: Alcohol dehydrogenase, cytochrome P-450 isoenzyme-1 (CYP2E1), and catalase[2]. Ethanol oxidation by CYP2E1 itself creates hydroxyethyl free radicals that interact with hepatocyte nucleic acids and proteins to make antigenic adducts such as malondialdehyde and acetaldehyde that elicit an immune response and cause direct oxidative injury of DNA and proteins[3].

Against the background of steatosis and existing liver damage, heavy and continued drinking in some patients causes AH. Two main mechanisms are involved: inflammation and oxidative stress.

PATHOGENETIC PATHWAYS LEADING TO HEPATIC INFLAMMATION

AH is a condition with features similar to systemic inflammatory response syndrome: fever, tender enlarged liver, leukocytosis, and increased hepatic blood flow. Initiating events include expression of gut-derived lipopolysaccharides (LPS), interaction of LPS with TLR4 receptors, activation of inflammatory signaling pathways, cytokine release, and Kupffer cells (Figure 1).

LPS, a component of the outer membrane of gram-negative bacteria interacts with immune cells and triggers inflammatory reactions with release of cytokines. Chronic alcohol exposure increases gut permeability and facilitates translocation of endotoxins from the intestinal lumen

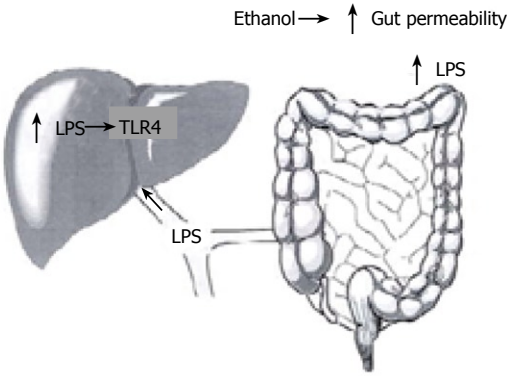

Figure 2 Link between gut derived bacterial lipopolysacaride and Toll like receptor-4 stimulation within the liver.

to the portal circulation (Figure 2). Increased levels of endotoxins and increase in gut permeability have been shown in patients with alcoholic liver disease[4]. Further, pretreatment with antibiotics or lactobacillus in animal models decreases the LPS-endotoxin and the severity of liver injury.[5,6]

Toll-like receptors (TLRs), important components of the innate immune system, function as pattern recognition receptors which recognize and bind proteins and toxins released by pathogens. There are many TLRs, but in alcoholic liver disease TLR4 is most relevant[7,8]. TLR4 signals activate early growth response 1 (EGR1, a transcription factor), nuclear factor-kappaB (NF-κB), and TLR4 adaptor (toll-interleukin-1-receptor-domain-containg adapter-inducing interferon-beta or TRIF)[9]. CD14 and TLR4 deficient mice are protected from alcoholic liver injury[10]. Interestingly, TLR4 is expressed by a number of other cells including hepatocytes, hepatic stellate cells, and sinusoidal epithelial cells which may further contribute to ALD[7,8,11]. Thus, TLR4 up regulation, in response to endotoxins, prompts Kupffer cells to release large amounts of TNF-α and NF-κB.

TLR4 acts through a pathway common to other TLRs, myeloid differentiation factor 88 (MyD88) pathway, as well as a specific and unique pathway to TLR4, TRIF signaling (the MyD88 independent pathway)[12]. In the MyD88 pathway, interleukin 1 receptor associated kinase (IRAK) and possibly TNF receptor associated kinase 6 (TRAF6) are recruited to the TLR4 complex by MyD88 and eventually express TNF-α and apoptosis transcription factor AP-1. The TRIF pathway (My88-independent) activates IRF-3, NF-κB and eventually IFN-β and TNF-α production[13]. IRF-3 may also bind to the promoter region and up regulate transcription of TNF-α[13].

NF-κB is a transcription factor that is translocated to the nucleus in response to stress signals and binds to the promoter region of pro-inflammatory genes[14]. Chronic alcohol intake primes the liver through continued NF-κB activation and increased TNF-α production in response to LPS, and murine models show increased binding of NF-κB to the DNA[15]. Monocytes from chronic alcoholic patients show increased NF-κB activation in comparison to controls[16]. Additionally, monocytes cultured from chro-

nic alcoholics show increased amounts of TNF in response to LPS stimulation[17]. Studies have shown that in rats chronically fed ethanol, injected LPS results in a much higher plasma level of TNF-α compared to controls[18,19].

Other pathways which are stimulated in this process are: (1) the signal transducer and activator transcription factor (STAT) pathway activated by interleukin-6 (IL-6) and interferons-LPS causes STAT3 to induce IL-10 production during acute alcohol exposure in monocytes[20]; (2) LPS stimulation of MAPK family members which include JNK (c-jun-N-terminal kinase), ERK (extracellular receptor activated kinases), and p38 culminates in NF-κB production and mRNA stabilization[21]; and (3) Changes in immune function accompany LPS-induced hepatic inflammation- CD4+ and CD8+ T lymphocyte infiltrates are found in 40% of patients with ALD[22]. It is thought that abnormal proteins may leak into the portal system and collect in germinal centers where the antigens are presented to CD4+ T-cells resulting in antibody creation against the proteins. Hepatic stellate cells can also present such antigens to CD4+ cells, and dendrites that scavenge dead hepatocytes may present antigens to CD8+ cells, thus providing numerous possible pathways by which oxidative stress can stimulate the immune system through both humoral and cellular mechanisms.

All these pathways result in recruitment of inflammatory cells (polymorphs and mononuclear cells) and cause necroinflammation. This is followed by Kupffer cell activation, hepatocyte ballooning, and apoptosis.

OXIDATIVE STRESS

Oxidative stress occurs when there is an imbalance between antioxidants and reactive oxidizing species[3]. Oxidative stress is indirectly measured through markers such as protein oxidation, lipid oxidation, DNA oxidation, and depletion of antioxidants. In AH, there is decreased production and increased depletion of antioxidants alongside an increase in production of reactive oxygen species(ROS), reactive nitrogen species, and peroxidized lipids.

Markers of oxidative stress increase with acute alcohol ingestion and in persons with AH[23]. Activated Kupffer cells and hepatocytes act as sources of free radicals in response to alcohol[24]. As alluded to earlier, CYP2E1 may increase 5-20 fold in patients with AH, leading to increased electron leakage and release of ROS causing oxidative stress, adduct formation and immunogenic responses[25]. Oxidative stress leads to damage of the mitochondria, endoplasmic reticulum (ER) stress and subsequent apoptosis, and increased lipid synthesis[3,26]. The ROS cause lipid peroxidation and the formation of Mallory bodies through breakdown of proteins. Other sources of oxidative stress include granulocytes from the inflammatory process catalyzed by the enzymes NADPH oxidase and myeloperoxidase which cause production of ROS, hepatic iron accumulation, and a decrease in antioxidants[3,27]. ROS can also activate ERK1/2, p38 MAPK kinases, and NF-κB which stimulates TNF-α, complementing the LPS-induced pathways of TNF-α production and creating a vicious cycle of inflammation and oxidative stress[28].

Mitochondria rely on transport of the powerful antioxidant glutathione from the cytosol. Alcohol consumption inhibits methionine conversion to S-adenosylmethionine (SAMe), the precursor for glutathione synthesis. Additionally, alcohol inhibits methionine synthase and folate which act as cofactors for methyl group transfers. Disruption of these pathways impairs the conversion of homocysteine to methionine, resulting in the accumulation of homocysteine, further disabling the redox balance of cells in favor of oxidative stress[2].

MISCELLANEOUS MECHANISMS AND PATHWAYS

Proteasomes degrade defective proteins and help in regulation of cell processes such as gene regulation and cell division. When the proteasomes do not work properly, proteins accumulate and enhance progression of liver disease[29]. In animal models of chronic alcohol feeding, proteasome activity decreases and serum levels of ubiquitin, involved in the degradation of defective proteins, increases[30]. Ubiquitin also accumulates in hepatocytes and appears as Mallory bodies on liver histology[31].

The unfolded protein response (UPR) is a series of signals triggered by the accumulation of unfolded proteins and is due to stress placed on ER[32]. UPR reduces protein synthesis and favors protein degradation as well as activation of Nfr2-mediated apoptosis signals[32]. UPR is aggravated by the accumulation of protein adducts and ROS as well as by the depletion of antioxidants such as glutathione[32, 33].

SAMe is the primary methyl donor and precursor to glutathione. In alcoholic hepatitis, there is a decrease in hepatic methionine levels and a 50-60% decrease in the activity of methionine adenosyl transferase, the enzyme which converts methionine to SAMe[34]. This causes a decrease in glutathione synthesis which results in impaired clearance of oxidative species such as 4-hydroxynonenal (marker of lipid peroxidation) and mitochondrial injury. Human and animal studies have suggested that SAMe replacement results in increased GSH and decreased markers of oxidation[35].

