Medical Management of Hepatic Vena Cava Syndrome (Based on New Concept of its Pathogenesis)

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1. Abstract
Hepatic Vena Cava Syndrome (HVCS) is a chronic obliterator disease of Inferior Vena Cava (IVC) at the site of hepatic vein opening characterized by long asymptomatic period, recurrent Acute Exacerbations (AE) and high incidence of hypersplenism, ascites, Liver Cirrhosis (LC) and Hepatocellular Carcinoma (HCC). The disease was previously labeled membranous obstruction of inferior vena cava and included under Budd-Chiari syndrome. It was considered congenital vascular anomaly and managed by surgery or endovascular procedures.

A new concept of pathogenesis of the disease was described recently that considered HVCS as bacterial infection induced evolving disease. The initial lesion a localized thrombophlebitis at the site of hepatic vein openings on resolution converts into stenosis or complete obstruction followed by dilation of the distal segment and development of cava-caval anastomosis. The obliterative lesion and cava-caval anastomosis persists the rest of the life. Patient remains asymptomatic for variable period till further bacterial infection results in recurrence of thrombophlebitis at the site which often extends into hepatic veins causing Acute Exacerbations (AE). Mild AE manifests clinically as jaundice and/or elevation of ALT/AST, and severe AE with large thrombus causing Hepatic Venous Outflow Obstruction (HVOO) as ascites. Organization of thrombophlebitis formed during recurrent AEs modifies the lesion in IVC into a thick obstruction. Patients with recurrent AEs develop mild splenomegaly and hypersplenism.

Sinusoidal hypertension that follows HVOO causes centrilobular hemorrhagic ischemic liver damage. It is followed by development of venocentric liver cirrhosis. Recurrent AEs with thrombophlebitis of intra-hepatic veins also cause LC. Development of LC and HCC was related to severity and frequency of AEs and not to the type and extent of caval obstruction. As such management of the disease had now shifted to treatment and prevention of AEs. This paper briefly reviews the surgical and endovascular treatment used at present and describes the new medical management.

2. Key Words: Ascites; Bacterial infection; Cirrhosis, Hepatocellular carcinoma; Hepatic Venous Outflow Obstruction; Hypersplenism
3. Introduction

Hepatic Vena Cava Syndrome (HVCS) is a chronic obliterative disease of Inferior Vena Cava (IVC) at the site of hepatic vein openings, characterized by long asymptomatic period, recurrent Acute Exacerbations (AE), and development of deep and superficial cava-caval anastomosis. The disease is complicated by ascites, hypersplenism, Liver Cirrhosis (LC) and Hepatocellular Carcinoma (HCC). HVCS was previously called membranous obstruction of inferior vena cava and was included under Budd-Chiari Syndrome (BCS) [1].

This disease was first reported from Europe and North America [2-12]. William Osler in 1896 gave a detailed account of the clinical and pathological findings of the disease [4]. According to Pleasants [7] of Johns Hopkins University Schenck first reported it in 1644 and many investigators between 17a to 19a centuries described the different cava-caval anastomosis that developed in the disease. Later in early 20a century the disease was reported from Japan [13-20]. Subsequently it becomes rare in both in Japan and the West with only occasional cases reported [21-31]. It was then described mainly from Asia and Africa [31-47]. Increase awareness of the condition and use of ultrasonography and color Doppler (US/CD) showed that the disease is endemic in China and Nepal among people living in poor hygienic condition [34,41,48]. In Nepal it was identified as a common cause of cirrhosis both in children and adults [49,50].

Etiology of the disease- congenital or acquired had been a subject of controversy for a long period. Congenital theory first suggested by Rosenblatt O et al. [3] in 1867 and popularized by Hirooka et al. [16] was accepted by many subsequent investigators. It was based on assumption that inferior vena cava a compound vessel formed by fusion of multiple blocks of embryonic veins is vulnerable to developmental anomalies. This theory influenced the management of the disease. Various surgical and later endovascular procedures to overcome the obstructive lesion in IVC were devised.

Kage et al. [51] who in 1992 studied the histopathology of the obliterative lesions in the IVC and the liver of 17 autopsied cases in Japan observed that hepatic veins were involved in all cases, and the lesions in IVC and hepatic veins were related to thrombosis and its sequel. They detected no evidence of congenital malformation. Parker et al. [12] based on analysis of reported 164 autopsied cases had made similar observations in the past. Okuda and colleagues [52] based on study of clinical and epidemiological profile of the patients reported from different countries and wide variation in topology of the caval lesion came to conclusion that the disease is acquired and is different from Budd-Chiari syndrome. Separate identity of the disease was subsequently established [53,54].

