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Preventive Measures for Cirrhosis of LIVER and its Progression



Sharad C Shah
Prasanna S Shah
Khyati P Shah

Foreword
CS Pitchumoni

JAYPEE

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2

Levels of Prevention



Please look in the right direction to prevent catastrophe

INTRODUCTION

Preventive medicine: Branch of medicine that is applied to 'Healthy' people for prevention of disease and promotion of health.

Primordial prevention: Prevention of the emergence of development of risk factors in continue or population groups in which it has not appeared.[1] Credit must be given to John Last to coin and describe primordial prevention. According to *John Last's Dictionary of Epidemiology,* the basic definition is "actions aimed at eradicating, eliminating, or minimizing the impact of disease or disability," In other words to me, Do not allow the background to occur that will bring the disease, e.g. crude example—do not buy the car so that no accident will occur.[1]

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Primary prevention: Action taken prior to the onset of the disease which removes the possibility that a disease will ever occur.[2]

> *Primary Prevention*
>
> Prevention strategies are aimed at reducing the prevalence of risk-taking behaviors associated with the development of chronic liver diseases.

Secondary prevention: Action which halts the progress of disease at its incurrent stage and prevents its complications"[3]

There are ways to prevent cirrhosis, because the disease progresses slowly, and hence we prevent it and treat them. Unfortunately, if the disease has already occurred **(Table 2.1)**, do not allow or halt or prevent its progression. Two major steps in this section:

1. Cirrhosis is the final stage attained by various chronic liver diseases after years or decades of slow progression. Undertake the measures to halt the march of the disease or its complications.

Table 2.1: Preventive strategies in cirrhosis

	Primary prevention	*Secondary prevention*	*Tertiary prevention*
Aims	Prevent cirrhosis	Detect cirrhosis at the earliest	Detect complications
Screening population	• Patients +ve for HBV and HCV • Chronic ethanol abusers • Obese individuals • Long-standing diabetes • Family members of patients with Wilson's disease, hemochromatosis, NASH, HBV, AIH	• Patient with chronic HBV/HCV infection • Chronic ethanol abusers • Obese individuals • Long-standing diabetes • Patients with Wilson's disease • Hemochromatosis • NAFLD/NASH • Autoimmune liver disease	All patients with cirrhosis
Screening tools	Liver function test and ultrasonography	Complete blood count, liver function test, ultrasonography, upper gastrointestinal endoscopy, fibroscan, liver biopsy	Upper gastrointestinal endoscopy, ultrasonography, ascitic fluid examination, alpha feto potein
Prevention strategy	Treat underlying cause	Treat underlying cause and screen for complications	Prophylactic beta-blockers or variceal band ligation, prophylaxis for spontaneous bacterial peritonitis

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; AIH, autoimmune hepatitis; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease.

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2. Take care that etiology is arrested or treated and removed. The underlying causes of cirrhosis determine its rate of progression, and are the focus of preventive efforts and treatment. Early detection of chronic liver disease, followed by individually tailored, risk-adapted treatment, is the best way to prevent it.

Tertiary prevention: All measures available to reduce or limit impairments and disabilities, minimize suffering caused by existing departures from good health and to promote the patient's adjustment to irremediable conditions.[4]

Levels of Prevention

Primordial Prevention

- Concentrate at adolscence or early childhood.
- Nonavailability of alcohol can be a true primordial prevention.

Primary Prevention

- Naltrexone, acamprostate, topiramate, baclofen for alcohol addiction.

Secondary Prevention

- Self-restriction.
- Control and halt progression of disease.

Tertiary Prevention

- Prevention of complications, morbidity, mortality and avoid transplant.

PRIMORDIAL PREVENTION

Eliminate background that allows the nucleus of the disease to set in; in other words primordial prevention means—do not allow the risk factors to come into the existence.

Concepts

In primordial prevention, it is essential to determine the backgrounds that allow the biological start of a disease. If we do not allow this biological start to set in a person, family or community, primordial prevention will occur. Primordial prevention can definitely show good results. It can be done by convincing high-risk groups of the effects of alcohol, obesity and importance of B virus vaccination.

