

the **S Q U A R E**

Healthcare **bulletin**



- ▶ *Hypertension- New Approach*
- ▶ *Hepatitis C*
- ▶ *Acute Abdomen*
- ▶ *Wilson Disease*
- ▶ *Vaccine Preventable Diseases*



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Contents

<i>Hypertension-New Approach</i>	Page 01
<i>Hepatitis C</i>	Page 02
<i>Acute Abdomen</i>	Page 10
<i>Wilson Disease</i>	Page 13
<i>Vaccine Preventable Diseases</i>	Page 16
<i>SQUARE in International Business</i>	Page 20

Editorial



Dear Doctor

Welcome to this edition of "the SQUARE" healthcare bulletin !

In this issue we have published a special feature on "Hypertension - New Approach" focusing on latest JNC 8 and ESH/ESC guidelines. We bring you all the details on "Hepatitis C", which can lead to permanent liver damage as well as cirrhosis, liver cancer and liver failure. We focused on "Acute Abdomen", which remains a challenge to surgeons and other physicians. Besides, we have an article on "Wilson Disease", a disorder of copper metabolism that can present with hepatic, neurologic or psychiatric disturbances or a combination of these, in individuals ranging from age three years to over 50 years. In addition, we have a special write-up on "Vaccine Preventable Diseases". The WHO reports licensed vaccines being available to prevent or contribute to the prevention and control of 25 vaccine-preventable infections. Moreover, we have our regular feature, "SQUARE in International Business".

Every effort has been made to make this issue interesting and we are quite sure that you will enjoy this as well.

We, on behalf of the management of SQUARE wish you all a safe, healthy and peaceful life.

Thank you !

Omar Akramur Rab

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Hypertension is a common cardiovascular condition worldwide. It is a major risk factor for a number of cardiovascular and other health problems. A large number of patients are diagnosed for the first time as “hypertensive” in each year. The huge numbers of newly diagnosed hypertensive patients need adequate control of their hypertension to prevent lifethreatening complications. For adequate and effective management of hypertension, multiple management guidelines have been published which are updated time to time, But, these recommendations are not a substitute for clinical judgment of an experienced physician.

When to Initiate Drug Treatment

According to the 2014 JNC 8 guideline, treatment of hypertension should be introduced among the general population aged ≥ 60 years when systolic blood pressure (SBP) ≥ 150 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg. In case of general population aged < 60 years, treatment should be started when SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. In the population aged ≥ 18 years with diabetes mellitus, anti-hypertensive drugs should be initiated when SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. In the population aged ≥ 18 years with chronic kidney disease (CKD) with or without diabetes mellitus, anti-hypertensive drug should be used when SBP is ≥ 140 mmHg or DBP ≥ 90 mmHg.

According to the 2013 ESH/ESC guideline, there is strong evidence of benefits from lowering of blood pressure by anti-hypertensive treatment in the elderly with initial SBP of ≥ 160 mmHg. In fit elderly patients < 80 years, anti-hypertensive treatment should be considered at SBP value ≥ 140 mmHg. In general non-elderly population, treatment should be started when SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. In the population with diabetes mellitus, treatment should be initiated when SBP ≥ 140 mmHg or DBP ≥ 85 mmHg irrespective of age. In population with CKD but no proteinuria, the drug should be commenced when SBP ≥ 140 mmHg or DBP ≥ 90 mmHg and with CKD with proteinuria when SBP ≥ 130 mmHg or DBP ≥ 90 mmHg.

Treatment Goal

According to the 2014 JNC 8 guideline, the blood pressure goal among the general population aged ≥ 60 years is SBP < 150 mmHg and DBP < 90 mmHg. In case of general population aged < 60 years the goal is SBP < 140 mmHg and DBP < 90 mmHg. In the population aged ≥ 18 years with diabetes, the goal is SBP < 140 mmHg and DBP < 90 mmHg. In the general population with CKD with or without diabetes mellitus, the goal is SBP < 140 mmHg and DBP < 90 mmHg.

According to the 2013 ESH/ESC guideline, in elderly hypertensive patients with SBP ≥ 160 mmHg the SBP goal is between 150 and 140 mmHg. In fit elderly patients < 80 years, the SBP goal is < 140 mmHg if treatment is well tolerated. In these two conditions, the DBP goal is < 90 mmHg. In general non-elderly population the goal should be SBP < 140 mmHg and DBP < 90 mmHg. In the population with diabetes mellitus, the goal blood pressure should be SBP < 140 mmHg and DBP < 85 mmHg. In population with CKD but no proteinuria the goal is SBP < 140 mmHg and DBP < 90 mmHg and with CKD with proteinuria the target is SBP < 130 mmHg and DBP < 90 mmHg.

Choice of Initial Anti-hypertensive Drug

According to the 2014 JNC 8 guideline, in general non-black population, initial drug therapy should include one of the four groups: *Thiazide-type diuretic*, *Angiotensin converting enzyme inhibitor (ACEI)*, *Angiotensin receptor blocker (ARB)* and *Calcium channel blocker (CCB)*.

On the other hand in the general black population, antihypertensive treatment should be started with a thiazide-type diuretic or a calcium channel blocker (CCB). In diabetic hypertensive patients, the initial anti-hypertensive drug should be a thiazide-type diuretic or an ACEI or an ARB or a CCB. In hypertension with CKD, the drug of choice is either ACEI or ARB.

According to the 2013 ESH/ESC guideline, in the general population (regardless of race) the suitable drugs for initial treatment should be one of the five groups: *Thiazide-type diuretics*, *Beta blockers*, *ACEI*, *ARB* and *CCB*.

In the hypertensive population with diabetes, the treatment of choice is either an ACEI or an ARB. In hypertensive patients with CKD with or without proteinuria, the primary choice of anti-hypertensive drug is an ACEI, or an ARB.

Combination of Anti-hypertensive Drug

According to the 2014 JNC 8 guideline, if target blood pressure is not achieved within expected time span, then first medication dose should be maximized before addition of a second drug. Another option is to add a second drug with the previous one. These two drugs may be used separately or as a fixed-dose combination. A third drug is necessary if hypertension is not controlled with the maximum doses of the two drugs. Failing to achieve the target may require another anti-hypertensive drug from other classes (e.g. β -blocker, aldosterone antagonist, or others). It should be kept in mind not to use an ACEI and an ARB together in the same patient.

According to the 2013 ESH/ESC guideline, in case of mild blood pressure elevation with low/moderate cardiovascular risk, initially a single drug is recommended. If blood pressure is not controlled, then the dose of 1st drug should be maximized. Another option is to switch the previous drug to a newer one which should be maximized if needed. Next approach is to use maximum doses of these two drugs in combination. After this step, a different drug combination from two other classes of drugs is suggested. Finally, three drugs in combination at full doses is advised. In case of marked blood pressure elevation with high/very high cardiovascular risk, initially two drugs in combination should be used. If blood pressure is not within the goal, then there are two options. The first one is to maximize the dose of this combination, then switch to different two drugs in combination from other two classes. The second option is addition of a third drug with initial combination. If the target is not still achieved, lastly three drug combination at full doses is recommended. It should be kept in mind not to use an ACEI and an ARB together in the same patient.

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www.ajmc.com
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Viral hepatitis is common worldwide. The viruses implicated for the causation of the condition are hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), hepatitis non A-E virus, Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), yellow fever virus etc. Some of them cause acute viral hepatitis whereas others are responsible for chronic viral hepatitis.

Hepatitis C virus causes viral hepatitis that is known as hepatitis C. It is also called type C hepatitis. HCV usually causes chronic viral hepatitis. This infection occurs worldwide. It is estimated that 160 million people of the world are chronically infected with HCV. It is one of the main causes of chronic liver disease, liver cirrhosis and hepatocellular carcinoma. The pathophysiology of the condition is now known. There is also development in the diagnostic procedures of the condition in the last two decades. These have brought significant improvements in the clinical care of the patients and prevention of infection. In spite of this, chronic infection by HCV is still not uncommon and associated with huge economic burden. Anti-viral vaccine effective against HCV is yet to be identified.

Virology

Hepatitis C virus is an enveloped positive sense RNA virus in the flavivirus group. It was discovered in 1989. The virus is characterized by high sequence heterogeneity. Seven HCV genotypes, numbered 1 to 7 and a large number of subtypes have been described. Genotypes and subtypes (which are identified by lowercase) differ among themselves by about 30% and 20% of their sequences, respectively.