Proponents of the acquired nature of the disease in the past had mentioned thrombophlebitis as the probable cause of the disease [8,13]. Shrestha et al. [55] in 2007 reported cases where bacterial infection induced thrombophlebitis of hepatic portion of the IVC on follow up converted into chronic obliterative lesion. A new concept of pathogenesis of the disease based on the bacterial infection was described in 2017 which explained all features of the disease [56].

Briefly, the liver that is kept in its position by intra-abdominal pressure virtually hangs on to IVC at the site where it is joined by the hepatic veins. IVC at this site is thus vulnerable to micro-endothelial damage during physical activities. Damaged endothelium at this site directly exposed to blood rich in coagulant coming from liver is thus prone to thrombosis and thrombophlebitis. Persons with bacteremia such as people with poor nutrition and chronic gut infection who develop translocation of bacteria [57] are thus prone to develop localized thrombophlebitis at this site. Patients with large thrombophlebitis that cause Hepatic Venous out Flow Obstruction (HVOO) manifest clinically as ascites. In others the acute lesions often go unnoticed. The lesion on resolution converts into localized stenosis with thick posterior wall followed by dilatation of distal segment and development of deep cava-caval anastomosis (Figure 1). Presence of extensive deep cava-caval anastomosis in the disease was documented by cavogram (Figure 2a,2b) and in autopsy studies [4,5,7,12]. Some at later stage also develop superficial collaterals seen as dilated veins in the body surface (Figure 3). The caval lesion and collaterals persists the rest of the life. Patient remains asymptomatic till another episode of bacterial infection cause recurrence of thrombophlebitis at the site causing Acute Exacerbation (AE). The thrombophlebitis extends into hepatic veins, and downward along the posterior wall and rarely upward into right atrium. During the course of the life patient may suffer recurrent episodes of AEs. Occurrence of thrombi of different ages in the IVC had been described in autopsy studies [12,17] and is recognized in patients by ultrasonography and color Doppler (Figure 4a,4b).
AE manifests clinically as jaundice and or elevation of ALT and AST and severe AE with HVOO as ascites. AE is associated with neutrophil leukocytosis, elevated level of C-reactive protein and/or bacteremia. Severe AE with ascites commonly follow postpartum infection or surgery or prolonged fever or diarrhea in patient with poor nutrition or alcoholics. Ascites in HVCS is associated with bacterial peritonitis [58] and about 10 % also develop pleural effusion [59]. About 11% patients with recurrent AEs develop mild splenomegaly and features of hypersplenism-reduced counts of WBC and platelets and anemia.

Ascites is caused by HVOO (Figure 5) [42]. HVOO results in sinusoidal hypertension with passage of protein rich fluid and RBC into the space of Disse and reflex reduction of arterial flow. The combined effect leads to development of hemorrhagic ischemia of centrilobular hepatocytes, which within a few months is followed by veno-centric cirrhosis [60]. Similarly recurrent mild AE with thrombophlebitic obstruction of medium-sized intra-hepatic veins lead to development of cirrhosis within a few years. Development of LC and HCC in HVCS related to severity and frequency of bacterial infection induced AEs and not to the type or extent of the oblitative lesion in IVC [49].

Real time ultrasonography and color Doppler examination of IVC and liver was found specific and sensitive in diagnosis of the disease [61,62]. The disease is diagnosed on detection of stenosis or complete obstruction of the IVC near the hepatic vein outlet with old organized thrombi of different ages along the posterior wall and abnormal blood flow pattern- continuous or biphasic instead of triphasic in IVC and hepatic veins. The procedure combined with routine hematologic, liver test and estimation of C-reactive protein helped in the recognition of AE. The procedure is simple and readily available, and has made cavogram and liver biopsy unnecessary for diagnosis of HVCS. Management of the disease is now based on treatment of bacterial infection induced AEs. This paper briefly reviews the surgical and endovascular treatment used at present and suggests a new medical management.

4. Surgical & Endovascular Treatment

Medical treatment in the past consisted of thrombolysis and/or anticoagulation [37,63]. Patients with ascites treated with this procedure had high mortality [37]. Medical treatment then was declared ineffective [38]. There was also a report of the disease
developing in a well anticoagulated patient [64]. And the treatment
directed to surgical decompression of the obstructed cava. At
early period non-definitive procedures as splenopneumonectomy was
used [34]. Definitive therapy began with the introduction of
transcardiac membranotomy [17,34]. Observation of obstructive
lesion several centimeters thick in majority of the patients, led to
introduction of shunt surgery. Various types of shunts as cavo-
atrial, meso-atrial, meso-caval were developed, followed later by
radical corrective procedures [65-69]. The aim of surgery was to
decompress the cava and regulate blood flow. Placing a synthetic
graft in a venous system however was difficult and was prone to
thrombosis despite long-term anticoagulation [35,69]. Extensive
surgery was associated with high operative mortality and
postoperative complications [17,69] and high failure rate. This led
some even to resort to liver transplantation [31,33,70].