Value of Primordial Prevention

It is essential to determine the background that allows the biological start of disease (like excess alcohol, obesity, history of familial chronic liver disease).In alcoholic cirrhosis, obviously the biological start is due to alcohol intake; abstinence should be emphasized by proper counseling, taking help of family members, lot of excellent campaigns in society for awareness of consequent ill effects. Longitudinal studies have confirmed the value of inciting factors in primordial

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prevention. By practicing behavioral changes, the disease will not be allowed to show its face. Data are convincing that appropriate lifestyle modification will prevent the disease including cirrhosis of liver of certain etiologies.

Examples

a. *Alcohol:* Lifestyle and avoidance of alcohol beginning from childhood is an important primordial prevention. The importance of lifestyle modification, which is also true for tobacco use to prevent coronary artery disease has been advocated by Gupte, et al.[5]
b. *Obesity:* Prudent behavior by individual community or group to avoid obesity, which is one of the major factors responsible for NASH, is the primordial prevention and subsequent liver deterioration. It may be advantageous to start obesity education in the children for proper habits. Primordial prevention aims towards maintaining BMI throughout childhood and adolescence.[6]
c. Viral B and C infection has become an important health issue. If we can achieve the goal of not-allowing virus to take footage in your body, then it would be a primordial prevention. In today's scenario, it is a public health priority, as there is considerable morbidity and mortality due to hepatitis-related complications. In 2010, the Institute of Medicine has directed an action for primordial prevention and "recommended to be prioritize it as a health concern."[7]

Population Effort

To avert or prevent "tidal wave" of life-threatening hepatitis death rate, Government of Australia called an act on hepatitis death rate. Hepatitis-related death rates are killing 1000 Australians every year, and the burden is increasing. It was national breaking news as reported by *news.com.au* on 24th September 2014.

Concern

There may be a concern of the practicality of implementing these changes. Is it cost effective? The feeling is that public policy, community efforts and pharmacological interventions are all likely to be cost effective and may be cost saving. Prevention of cirrhosis obviously will provide great stride in developing healthier, more productive society. Approach based on the concept of AHA statement on "value of primordial and primary prevention of cardiovascular disease".[8]

Cirrhosis is a worldwide problem that is associated with a substantial economic burden. Hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and alcoholic liver disease are the main causes of cirrhosis, but cost-effective preventive strategies are only available for HBV infection. This paper highlights the publications which evaluate the cost-effectiveness of strategies that prevent or treat the main causes of cirrhosis as well as publications that assess the impact of quality of life on the overall cost burden of the disease.

Screening and Prevention

Hepatitis B testing in asymptomatic patients should be considered in:

- Men who have sex with men

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- Sex workers (of either sex)
- Intravenous drug users
- HIV-positive patients
- Sexual assault victims
- People from countries where hepatitis B is common
- 'Needle-stick' victims
- Sexual partners of people who either have or who are at high risk of having hepatitis B
- Workers with occupational risk, e.g. healthcare workers
- If nonimmune, consider vaccination. If found to be chronic carriers, consider referral for therapy.

  It can be done by education and conviction of benefits.

Important methods of primordial prevention are taking care of general environment, sanitary measures and good-eating habits and maintaining safe water and food supply. This is not likely to cause viral A/E hepatitis. Contaminated water with hepatotoxic effluent should be disposed of very carefully and scientifically so that it does not cion and contaminate drinking water. It would be essential to emphasize the importance of sanitary measures to young minds. This clan can further the message to their close relations and friends **(Fig. 2.1)**.

Catch them young to give preventive advice of good habits and not to acquire bad habits so that they do not develop liver injury, jaundice, and furtherance to cirrhosis. They should also be guided for hepatitis vaccine, restrain entering of B virus in the body.

Methods for Implementation of Primordial Prevention

- Taking care of general environment
- Sanitary measures



Fig. 2.1 Children from a remote village acquiring excellent knowledge and qualifications (Kanyashala Girls High School at remote place Akol, Belgaum, Karnataka, India—Lecture given by Dr Sharad Shah)

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- Good-eating habits
- Maintaining safe water and food supply.

Primordial prevention of obesity: It would mean massive campaign to see that everybody is made aware of bad effects of obesity and everybody makes a determined effort to remain thin and fit.