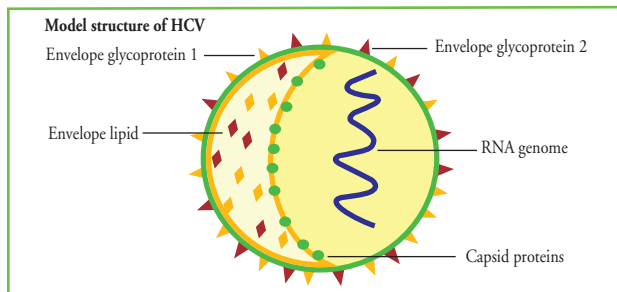


Figure: Hepatitis C Virus

Genotype 1 is the most prevalent genotype worldwide, with a higher proportion of subtype 1b in Europe and 1a in the USA.

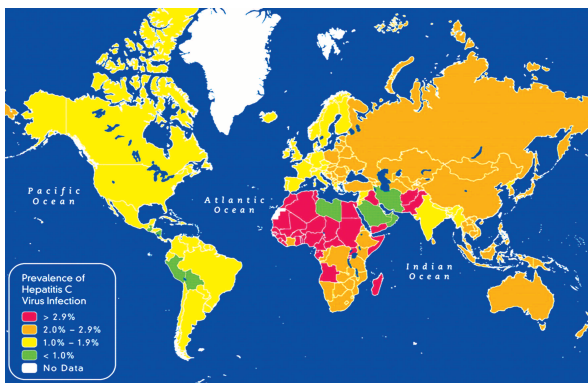


Figure: Global prevalence of Hepatitis C

Genotype 3a is highly prevalent in the people who inject drugs (PWID). Genotype 4 is also being found increasingly in PWID.

Genotype 2 is found in clusters in the Mediterranean region, while 5 and 6 are rare in Europe. The novel genotype 7 was identified in patients from Canada and Belgium, possibly infected in Central Africa. The identification of HCV genotypes and subtypes is not only of epidemiological interest, but also it determines the type and duration of antiviral therapy.

Routes of Transmission

- ❑ Up to the 1990's, the principal routes of HCV infection were blood transfusion. Currently, screening of blood products for HCV by means of enzyme immunoassay (EIA) and polymerase chain reaction (PCR) has virtually eradicated transfusion associated hepatitis C in developed countries.
- ❑ Transmission of HCV by unsafe injection procedures and intravenous drug abuse remains a major route both in developed and developing countries. Sharing paraphernalia, unstable housing, frequent cocaine use and history of imprisonment are responsible for incident cases in developed countries.
- ❑ Tattooing or acupuncture with unsafe materials, are also implicated in occasional HCV transmissions.
- ❑ New HCV infections are infrequently related to unsafe medical or surgical procedures. The risk of acquiring HCV by needle sticks is about six times higher than that for HIV (1.8% versus 0.3%).
- ❑ The risk of prenatal and heterosexual transmission of HCV is low, while male homosexual activity has become an important route of transmission in Western countries.

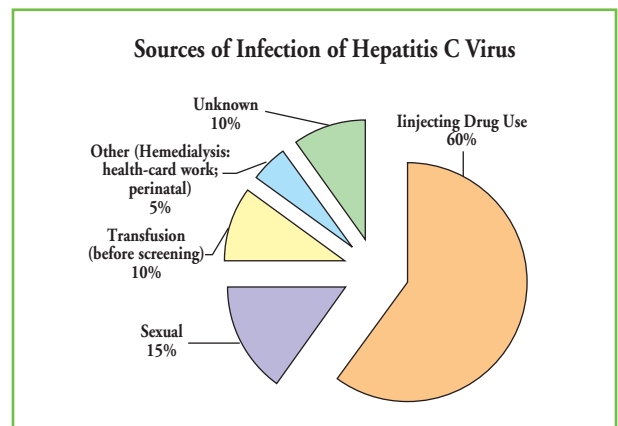


Figure: Sources of infection of HCV

Natural History of HCV Infection

Infection of liver parenchyma by HCV progresses through acute phase and chronic phase leading to various complications.

Acute Hepatitis C:

Acute HCV infection refers to the presence of clinical signs or symptoms of hepatitis within six months of presumed HCV exposure. Most individuals are unaware of when they became infected and are only identified when they develop chronic liver disease. Acute HCV infection is asymptomatic in most cases. In the US, 15% cases of acute viral hepatitis occur due to HCV whereas in Europe, HCV is responsible for 10% cases. Hepatocyte damage is believed to result from damage to the virus-infected cells by CD8+ cytotoxic T cells.

After an incubation period of 2-26 weeks (with a mean onset of 7 to 8 weeks), patients may complain of non-specific symptoms e.g., fatigue, low-grade fever, anorexia, nausea, arthralgia, myalgia etc. Jaundice usually follows the initial symptoms. Vomiting and diarrhea may follow and abdominal discomfort is common. The liver is often tender but only minimally enlarged. Acute infection may also cause dark urine and pale stool. Progression to persistent or chronic infection occurs in about three quarters of cases.

□ Chronic Hepatitis C :

Persistent infection and chronic hepatitis are the hallmarks of HCV infection. Chronic hepatitis C is defined as inflammation of liver parenchyma by HCV for 6 months or more. Only exceptionally does infection clear spontaneously in the chronic stage. Chronic hepatitis C proceeds towards cirrhosis over several decades through hepatic fibrosis. On average, 10-20% of patients develop cirrhosis over 20-30 years of infection. Once at the cirrhotic stage, the risk of developing hepato-cellular carcinoma (HCC) is approximately 1-5% per year. The prevalence of anti-HCV antibodies among patients with cirrhosis ranges from 11-61%. Similarly, the prevalence of anti-HCV antibodies in patients with HCC ranges from 18-64%. Overall, the standardized mortality rate in anti-HCV positive persons ranges from 1.6 to 4.5 and was as high as 25 in a recent study from Scotland. In countries where injecting drug use is the major risk factor for HCV infection, 20-25% of deaths among HCV-infected individuals are from liver disease.

The presence of some co-factors can accelerate the fibrotic process in the liver. Proven co-factors for fibrosis progression include older age at infection, male gender, chronic alcohol consumption, cannabis use, obesity, insulin resistance, type 2 diabetes mellitus and immunosuppression. Coffee intake is associated with reduced inflammation, less advanced fibrosis and reduced risk of developing HCC. For all of the above reasons, the modification of co-factors is also important in the management of chronic HCV infection.

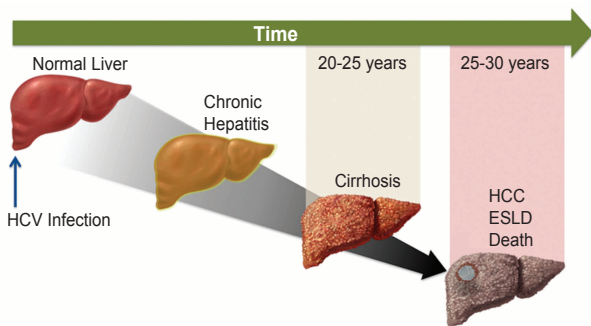


Figure: Natural Course of HCV Infection

Diagnostic Investigations of Acute and Chronic Hepatitis C

The diagnosis of HCV infection is based on the detection of both HCV antibodies and HCV RNA in the presence of signs of chronic hepatitis, either by elevated ALT or by histology.

- The detection of HCV RNA by PCR is very much helpful in the diagnosis of acute and chronic HCV infections.
- Anti-HCV antibodies are detectable by enzyme immunoassay (EIA) in the vast majority of patients with HCV.

- The diagnosis of acute hepatitis C can be confidently made only if seroconversion to anti-HCV antibodies can be documented. But, anti-HCV antibodies may be undetectable in early acute hepatitis C and in profoundly immunosuppressed patients. In these cases, acute hepatitis C can be suspected if the clinical signs and symptoms are compatible with acute hepatitis C (ALT > 10 times the upper limit of normal, jaundice) in the absence of a history of chronic liver disease or other causes of acute hepatitis, and/or if a likely recent source of transmission is identifiable.
- Chronic hepatitis C is diagnosed if HCV RNA is found in the serum beyond 6 months of infection.
- Following spontaneous or treatment induced viral clearance, anti-HCV antibodies persist in HCV RNA but may decline and finally disappear in some individuals. Anti-HCV positive, HCV RNA negative individuals should be retested after 3 months to confirm a recovered infection.