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S- Editor Zhang HN **L- Editor** Hughes D **E- Editor** Zhang L

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v3.i5.118

World J Hepatol 2011 May 27; 3(5): 118-120
ISSN 1948-5182 (online)

TOPIC HIGHLIGHT

Ashwani K Singal, MD, *Series Editor*

Symptoms and signs of acute alcoholic hepatitis

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Received: October 28, 2010 Revised: March 8, 2011
Accepted: March 15, 2011
Published online: May 27, 2011

Abstract

Although there is not one specific sign or symptom related to alcoholic hepatitis (AH), a constellation of symptoms and signs can help make the diagnosis of AH with reasonable accuracy. Documentation of chronic and active alcohol abuse is paramount in making a diagnosis of AH. Clinical presentation after abstinence for more than 3 m should raise doubts about the diagnosis of AH and dictate the need for considering other causes of liver disease, decompensation of alcoholic cirrhosis, sepsis and malignancy as the cause of patient's clinical profile.

Key words: Alcoholic hepatitis; Alcoholic liver disease; Clinical features; Symptoms and signs

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Basra G, Basra S, Parupudi S. Symptoms and signs of acute alcoholic hepatitis. *World J Hepatol* 2011; 3(5): 118-120 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i5/118.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i5.118

INTRODUCTION

A typical patient with alcoholic hepatitis (AH) provides a history of an average daily consumption of over 80 g of ethanol for over 5 years[1]. However, the duration of excessive drinking before the onset of liver disease could vary from 3 mo to 36 years. One study had evidence of liver disease with excessive drinking of less than 1 year duration[2]. Not uncommonly, patients may have ceased alcohol consumption several weeks before the onset of symptoms[3]. However, abstinence of more than 3 mo is unlikely to be associated with the diagnosis of AH.

Although the peak age distribution of AH is 40-60 years of age, the disease has been seen in a patient as young as 20 years and as old as 80 years[2]. Gender distribution of the disease varies across different studies with a male predominance in one study[4]. However, in another study of 169 patients, females contributed to more than 60% of cases[2]. This conclusion may be related to a higher number of black women in this series. However, when the data are combined across different series, the gender distribution was found to be equal[1]. A higher risk of liver injury may be associated with an individual's racial and ethnic heritage[5]. Racial distribution across studies shows that 70%-80% of cases are seen among whites and 20%-30% among blacks. The rates of alcoholic cirrhosis are higher in African-American and Hispanic males compared to Caucasian males and the mortality rates are highest in Hispanic males[6]. These differences do not appear to be related to differences in amounts of alcohol consumed[7].

Clinical features of acute AH can be subdivided into four broad headings.

Table 1 Common signs and symptoms amongst hospitalized patients with alcoholic hepatitis

Symptom or Sign	% of patients	
	Mendenhall *et al*[1] (*n* = 363)	Lischner *et al*[2] (*n* = 169)
Hepatomegaly	87	81
Jaundice	60	37
Ascites	57	35
Hepatic encephalopathy[a]	45	18
Splenomegaly	26	
Fever	23	56
GI hemorrhage	10	23
Malnutrition[b]	90	56
Esophageal varices		12
Abdominal pain	18	

[a]Defined as altered consciousness, coma, and/or asterixis; [b]Defined as muscle wasting, weight loss, low albumin, amenorrhea, or pellagra.

FEATURES SPECIFIC TO EXISTING ALCOHOLIC HEPATITIS

Although clinical jaundice is present in 40%-60% cases (Table 1), hyperbilirubinemia is present in almost every patient with AH and is considered a cardinal feature of this disease. Other symptoms reported in AH patients include right upper quadrant pain, fever, tachycardia and tender enlarged liver. Fever should be attributed to AH after excluding infection and malignancy. Hepatic bruit due to increase in blood flow is characteristic of AH. However, its reported frequency varies across different studies. This is not a common finding and in a large series was seen in only about 2% of cases[8]. However, demonstration of increased blood flow using Doppler Duplex examination was useful for diagnosis of AH in one study[9]. Presence of hepatic bruit should be further worked up before labeling it AH related since coexistent HCC can contribute to the hepatic bruit. Other non-specific symptoms may be associated such as nausea, vomiting, malaise and anorexia. The frequency of these symptoms and signs varies with the severity of disease with a higher frequency in patients with severe disease. With a more severe disease, patients may have associated complications such as hepatic encephalopathy, renal failure or hepatorenal syndrome, ascites due to portal hypertension and bleeding tendencies due to coagulopathy and/or thrombocytopenia. Malnutrition is frequently seen in these with a frequency of up to 90% in one series[1]. This could be due to protein calorie malnutrition, Kwashiorkor or generalized caloric under nutrition or Marasmus. Patients should be examined for clinical signs of malnutrition such as reduced muscle mass, decreased triceps skin fold thickness, swelling on legs or edema of feet in the absence of ascites, decreased mid arm muscle circumference and hypoalbuminemia. This is important as many studies have shown a correlation between malnutrition and negative outcome of the disease[10,11]. Malnutrition is also a risk factor for the occurrence of infections which patients with alcoholic hepatitis are prone to.

FEATURES DUE TO UNDERLYING CIRRHOSIS

Concomitant cirrhosis is present in about 50%-60% cases with AH[12]. Hence, these patients may have features of cirrhosis such as spider angiomas, palmar erythema, ascites and variceal bleeding. Other commonly noted features are Dupuytren's contracture, gynecomastia and loss of pubic or axillary hair, parotid gland enlargement and testicular atrophy in males and amenorrhea with infertility in females. Although these are seen more commonly with alcoholic cirrhosis, these are not specific or sensitive for diagnosis of alcohol related cirrhosis.

ASSOCIATED DISEASES

As alluded to earlier, patients with alcoholic liver disease are prone to development of infections. Increased gut permeability and transmigration of gut bacteria, associated malnutrition and depressed innate immunity are some of the reasons that make alcoholics more prone to infections[13-18]. In one series, about a third of patients had infections with the urinary tract being the most common site of infection in about 23% cases[2]. Other common infections are spontaneous bacterial peritonitis, bacterial pneumonia, tuberculosis, septicemia and lung abscess. Other associated conditions are gastrointestinal bleeding (10%-22%), alcoholic gastritis (10.7%), pancreatitis (8.8%-11.4%), neuropathy (10.0%), cardiomyopathy (2.4%), diabetes mellitus (10.7%) and cancer (3.6%)[1,2].

SIGNS OF ALCOHOL WITHDRAWAL

Patients with AH may also present with withdrawal symptoms. Mild to moderate symptoms include irritability, anxiety, headache, sweating, tachycardia and hand tremors with clammy skin. Severe symptoms include delirium tremens in which the patient is confused and may have visual hallucinations along with agitation, convulsions and fever. The frequency of alcohol withdrawal is inversely proportional to the severity of alcoholic hepatitis with 35% cases with mild disease and 15% of severe disease[1].

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S- Editor Zhang HN **L- Editor** Roemmele A **E- Editor** Zhang L

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v3.i5.121

World J Hepatol 2011 May 27; 3(5): 121-124
ISSN 1948-5182 (online)

TOPIC HIGHLIGHT

Ashwani K Singal, MD, *Series Editor*

Acute renal dysfunction in patients with alcoholic hepatitis

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Received: October 28, 2010 Revised: March 6, 2011
Accepted: March 13, 2011
Published online: May 27, 2011

Abstract

Acute renal dysfunction is common in patients with alcoholic hepatitis (AH). Its presence leads to higher mortality in these patients. Despite advances in medical care, the outcome has changed little over the past decades. Studies using Pentoxifylline and molecular adsorbent recirculation system have shown encouraging data in small studies. Further larger well designed studies are needed to assess these modalities of treatment for the treatment of AH.

Key words: Acute renal dysfunction; Alcoholic hepatitis; Renal failure; Hepatorenal syndrome

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Arora R, Kathuria S, Jalandhara N. Acute renal dysfunction in patients with alcoholic hepatitis. *World J Hepatol* 2011; 3(5): 121-124 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i5/121.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i5.121

INTRODUCTION

Renal dysfunction can present as acute kidney injury (AKI), defined as an abrupt or rapid decline in renal function, or as chronic kidney disease secondary or concomitant to liver dysfunction. In this chapter we will discuss mechanisms, clinical features and management of AKI in patients with alcoholic hepatitis (AH).

AKI is common among hospitalized patients[1,2], affecting 3%-7% of hospital admissions and 25%-30% of intensive care unit admissions. Patients with AH may have underlying cirrhosis in about 70% of cases[3]. Therefore, AKI in patients with AH could occur due to decompensation of underlying cirrhosis or due to mechanisms peculiar to AH.