For primordial prevention, it is essential to determine the background that allows the biological start of a disease (like excess alcohol, obesity, history of familial chronic liver disease). Obviously, the biological start is due to alcohol intake, it should be emphasized by proper counseling, taking help of family members, and lot of excellent campaign in society for awareness of consequent bad effects. Children and adults must avoid getting obese or lose weight so that there is no chance of the person to develop deposits of fat in the liver which will lead to NAFLD to NASH to cirrhosis. Avoiding obesity is primordial prevention. Do not allow the biological predisposition to an illness. For primordial prevention of virus B problem, obviously the answer is mass vaccination or vaccination at birth for all newborn, which is compulsory or practiced in many countries including India.

In Brazil, a lot of attention has been given to loss of productive years of life (PYL) due to premature mortality attributed to cirrhosis of liver. One of the major factors is alcoholism, which is considered as a risk factor related to life style. They feel "Population strategies may be adopted at early ages in an effort to bring about primordial prevention." For their publication, they have defined the term primordial prevention as "Prevention of the risk factor (alcoholism) for cirrhosis of the liver".[9]

PRIMARY PREVENTION

Prevention strategies are aimed at reducing the prevalence of risk-taking behaviors associated with the development of chronic liver diseases. Treatment of any underlying chronic liver disease would logically restrain the progression to cirrhosis. Appropriate screening of family to detect genetically transmitted cirrhosis and intercept its occurrence by proper guidance in siblings is advocated.

Etiology of Cirrhosis of Liver (Fig. 2.2)

It is important to know the etiology of cirrhosis, since it can predict complications and direct treatment decisions. It also allows the discussion of preventive measures, e.g. with family members of patients with alcoholic cirrhosis or chronic viral hepatitis, and consideration of (genetic) testing and preventive advice for relatives of patients with genetic diseases, such as hemochromatosis or Wilson's disease. Frequently multiple etiological factors contribute to the development of cirrhosis, as exemplified in epidemiological studies that identified regular (moderate) alcohol consumption, age above 50 years, and male gender as risk factors in chronic hepatitis C, or older age obesity, insulin resistance/type 2 diabetes, hypertension and hyperlipidemia (all features of the metabolic syndrome) in NASH.[10]

Family members of patients with cirrhosis secondary to hemochromatosis (with iron studies, LFTs, and genetic testing for the HFE mutation) or Wilson's disease should have genetic testing, if available, ceruloplasmin, 24-hour urinary

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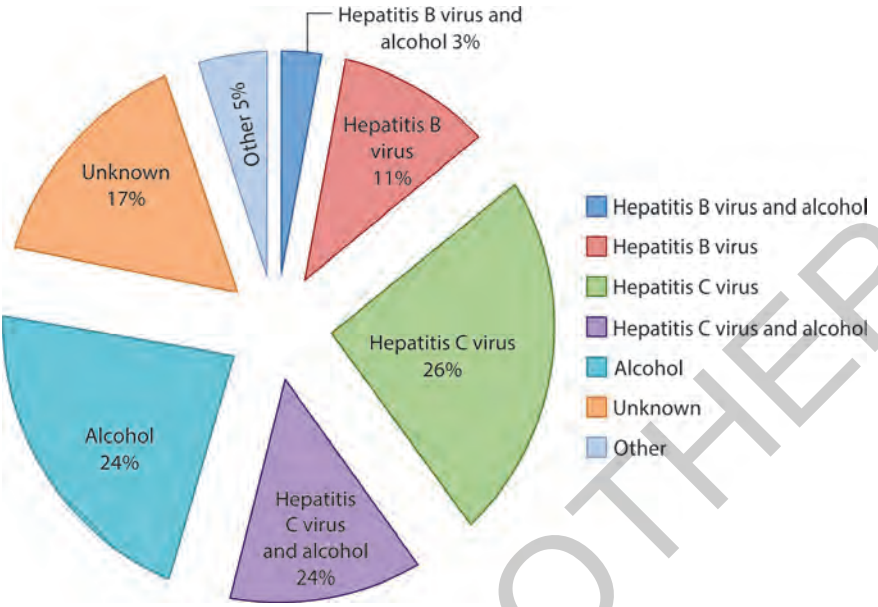

Fig. 2.2 Different etiologies of cirrhosis

copper, and slit-lamp examination looking for Kayser-Fleischer rings in order to initiate monitoring and treatment in affected people in an endeavor to reduce the risk of future cirrhosis.