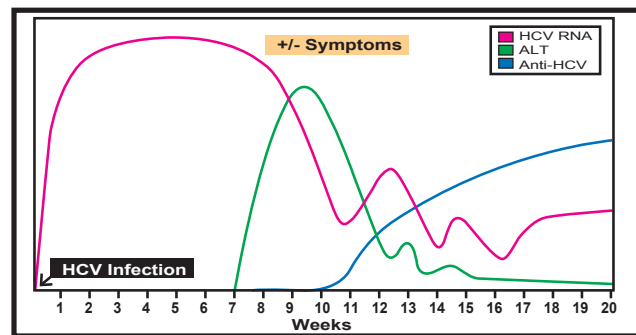


Figure: Laboratory finding in HCV infection

Pre-therapeutic Assessment of Patients with Chronic Hepatitis C

Before initiation of anti-HCV treatment, the causal relationship between HCV infection and liver disease must be established. Moreover, the severity of liver disease should be assessed and baseline virological parameters that will be useful to tailor therapy should be determined.

□ Causes of liver disease :

Other causes of chronic liver disease or factors which are likely to affect the natural history or progression of liver disease should be identified. All patients should be tested for other hepatotropic viruses, particularly HBV. Alcohol consumption should be assessed and quantified, and the patient should be counseled to stop any use of alcohol. Possible co-morbidities, including co-infection with HIV, autoimmunity, genetic or metabolic liver disease (hemochromatosis, diabetes, obesity) and the possibility of drug-induced hepatotoxicity should also be assessed.

□ Assessment of severity of liver disease :

Evaluation of disease severity should be performed regardless of ALT patterns. Identification of patients with cirrhosis is of particular importance, as the likelihood of response to therapy and post-treatment prognosis are proportional to the stage of fibrosis. The absence of significant fibrosis may also have important implications for the choice or timing of therapy. Assessment of the stage of fibrosis is not a requirement in patients with clinical evidence of cirrhosis. Liver biopsy remains the reference method in indicated patients where the risk of complication is very low (1/4000 to 1/10000).

Based on abundant literature, non-invasive methods (biomarkers of fibrosis) can now be used instead of liver biopsy to assess liver disease severity prior to therapy at a safe level of predictability. These are of particular interest in patients with clotting abnormalities. Liver stiffness measurement can be used to assess liver fibrosis in patients with chronic HCV. But histology may be required in cases of known or suspected mixed etiologies (e.g., HCV infection with HBV infection, metabolic syndrome, alcoholism or autoimmunity). Patients with likely cirrhosis should be screened for HCC.

□ HCV titer and genotype determination :

HCV quantification is indicated for the patient who may undergo antiviral treatment. HCV quantification should be made by reliable sensitive assay, and levels should be expressed IU/ml. The HCV genotype should also be assessed prior to treatment initiation as current treatment plan is somewhat varies depending up on the genotype of HCV.

□ Determination of host genetics :

IL28B genotyping may provide useful information for making clinical decisions in selected patients with genotype 1 or 4. A favorable IL28B genotype identifies patients who are more likely to achieve a rapid virological response (RVR) and who have a significant chance of cure with dual therapy. In selected cases with genotype 1, it may assist the physician and patient in management decision. The negative predictive value of an unfavorable IL28B genotype is not sufficient to be considered a futility rule.

The Current Standard of Treatment for Chronic Hepatitis C

At present three antiviral agents are used for the treatment of chronic hepatitis C in different combinations. These are interferons, ribavirin and protease inhibitors (Boseprevir/ Telaprevir). Some important factors such as goals of treatment, indications and contraindications of treatment, available drug regimens, adverse effects of treatment should be kept in mind.

□ Goals of anti-HCV treatment :

The primary goal of anti-HCV therapy is to cure the infection in order to halt disease progression, prevent complications of HCV-related liver disease (including liver inflammation, fibrosis, cirrhosis, HCC), extrahepatic diseases and death. Treatment of HCV is generally associated with resolution of liver disease in patients without cirrhosis. Long-term follow-up studies have shown that the infection is cured in more than 99% of patients who achieve a sustained virological response (SVR), defined as undetectable HCV RNA 24 weeks after treatment completion. The validity of using undetectable HCV RNA at 12 weeks after the end of therapy (SVR12) has been accepted by regulators in the US and Europe, given that the concordance with SVR24 is 99%. Patients with cirrhosis remain at risk of life-threatening complications e.g., hepatocellular carcinoma, albeit at a lower rate, even after viral infection has been eradicated.

□ Contraindications to anti-HCV treatment :

Treatment of chronic hepatitis C with pegylated interferon (PegIFN) and ribavirin (RBV) containing dual therapy is absolutely contraindicated in patient with uncontrolled depression, psychosis and epilepsy. These are also contraindicated in patients with decompensated

cirrhosis and severe concurrent medical illness. Pregnant women or couples unwilling to comply with adequate contraception should not take these drugs. The same contraindications apply to protease inhibitor-based triple therapy as to dual therapy. In patients with compensated cirrhosis, treatment should be administered with special care as the incidence of side-effects is significantly increased in triple therapy, especially when serum albumin is < 3.5 g/ dL or platelets < 100,000/ mm³ before starting treatment.

□ Indications of anti-HCV treatment :

All treatment-naïve patients with compensated chronic liver disease related to HCV, who are stable and willing to be treated and who have no contraindications to treatment, should be considered for therapy. Treatment should be scheduled, rather than deferred, in patients with advanced fibrosis (METAVIR score F3 to F4) and in those patients with clinically significant extrahepatic manifestations (symptomatic cryoglobulinemia or HCV immune complex nephropathy). Patients who have treatment deferred should be considered for reassessment at a regular basis for evidence of disease progression, to reconsider the indication for treatment and to discuss new therapies as they emerge. For patients with minimal or no fibrosis, the timing of therapy is debatable and should be individualized.

□ Current treatment regimens :

a. Anti-HCV therapy against HCV genotype 1 :

From 2001 to 2011, either of the two pegylated interferons, PegIFN- α 2a & PegIFN- α 2b, administered subcutaneously once weekly in combination with oral RBV were the standard of care for treatment of HCV genotype 1 infection. With this regimen, patients had SVR rates of approximately 40% in North America and 50% in Western Europe. This dual therapy may be appropriate for selected treatment-naïve patients with baseline features predicting a high likelihood of RVR and SVR to PegIFN/RBV. Cost savings and better tolerability of dual therapy must be taken into account. Moreover, occasional patients may have co-morbid conditions that require medication known or predicted to have adverse drug-drug interaction with the PIs.

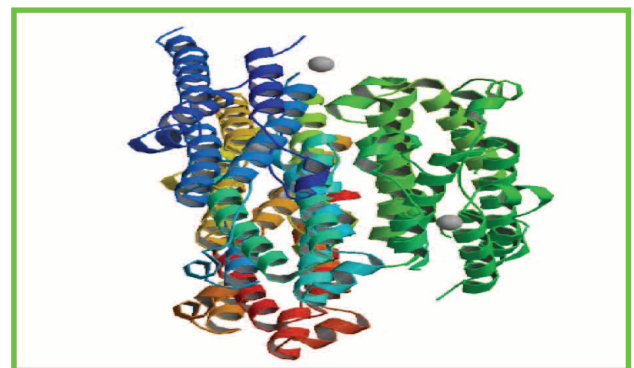


Figure: Interferon alpha

In 2011, the two protease inhibitors, telaprevir (TVR) and boceprevir (BOC), had been licensed for use only in HCV genotype 1 infection along with dual therapy. These two drugs are first-generation direct acting antivirals (DAAs), both targeting the HCV NS3/4A serine protease.

The triple therapy regimens have proven the efficacy for treatment-naïve and for treatment-experienced patients, including previous null responders to dual PegIFN/RBV therapy. In the phase III trials of BOC and TVR in HCV 1 treatment-naïve patients, triple therapy regimens achieved much higher SVR rates than dual therapy.

Ribavirin is a synthetic guanosine (purine) analog. The drug is first converted to the 5'-phosphate derivatives, the major product being the compound ribavirin-triphosphate. It inhibits guanosine triphosphate formation by blocking RNA-dependent RNA polymerase and thus, preventing 5'-capping of messenger RNA. It is active against a broad spectrum of RNA and DNA viruses e.g. hepatitis C virus, respiratory syncytial virus, Lassa fever virus etc. Ribavirin is effective orally and intravenously. Absorption is increased if the drug is taken with a fatty meal. An aerosol is used in certain respiratory viral conditions, such as the treatment of RSV infection. Side effects reported for oral or parenteral use of ribavirin have included dose-dependent transient anemia. Elevated bilirubin has been reported. Because of teratogenic effects in experimental animals, ribavirin is contraindicated in pregnancy.