In 1974 Eguchi et al. [71] introduced balloon membranotomaty.
Endovascular procedures proved safer, less invasive and cost-
effective. And the trend in the management later shifted to
Percutaneous Transluminal Angioplasty (PTA) and stenting
[33,35,71-77]. Obstructed hepatic vein outlets also had been
dilated. IVC stenting not uncommonly precipitated hepatic vein
obstruction with development of ascites and variceal bleeding
[35] or became thrombosed. Persistence of ascites after surgery
despite evidence of proved patency of the shunt [73] and its
reoccurrence 8 months after endovascular procedure despite the
evidence of vein patency [74] had been reported. Ascites was the
major immediate complications in large series managed by
surgery and endovascular procedures [31,35].

Table 1: Comparison of outcome of Surgical and Proactive Medical Management in Children with HVCS.

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<tr>
<td>1. Subject</td>
<td>22: 18 operated (9 European &amp; 9 North African)</td>
<td>178</td>
</tr>
<tr>
<td>2. Procedures</td>
<td>Mesocaval shunts in 14, others 4</td>
<td>Proactive medical treatment</td>
</tr>
<tr>
<td>3. Follow-up</td>
<td>Average: 4 years</td>
<td>Average 5 yrs (1mo-16yrs)</td>
</tr>
<tr>
<td>4. Mortality</td>
<td>Operative: 5 (27.7%)</td>
<td>2 (1.1%): 1 at 1mo &amp; 4 yrs each from severe AE.</td>
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<tr>
<td>4. Complications</td>
<td>Post operative complications: ascites in all 13 surviving patients, 7 had pleural pericardial effusion, hemoptoemia, pneumonitis, acute hepatitis etc; 7 late complications like thrombosis of IVC, stenosis of shunt, nephrotic syndrome etc.</td>
<td>AE: fever with jaundice or ascites or variceal bleeding - average once a year per patient - responded to medical treatment. Frequency of AE diminished with follow up</td>
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<tr>
<td>5. Liver cirrhosis</td>
<td>5 (26.3%): 3 detected at operation 2 developed at follow-up</td>
<td>49 (27.5%): 28 developed at average 1.9mo; and 21 developed at 3.4 yrs follow up period</td>
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Operative liver biopsy showed 78% of the adult [20,68], and
16.6% of child [31] patients already had developed LC. Further,
LC [31] and HCC [20,35,68] continue to develop even after the
procedures. The procedures were costly, associated with
significant mortality and complications (Table 1a & 1b) and
also had failed to prevent major complications of the disease.

Table 2: Outcome of Surgical or Endovascular procedures & Pro-active Medical Management in Adult HVCS

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<tbody>
<tr>
<td>1. Subject</td>
<td>2677 patients (1981-2003)</td>
<td>56 patients</td>
</tr>
<tr>
<td>2. Procedures</td>
<td>Surgery: 1275, PTA/Stent: 1289</td>
<td>Proactive medical treatment</td>
</tr>
<tr>
<td>3. Follow-up</td>
<td>Long term follow-up in 382 patients</td>
<td>14.8 ± 9 years</td>
</tr>
<tr>
<td>4. Mortality</td>
<td>9.5% (operative 5%, late 4.5%); 24 died from HCC</td>
<td>4 (7.1%) patients died from severe AE (average age 45 yrs) 6 from HCC (average age 57yrs); 3 natural cause (average age 78 yrs, 1 from bronchial carcinoma)</td>
</tr>
<tr>
<td>5. Complications</td>
<td>Post operative: Ascesis in 29, other include pleural effusion, hemoptoemia, Pulmonary, abscesses, cardiac tamponad, encephalectomy</td>
<td>AEs total 144 episodes: Fever with jaundice or ascites average once a year per patient: responded to medical treatment. Frequency of AE diminished during follow up</td>
</tr>
<tr>
<td>6. LC &amp; HCC</td>
<td>24 (6.2%) developed HCC</td>
<td>44(78%) developed LC &amp; 6 (11%) developed HCC Development of LC related severity &amp; frequency of AE. &amp; HCC related to frequency of AE and long duration of disease.</td>
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Nakamura et al. [14] as long back as 1968 had raised doubt
about the need of surgery in the disease because of long survival
of the patients on conservative management. Cavographic [49] and
autopsy studies [4,5,7,12] showed presence of extensive internal cava-caval collaterals in these patients. Azygos vein was
found always dilated to the size of IVC or bigger [4].
Understanding of the new pathogenesis of the disease and study
of collaterals thus failed to support the continued use of these
invasive procedures for the treatment of HVCS.