Common risk factors leading to chronic liver injury can be identified in most patients with cirrhosis, but approximately 5% of patients have no apparent risk factors. Understanding the pathogenesis of cirrhosis formation is essential to develop new diagnostic and therapeutic tools and for its prevention. The identification of genetic risk factors associated with cirrhosis is one of the possible way to approach this issue. Evidence supporting the role of genetic risk factors has been accumulating during the past years, and recently it has been also suggested that telomere shortening may represent a genetic risk factor.[11]

Understanding the complex pathogenesis of cirrhosis is important for its prevention and to identify new diagnostic tools as well as new therapeutic options; one of the possible approaches to this issue might be to understand the genetic bases of cirrhosis.

- Kindly take care of:
  - Excessive alcohol consumption
  - Intravenous drug use
  - Unprotected intercourse
- Methods of primary prevention include:
  - Vaccination programs for hepatitis A and B and theoretically (as is done in tuberculosis) oral drugs to prevent viral hepatitis particularly hepatitis C
  - Public health strategies to control the rising incidence of obesity
  - Treatment of any underlying chronic liver disease to prevent the progression to cirrhosis
  - Screening of blood donors and products for viral hepatitis.

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Patient Education Recommendations for Preventive Care in Chronic Liver Disease are described by Riley TR III, and Bhatti AM.[12]

1. Avoid alcohol of all types (beer, wine, liquor, mixed drinks).
2. Receive vaccinations against hepatitis A and B, if not already immunized (your doctor can check blood investigations to determine this). Also receive a one-time pneumovac and yearly flu shots at fall time.
3. Avoid liver-toxic medications, such as over-the-counter painkillers (aspirin-like medications). Tylenol (acetaminophen) in less than 2 g per day is safest (one extra-strength every 6 hours). Review all other medications with your doctor.
4. Avoid iron supplementation unless your doctor has shown that you are iron deficient (If you take a multivitamin, use a brand that does have iron as an ingredient).
5. Eat a proper, "heart smart" diet; this is good for your liver as well as your heart.
6. Once cirrhosis develops, get screened yearly with upper GI endoscopy to follow your risk of bleeding and with ultrasound to detect liver cancer.
7. Inform all of your healthcare providers that they can acquire your liver disease. Consider wearing a medical alert bracelet cautioning others.[13]

Endoscopy Set-up. Extremely useful to detect varices in the early and late stages and can be treated and pre-empt the threat of bleed.

Balance your diet, rest, avoiding alcohol, acquiring virus B and C and becoming too fat.

Treatment of Hepatitis C

An estimated 3–4 million persons in the US are chronically infected with HCV, and approximately half are unaware of their status. These individuals may ultimately progress to advanced liver disease and/or hepatocellular cancer. However, those outcomes can be staved off by treatment, which is rapidly improving and offers the potential of a cure to more patients than has been previously possible (*Source*: HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Infectious Diseases Society of America).

- Public health strategies to control the rising incidence of obesity.
- Treatment of any underlying chronic liver disease to obviate the progression to cirrhosis.
- Screening of blood donors and products for viral hepatitis.
- Safeguard transmission to child by screening them for HBV, HCV and HIV.

Usually, there are no symptoms for chronic liver disease. It may be picked up after blood investigations mainly alanine aminotransferase (ALT) which denotes the hepatic inflammation and gamma-glutamyltransferase (GGT) which indicates cholestasis and impaired hepatic metabolism. Patient may present to primary physician, even the patient is asymptomatic. In that case, primary care taker must take good history of risk factors such as alcohol consumption, possibility of viral hepatitis by needle sharing or working with blood products in hospital or blood-bank services, dialysis units. He may also ask for any familial trait for developing metabolic causes of cirrhosis. If so primary physician can explain the patient about the risk factor



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Fig. 2.3 Spread of virus B, C and D. In India use of common razor is not uncommon

and keep them under observation, and thereby can stop the patient to develop cirrhosis of liver.