PATHOPHYSIOLOGY OF AKI IN ALCOHOLIC HEPATITIS

Mechanisms for AKI due to underlying cirrhosis

AH and cirrhosis are associated with systemic arterial vasodilation because of increased endogenous vasodilators, especially nitric oxide and 3', 5' cyclic guanosine monophosphate[4]. Systemic arterial vasodilation causes a decrease in systemic vascular resistance (SVR) leading to high cardiac output and hyperdynamic circulation[5]. Increase in cardiac output may be insufficient to keep up with a drop in SVR leading to hypotension. Further insult in the form of sepsis or decreased cardiac output may overcome renal blood flow autoregulation, rendering patients prone to pre-renal AKI and acute tubular necrosis (ATN).

In patients with cirrhosis there is increased splanchnic pooling of blood due to portal hypertension. Decreased effective circulatory blood volume leads to activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system. Arginine-vasopressin leads to salt and water retention, further worsening edema and ascites. In addition, there is intense vasoconstriction in an attempt to maintain blood pressure and perfusion to vital organs[6,7].

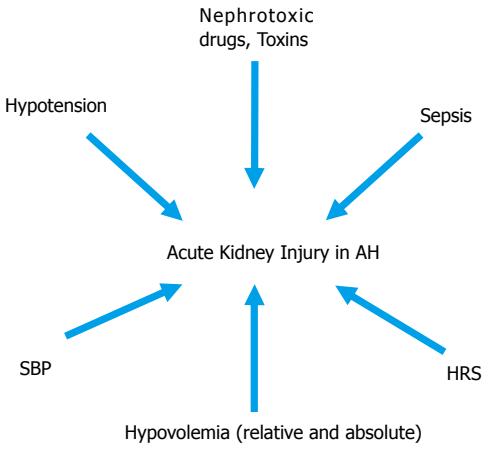

Figure 1 Potential cause of acute kidney injury in alcoholic hepatitis. AH: Alcoholic hepatitis; SBP: Spontaneous bacterial peritonitis; HRS: Hepatorenal syndrome.

Decompensation due to hypovolemia or GI bleeding can make this worse, causing further reduction in glomerular filtration rate (GFR) and predisposing the patient to AKI.

Mechanisms peculiar to alcoholic hepatitis

A number of studies have shown increased gut permeability to endotoxin, bacterial endotoxins and other macromolecules[8,9]. Gut leakiness leading to endotoxemia is a key cofactor for alcoholic steatohepatitis in rats[10]. Bacterial endotoxin (Lipopolysaccharide, LPS) is recognized by Toll-like receptor 4 complex in the liver, which results in increased production of cytokines such as tumor necrosis factor (TNF-α), interleukin (IL)-6, IL-1β and IL-8[11-13]. Studies have shown a linear relationship between TNF-α receptors and mortality from AH[14]. Pentoxifylline is a non-specific phosphodiesterase inhibitor with anti-inflammatory (by TNF-α inhibition) and anti-fibrogenic properties and has been shown to reduce mortality in patients with severe alcoholic hepatitis by significant reduction in the development of hepatorenal syndrome[15]. Elevated TNF-α is significantly associated with chronic kidney disease and proteinuria[16,17].

CAUSES OF ACUTE KIDNEY INJURY IN ALCOHOLIC HEPATITIS

Pre-renal

Patients with AH and cirrhosis may have reduced effective circulatory blood volume and functional hypovolemia. Patients are more susceptible to develop pre-renal azotemia in the presence of true hypovolemia, gastrointestinal bleeding, large volume paracentesis, infections and nonsteroidal anti-inflammatory drugs (NSAIDs)[18-21].

Intrinsic renal

The potential intrinsic causes of AKI in AH are nephrotoxic drugs (e.g. amino glycosides, diuretics and NSAIDs)[22-24], toxins and infections[18]. Rhabdomyolysis[25] and jaundice[26,27] leading to hyperbilirubinemia[28] have also been suggested as causes of intrinsic renal dysfunction. One third of patients with spontaneous bacterial peritonitis (SBP) develop renal dysfunction as a result of reduced effective circulatory volume[29]. Patients with alcohol-induced liver cirrhosis are believed to develop intrinsic renal disease in addition to the above insults[30]. If left untreated, any cause of pre-renal AKI can lead to ATN. (Figure 1)

Hepatorenal syndrome

Hepatorenal syndrome (HRS) is a functional form of renal failure that develops in patients with advanced cirrhosis and ascites. HRS is usually accompanied by severe renal arterial and arteriolar vasoconstriction in the presence of systemic and splanchnic arterial vasodilation leading to low renal perfusion and GFR. HRS can present either as Type-1 (acute developing over few days) or Type-2 (slower in onset over weeks to months)[31]. Patients with AH usually develop type Ⅰ HRS and, without treatment, these patients have a median survival of only 2 wk[32].

DIAGNOSTIC APPROACH TO RENAL DYSFUNCTION IN ALCOHOLIC HEPATITIS

Clinical evaluation

Recent exposure to nephrotoxic drugs, radio contrast agents, surgical or interventional procedures and history of gastrointestinal hemorrhage, vomiting and diarrhea should be excluded. Evaluation should rule out true hypovolemia, infections and sepsis. A complete history and physical can help to exclude vascular and immunological causes of AKI (Table 1, 2). Tense ascites can cause abdominal compartment syndrome defined as intra-abdominal pressure (IAP) of > 20 mmHg and abdominal perfusion pressure < 60 mmHg resulting in decreased renal vein blood flow and renal dysfunction[33]. IAP can be evaluated by intravesical method[34]. Anuria is suggestive of post-renal cause.

Urine evaluation

Microscopic and chemical urinalysis can yield important information for establishing diagnosis. Presence of pigmented granular casts and red blood cell casts (RBC casts) are suggestive of ATN and glomerulonephritis (GN) respectively[35,36]. In contrast, the urine in pre-renal and HRS is generally unremarkable.

Laboratory evaluation

Low urine sodium (< 20 mmol/L) and a high urine osmolality (> 500 mOsm/kg) are suggestive of pre-renal causes or HRS. In contrast, high urine sodium (> 40 mmol/L) and low urine osmolality (< 350 mOsm/kg) suggest intrinsic renal disease or ATN[37,38]. Patients with AKI and advanced liver disease have higher incidence of hyponatremia, SBP, hepatic encephalopathy and higher levels of serum bilirubin, aspartate aminotransferase, alanine aminotransferase, and white cell counts [18].

Table 1 International Club of Ascites criteria for the diagnosis of hepatorenal syndrome

1	Presence of cirrhosis and ascites
2	Serum creatinine > 1.5 mg/dL (or 133 mmol/L)
3	No improvement of serum creatinine (decrease equal to or less than 1.5 mg/dL) after at least 48 h of discontinuing diuretics
4	Withdrawal and volume expansion with albumin (recommended dose: 1 g/kg per day up to a maximum of 100 g of albumin/d)
5	Absence of shock
6	No current or recent treatment with nephrotoxic drugs
7	Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/d, microhematuria (> 50 RBCs/high power field), and/or abnormal renal ultrasound scanning

Table 2 Urinalysis findings in various etiologies of acute kidney injury

AKI type		UA	Urine sodium (mEq/L)	FENA	BUN:Creatinine ratio
Pre-renal		Normal or hyaline casts	< 20	< 1	⩾ 20:1
Intrinsic renal					
	ATN	Muddy brown casts	> 40	⩾ 1	
	GN	Dysmorphic RBC and RBC casts	< 20	< 1	
	AIN	WBC casts and eosinophils	> 20	⩾ 1	
Post-renal		Normal or hematuria	>20	Variable	⩾ 20:1

ATN: Acute tubular necrosis; GN: Glomerulonephritis; AIN: Acute interstitial nephritis; RBC: Red blood cells; WBC: White blood cells; FENA: Fractional excretion of sodium.

MANAGEMENT

Pre-renal and renal

Initial management is similar to the management of AKI of any etiology and includes correction of hypovolemia, electrolyte abnormalities, coagulation disorders and gastrointestinal bleeding. Patients with liver disease are susceptible to develop renal toxicity with diuretics, NSAIDs and amino glycosides[22-24]. The utmost attention should be paid to volume status of patients as they may need fluid challenge to rule out pre-renal hypovolemia as the cause of renal dysfunction. Since the deterioration in patients with advanced liver disease and ascites is associated with SBP and sepsis, one should be vigilant as infection may be the precipitous cause. Renal adjustment of antibiotic dosage may be required secondary to renal dysfunction. If suspected, SBP should be ruled out by performing paracentesis in a patient with ascites. Patients with ascites and other signs and symptoms of fluid overload may require sodium and fluid restriction in addition to frequent paracentesis and albumin administration[39].