4.1. Medical Management based on Bacterial Infection Theory

4.1.1. Management of Severe AE with ascites: Medical
management based on the bacterial infection theory had been
used in Nepal since many years [49,50,54,63]. HVCS patients have long
asymptomatic period with occasional AEs precipitated by bacterial
infection and long survival if no complication occurs. Severe AE
with ascites and jaundice carried high mortality. It was frequently
precipitated by puerperal sepsis, surgery, or chronic bacterial
diarrhea or prolonged low grade fever in person with poor
nutrition or history of alcohol abuse [9,31,35,78,79].
Surgery and endoscopic procedures are known to cause transient bacteremia [80]. US/CD of patients with ascites showed evidence of HVOO- hepatomegaly with obstruction to blood flow at the orifices by large recent thrombus in IVC (Figure 5) and evidence of bacterial peritonitis - free-floating particles in the peritoneal cavity that settles on standing; or thick peritoneum or adhesions or loculations [54].

Blood and ascitic fluid for examinations are collected on the first visit. About 15 ml of blood and ascitic fluid each is inoculated at bedside in separate blood-culture bottles for aerobic organisms. Ascitic fluid is also collected in an ethylenediaminetetraacetic acid anticoagulant tube for routine examinations that include total and differential white blood cell count, absolute neutrophil count, presence of red blood cell and estimation ascitic fluid protein and albumin. Blood is examined for routine hematology, liver, renal tests and estimation of C-reactive protein. Ascitic fluid has high protein (3.5 to 6.5 g per cent), high absolute neutrophil counts and positive culture for aerobic organism and high serum ascitic fluid albumin gradient [58]. Blood test shows neutrophil leukocytosis with high level of C-reactive protein and/or bacteremia and mild to moderate elevation of serum bilirubin, and ALT/AST. Even HVCS patients with hypersplenism develop neutrophil leukocytosis during severe AE returning to neutropenia at follow-up.

Patient is put on high dose oral antibiotic e.g. ciprofloxacin 750 mg twice a day; and diuretics spironolactone 100 mg and frusenamide 40 mg daily with dietary restriction of sodium. Further choice of antibiotic is decided after the culture report. After initial high dose for two weeks ciprofloxacin 500 mg twice daily is continued for a month or till C-reactive protein and white blood cell count returns to normal if the later is delayed. Dose and combination of diuretics is adjusted based on the response to the drug/s and presence of edema legs. Large volume paracentesis is avoided, as it removes the fluid rapidly but does nothing to correct the underlying cause and is associated with loss of body protein. Removal of 4L of ascitic fluid in a HVCS patient translates to loss of 140 to 260g protein.

Alcoholics and patients with poor nutrition require alcohol abstention and nutritional food supplements. Some patients have low level of serum albumin. It is partly due to impaired synthesis and partly due to redistribution in the ascitic compartment [81]. Response to treatment with intravenous albumin to maintain normal serum level was poor. It was observed that about 4% of the intravenously injected albumin tagged with radioactive iodine is transferred from the circulating blood to ascitic fluid per hour [82]. Albumin infusion was followed by increased albumin concentration and the colloid osmotic pressure of ascitic fluid within 24 hours [83] resulting in no net change after a week. Slow but sustained positive result was achieved by improving nutrition [84]. Prolong prothrombin time seen in a few patients responds to parenteral vitamin K supplement. Patient with high grade esophageal varices are treated with variceal ligation. Low grade transient portal hypertension responds to the medical treatment without a need for additional therapeutic measures. The grade of esophageal varices decreased spontaneously within a few months.

4.1.2. Prevention of AE: Recurrence of ascites was prevented by adopting good food and water hygiene, maintenance of good nutrition, avoidance of alcohol and management of any focus of infection like gall stone or chronic pelvic or recurrent urinary tract infection. Management of the disease is based on zero tolerance to bacterial infection. Long term prophylactic antibiotic to prevent AE is not recommended as its use may add risk of development of antibiotic resistant peritonitis or emergence of peritonitis with gram positive organism as in cirrhosis [85]. However, short course prophylactic antibiotic is used before surgery or endoscopic procedures in HVCS patients.