Interferons are naturally occurring glycoproteins with a multiplicity of actions, including antiviral, immunomodulatory and antiproliferative effects. Interferons are produced by virus-infected cells, macrophages and lymphocytes. Their production is stimulated by a number of factors, including viral nucleic acid. They induce complex set of biochemical pathways. At least three types of interferon exist such as interferon- α , interferon- β and interferon- γ . Interferon- α has been approved for treatment of hepatitis B and C, condylomata acuminata, and cancers such as hairy-cell leukemia and Kaposi's sarcoma. Interferon- β has some effectiveness in the treatment of multiple sclerosis. They have been synthesized commercially by either culture of lymphoblastoid cells or by recombinant DNA technology and are licensed for therapeutic use. The potency of IFN- α has been enhanced by coupling the protein with polyethylene glycol. The larger pegylated-molecule delays absorption from the injection site, lengthening the duration of action of the drug and also decreases its clearance.

In SPRINT-2 study of BOC, one group of patients received PegIFN/RBV dual therapy plus placebo for 48 weeks. Another group of patients received 4 weeks of dual therapy followed by 44 weeks of BOC-containing triple therapy. The third group of patients received 4 weeks of dual therapy followed by response-guided BOC-containing triple therapy where duration of treatment was guided by on-treatment virological response (the patients who were HCV RNA undetectable at week 8 and 24 weeks stopped all drugs at week 28, while who were HCV RNA detectable at any time point between week 8 and 24 stopped BOC at 28, but then continued dual therapy for a total treatment duration of 48 weeks). The SVR in these 3 groups of patients were 38%, 66% and 63% respectively. So, higher SVR were achieved with triple therapy than dual therapy. The response-guided short-duration therapy should be avoided in the presence of cirrhosis.

In ADVANCE study of TVR, treatment-naïve patients were enrolled and randomized into three groups. Group 1 received PegIFN/RBV

plus placebo for 48 weeks. Group 2 received 8 weeks of triple therapy (T8PR) followed by response-guided tail of dual therapy. Group 3 received 12 weeks of triple therapy (T12PR) followed by response-guided tail of dual therapy. In both T8PR and T12PR arms, treatment duration was based on HCV RNA values at week 4 to 12. Patients in whom HCV RNA was undetectable at week 4 to 12, the so-called extended rapid virological response (eRVR), treatment was stopped at week 24, while those in whom HCV RNA was detectable at either this time points, continued dual therapy up to 48 weeks. The SVR rates in group 1, 2 and 3 were 44%, 69% and 75% respectively. So, triple therapy is associated with higher SVR than dual therapy.

In ILLUMINATE study, the patients with an eRVR were enrolled. One group received TVR-containing triple therapy for 12 weeks followed by dual therapy for another 12 weeks. Another group received TVR containing triple therapy for 12 weeks followed by dual therapy for 36 weeks. The SVR rates 92% in the first group and 87.5% in the second group. Based on the results of these 2 studies, overall treatment duration with triple therapy containing TVR can be shortened to 24 weeks in naïve patients with an eRVR, while treatment needs to be continued until week 48 in those without an eRVR.

Drug Dosing in HCV Genotype 1 Therapy :

PegIFN- α 2a should be used at the dose of 180 μ g/week subcutaneously whereas PegIFN- α 2b should be used at the weight-based dose of 1.5 μ g/kg/week subcutaneously. In triple therapy, ribavirin dose should be 1000-1200 mg/day orally based on body weight for PegIFN- α 2a and 800-1400 mg/day orally based on body weight for PegIFN- α 2b. TVR dose is 750 mg every 8 hourly orally, though recently presented clinical trial data showed that 12-hourly dosing (1125 mg 12 hourly) does not have inferior efficacy. BOC dose is 800 mg at 7-9 hourly or qally. Both the PIs need to be taken with food. Each TVR dose needs to be taken with a 20 g fat containing snack.

b. Anti-HCV therapy against HCV genotypes 2, 3, 4, 5 or 6 :

In patients infected with HCV genotypes 2, 3, 4, 5 or 6, the standard of care regimen consists of the combination of either of the two PegIFN- α with ribavirin. PegIFN- α 2a should be used at the dose of 180 μ g/week whereas PegIFN- α 2b should be used at the weight based dose of 1.5 μ g/kg/week. The ribavirin dose depends on the HCV genotype. Patients infected with HCV genotypes 4, 5 and 6 should receive a weight-based dose of ribavirin i.e. 15 mg/kg body weight. Patients infected with genotypes 2 and 3 can be treated with a flat dose of 800 mg of ribavirin daily, but those with a body mass beyond 25 or who have baseline factors suggesting low responsiveness (insulin resistance, metabolic syndrome, severe fibrosis or cirrhosis, older age) should receive a weight-based dose of ribavirin. Patients with genotype 2 or 3 infection are more responsive to the current standard dual therapy than genotype 1. The rates of SVR for genotype 2 or 3 infection are similar in patients treated for 24 or 48 weeks; thus, for these patients 24-week treatment is generally considered appropriate. There is no indication to the use of first-generation PIs in patients with non-1 genotype HCV infection.

Adverse Effects of Anti-HCV Therapy

Almost all patients receiving hepatitis C antiviral therapy will experience some treatment-related adverse effects. Close monitoring is crucial throughout the treatment. Poor tolerability can lead to early treatment discontinuation. The addition of PI to PegIFN/RBV is associated with an increased incidence of adverse events, requiring discontinuation of the PI in 10-21% of patients. Commonly encountered adverse effects are :

❑ Anemia :

In clinical trials, significant anemia (hemoglobin < 10 g/dL) occurred nearly twice as frequently in triple therapy than dual therapy.

❑ Neutropenia :

Anti-HCV treatment-related neutropenia is more with BOC-based triple therapy than dual therapy. Initial management should consist of PegIFN dose reduction.

❑ Rash and skin reactions :

Mild-to-moderate rash occurred in more than half of the patients receiving TVR, with severe rash occurring in up to 7% of patients and requiring discontinuation of therapy in approximately 6%. Rash often developed within 1 month of TVR initiation and required 4-6 weeks after TVR discontinuation to resolve. Rashes were primarily eczematous, maculopapular or papular, lichenoid and pruritic. Mild to moderate rash can be treated with oral antihistamines and/or topical corticosteroids. Systemic steroids are contraindicated in combination with TVR. If rash become severe (> 50% of BSA), TVR should be stopped. All HCV therapy should be discontinued immediately for any rash associated with significant systemic symptoms, including evidence of internal organ involvement (e.g., hepatitis, nephritis), facial edema, mucous membrane erosions or ulceration, target lesions, epidermal detachment, vesicles or bullae. The patient should be promptly referred for urgent dermatological consultation.

❑ Anorectal features

Anorectal symptoms, such as, hemorrhoids, anorectal discomfort, anal pruritus, and rectal burning, were reported by approximately 25% of patients receiving TVR. These are usually mild to moderate in severity and rarely require treatment discontinuation. Symptomatic treatment with topical steroids or local anesthetic can be considered.

❑ Elevated uric acid levels

Elevated uric acid levels occurred in up to 73% of patients receiving TVR, with onset during the first 2 weeks of therapy. In patients receiving TVR, uric acid levels should be measured at baseline, at weeks 2, 4, 8, 12 and as clinically indicated. Treatment with allopurinol can be considered if uric acid level is > 10 mg/dl.

❑ Elevated bilirubin levels

Elevated bilirubin levels occurred more frequently in TVR-treated patients than those treated with PegIFN/RBV alone, but were not accompanied by liver dysfunction. The steepest increase in bilirubin occurred during the first 1-2 weeks of TVR therapy. In patients receiving TVR, bilirubin level should be measured at baseline, at weeks 2, 4, 8, 12 and as clinically indicated.

Monitoring of Therapy

Efficacy of anti-HCV therapy should be monitored which is based on repeated measurement of HCV RNA levels. The same assay, ideally from the same laboratory, should be used in each patient to measure HCV RNA at different time points, in order to assure consistency of results.

In dual therapy, HCV RNA levels should be assessed at baseline, week 4, week 12, week 24, end of treatment and 12 or 24 weeks after the end of therapy to assess the SVR. In triple therapy with BOC, HCV RNA should be measured at weeks 4, 8, 12, 24, end of treatment, and 12 or 24 weeks after the end of therapy. In triple therapy with TVR, HCV RNA should be assessed at weeks 4, 12, 24, end of treatment, and 12 or 24 weeks after the end of therapy. Based on HCV RNA level after initiation of treatment, the responses may be divided as follows:

- ❑ The rapid virological response (RVR) is defined as an undetectable HCV RNA at week 4 of therapy.
- ❑ The early virological response (EVR) is defined as an undetectable HCV RNA, which is at week 12 of therapy.
- ❑ The delayed virological response (DVR) is defined as a more than 2 log₁₀ drop with detectable HCV RNA at week 12 and undetectable HCV RNA at week 24.