Hepatorenal syndrome

HRS is a diagnosis of exclusion. Liver transplantation, often combined with kidney transplantation, is the definitive treatment option. However, as patients with AH are active drinkers, they are not suitable candidates[40].

Vasopressin analogues (terlipressin and orlipressin) have been used in the management of HRS. Their mechanism of action is to induce systemic and splanchnic vasoconstriction leading to increased renal blood flow. Since terlipressin is not available in the United States, other agents such as somatostatin analogues (octreotide) and alpha-adrenergic agonists (midodrine) are used for management of HRS[41,42].

If the patient is non-responsive to vasoconstrictor therapy, a transjugular intrahepatic porto-systemic shunt (TIPS) may result in improvement in renal function in patients with HRS[42]. TIPS is currently recommended only in patients who are eligible for liver transplant.

Patients should be evaluated for Renal Replacement Therapy (RRT) in the event of acute decompensation resulting in metabolic acidosis, electrolyte imbalance and volume overload. RRT has a high incidence of side effects in these sick patients, including arterial hypotension, coagulopathy and gastrointestinal bleeding. Because of the high mortality of HRS, it should be offered as a bridge only to those with the possibility of hepatic recovery or liver transplantation. The three common RRT modalities available are Peritoneal Dialysis, Intermittent Hemodialysis (IHD) and Continuous Renal Replacement Therapy (CRRT). PD is usually contraindicated, secondary to ascites in these patients. CRRT is the preferred modality in these patients since it has an advantage over IHD of better cardiovascular, hemodynamic and Intracranial Pressure stability. The molecular adsorbent recirculation system has shown promising result in patients with AH but needs further evaluation[43-45].

PREVENTION

In patients with spontaneous bacterial peritonitis, administration of albumin in addition to antibiotic therapy (intravenous cefotaxime) significantly lowers the occurrence of HRS and death compared to antibiotics alone[46]. The benefit is believed to be due to plasma volume expansion with intravenous albumin preventing reduction in effective arterial blood volume. As discussed above, in patients with AH, the use of pentoxifylline reduces the incidence of HRS and mortality[15,47].

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S- Editor Zhang HN **L- Editor** Roemmele A **E- Editor** Zhang L

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v3.i5.125

World J Hepatol 2011 May 27; 3(5): 125-129
ISSN 1948-5182 (online)

TOPIC HIGHLIGHT

Ashwani K Singal, MD, *Series Editor*

General aspects of the treatment of alcoholic hepatitis

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Received: October 28, 2010 Revised: March 6, 2011
Accepted: March 13, 2011
Published online: May 27, 2011

Abstract

General measures for treating patients with alcoholic hepatitis (AH) are similar irrespective of the disease severity. Alcohol abstinence is the cornerstone of treatment and can be achieved with appropriate social support, Alcoholics Anonymous and sometimes pharmacological therapy. Alcohol withdrawal should be anticipated and treatment initiated to prevent this complication. Treatment for complications of cirrhosis should be as for any other patient with cirrhosis. AH patients are particularly prone to infections and malnutrition. These should be identified and treated appropriately using broad spectrum antibiotics and nutritional support respectively.

Key words: Alcoholic hepatitis; Alcohol abstinence; Alcohol withdrawal; Nutritional support; Complications of cirrhosis; Malnutrition; Treatment

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Babianeux MJ, Anand BS. General aspects of the treatment of alcoholic hepatitis. *World J Hepatol* 2011; 3(5): 125-129 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i5/125.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i5.125

INTRODUCTION

The approach to general treatment of patients with acute alcoholic hepatitis (AH) is similar irrespective of the disease severity.

ABSTINENCE FROM ALCOHOL

Abstinence is of paramount importance in the treatment of AH and has been shown to significantly improve long-term survival[1,2]. The success rate of achieving abstinence varies from 30%-90%. The most important factor associated with long-term abstinence is the patient's awareness of the consequences of alcohol consumption. Other factors such as adequate social support, lack of illicit drug use and appropriate psychiatric evaluation and help predict successful outcome[3]. Incorporation of behavior modification and support groups, such as Alcoholics Anonymous, increases the likelihood of sustained sobriety and is recommended for patients who have difficulty in abstaining.

Pharmacological therapy such as naltrexone (an opioid receptor antagonist), acamprosate (GABA analog) and baclofen (GABA agonist) can be used to maintain abstinence[4]. However, only baclofen has been tried in patients with cirrhosis and liver failure. In the study reported from Italy, patients with alcoholic decompensated cirrhosis were randomized to receive baclofen (n = 42) or placebo (n = 42). At the end of 3 m, results by intention to treat analysis favored baclofen with a higher proportion of patients remaining abstinent (71% *vs* 29%; P = 0.0001) and longer cumulative abstinence duration (63 d *vs* 31 d; P = 0.001).

Table 1 General approach to treatment of a patient with alcoholic hepatitis

Complication	Initial evaluation	Treatment	Treatment for refractory cases
Alcohol withdrawal	History of alcohol abuse Ethanol level	Fluid hydration Benzodiazepines Glucose supplementation Vitamin replacement	ICU placement IV benzodiazepines Propofol Phenobarbital Endotracheal intubation
Ascites	LFTs, ascetic fluid analysis, CT abdomen	Diuretics IV albumin Paracentesis	TIPS Liver transplantation
Altered mental status	CBC/BMP LFTs NCCT head Pancultures Lumbar puncture	IV antibiotics Lactulose Treat precipitant	Rifa × imin
Variceal bleeding	CBC LFTs	Blood transfusion octreotide Prophylactic antibiotics EVL	TIPS Shunt surgery for compensated cirrhosis
Infection	CBC/BMP Pancultures	Antibiotics for gram negative coverage	Broad spectrum antibiotics covering both gram positive and negative organisms
Malnutrition	Weight comparison Serum albumin	Oral supplementation	PEG placement Nutritionist consultation

CBC: Complete blood count; BMP: Basic metabolic panel; EVL: Endoscopic variceal ligation; TIPS: Transjugular intrahepatic portosystemic shunt.

No side effects were reported with the use of baclofen in these patients with advanced cirrhosis[5].

MANAGEMENT OF ALCOHOL WITHDRAWAL

In patients with a history of alcohol abuse, it is crucial to recognize symptoms of alcohol withdrawal which may include insomnia, irritability, nausea, vomiting, headache, anxiety, cardiac arrhythmia, hypoglycemia and diaphoresis. Rarely, withdrawal tonic clonic seizures may occur which can proceed to delirium tremens (DT). Symptoms can present within six hours of alcohol cessation in the presence of significant serum alcohol levels. Electrolyte abnormalities such as hypokalemia, hypomagnesemia, hypophosphatemia and hypoglycemia are common due to poor intake or concomitant diarrhea.

Alcoholics are also prone to anion gap acidosis due to hormonal disturbances with relative insulin deficiency and high cortisol levels. Anion gap acidosis should, however, be differentiated from lactic acidosis and sepsis as these are also common in alcoholics. Pure acidosis due to fasting and hypoglycemia reverses with administration of appropriate fluids. Hypoglycemia should only be corrected after the administration to thiamine to avoid precipitation of Wernicke's encephalopathy presenting with confusion, delirium and ophthalmoplegia, a consequence of thiamine deficiency which can be prevented by supplementation with thiamine and folic acid.

DT, defined by hallucinations, disorientation, cardiac arrhythmia, hypertension, fever, agitation and diaphoresis, usually occurs 48-96 h after the patient's last alcohol drink. Risk factors for the development of DT include chronic alcohol use, history of DT in the past, elevated serum alcohol levels and presence of concomitant illness Mortality rate of DT approaches 5% and is usually due to arrhythmia and complicating illness (pancreatitis, hepatitis or pneumonia). Benzodiazepines are used for prophylaxis and acute withdrawal. Lorazepam and oxazepam are the preferred drugs in patients with liver disease due to their relatively short half life. Intravenous administration is preferred in the setting of acute withdrawal due to rapid absorption and achievement of therapeutic levels. Intramuscular administration is not recommended due to inconsistent absorption rates. Refractory DT may be treated with the addition of phenobarbital to benzodiazepine therapy. Propofol has also been utilized to control symptoms. Patients who require phenobarbital or propofol will likely need endotracheal intubation and mechanical ventilation.

TREATMENT OF COMPLICATIONS OF CHRONIC LIVER DISEASE

Individuals with alcoholic hepatitis may have underlying cirrhosis and may frequently have complications with decompensated cirrhosis such as ascites, infection, variceal bleeding, altered mental status and renal complications (Table 1).