Examples of Primary Prevention

Major risk factors for hepatitis B and C virus infections include high-risk sexual behavior history of intravenous drug use. Additional risk factors for hepatitis B and/or C virus infection include improperly tested blood for that virus. Blood transfusion, hemodialysis, tattoos, and being the child of a mother infected with hepatitis B or C virus **(Fig. 2.3)**. All pregnant women should be screened for hepatitis B virus. In India, vaccination against hepatitis B is given at birth and is included now in universal vaccination program. In India, viral A and E hepatitis is common. Pregnant women should be advised/warned not to eat or drink water outside to avoid viral E hepatitis as there are enough reports giving high mortality of 20% in these cases.

Treatment of severe acute: Hepatitis E can be achieved by oral Ribavarin for 6 months. Occasionally, it can also be treated by Peginterferon. Acute phase serum glutamic-pyruvic transaminase (SGPT) levels were higher in chronic infection.[14]

Patients with virus C cirrhosis, who require transplant, it will be mandatory to start antiviral-C treatment before transplant. Unfortunately in spite of all the precautions recurrence of hepatitis C infection can occur in the newly transplanted liver. It avoids graft infection and may improve liver function tests (LFT). Advantage of this implementation should be confirmed by all the tests including anti-HCV, viral load in post-transplant period. The importance of treatment of virus C before transplant and after transplant has been highly advocated. There are new direct antiviral agents which is a major treatment advance. However, there is an advancement in treatment of virus C. In patients with long-standing cirrhosis with decompensation treatment may be delayed after transplant. Usually, it is possible to know the degree of damage to liver and

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the presence of viral C on histological basis. In the patients, the treatment would be effecatious in the early stage of cirrhosis. The choice of anti-viral therapy will be partly based on the decree of liver damage and renal status as well as the tolerability of the drug.[15]

It is highly recommended for all healthcare workers, as well as people who are infected with human immunodeficiency virus or hepatitis C virus, or who participate in high-risk sexual activity or use intravenous drugs should have vaccine to prevent hepatitis A and B. vaccines are have been available for decades; vaccination against hepatitis C virus has not yet been proven effective in humans.[16,17]

SECONDARY PREVENTION

When unfortunately the disease has taken foothold, not allowing it to progress is secondary prevention. Wikipedia has defined secondary prevention as "Methods to diagnose and treat existent disease in early stages before it causes significant morbidity".

Secondary Prevention

Preventing cirrhosis by early detection of chronic liver disease, followed by individually tailored, risk-adapted treatment would be a good start for secondary prevention.

Taking care of foothold by the etiology is a primary prevention.

Secondary prevention will be not to allow the etiology to progress and endanger occurrence of cirrhosis. It would avoid progression of disease, and it may be achieved by avoidance of progression of disease *per se* or removing the underlying reason or not allowing the etiology to progress and cause further damage **(Flow chart 2.1)**.

Course of chronic liver disease: Worsening hepatic fibrosis leads to cirrhosis, which can become decompensated and lead, in turn, to hepatocellular carcinoma. Timely intervention can prevent progression to the next disease stage. In particular, it can prevent hepatocellular carcinoma. Appropriate treatment can bring about the regression of disease from a worse stage to a better one. Even cirrhosis can regress, but hepatocellular carcinoma cannot.

It also would mean to identify risk factors and assessment of liver damage. The etiological condition like virus B and C can be cured (!) with interferon with ribavirin. Virus B can be treated with long-term treatment to prevent cirrhosis! And similarly hepatitis C (in near future) can be treated with oral long-term nucleotide structure. This will bring out good secondary prevention. Close contact must be apprehended about the infection and how to avoid it.

Methods to achieve secondary prevention are:

1. Eradicate the etiology.
2. Do not allow the etiology to progress to cirrhosis (an example of a dream which may be achieved by oral treatment of virus C).
3. Use safe drugs in cirrhosis.

In a recent review, Lewis and Stine provided recommendations, on the safe use of medications in patients with cirrhosis.