In dual therapy, treatment should be stopped at week 12 if the HCV RNA decrement is less than 2 log₁₀ IU/ml as SVR rate achieved by treatment continuation in these is less than 2%. In patients with detectable HCV RNA at week 24, there is a very small chance of SVR (1-3%). In triple therapy with BOC, all drugs should be stopped if HCV RNA is > 100 IU/ml at treatment week 12 and if HCV RNA is detectable at treatment week 24. In TVR-based regimens all drugs should be stopped if HCV RNA > 1000 IU/ml at week 4 or 12 of therapy.

Measures to Improve Treatment Success Rate

Success of anti-HCV treatment depends on some factors. Some measures are shown to improve treatment success with significantly higher SVR rates. These are :

❑ Treatment adherence :

Full adherence to both PegIFN- α and ribavirin is associated with improved SVR rates. Adherence to HCV therapy has been defined as receipt of $\geq 80\%$ of scheduled PegIFN/RBV doses for $\geq 80\%$ of the treatment period. Before starting antiviral therapy, patients must be instructed about the schedule and side-effects to be expected during treatment. Patients should also be instructed about the preventive and therapeutic measures to ameliorate these side-effects. The key element of effective HCV clinical management is access to a multidisciplinary team. HCV infected patients should be counseled for the importance of adherence for attaining an SVR.

❑ Correction of co-factors :

High body weight (BMI) adversely influences the response to dual therapy, even after dose adjustments. So, body weight reduction prior to therapy is recommended. The HCV life cycle is tightly linked to lipid metabolism.

Thus, some cholesterol lowering drugs have been shown to inhibit HCV replication and may improve response rate to treatment. Alcohol consumption has a negative impact on treatment adherence. So, patients should therefore be advised to stop or to reduce alcohol consumption. Insulin resistance and type 2 diabetes mellitus, independently of their pathogenesis, accelerate progression of liver disease and increase the risk for the development of HCC. They also reduce response to the standard combination of Peg IFN/RBV. HCV infection per se does not carry an increased risk of metabolic syndrome, but it is able to perturb glucose homeostasis. HCV may also cause hepatic steatosis. So, both lifestyle and pharmacological measures are warranted in chronic hepatitis C with metabolic alterations.

□ Supportive therapy :

Anemia with anti-HCV therapy is common and more profound during PI-based triple therapy than dual therapy. In anemia due to dual therapy, hematological growth factors are helpful. In anemia due to triple therapy, ribavirin dose reduction should be the initial response as this does not influence SVR rate. If this does not improve hemoglobin level, hematological growth factor should be administered. Recombinant erythropoietin can be used to maintain or to improve hemoglobin levels. It can be administered when hemoglobin level is below 10 g/dL and titrated thereafter into maintenance hemoglobin levels between 10 and 12 g/dL. Administration of granulocyte colony stimulating factor (G-CSF) may enable patients to remain on or resume optimal anti-HCV therapy in neutropenia during therapy.

Treatment discontinuation rates due to thrombocytopenia are rare and patients with low platelet counts can generally be initiated on dual therapy without an increase in major bleeding episodes. Thrombopoietin receptor agonists (romiplostin, eltrombopag) can raise blood platelet levels. Portal vein thrombosis is a potential and feared complications of raised platelet count in this setting, particularly in patients with advanced cirrhosis.

Depression has a severe adverse impact on health-related quality of life during dual therapy and is a frequent reason for treatment discontinuation. Patients with a history and/or signs of depression should be seen by a psychiatrist before therapy initiation. Antidepressant therapy should be initiated during antiviral therapy if felt appropriate and follow-up is required to decide whether IFN treatment interruption is needed. There is conflicting data about the use of prophylactic antidepressants. SSRI or SNRI work best in this condition. Sleep deprivation should be treated with anxiolytics. Many patients have co-morbid medical and psychiatric conditions, which may affect their adherence to antiviral therapy or worsen while on antiviral therapy.

Post-treatment Follow-up After Successful Treatment

Non-cirrhotic patients who achieve an SVR should be retested for HCV RNA at 48 weeks post-treatment. If HCV RNA is still not detected, the infection can be considered as definitely eradicated and HCV RNA need not be retested. As hypothyroidism may occur after stopping therapy, TSH levels should be assessed 1 and 2 years after treatment. Patients with pre-existing co-factors of liver disease (e.g. alcohol intake, type 2 diabetes mellitus) should be carefully and

periodically assessed. Cirrhotic patients who achieve an SVR should remain under surveillance for HCC every 6 months by ultrasonography and for esophageal varices by endoscopy if they were present at pre-treatment endoscopy.

There remains some concern that re-infection due to recurrent or persistent risk behavior may negate the potential benefit of treatment. Reported rates of re-infection following successful HCV treatment among patients at high risk, such as PWID, have been found which estimates of 1-5% risk per year. So, monitoring for HCV re-infection through annual HCV RNA assessment should be undertaken on PWID with ongoing risk behavior.

Retreatment of Non-SVR to PegIFN and Ribavirin

There are substantial number of patients with genotype 1 hepatitis C virus who have had previous therapy with standard dual therapy but have not achieved an SVR. These patients can broadly be divided into three groups according to the pattern of response and virological failure during dual therapy.

These divisions are :

- Virological relapse : Patients who have undetectable HCV RNA at the end of treatment, but do not achieve an SVR.
- Virological partial response : Patients who have a > 2 log IU/ml drop in HCV RNA by 12 weeks of treatment, but never achieve undetectable HCV RNA.
- Virological null response : patients who have a < 2 log IU/ml drop in HCV RNA by 12 weeks of treatment.

For HCV genotype 1 patients who have previously had virological failure with dual therapy, there is a significant benefit in retreatment by PI-containing triple therapy. Patients with cirrhosis and prior null responders have a lower chance of cure and should not be treated with response-guided therapy with PI. Patients infected with HCV genotypes other than 1 and who failed on prior therapy with non-pegylated IFN- α , with or without ribavirin, can be re-treated with PegIFN/RBV dual therapy.

Treatment of Patients with Severe Liver Disease

□ Hepatic cirrhosis :

Antiviral therapy is strongly indicated in patients with conserved liver function (Child-Pugh A). In patients with Child-Pugh B cirrhosis, antiviral therapy may be offered on an individual basis in experienced centers. Patients with Child-Pugh C cirrhosis should not be treated with IFN- α -based regimens, due to a high risk of life-threatening complications. Several large cohort studies and meta-analyses have shown that an SVR in patients with advanced fibrosis is associated with a significant decrease of the incidence of clinical decompensation. The SVR rates with both the dual or triple therapy are lower in patients with advanced fibrosis or cirrhosis than in patients with mild to moderate fibrosis.

A significant rate of side-effects are seen during treatment of cirrhotic patients with PI-containing regimens, especially those with a platelet count < 100,000/mm³ and serum albumin levels < 3.5 g/dL at baseline.

There is no role for current triple therapy with decompensated liver disease. Irrespective of the achievement of an SVR, patients with cirrhosis should undergo regular surveillance for the occurrence of HCC and for portal hypertension, as the risk of complications is decreased but not abolished when HCV infection has been eradicated.

❑ **Patients with an indication for liver transplantation :**

Liver transplantation is the treatment of choice for patients with end-stage liver disease. Hepatitis C recurrence due to graft re-infection is universal after transplantation. Antiviral therapy in patients awaiting transplantation prevents graft re-infection if SVR is achieved.

❑ **Post-liver transplantation recurrence :**

Recurrence of HCV infection is universal in patients with detectable HCV RNA at the time of liver transplantation. The course of HCV-related liver disease is accelerated in liver transplant recipients and approximately one third of them develop cirrhosis within 5 years following transplantation. Successful anti-HCV therapy has been shown to have a positive impact on both graft and patient survival. Patients with post-transplant recurrence of HCV infection should be considered for therapy once chronic hepatitis is established and histologically proven. The presence of significant fibrosis or portal hypertension one year after transplantation is predictive of rapid disease progression and graft loss, and urgently indicates antiviral treatment. With dual therapy, the likelihood of an SVR in the post-transplant patients is in the order of 30% overall. PIs are potent inhibitors of hepatic cytochrome P450 3A4, the main enzyme responsible for tacrolimus and cyclosporine metabolism. Thus, commencement of a PI-containing regimen requires an immediate and profound dose reduction of these immunosuppressive drugs.