Ascites

Large volume paracentesis (LVP) is indicated for removal of fluid due to diuretic or diet noncompliance or ascites refractory to diuresis. Large volume paracentesis (removal of over 4-5 L) requires infusion of 6-8 g of albumin for every liter of ascites removed above the minimum. Another option for patients with refractory ascites is the use of transjugular intrahepatic portosystemic shunt (TIPS). Meta-analysis of randomized studies comparing paracentesis and TIPS have shown better control of ascites with less frequent accumulation and significantly impro-

ved transplant free survival with TIPS compared to LVP (year 1: 63% *vs* 52% and year 2: 49% *vs* 35%)[6]. However, increased frequency of hepatic encephalopathy occurred with TIPS compared to LVP (39 ± 21% *vs* 23 ± 14%; $P < 0.05$). After initial placement acute deterioration of hepatic function, increased cardiac output and decrease in vascular resistance is expected with TIPS but resolves approximately 3 mo later. Therefore, TIPS should be avoided in patients with a model for end-stage disease (MELD) score > 18 or Child Pugh class > 9[7-9].

Hepatic hydrothorax develops in approximately 5%-10% of cirrhotic patients. It occurs on the right side in 90% cases. Fluid seeps through defects in the diaphragm and the accumulated fluid in the pleural cavity has features similar to ascitic fluid[10]. Because of the potential for occurrence of volume and electrolyte disturbances in these patients, the placement of a chest tube should be avoided[11].

Altered mental status

Changes from baseline mentation are common in acute alcoholic intoxication and liver disease. Neurological disorders may stem from malnutrition (thiamine deficiency), ethanol neurotoxicity or acute intracranial abnormality (hemorrhagic or ischemic stroke). Metabolic disorders such as hypoglycemia, hyponatremia or hepatic encephalopathy are additional considerations. Infectious causes such as spontaneous bacterial peritonitis, meningitis or sepsis if suspected require empirical antibiotic coverage. At initial presentation, the patient should have a non-contrast head CT, preferably before lumbar puncture, if clinically indicated. Blood cultures, urinalysis, urine culture and ammonia level should be obtained along with CBC to evaluate acute decrease of hemoglobin or infection and BMP for metabolic abnormalities. Supplementation of thiamine and water soluble vitamins (pyridoxine and folate) should be administered. A major cause of altered mental status in liver disease is noncompliance with medical management. Typical management is the administration of lactulose with a goal of 2-3 bowel movements daily. Many patients are noncompliant with therapy due to the inconvenience of having frequent bowel movements, thus leading to frequent episodes of encephalopathy. Rifaximin is also utilized in the prevention of encephalopathy and has been shown in placebo controlled studies to have higher rates of remission and reduction of hospital admissions due to hepatic encephalopathy[12].

Variceal bleeding

A potential complication of portal hypertension is the development of esophageal and gastric varices. Mortality from esophageal variceal bleeding approaches 20%-40% and in hospital mortality remains about 20% despite optimal medical management[13]. Mortality from gastric variceal bleeding exceeds 50% and, as with esophageal varices, the outcome is linked to factors such as CTP class and the size of varices[14]. Screening for primary prevention is recommended for all patients presenting with cirrhosis. The presence and characteristics of the varices are predictors of bleeding. These include distance from the gastroesophageal junction (proximal *vs* distal), color (blue or white), size and presence of red streaking/hematocystic spots.

Primary prophylaxis can be achieved with nonselective beta blockers such as propranolol for patients with large varices. Individuals who cannot tolerate or are non-compliant to beta blockers have a high risk of bleeding and may benefit from endoscopic variceal ligation.

Acute variceal bleeding can lead to encephalopathy and the patient's airway should be secured at presentation. Pharmacological therapy aims to control acute bleeds from systemic vasoconstriction. Commonly, somatostatin or octreotide infusions are utilized to control active variceal bleeding. Both drugs have an excellent safety profile and studies have shown favorable control of acute bleeding with somatostatin and octreotide versus placebo or vasopressin. The use of these drugs is also comparable to early balloon therapy or endoscopy[15-18]. Current guidelines recommend infusion of somatostatin or octreotide in addition to balloon tamponade, sclerotherapy or endoscopic banding to reduce the risk of recurrent bleeding[19-21]. Patients who are unresponsive to initial pharmacological or endoscopy treatments should be considered for TIPS procedure or surgery as an alternative. Empirical coverage with Cefotaxime or a third generation cephalosporin is recommended during active bleeding to prevent infections, especially spontaneous bacterial peritonitis.

Special considerations

Infection: Alcoholics are more susceptible to infections than other patients with liver disease because of malnutrition, immunosuppression and altered macrophage function. Common infections include pneumonia, meningitis, urinary tract infections, bacteremia and spontaneous bacterial peritonitis. Patients with cirrhosis are also susceptible to fungal infections and *Vibrio vulnificus* or *Listeria monocytogenes*. Cirrhotic patients who are suspected to have an infection should have a proper work up with a chest x-ray, blood cultures and urine analysis and culture. If the physical exam is positive for CNS abnormalities, a lumbar puncture should also be considered. Ascites should be sampled and sent for culture and cell count. An absolute neutrophil count of > 250 in the ascitic fluid of a cirrhotic patient indicates spontaneous bacterial peritonitis (SBP)[22]. The most frequently isolated organisms are enterobacteriaceae but gram positive organisms such as *Streptococcus pneumonia* and *Enterococcus* can also be isolated[22]. Initial antibiotic choice includes a third generation cephalosporin or beta lactam/lactamase. Amino glycosides should be avoided due to the risk of renal toxicity. Intravenous albumin (1.5 g/kg at diagnosis and 1 g/kg 48 h post diagnosis) can also be administered upon clinical suspicion or laboratory confirmation of SBP to prevent potential renal complications and reduce mortality[23]. Bacterial infection or sepsis from upper gastrointestinal bleeding occur in about 20% of patients and should also be treated with empirical antibiotics. Database reviews and trials have demonstrated that overall

complications, recurrent bleeding and mortality from infections were reduced in patients with cirrhosis hospitalized for gastrointestinal bleeding[24-26].

Renal failure: Renal failure is an important cause of mortality among patients with AH and will be discussed separately in another section.

Malnutrition: Patients with AH frequently present with protein caloric malnutrition due to a number of factors such as: poor intake, direct interference with small intestinal absorption and alcoholic diarrhea[27]. Nutritional status directly correlates with survival and patient outcome; thus, maintaining an adequate nutritional status in patients with alcoholism and alcoholic hepatitis is paramount[28].

Many studies have assessed the role of nutritional supplementation in the treatment of AH. A randomized control trial compared corticosteroid therapy (40 mg/d) with enteral diet (2000 kcal/d) and the outcomes were assessed at 28 d, 1 year and death. The study concluded that the overall mortality in both groups were similar; however, the enteral nutrition group had a lower incidence of infections[29]. Investigational studies have evaluated the use of anabolic steroids such as oxandrolone and testosterone in addition to high protein diets. In a trial of 263 patients with moderate to severe AH, patients were randomized to receive prednisolone, oxandrolone or placebo. Mortality was not significantly different between placebo and steroid therapy in the first 30 d; however, the group receiving oxandrolone and nutritional supplementation had a better outcome compared to oxandrolone alone[30,31]. It is important to achieve nutritional goals with positive nitrogen balance to improve survival; therefore, an energy intake of 35-40 kcal/kg per day and protein intake of 1.2-1.5 g/kg per day is recommended. Proteins should not be restricted, even in patients with encephalopathy provided they can tolerate the protein load and encephalopathy does not worsen. The use of a daily caloric count and the help of a professional dietitian are crucial in detecting patients who are unable to meet the desired needs and subsequently require additional supplementation[32,33]. Enteral supplementation is preferred and placement of enteral tubes, even in patients with esophageal varices, can successfully achieve the desired nutritional goals[34].

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S- Editor Zhang HN **L- Editor** Roemmele A **E- Editor** Zhang L

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v3.i5.130

World J Hepatol 2011 May 27; 3(5): 130-136
ISSN 1948-5182 (online)

BRIEF ARTICLE

Bacteremia and "Endotipsitis" following transjugular intrahepatic portosystemic shunting

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Received: November 22, 2010 Revised: March 27, 2011
Accepted: April 3, 2011
Published online: May 27, 2011

Abstract

AIM: To identify all cases of bacteremia and suspected endotipsitis after Transjugular intrahepatic portosystemic shunting (TIPS) at our institution and to determine risk factors for their occurrence.

METHODS: We retrospectively reviewed records of all patients who underwent TIPS in our institution between 1996 and 2009. Data included: indications for TIPS, underlying liver disease, demographics, positive blood cultures after TIPS, microbiological characteristics, treatment and outcome.