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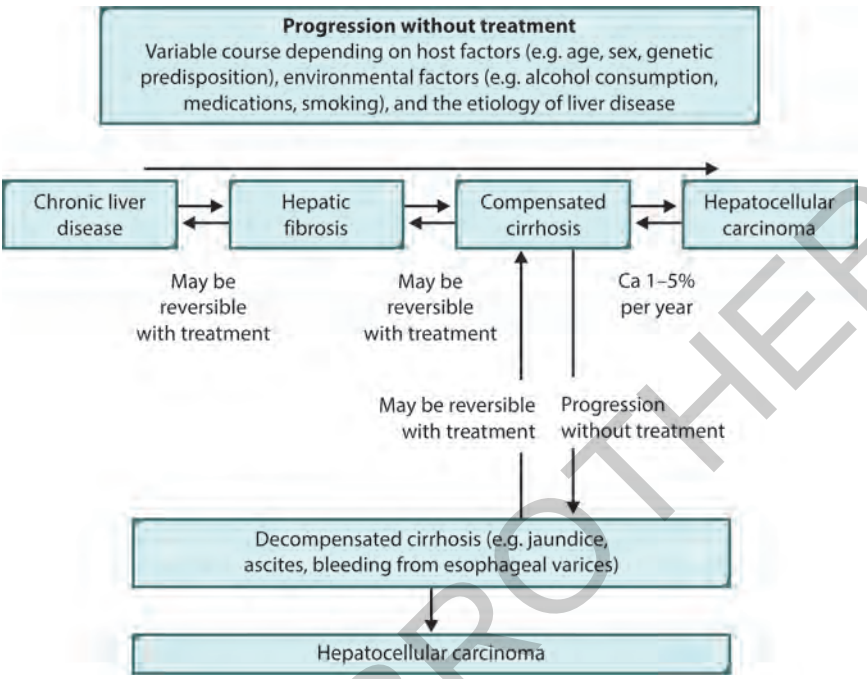
Flow chart 2.1 Progression without treatment



Lower medications doses should generally be used, particularly in patients with significant liver dysfunction.

Opioid analgesics, anxiolytics, and sedatives, which can precipitate hepatic encephalopathy, should be used cautiously.

Nonsteroidal anti-inflammatory drugs (NSAIDs), which can cause renal failure and gastrointestinal (GI) bleeding in patients in cirrhosis, should not be used.

Paracetamol (acetaminophen)–low doses (2–3 g or less, daily) for short periods, paracetamol can be used safely as a first-line pain treatment.

It is a weaker analgesic and may require use of other drugs like tramadol 25 mg TDS and for severe pain fentanyl can be given as skin patches (20 mg), but should be avoided as it can be addictive. There will be search for newer safe drugs without hepatotoxicity. Lots of newer drugs are being constantly introduced for many illnesses. We should look out for possible hepatotoxicity of these drugs. For example, lemotrigin or topiramet used as anticonvulsant are better tolerated. Fluoxetine is better tolerated in cirrhosis as antidepressant. Some of the drugs can be used with modified dose schedule.[18] Similar caution is to be taken in patients who have to undergo surgery. Dynamic readjustment in body may require modification of drug doses.

Statins are safe in patients with cirrhosis[18] and there is a significant increase in hepatic blood flow with simvastatin 40 mg per day. However, further studies are necessary.

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Proton-pump inhibitors and histamine-2 blockers should be used only for valid indications, since they may lead to serious infections in patients with cirrhosis.[18]

Early Detection of Chronic Liver Diseases by Screening of Population

Lot can be done to screen the patients for the incidental existence of cirrhosis. There are nearly 40% of cirrhotics, who are accidentally detected. It should also be seriously considered in people who have prolonged consumption of alcohol, hepatotoxic medications or history of receiving blood or blood products. Patient may be discovered to have cirrhosis for the first time when they when they present with complications like bleed or encephalopathy or hepatocellular carcinoma (HCC).

So, determined effort has to be made for diagnosis of cirrhosis in the population, who has not been suspected to have cirrhosis for themselves. Author personally feels that every liver or gastroenterology unit or any general hospital should have a very laid out program to screen every individual who comes to their institution should be screened for cirrhosis of liver.