Treatment of Hepatitis C in Special Groups

❑ **HIV co-infection :**

Progression of liver disease is accelerated in patients with HIV-HCV co-infection, in particular for those with a low CD4+ cell count and impaired immune function. For this reason, early antiretroviral therapy should be considered in patients with HIV-HCV coinfection. CD4+ cell count should be improved using highly active antiretroviral therapy (HAART) prior to commencing anti-HCV treatment. During PegIFN/RBV therapy, use of stavudine, zidovudine and didanosine should be avoided. Recently published data do not contraindicate the use of abacavir with ribavirin. Liver disease severity should be assessed prior to therapy by means of a liver biopsy or by non-invasive assessment (serological tests). Published data do not clearly define the preferred dose of ribavirin and the optimal duration of treatment. Fixed dose 800 mg/day or weight-based ribavirin may be used. The duration of treatment should be adjusted with virological responses at weeks 4 and 12. For patients with serum HCV RNA negativity at 4 weeks, a 24 week duration of therapy may be sufficient. For those who achieve an EVR, but not RVR, 48 weeks duration is recommended regardless of HCV genotypes.

HIV-positive patients who are infected with HCV genotypes 1 should be treated with anti-HCV triple therapy including PegIFN, ribavirin and TVR/BOC. Permitted HIV antivirals included neocleoside analogues, efavirenz, raltegravir and selected ritonavir-boosted HIV protease inhibitors. Acute HCV in HIV-infected individuals should be treated with dual therapy.

❑ **HBV co-infection :**

In patients with HCV-HBV co-infection, the HBV DNA level is often low or undetectable although it may fluctuate widely, and HCV is usually the main driver of chronic hepatitis activity. Hepatitis delta virus infection should also be sought. When HCV is replicating and causes liver disease, it should be treated with PegIFN/RBV following the same rules as applied to mono-infection. There is potential risk of HBV reactivation during or after HCV clearance. In that case or if HBV replication is detectable at a significant level, concurrent HBV nucleoside/nucleotide analogue therapy may be indicated. There is no information on the use of PI based triple therapy in this population of patients, though HCV-PIs should be used for treatment of patients who are co-infected by HBV and HCV genotype 1.

❑ **Hemodialysis patients :**

HCV infection is prevalent in the hemodialysis patients and is associated with an increased risk of all-cause and liver-related mortality. Cardiovascular disease remains the main cause of death in dialysis patients irrespective of HCV status. PegIFN- α 2a at the dose of 135 μ g/week in this setting can be used and may be associated with improved SVR rates. Combination treatment with PegIFN/RBV can be considered by experienced physicians. A recently presented study in 36 hemodialysis patients with HCV genotype 1 showed that PI-based triple therapy had superior efficacy than PegIFN/RBV dual therapy but the 1st was associated with more anemia.

❑ **Non-hepatic solid organ transplant recipients**

HCV positivity is associated with impaired renal graft and increased all-cause and liver-related mortality. HCV-related glomerular disease and increased risk of diabetes will affect graft outcome. HCV-associated liver damage may be accelerated by immunosuppression, and IFN- α may precipitate renal graft rejection. Assessment of liver fibrosis stage in all HCV-positive renal transplant candidates is advisable as cirrhosis is an important predictor of poor post-transplant survival. Treatment of chronic HCV infection with PegIFN/RBV in kidney transplant recipients is associated with a risk of acute or chronic graft rejection of 30% or more, resulting in graft loss and reduced patient survival. HCV treatment before kidney transplant may avoid liver-related mortality in the post-transplant patient and may prevent HCV-specific causes of renal graft dysfunction. For patients with established cirrhosis who fail HCV antiviral treatment, isolated renal transplantation is contraindicated and consideration should be given to combined liver and kidney transplantation.

Data on HCV infection after heart transplantation are scarce and controversial. International guidelines list chronic HCV infection as a contraindication to lung transplantation. No data are available on the impact of HCV infection and its treatment after pancreas or small bowel transplantation.

❑ **Active drug addicts :**

The prevalence of HCV among PWID is ~65% and >80% among long-term PWID. HCV genotypes 1a, 1b & 3a are common among PWID, while 4d is common in Europe and 6 in Southeast Asia.

Factors associated with HCV among PWID include female gender, ethnicity, unstable housing, frequent use of injecting cocaine, imprisonment, injecting networks and sharing injecting equipments.

No liver toxicity is reported for heroin or methadone. Buprenorphine occasionally increases transaminases. Daily cannabis use may be associated with more advanced liver fibrosis. Heavy alcohol consumption is associated with a higher risk of cirrhosis. Tobacco smoking may increase inflammation and fibrosis progression.

HCV treatment can be considered for PWID, provided they wish to receive treatment and are able and willing to maintain regular appointments. Implementation of HCV treatment for PWID could reduce transmission. There are some factors for low adherence of treatment such as frequent drug use during therapy, history of psychiatric disease, low educational level, unstable housing, poor social functioning, older age, minor ethnicity, co-morbid medical disease, advanced liver disease etc. But recent drug use at treatment initiation or occasional drug use during treatment do not seem to impact adherence, treatment completion or SVR. In adherent patients, alcohol use has no negative impact on SVR. Midazolam, alprazolam, sertraline, mirtazapine, heroin, methadone show important drug-interaction with PIs (more with telaprevir). Escitalopram, zolpidem, olanzapine, fluoxetine, paroxetine are considered without significant side-effects. Amphetamine, barbiturates and ecstasy should also be avoided as overdose of these agents may be fatal due to hyperthermia, cardiac arrhythmia or liver failure.

□ Hemoglobinopathies :

Thalassemia major is frequently associated with hepatitis C as the condition requires blood transfusion. Though transmission of HCV by blood and blood products are rare in developed countries now-a-days, cases are prevalent in countries where screening of donated blood is suboptimal. Chronic HCV infection is also frequent in individuals with sickle cell anemia. These patients can be treated with Peg-IFN/RBV dual therapy with higher incidence of anemia. Growth factors and blood transfusions are sometimes needed to treat anemia.

Follow-up of Untreated Patients and of Patients with Treatment Failure

Untreated patients with chronic hepatitis C and those who failed to respond to previous treatment should be regularly followed. The reason(s) should be clearly documented. For patients who have failed prior treatment with Peg IFN/RBV or PI-based triple therapy, the pattern of virological response and failure should be carefully documented. Previous guidelines recommended performing a liver biopsy every 3 to 5 years. With non-invasive methods, more frequent screening can be performed. Thus, untreated patients should be assessed every 1 to 2 years with a noninvasive method. Patients with cirrhosis should undergo specific screening for hepatocellular carcinoma every 6 months.

Treatment of Acute Hepatitis C

Most patients with acute hepatitis C are asymptomatic, but a high rate of chronic infection is expected (50-90%). Symptomatic disease, female gender, a young age and genetic polymorphisms in IL28B have been associated with spontaneous viral clearance but none of these parameters accurately predicts spontaneous resolution at the individual level.

Patients with acute hepatitis C should be considered for antiviral therapy in order to prevent progression to chronic hepatitis. High SVR rates (> 90%) have been reported with PegIFN- α 2a at the dose

of 180 μ g/ week or IFN- α 2b at the dose of 1.5 μ g/kg/week monotherapy in series of symptomatic patients, regardless of the HIV genotype. Combination therapy with ribavirin does not increase the SVR rate in this setting, but may be considered during treatment in patients with slow response and other negative predictors of treatment response. No data are available on the use of triple therapy in this group. The ideal time point for starting therapy has not been firmly established. Some clinicians suggest that the onset of ALT elevation, with or without clinical symptoms, may be the ideal time point for treatment. It has also been suggested that patients should be followed with 4-weekly HCV RNA quantification and that only those who remain HCV positive at 12 weeks from onset should be treated. Treatment duration should be of 24 weeks. Patients who fail to achieve an SVR with this regimen may be retreated for 48 weeks, with or without ribavirin at the usual doses. For those with genotype 1 infection who fail to respond to IFN- α mono-therapy, PI-based triple could be considered. There is currently no indication for administering IFN- α as post-exposure prophylaxis in the absence of documented HCV transmission.

Perspective of New and Emerging Treatments

The two protease inhibitors, Boceprevir and Telaprevir, have changed but not transformed the management of chronic HCV infection. But the outcome of triple therapy involving PI remains dependent on the interferon, sensitivity of the patients and viral genotype. Side-effects of triple therapy are significant, particularly in patients with cirrhosis. Clinical trials of drug combinations, including IFNfree regimens are going on. It is optimism that emerging antiviral drugs will treat all HCV genotypes, with cure for the majority and with few side-effects in short duration therapy. It is a realistic expectation as there are some shortcomings of currently used dual and triple therapy. It also seems likely that there will be a steady flow of drugs in future, but many of which will have little exposure to the difficult-to-treat groups with cirrhosis, liver failure, renal failure or HIV con-infection and other form of immunosuppression. Clinicians need to acquire the appropriate expertise, develop an appropriate service for delivery and guarantee adequate and proportionate funding to manage the cohort. Failure to deliver on any of these aspects will limit the recent and ongoing developments in drug development against HCV.