RESULTS: 49 men and 47 women were included with a mean age of 55.8 years (range 15-84). Indications for TIPS included variceal bleeding, refractory ascites, hydrothorax and hepatorenal syndrome. Positive blood cultures after TIPS were found in 39/96 (40%) patients at various time intervals following the procedure. Seven patients had persistent bacteremia fitting the definition of endotipsitis. Staphylococcus species grew in 66% of the positive cultures, Candida and enterococci species in 15% each of the isolates, and 3% cultures grew other species. Multi-variate regression analysis identified 4 variables: hypothyroidism, HCV, prophylactic use of antibiotics and the procedure duration as independent risk factors for positive blood cultures following TIPS ($P <$ 0.0006, 0.005, 0.001, 0.0003, respectively). Prophylactic use of antibiotics before the procedure was associated with a decreased risk for bacteremia, preventing mainly early infections, occurring within 120 d of the procedure.

CONCLUSION: Bacteremia is common following TIPS. Risk factors associated with bacteremia include failure to use prophylactic antibiotics, hypothyroidism, HCV and a long procedure. Our results strongly support the use of prophylaxis as a means to decrease early post TIPS infections.

Key words: Tips; Bacteremia; Ascites; Bleeding; Liver Insufficiency

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Mizrahi M, Roemi L, Shouval D, Adar T, Korem M, Moses A, Bloom A, Shibolet O. Bacteremia and "Endotipsitis" following transjugular intrahepatic portosystemic shunting. *World J Hepatol* 2011; 3(5): 130-136 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i5/130.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i5.130

INTRODUCTION

Transjugular intrahepatic portosystemic shunting (TIPS) is a procedure that uses minimally invasive image guided techniques to decompress the portal system and reduce portal hypertension. TIPS was first described as a research technique in 1969 and gained clinical acceptance in the early 1990s[1,2]. The most common indications for TIPS are for the treatment of variceal bleeding[3-5], and refractory ascites[6-8]. Other less common indications include: Budd-Chiari syndrome[9,10], hepatorenal syndrome[11,12], veno-occlusive disease[13] hepatic hydrothorax[14], non-variceal bleeding and pre-operative portal decompression[15].

The widespread use of the TIPS procedure has led to the recognition of multiple complications, both systemic and local. Systemic complications include hepatic failure, encephalopathy, sepsis and death. Local complications are less frequent but include laceration of vessels, massive hemorrhage and pneumothorax, as well as prosthesis-associated complications such as occlusion, migration and misplacement[16-18].

Bacteremia associated with endovascular infection of TIPS stents is an infrequently reported serious complication[19]. The term "endotipsitis" was proposed by Sanyal and Reddy[20], who defined it as: (1) the presence of continuous bacteremia indicating an infectious focus in continuity with the venous circulation and (2) failure to find an alternate source of infection despite an extensive search. While fever and transient bacteremia have been described in 2% to 25% of the patients after TIPS[21,22], the overall incidence of "endotipsitis" is unknown because of its rarity, lack of uniform definition and the unknown number of total TIPS procedures. The purpose of this study was to identify all cases of bacteremia and suspected endotipsitis after TIPS at our institution and to determine risk factors for their occurrence. We analyzed data from all the patients who underwent TIPS in our institution over a 13 year period (1996-2009).

MATERIALS AND METHODS

Patients

We retrospectively reviewed the records of all patients who underwent TIPS between January 1996 and January 2009 at a single tertiary referral center the Hadassah-Hebrew University Medical Center in Jerusalem, Israel.

Clinical information

Data recorded included age, sex, underlying liver disease, other co-existing diseases, indications for TIPS, positive blood cultures after TIPS, time between TIPS and occurrence of bacteremia, type of microorganism isolated, extent of diagnostic work-up, type of treatment and outcome. Also recorded was the duration of the TIPS procedure, direct portal venous pressure before and after procedure, use of prophylactic antibiotics and length of hospitalization after procedure. The severity of chronic liver disease was assessed by the MELD score[23], and Child-Pugh-Turcotte (CPT) score[24],.

Definitions

We used the definition used by Sanyal *et al*[20] for persistent bacteremia as fever with at least two positive blood cultures in which the same organism grew. Non-persistent bacteremia was defined as fever with multiple/single positive cultures of any organism over the study time period.

Highly suspected "endotipsitis" was defined as persistent bacteremia with vegetations or occlusive thrombus within the TIPS, or a patent TIPS, with no other obvious source of infection. Because there is no definition in the literature of the time span between the TIPS procedure and the bacteremia, we did not limit the time until the first bacteremia.

Underlying liver disease, concomitant medical conditions, treatments, extent of diagnostic work-up and complications were individually collected from patient's files. Laboratory data was collected from the hospital's computerized laboratory results. Outcome data was collected from the Israeli national registry and individually from other medical centers in Israel.

Statistical analysis

The Pearson Chi-square test, as well as the Fisher's exact test, were used to test the association between any two categorical variables. Comparison of continuous variables between two independent groups was performed by application of the two-sample *t*-test. The multiple stepwise logistic regression model was applied in order to test which variables simultaneously influence the development of bacteremia and endotipsitis post TIPS procedure. Continuous variables are presented as mean ± SD. All statistical tests were two-tailed, and a p-value of 5% or less was considered statistically significant.

RESULTS

We identified 96 patients who underwent TIPS between 1996-2009. There were 49 males and 47 females, with a mean age of 55.8 years (range 15-84). Patient characteristics are summarized in (Table 1). Indications for TIPS were: variceal bleeding in 51 patients (53%), refractory ascites in 41 patients (42%), hepatic hydrothorax in 4 patients (4%) and hepatorenal syndrome in one patient (1%). One patient had both bleeding and refractory ascites. The underlying liver disease was HCV in 31 patients (32.3%), HBV in 17 patients (17.7%), cryptogenic cirrhosis in 18 patients (18%), Budd-Chiari syndrome in 10 patients (10%), non-alcoholic steatohepatitis in 5 patients (5%), and miscellaneous causes in 15 patients (18%). One patient was a chronic carrier of both HBV and HCV. The mean MELD and CPT scores at the time of TIPS were 14.04 (range 6-32), and 9 (range 5-13) respectively. The mean procedure duration was 85.2 min (range 26-300 min).

We identified 39/96 (40%) patients with positive blood cultures. Twenty four of the positive blood cultures (62%) occurred within 60 days of the procedure. Thirty-two were non-persistent (13 single, 19 multiple) and 7 Persistent.

Table 1 Patients characteristics

Group characteristics		No bacteremia	Positive culture	Persistent bacteremia	*P* value
Number of patients		57	32	7	*P* = NS
Gender (M/F)		30/27	19/20	3/4	*P* = NS
Mean age at time of procedure (years) (range)		55.76 ± 13.44	55.89 ± 13.62	55.85 ± 13.38	*P* = NS
Underling liver disease	HCV	13 (21.05%)	12 (37.5%)	6 (85.7%)	*P* < 0.004
	HBV	12 (21.05%)	4 (12.5%)	1 (14.2%)	*P* = NS
	Cryptogenic	13 (22.8%)	5 (15.6%)	None	*P* = 0.08
	Budd-Chiari	7 (12.28%)	3 (9.3%)	None	*P* = 0.08
	NASH	3(5.26%)	2 (6.25%)	None	*P* = NS
	Miscellaneous	10 (17.54%)	6 (18.75%)	None	*P* = NS
	Variceal bleeding	30 (31.2%)	9 (28.1%)	4 (57.1%)	*P* = 0.056
Indication for TIPS	Refractory ascites	27 (28.12%)	21 (23.95%)	2 (28.57%)	*P* = NS
	Hepatic hydrothorax	1 (1.04%)	None	1 (14.2%)	*P* = NS
	Hepatorenal syndrome	2 (2.08%)	1(1.04%)	None	*P* = NS
Time of procedure (min), mean (range)		70 ± 37	85 ± 51	109 ± 58	*P* < 0.039
MELD, mean (range)		13.96 (6-32)	14.11 (6-32)	16.5 (9-22)	*P* = NS
CPT, mean (range)		8.19 (5-13)	9.23 (5-13)	12 (9-13)	*P* < 0.001
Hypothyroidism		7 (12.28%)	17 (53.1%)	6 (85%)	*P* < 0.001
Failure to use prophylactic antibiotics		7 (12.28%)	18 (56.25%)	6 (85%)	*P* < 0.001

M/F: Male/Female; CPT: Child-Pugh-Turcotte; MELD: Model for End-stage Liver Disease; TIPS: Transjugular intrahepatic portosystemic shunting; NASH: Nonalcoholic steatohepatitis.