In India, hepatitis B is linked to 60% of cases of hepatocellular carcinoma and 80% of cases of cirrhosis of the liver. There has to be a massive campaign for the population or individuals to be ready to undergo these properly tailored methods of investigations.

Satisfactory Clinical Examination (Figs 2.4 to 2.9)

One of the classical sign/finding is the appearance of spider nevi which blanch on pressure.

Wikipedia—"Laennec's cirrhosis is named after René Laennec, a French physician and the inventor of the stethoscope. It is a disease of the liver in which the normal lobular architecture is lost, with fibrosis and later nodular regeneration. Laennec's cirrhosis can be associated with inflammatory polyarthritis, most commonly affecting the shoulders, elbows and knees. Osteoporosis, soft tissue swelling in peripheral joints and sometimes calcific periarthritis are seen".

In the developed world, Laennec's cirrhosis most commonly affects middle-aged males, typically ages 40–60. This is the most common form of cirrhosis in the US. In African and Asian areas of the world, vast numbers of children are also afflicted.

We may find florid cirrhotic or its complications or predisposing attributes that lead to cirrhosis like alcohol, NASH, viral B or C affectations. With proper treatment, it is possible to halt progression of cirrhosis. These affected individuals can have primary, secondary tertiary prevention. Until today cirrhosis is uniformly the end stage of liver disease. There is no defined method to reverse the process and make a normal organ once again. However, there is a major hope of reversing the pathogenesis (discussed in a later section). In most patients, the dynamic process of progressive fibrosis, which could ultimately lead to cirrhosis, can be interrupted by the timely recognition of the risk, followed by appropriate treatment.

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Fig. 2.4 Gynecomastia is seen in male patients—the breast enlargement with glandular subcutaneous tissue under the nipple and aerola—better felt on palpation

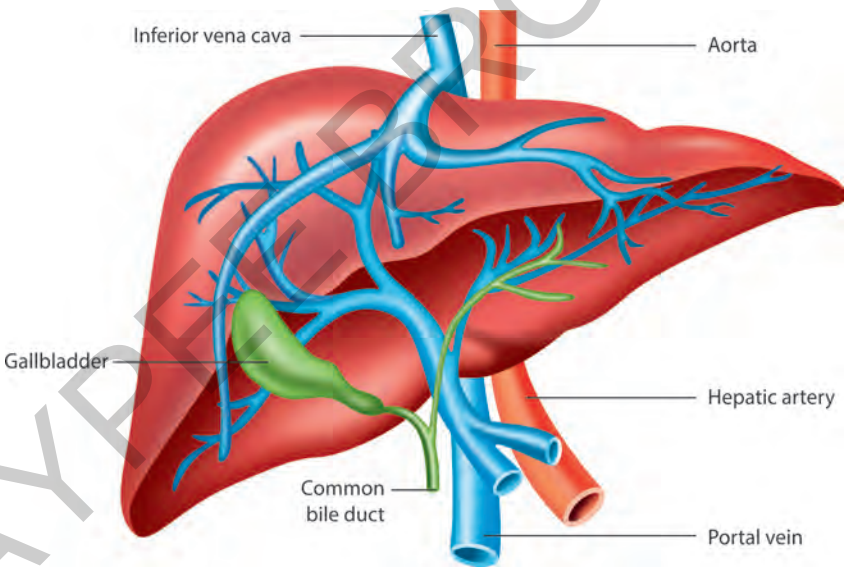

Fig. 2.5 Anatomical view of liver. Note smooth surface

Preventing cirrhosis by early detection of chronic liver disease, followed by individually tailored, risk-adapted treatment would be a good start for secondary prevention.[19]

Screening for chronic liver disease should be performed in all the individuals afflicted with risk factors leading to cirrhosis, particularly, (1) Chronic alcoholics, patients with long-standing diabetes mellitus, obese individuals, and patients with hepatitis B and hepatitis C infections, as well as (2) First degree blood