Prevention of Hepatitis C

No vaccine is available to prevent HCV infection, nor does immune globulin provide protection. Before traveling to a high risk areas, people should take precautions not to acquire the disease. Care must be taken during the use of medical, surgical, and dental equipment. Any instrument that has not been adequately sterilized or disinfected should not be used. Unsafe injection practices (such as reuse of disposable needles and syringes) must be avoided. Clinicians There are still a few areas of the world, such as parts of Asia and Africa, where blood donors may not be screened for HCV. So, all blood and blood products are needed to be screened adequately before transfusion.

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Acute abdomen is very common and a clinical emergency. It denotes any sudden, spontaneous, non-traumatic abdominal condition that usually warrants immediate management including urgent abdominal surgery. This condition is usually manifested by sudden onset of abdominal pain, gastrointestinal symptoms and varying degrees of local and systemic reactions. There are few specific tests or examinations which may be relied upon to give clear-cut answers as to the exact cause of the acute condition. But the diagnosis can be reached by accurate and detailed history, a careful physical examination and some selected investigations. Any changes of the patient's clinical feature during gathering the evidences should be evaluated carefully.

Etiology

Acute abdomen may arise from a large number of pathological conditions. These conditions can be broadly divided into inflammatory, mechanical, vascular and some other conditions.

<p>A. Inflammatory conditions :</p> <ul style="list-style-type: none"> ❑ Acute appendicitis ❑ Acute pancreatitis ❑ Acute cholecystitis ❑ Acute pyelonephritis ❑ Meckel's diverticulitis ❑ Perforated peptic ulcer ❑ Peritonitis ❑ Acute diverticulitis ❑ Pelvic inflammatory disease 	<p>B. Mechanical conditions:</p> <ul style="list-style-type: none"> ❑ Paralytic ileus ❑ Volvulus ❑ Intussusception ❑ Obstructed and strangulated hernia ❑ Acute renal colic ❑ Acute ureteric colic ❑ Acute retention of urine ❑ Testicular torsion ❑ Malrotation of gut in neonates ❑ Duodenal atresia ❑ Meconium ileus ❑ Massive worm infestation in children
<p>C. Vascular conditions :</p> <ul style="list-style-type: none"> ❑ Acute gastrointestinal hemorrhage ❑ Mesenteric infarction ❑ Abdominal aortic aneurysm 	<p>D. Other conditions:</p> <ul style="list-style-type: none"> ❑ Ectopic pregnancy ❑ Acute myocardial infarction ❑ Lower lobe pneumonia ❑ Sickle cell crisis ❑ Inflammatory bowel disease ❑ Hepatitis ❑ Enteric fever ❑ Acute intermittent porphyria ❑ Placenta percreta ❑ Phytobezoar

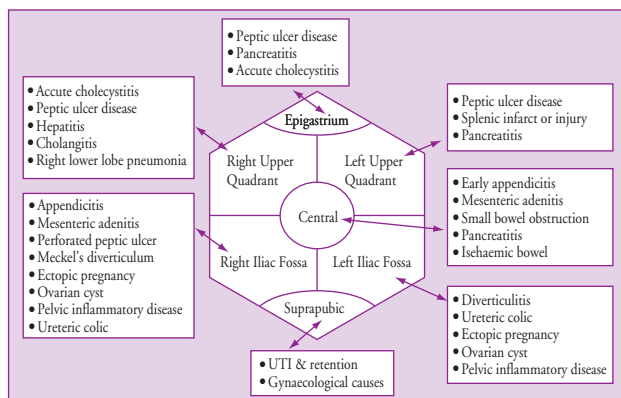


Figure: Acute abdominal conditions

Pathophysiology of Some Acute Abdominal Conditions

Acute Appendicitis

Inflammation in the appendix has the same features and follows the same course as inflammation elsewhere in the gut. The essential element causing inflammation of the wall of the appendix is invasion by bacteria. The usual organisms in the inflamed appendix are colon bacilli and streptococci. The earliest lesion is a superficial ulceration of the mucosa. Spread then occurs from the mucosa to the muscle layers and the serosa and the lumen may become filled with pus. Obstruction of the lumen is the subsequent pathological features. Interference with circulation leads to areas of necrosis and perforation of the appendix, with spread of infection to the peritoneal cavity. If the infection becomes walled off around the appendix, a localized abscess may result, otherwise a generalized peritonitis is the feature.

Acute Cholecystitis

Inflammation of the wall of the gall bladder occurs due to chemical damage from the action of concentrated bile, promoted by an obstruction of the cystic duct. Bacterial infection with streptococci or colon bacilli may supervene. The mucosa shows areas of ulceration and necrosis and leukocytes are present in the wall. Pus may fill the cavity, with an empyema of the gall bladder. Necrosis and rupture may occur.

Acute Small Intestinal Obstruction

Acute obstruction of the small bowel in adults is caused most commonly either by incarcerated hernia or by post-operative paralytic ileus. Post-operative adhesions within the peritoneal cavities may also cause acute small bowel obstruction. In newborns, congenital problems such as atresia and meconium ileus are important causes of obstruction. In young children, intussusception is encountered with frequency. Pain is usually sudden in onset, severe, and spasmodic in nature because it results from vigorous peristaltic activity of the bowel as it attempts to propel the intestinal contents through the site of obstruction. Vomiting occurs early in high intestinal obstruction and is copious in amount containing gastric contents, followed by small intestinal contents, usually bile colored. If persistent vomiting occurs, and if the obstruction is in the lower part of the small bowel, the vomitus becomes fecal in character. In children with intussusception, this fecal material contains bloody mucus which gives it the characteristic "red currant jelly" appearance.

Perforated Duodenal Ulcer

Perforation of a duodenal ulcer is one of the important causes of the development of sudden severe abdominal pain. Typical history involves a male usually between 20 and 40 years of age who has a history of episodes of epigastric distress relieved by milk and antacids. The episode of perforation is usually dramatic, with sudden, severe mid-epigastric pain which spreads rapidly to involve the entire abdomen. The pain is so severe and prostrating that the patient may faint.

Peritonitis

The peritoneal cavity, lined by serous peritoneal membranes which cover the viscera and the parietal walls, is a closed sac except for the openings of the fallopian tubes in the female.

General inflammation of the peritoneal cavity is usually caused by bacterial invasion, which may result by spread: 1) from a ruptured viscus such as a perforated peptic ulcer or gangrenous appendix; 2) through an ischemic and necrotic but unruptured bowel wall, as in strangulated hernia, mesenteric occlusion or volvulus; or 3) as a result of extension of infection from abdominal organs such as on liver abscess or pelvic inflammatory disease. The majority of cases of peritonitis involve organisms found in the normal flora of the gastrointestinal tract. Perforation of a hollow viscus is most frequently the source of entry of these organisms. The peritoneal infection may become walled off and limited to a localized area as in an appendiceal abscess, or there may be generalized peritonitis, which may be a serious and life-threatening condition.

Acute Pancreatitis

Acute pancreatitis may be difficult to distinguish from a perforated ulcer. Many patients with pancreatitis have either a history of alcoholism or gallstone disease. The onset of pancreatitis is more gradual and is often associated with prodromal episodes of epigastric distress 2-3 weeks before the onset of the severe pain which is constant, epigastric in location and radiates to the back.

Rupture Abdominal Aortic Aneurysm

Rupture of the abdominal aortic aneurysm may produce sudden severe prostrating pain, but the picture of blood loss and shock predominates quickly, suggesting the true nature of the catastrophe which may be rapidly fatal.

Acute Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) comprises a spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, tubo-ovarian abscess and pelvic peritonitis. It is common in sexually active young women. Sexually transmitted organisms, especially *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, are implicated in many cases. However, microorganisms that comprise the vaginal flora (e.g., anaerobes, *Gardnerella vaginalis*, *Haemophilus influenzae*, enteric Gram-negative rods, and *Streptococcus agalactiae*) also have been associated with PID. In addition, cytomegalovirus, *Mycoplasma hominis*, *Ureaplasma urealyticum* and *Mycoplasma genitalium* might be associated with some cases of PID. All women who have acute PID should be tested for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* and should be screened for HIV infection. A diagnosis of acute PID is difficult to diagnose because of the wide variation in the symptoms and signs and many women with PID have subtle or mild symptoms. Many episodes of PID go unrecognized. PID should be differentiated from other common causes of lower abdominal pain (e.g., acute appendicitis, acute cystitis, ectopic pregnancy, and functional pain). Pelvic examination may reveal uterine or adnexal tenderness. Examination of endocervical discharge may reveal excess leukocytes and microorganisms. Systemic features are common. ESR and CRP are usually elevated. Transvaginal sonography or magnetic resonance imaging techniques may show thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex. Doppler studies may suggest pelvic infection (e.g., tubal hyperemia).