Table 2 Microbiological characteristics

Microorganism	Frequency (%)
Staphylococcus aureus	41
Staphylococcus coagulase negative	26
Enterococci species	15
Candida species	15
Others	3

Staphylococcus species were isolated from 26/39 patients (66% of all positive cultures). Sixteen of 39 patients had Staphylococcus aureus (41%) and 10 patients coagulase negative Staphylococcus (26%). Enterococcus and Candida species were each isolated from 6 patients (15% of the positive cultures). Streptococcus viridans grew from 1 patient (3 %)(Table 2). The median length of time to the first bacteremia following TIPS was 38 d (range 8-562 d, mean 151 d). Although 13 of the early bacteremias (within 120 d of the procedure), were due to Staphylococcus aureus this did not reach statistical significance because of the low incidence of other bacterial species in early cultures.

Organisms isolated from the 7 patients with persistent bacteremia that were highly suspected for endotipsitis, included 3/7 patients with entrococci (42%), 2/7 patients with Staphylococcus aureus (29%) and 2/7 patients with Candida albicans (29%). All the patients with highly suspected endotipsitis underwent a work up including: abdominal US, chest-abdomen-pelvic CT and transthoracic echocardiography. Further work-up in selected cases included transesophageal echocardiogram in 2/7 patients, bone scan in 4/7 and bone-marrow and liver biopsy in 2/7 patients. Six out of the 7 patients did not have indwelling central vein catheters at the time of bacteremia. One patient had an indwelling catheter prior to the diagnosis of bacteremia; however bacteremia persisted after removal of the catheter. No underlying cause for bacteremia other then TIPS infection was identified. TIPS thrombosis was diagnosed in 4/7 (57%) patients with persistent bacteremia including the patient with the indwelling intra-venous catheter.

In the entire study group, the mean survival time after the TIPS procedure was 965 d (range 4-3072, median 609 d). Sixty-seven patients (70%) died during the study period and 15 patients underwent cadaveric liver transplantation. Of those 15 patients, 11 died during the study period with a mean survival for transplanted patients after TIPS of 1261 d (range 15-3585, median 542 d). In the persistent bacteremia group (n = 7), two patients underwent cadaveric liver transplantation while receiving antibiotics with negative cultures, 4 died of infectious complications associated with their suspected endotipsitis and one recovered following prolonged antibiotic treatment and is currently alive. There was no difference in survival rates between patients with persistent bacteremia and non-persistent bacteremia and between the group with bacteremia and without bacteremia.

Assessment of risk factors

The following variables were not associated with increased risk of bacteremia in our study: age, sex, portal venous pressure after the procedure, type of microorganism and MELD score.

Univariate analysis identified the following variables as risk factors for bacteremia following TIPS: indication for TIPS procedure, duration of procedure, lack of prophylactic antibiotic treatment before the procedure, pre-procedure portal pressure, hypothyroidism, HCV and CPT score.

Four variables were identified as independent risk factors for bacteremia by multivariate analysis: failure to

use prophylactic antibiotics, the duration of the TIPS procedure and HCV or hypothyroidism as the underlying liver or concurrent disease.

Patients with highly suspected endotipsitis had a higher CPT score (12 ± 1.51 *vs* 8.72 ± 1.69, $P < 0.0001$), and a trend towards longer hospitalization post the TIPS procedure (16.8 ± 11.82 d *vs* 10 ± 6.31 d, $P < 0.08$), compared to patients with transient bacteremia and patients without bacteremia.

There were 31/96 (31%) patients who did not receive prophylactic antibiotics before the procedure. It is important to mention that until the year 2000 prophylactic antibiotic treatment was not a required part of our TIPS protocol. Bacteremia was significantly more common in the group that did not receive prophylaxis as compared to those that received it; 24/31 (77%) *vs* 15/65 (23%) ($P < 0.001$, adjusted OR 10.682, 95% CI: 2.22-51.3). In the group that was highly suspected of endotipsitis 4/7 patients did not receive prophylaxis. The reduction in the number of bacteremias, was attributed mainly to prevention of early staphylococcal infections. 17/24 (70%) of infections in the group with bacteremia that did not receive prophylaxis were due to staphylococcal infections (13 Staphylococcus aureus and 4 coagulase-negative Staphylococci) that occurred within 120 d of the procedure ($P < 0.002$, as compared to late infection).

There was a linear increase in the number of positive blood cultures following TIPS with increased duration of procedure ($P < 0.001$, adjusted OR 1.015; 95% CI: 1.001-1.030).

Two other variables associated with increased risk of bacteremia were HCV and hypothyroidism. There were 31 HCV patients in our cohort, 18 (60%) had bacteremia as compared with 5/17 (30 %), 3/10 (30 %) 5/18 (27%), 8/21 (38%), in the HBV, Budd-Chiari and cryptogenic cirrhosis, NASH and miscellaneous groups ($P < 0.005$) respectively. There were 30 patients with hypothyroidism in our cohort. Patients were considered to have hypothyroidism if they had the diagnosis in their medical charts, if they were treated with thyroid hormone replacement or if they were found to have elevated thyroid stimulating hormone (TSH) levels in their laboratory results. 24/30 (80%) had bacteremia (single and persistent) as compared with 15/66 (22%) in the euthyroid patients ($P < 0.00003$, adjusted OR 15.67; 95% CI: 2.94-83.47).

DISCUSSION

Bacteremia is a serious complication following TIPS. "Endotipsitis" is the term used to describe persistent bacteremia stemming from endovascular infection of the TIPS stent. The incidence and risk factors associated with bacteremia and/or endotipsitis following TIPS are currently unknown[25]. We retrospectively identified 39 episodes of bacteremia in 96 patients who underwent TIPS in a single center over a 13-year period. We identified seven cases of persistent bacteremia highly suspected for endotipsitis and 32 episodes of non-persistent bacteremia. Multivariate analysis identified 4 variables as independent risk factors for bacteremia following TIPS. To the best of our knowledge this is the first longitudinal study to assess variables associated with this previously under-reported and poorly understood entity.

We first looked at bacterial isolates from patients with bacteremia following TIPS. The majority of pathogens isolated were staphylococci and enterococci species. These pathogens are consistent with isolates reported in previously published data and with data from other endovascular infections[19,20].

The median length of time between TIPS and the first bacteremia was 38 d. We did not find a correlation between re-intervention such as "TIPSogram", stent angioplasty or re-stenting following the initial procedure and the occurrence of bacteremia. Previous reports have suggested that endotipsitis can occur at any time following the initial procedure with periods reported in the literature ranging from 6 d to 10 years[19]. It was also previously suggested that the pathogens identified following TIPS may differ between early (less than 120 d following the initial procedure) and late episodes (more than 120 d following the initial procedure). In the present study 24 (62%) of the bacteremia episodes were within 60 d of the procedure. The majority of early isolates were Staphylococcus aureus; however, due to the small numbers of other bacterial species, this did not reach statistical significance. Therefore, although there was no correlation between type of bacterium and the timing of bacteremia following the initial procedure, it is possible that Staphylococcus will emerge as the predominant bacterium in early post-TIPS bacteremia.

We identified four variables that were independent risk factors for bacteremia following TIPS. Failure to use prophylactic antibiotics was associated with increased risk of bacteremia. During the 1996-2000 period we did not routinely use prophylactic antibiotics before the procedure. From 2000 onwards, based on reports by Gulberg *et al* and Dravid *et al*[8,26], we started using a single dose of cefazolin for ambulatory patients, or a single dose of vancomycin for hospitalized patients. Following the initiation of prophylactic treatment we observed a marked reduction in the incidence of bacteremia. This reduction was mainly attributed to a reduction in early staphylococcal infection.

There are no formal recommendations regarding antibiotic prophylaxis prior to TIPS. However, if we draw comparison from other endovascular infections, the recent guidelines of the American Heart Association concerning prevention of endocarditis state that prophylaxis is needed when prosthetic material is present during the first 6 mo after the procedure[27]. Several reports suggest that portions of the TIPS stent do not undergo endothelialization and remain exposed indefinitely. These exposed segments may form areas of attachment for bacteria[28,29]. We therefore currently use prophylaxis during the initial procedure and during repeated TIPS manipulations. A single prior report assessed the efficacy of a second generation cephalosporin as prophylaxis prior to TIPS and found that it did not

decrease the incidence of infection, thereby casting doubt on the efficacy of prophylaxis[21]. However antibiotic prophylaxis is nowadays considered standard care[30,31]. Our results strongly support the use of prophylaxis as a means to decrease early infections post-TIPS.