4.1.3. Treatment of hypersplenism: About 11% of HVCS patients develop mild to moderate splenomegaly with high incidence of hypersplenism- low count of platelet and/or granulocyte and anemia in peripheral blood. Patients with splenomegaly and hypersplenism had high incidence of AEs, high incidence of ascites and high incidence of LC. At early stage patient with relatively low WBC count are usually able to mobilize granulocyte to deal with infection. Patient with very low WBC count with frequent bacterial infection is treated with granulocyte colony-stimulating factor (Filgrastim). Filgrastim 300 mcg is administered subcutaneously once or twice a week to maintain normal granulocyte count. One large randomized controlled trial of effect of Filgrastim in patient with liver transplantation showed a significant increase in neutrophil counts in the treatment group but no beneficial effects on infection rates or survival [86]. Patients with very low platelet count may have problem of variceal bleeding during AE. Platelet infusion is often used. As infused platelets are rapidly sequestrated in enlarged spleen with only 20% still present in circulation at 2 hours compared with 60% in normal subjects [87], prophylactic platelet infusion is used only during or shortly before invasive elective procedures to maximize its effectiveness.

Anemia usually causes no problem. Erythropoietin has been extensively used in chronic renal failure with anemia. It also increases platelet count in about 25% in patient with alcoholic cirrhosis [88]. It is used in patients with severe thrombocytopenia and anemia. Injection darbepoetin alfa 400 mcg subcutaneously once a week is used. Patient is insured of adequate iron store before its use. Patient with severe hypersplenism with recurrent AEs is considered for
elective splenectomy or splenic embolization.

4.14. Management of HVCS induced cirrhosis and HCC: HVCS induced cirrhosis is characterized by relatively preserved hepatocellular function [39,42] with good long term prognosis [91]. HVCS induced LC may be identified at US/CD from presence one or more of the following features - dilated HVs, membrane or stenosis of hepatic veins, loss of a segment or complete loss of right hepatic vein and presence dilated right inferior hepatic vein or collaterals in and around liver or calcified focus in liver or thick layer of perihepatitis and thick edematous or thick gallbladder wall [91]. Jaundice, ascites and transient portal hypertension continue to occur from severe AE that responds to medical treatment. Liver biopsy in these patients shows acute congestive change in the background of cirrhosis [12,39]. Development of ascites and jaundice in HVCS induced cirrhosis is thus not an indicative of hepatic decompensation and not an indication of liver transplantation as in LC due to alcohol or chronic viral infection [89]. Long term prognosis of HVCS induced cirrhosis is good and further progression of cirrhosis may be prevented with medical management of AE.

Study of LC and HCC in Nepal showed that HVCS is a common co-morbid condition with chronic hepatitis B or chronic hepatitis C or alcohol [90]. As cirrhosis develop more rapidly due to HVCS than by alcohol or chronic viral infection, an attempt to establish the actual cause of cirrhosis in these patients is necessary because the management and prognosis of HVCS induced cirrhosis is different. Incidence of HCC in patients with HVCS is about 10% similar to other chronic liver diseases [49]. Serial assay of serum alpha fetoprotein level helps in early diagnosis of HVCS induced HCC [32,92]. Histologically it is well differentiated, often in the background of dense fibrosis that rarely invades the portal vein or bile ducts [32,49,92]. The median survival period of HVCS-induced HCC is significantly higher than chronic hepatitis B virus associated HCC. It is managed by percutaneous ethanol injection or radiofrequency ablation or transcatheter arterial chemoembolization [32,92].

5. Conclusions

HVCS is a bacterial infection induced chronic obliterative disease of IVC at the site of hepatic vein outlet clinically characterized by chronicity with long asymptomatic period and recurrent AEs precipitated by clinical or subclinical bacterial infection. Development of complications like ascites, hypersplenism, LC and HCC is related to severity and frequency of bacterial infection induced AEs. US/CD examination of liver and IVC combined with simple blood tests helps in diagnosis of the disease and AE. Minor AE responds to treatment with antibiotic. Severe AE is treated with high dose prolonged oral antibiotic and diuretics.

Early recognition and treatment of severe AE is important as it is associated with high mortality and rapid development of LC. Prevention or early treatment of AE helps in prevention or further progression of LC. Jaundice, ascites and variceal bleeding in HVCS induced cirrhosis is often due to bacterial infection induced AE and not due to decompensation. It responds to medical treatment. Surgical or endovascular procedure to correct the obliterative lesion in IVC is considered unnecessary.

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7. Conflict of Interest: None

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