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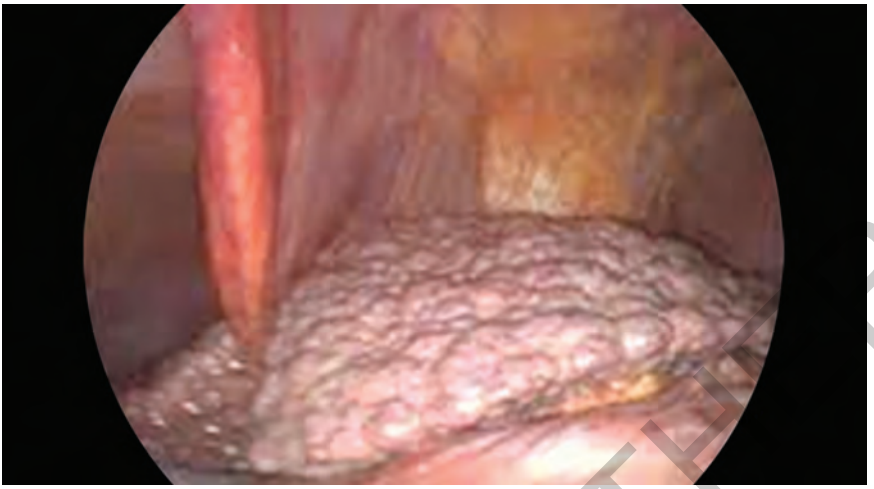

Fig. 2.6 Laparoscopic view of cirrhotic liver. Note the nodular (hobnob) surface that indicates cirrhosis of liver and liver biopsy will give authoritative confirmed diagnosis *(Contributed by Dr TE Udwadia)*



Fig. 2.7 Advanced cirrhosis nodular surface, splenomegaly and ascites. Well-pronounced classical appearance/picture of advanced Laennec's cirrhosis of liver. *(Image contributed by Dr Anirudh Kohli)*

relatives of patients with hemochromatosis, Wilson's disease, nonalcoholic steatohepatitis (NASH)-related cirrhosis, autoimmune hepatitis (AIH), and HBV-related cirrhosis. So that treatment at very early stage will halt the build-up of cirrhosis.

Taking exemplary advantage of the natural history of cirrhosis for secondary prevention is discussed further.

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Preventive Measures for Cirrhosis of LIVER and its Progression

Salient Features

- Covers the prevention of cirrhosis, the stages of levels of prevention, and each aspect of cirrhosis at all stages
- Includes figures, diagrams at appropriate places and chapters and references to cover the topic on broader base
- Useful to the doctors and teaching staff who teach preventive services and lay people in general
- A small hint is given as reversing the fibrosis, which will be the best boon for humanity



Sharad C Shah did his MBBS and MD from Grant Medical College and achieved MRCP both from Edinburgh and Glasgow, UK. He was appointed as Honorary Gastroenterologist and an Honorary Assistant Professor of Medicine, Grant Medical College and JJ Hospital, Mumbai, Maharashtra, India, and was also attached to Sir HN Hospital, Mumbai.

He is one of the senior most celebrities in the field of gastroenterology. He has been teacher of excellence and has groomed a plenty of doctors, postgraduate students in the field of gastroenterology, which is an important branch of medicine in India. He also has been an Examiner for postgraduate degrees in gastroenterology in India at various universities. He has lectured at the World Meet in Brazil (through an NGO nomination) on Prevention in Gastroenterology, stating on the fact that Preventive Gastroenterology should be made very interesting and rewarding. He has many laurels; to quote a few: (1) Henry Dimmock Medal, (2) Research grant by Mumbai University, etc. His clinical work does not distinguish between rich and poor. His dedication to his profession, teaching and care of patient is exemplary. He has to his credit teaching hundreds of undergraduate and postgraduate students.



Prasanna S Shah is a Consultant Gastroenterologist and Endoscopist, Breach Candy, Jaslok and Saifee Hospitals, Mumbai, Maharashtra, India. He has written several papers and monograms, the important one being Management of Acute Pancreatitis. He is a teacher for the intragastric balloon placement for obesity in India and has to his credit the highest placements in the country.



Khyati P Shah is a Physician and Medical Research Officer, Breach Candy Hospital, Mumbai, Maharashtra, India. She has been closely associated as Clinical Assistant to Dr Farokh E Udwadia for almost 15 years.

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