Of interest is the question of whether use of coated versus uncoated stents alters the prevalence, course or susceptibility to bacteremia and endotipsitis. Use of polytetrafluoroethylene coated stents was first reported in 1995[32], however their widespread use has only been recent. Covered stents improve TIPS patency, reduce the rate of encephalopathy and the need for re-intervention[33,34]. It is therefore possible that they alter the susceptibility to bacteremia and the development of endotipsitis. We had only 4 patients with covered stents in our cohort (none had bacteremia) and cannot assess its impact on bacteremia in patients following TIPS procedure. This variable will have to be assessed in future randomized prospective studies.

The second independent risk factor for bacteremia was the duration of the procedure. This variable, which has not been previously reported as a risk factor associated with TIPS, has been shown to be an independent risk factor for bacteremia in numerous other surgical procedures including lung surgery[9], total abdominal hysterectomy[35], and others[36], as well as in non-surgical interventions such as percutaneous transluminal coronary angioplasty[37].

The two final variables associated with an increased risk of bacteremia were hypothyroidism and HCV. We could not find a direct association between hypothyroidism and infection. However, it has been previously reported that hypothyroidism decreases portal venous flow in animal models, and may be associated with a hypercoagulable state. These effects may increase the risk of bacterial adhesion to the stent thereby increasing the risk of infection as well as stent thrombosis[38,39].

The association between HCV and infection has been previously suggested[40]. Bacterial infections are very common in patients with HCV cirrhosis, accounting for up to 15% of hospitalizations[41]. Recently HCV was shown to be associated with an increased rate of bacteremia in hemodialysis patients with tunneled catheters[42].

We found no difference in survival between patients with persistent bacteremia, non-persistent bacteremia and without bacteremia. This finding may be attributed to the high overall mortality in our cohort of patients with very advanced liver disease, as well as to the size of our persistent bacteremia group which was not large enough to detect small changes in survival rates.

Our study has several limitations. It is retrospective and suffers from inherent problems associated with this study design. Some of the patients that underwent TIPS in our hospital may have presented with TIPS-related infections in other hospitals. Some of the data collection was incomplete. However the majority of the data was parametric and collected using computerized systems, and we specifically noted any missing data. Finally, due to the rarity of bacteremia and endotipsitis, it is unlikely that prospective studies to assess its incidence and risk factors will ever be conducted.

In summary, bacteremia and "endotipsitis", following TIPS is an emerging and probably under-recognized infectious disease. We identified four independent risk factors for bacteremia following TIPS including, lack of prophylactic antibiotics, prolonged procedure, HCV and hypothyroidism. As was previously shown the bacteremia and specifically endotipsitis can present as an early infection within days or weeks after TIPS or as a late infection, appearing months to years after the initial procedure. Multiple causative agents were implicated without a single bacterium emerging as a predominant pathogen. Endotipsitis should be considered in any patient with a TIPS and a persistent bloodstream infection that is not clearly attributable to another source. Antibiotic prophylaxis and an effort to shorten procedure duration should reduce the risk of endotipsitis.

COMMENTS

Background

Transjugular intrahepatic portosystemic shunting (TIPS) is a procedure that uses minimally invasive image guided techniques to decompress the portal system and reduce portal hypertension. The most common indications for TIPS are for the treatment of variceal bleeding, and refractory ascites, other less common indications include: Budd-Chiari syndrome, hepatorenal syndrome, veno-occlusive disease hepatic hydrothorax, non-variceal bleeding and pre-operative portal decompression.Systemic complications of TIPS procedure include hepatic failure, encephalopathy, sepsis and death. Local complications are less frequent but include laceration of vessels, massive hemorrhage and pneumothorax, as well as prosthesis-associated complications such as occlusion, migration and misplacement. Bacteremia associated with endovascular infection of TIPS stents is an infrequently reported serious complication.

Research frontiers

The widespread use of the TIPS procedure has led to the recognition of multiple complications, both systemic and local, with more frequent reports of bacteremia following TIPS procedure.

Innovations and breakthroughs

In the area of TIPS and bacteremia a lot of details are missing as prospective randomized control trails are impossible. For this reason, any trial prospective or retrospective is valuable for understanding the prevalence and outcome of bacteremia complications.

Applications

In this study 49 men and 47 women were included with a mean age was 55.8 years (range 15-84). Indications for TIPS included variceal bleeding, refractory ascites, hydrothorax and hepatorenal syndrome. Positive blood cultures after TIPS were found in 39/96 (40%) patients at various time intervals following the procedure. Seven patients had persistent bacteremia fitting the definition of endotipsitis. Staphylococcus species grew in 66% of the positive cultures, Candida and enterococci species in 15% each of the isolates, and 3% cultures grew other species. Multi-variate regression analysis identified 4 variables: hypothyroidism, HCV, prophylactic use of antibodies and the procedure duration as independent risk factors for positive blood cultures following TIPS ($P < 0.0006$, 0.005, 0.001, 0.0003, respectively). Prophylactic use of antibiotics before the procedure was associated with a decreased risk for bacteremia, preventing mainly early infections, occurring within 120 of the procedure. Our data comprise the largest cohort presented to date and provide readers with insight into the risk factors for bacteremia and ways in which such complications can be prevented.

Terminology

Transjugular intrahepatic portosystemic shunting (TIPS) is a procedure that uses minimally invasive image guided techniques to decompress the portal system and reduce portal hypertension. TIPS was first described as a research technique in 1969 and gained clinical acceptance in the early 1990s

Peer review

This study is of interest because it introduces new knowledge regarding the risk factors for bacteremia post TIPS procedure.

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World J Hepatol 2011 May 27; 3(5): I
ISSN 1948-5182 (online)

Acknowledgments to reviewers of *World Journal of Hepatology*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Hepatology*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

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World J Hepatol 2011 May 27; 3(5): I
ISSN 1948-5182 (online)

Events Calendar 2011

January 14-15, 2011
AGA Clinical Congress of Gastroenterology and Hepatology: Best Practices in 2011
Miami, FL 33101, United States

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011
San Francisco, CA 94143, United States

January 27-28, 2011
Falk Workshop, Liver and Immunology, Medical University, Franz-Josef-Strauss-Allee 11
Regensburg 93053, Germany

January 28-29, 2011
9. Gastro Forum München
Munich, Germany

February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference
Sydney, NSW, Australia

February 17-20, 2011
APASL 2011-The 21st Conference of the Asian Pacific Association for the Study of the Liver
Bangkok, Thailand

February 22, 2011-March 04, 2011
Canadian Digestive Diseases Week 2011
Vancouver, BC, Canada

February 24-26, 2011
Inflammatory Bowel Diseases 2011-6th Congress of the European Crohn's and Colitis Organisation
Dublin, Ireland

March 3-5, 2011
42nd Annual Topics in Internal Medicine
Gainesville, FL 32614, United States

March 7-11, 2011
Infectious Diseases: Adult Issues in the Outpatient and Inpatient Settings
Sarasota, FL 34234, United States

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011
Birmingham, England, United Kingdom

March 17-20, 2011
Mayo Clinic Gastroenterology & Hepatology 2011
Jacksonville, FL 34234, United States

March 18, 2011
UC Davis Health Informatics: Change Management and Health Informatics, The Keys to Health Reform
Sacramento, CA 94143, United States

March 25-27, 2011
MedicReS IC 2011
Good Medical Research, Istanbul, Turkey

March 26-27, 2011
26th Annual New Treatments in Chronic Liver Disease
San Diego, CA 94143, United States

April 25-27, 2011
The Second International Conference of the Saudi Society of Pediatric Gastroenterology, Hepatology & Nutrition
Riyadh, Saudi Arabia

May 7-10, 2011
Digestive Disease Week
Chicago, IL 60446, United States

May 19-22, 2011
1st World Congress on Controversies in the Management of Viral Hepatitis (C-Hep), Palau de Congressos de Catalunya, Av. Diagonal, 661-671
Barcelona 08028, Spain

May 21-24, 2011
22nd European Society of Gastrointestinal and Abdominal Radiology Annual Meeting and Postgraduate Course
Venise, Italy

May 25-28, 2011
4th Congress of the Gastroenterology Association of Bosnia and Herzegovina with international participation, Hotel Holiday Inn,
Sarajevo, Bosnia and Herzegovina

June 11-12, 2011
The International Digestive Disease Forum 2011
Hong Kong, China

June 13-16, 2011
Surgery and Disillusion XXIV
SPIGC, II ESYS
Napoli, Italy

June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer
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October 19-29, 2011
Cardiology & Gastroenterology Tahiti 10 night CME Cruise
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19th United European Gastroenterology Week
Stockholm, Sweden

October 28-November 2, 2011
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World J Hepatol 2011 May 27; 3(5): I-V
ISSN 1948-5182 (online)

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Name of journal

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

Indexed and Abstracted in

PubMed Central, PubMed, Digital Object Identifer, and Directory of Open Access Journals.

Published by

Baishideng Publishing Group Co., Limited

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean ± SD or mean ± SE.

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