Acute Ectopic Pregnancy

An ectopic pregnancy is one that occurs anywhere outside the uterus. By far the most common place for ectopic pregnancy is the Fallopian tubes. Fertility treatments and intrauterine contraceptive devices (IUCDs) are the most important associated risk factors. Pelvic inflammatory disease may cause complete tubal occlusion or delay the transport of the embryo so that implantation occurs in the tube. Adhesions from infection and inflammation from endometriosis may play a part. Right-sided tubal pregnancy is more common than left-sided. This is thought to be from spread of infection from appendicitis. Where an IUCD or progestogen-only oral contraceptives, including emergency contraception fails, the risk of a pregnancy being ectopic is greater than with other forms of contraception. 30% of ectopic pregnancies present before a period has been missed. Symptoms and signs of ectopic pregnancy can resemble those of other more common conditions, including urinary tract infections and gastrointestinal conditions. Most common symptoms are abdominal pain, pelvic pain, history of amenorrhea or missed period, vaginal bleeding (with or without clot). Other symptoms may be dizziness, faintness, syncope, hypotension, tachycardia, passage of tissues. There may be a history of a previous ectopic pregnancy. Acute ectopic pregnancy must be differentiated from incomplete abortion. In the latter condition, vaginal bleeding is the predominant feature and pain may come later as the cervix dilates. In ectopic pregnancy, pain usually comes first and if vaginal bleeding occurs it is of much less significance.

Clinical Features

Clinical features of acute abdomen vary depending up on the underlying pathophysiological process.



Figure: "Red Currant Jelly" stool in intussusception

- ❑ Acute abdominal pain is the dominant feature in most of the cases. This pain is usually severe. It may be localized (duodenal point tenderness in peptic ulcer or MaBurney's point tenderness in appendicitis) or generalized e.g., in peritonitis. Radiation of pain to other sites may also occur e.g., to the back in acute pancreatitis and to the groin in ureteric colic.
- ❑ Muscle guarding is also common in association with pain
- ❑ Nausea and vomiting are also common; hematemesis in gastrointestinal bleeding

- ❑ Systemic features e.g., fever, hypotension, tachycardia, tachypnoea, headache
- ❑ Diarrhea may occur; constipation is also a feature in some cases
- ❑ Abdominal distension in obstruction
- ❑ Absent bowel sound in obstruction
- ❑ Some specific signs in different condition e.g., positive Murphy's sign in acute cholecystitis, rebound tenderness in acute appendicitis etc.

Red Flags that Raise Suspicion of Serious Pathology

- ❑ Hypotension
- ❑ Confusion/impaired consciousness.
- ❑ Signs of shock
- ❑ Signs of dehydration
- ❑ Rigid abdomen.
- ❑ Patient lying very still or writhing

Initial Assessment

- ❑ A detailed history such as demographic details, occupation, medication history, previous medical history, history of previous surgery, obstetrical & gynecological history and other relevant history depending up on the presenting condition.
- ❑ Initial physical examination is also very important to assess the patient and to reach the diagnosis. General physical examination should include observation of the patient's outlook, pulse, blood pressure, respiratory rate and pattern, temperature, anemia, hydration status, GCS if altered consciousness etc.
- ❑ Abdominal examination should be in detail. Inspection of abdomen may reveal some clues e.g., Cullen sign, Grey Turner sign etc. Auscultation of abdomen may reveal absent bowel sound (in paralytic ileus, generalized peritonitis or intestinal obstruction), high-pitched and tinkling bowel sounds suggest sub-acute intestinal obstruction. Abdominal and iliac bruits may be found in abdominal aortic aneurysm. Abdominal palpation should be started gently away from the pain, then deep palpation towards the site of pain. Any tenderness, mass, enlarged organ, muscle guarding should be identified if present. Hernial orifices and external genitalia must be examined. Regional lymph nodes should also be palpated for evidence of enlargement. Patients who display tenderness to percussion are likely to have generalized peritonitis.
- ❑ Rectal or pelvic examination may be performed when needed.
- ❑ Examination of other systems may be needed when relevant

Initial Investigations

This is mainly relevant to patients being assessed in emergency departments or secondary care. Many tests are non-specific and must be interpreted in the clinical context and with appropriate medical/surgical expertise. Some tests may reveal the underlying pathology.

- ❑ Tests on blood may include full blood counts, urea & electrolytes, liver enzymes, serum amylase and lipase, random plasma glucose, serum calcium, coagulation screening etc.
- ❑ Blood grouping and cross-matching
- ❑ Blood culture

- ❑ Pregnancy test in women of childrenbearing age
- ❑ Urine routine examination
- ❑ Radiology may include abdominal X-ray (erect posture AP view or if not possible supine posture lateral view), chest X-ray PA view, abdominal and pelvic ultrasonogram. CT scan and MRI may be required rarely.
- ❑ ECG and cardiac enzymes should be checked in relevant conditions

Management

Acute abdomen requires urgent management. This usually includes symptomatic and supportive measures as well as specific measures.

Symptomatic and supportive measures :

- ❑ Patients should be kept at rest
- ❑ Patient should not be allowed to eat or drink
- ❑ Oxygen therapy if the patient is in shock
- ❑ Intravenous fluid and electrolytes should be given; blood transfusion may be required in some cases
- ❑ Naso-gastric tube insertion for gastric decompression may be needed in case of obstruction
- ❑ Analgesics, usually in the form of injection should be given to relieve pain
- ❑ Antispasmodics are used if there is colicky pain
- ❑ Antiemetic injections for vomiting are necessary in many conditions

Specific measures :

Specific measures for acute abdomen depend up on the underlying condition. Some conditions can be treated conservatively with symptomatic-supportive measures plus broad spectrum antibiotics. These conditions include acute cholecystitis, acute pancreatitis, acute pyelonephritis, acute pelvic inflammatory disease etc. Some conditions require emergency surgical intervention e.g., acute appendicitis, perforation of abdominal viscus, acute ectopic pregnancy, obstructed hernia, large gut volvulus etc. Appropriate reviews from Gynecologist may be sometimes needed e.g., in acute ectopic pregnancy or tuboovarian abscess.

Acute Abdomen in Older Patients

Acute abdomen usually shows less specific symptoms and signs in this group of patients. Morbidity and mortality in older patients presenting with acute abdomen is high. Aortic aneurysm and bowel ischemia are more prevalent in the elderly. Angiodysplasia of the colon is more common and can cause lower gastrointestinal hemorrhage. Medical causes of abdominal pain are encountered more frequently. The 'Top 5' medical causes of an acute abdomen to consider in older patients are inferior myocardial infarction, lower lobe pneumonia, diabetic ketoacidosis or hyperosmolar nonketotic coma, pyelonephritis and inflammatory bowel disease. Biliary tract disease, including cholecystitis, is the most common indication for surgery in older patients with abdominal pain.

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- [www.ece.ncsu.edu/acute abdomen](http://www.ece.ncsu.edu/acute%20abdomen)
- www.cdc.gov

Wilson disease is an autosomal recessive genetic disorder in which copper accumulates in tissues; This manifests as neurological or psychiatric symptoms and liver disease. The condition is due to mutations in the Wilson disease protein (ATP7B) gene. A single abnormal copy of the gene is present in 1 in 100 people who do not develop any symptoms (they are carriers). Symptoms usually appear between the ages of 6 and 20 years, but cases in much older people have been described. It is named after Samuel Alexander Kinnier Wilson (1878–1937), the British neurologist who first described the condition in 1912.

Epidemiology

The worldwide prevalence of Wilson disease is estimated 1 in 30,000 with a gene frequency of 0.56% and a carrier frequency of 1 in 90. A Slavic type has a late age of onset predominantly with neurological features. There is a juvenile type, which occurs in Western Europeans and several other ethnic groups. This has onset before age 16 years and mainly affects the liver. There is also a rare atypical type in which heterozygotes have only half the normal level of caeruloplasmin. The most common mutation in patients from Europe is H1069Q. A unique 15-bp deletion in the 5-prime region is frequent in Sardinia. M645R is common in Spain and R778L is often found in patients from eastern Asia.

Genetics

The condition is inherited in an autosomal recessive pattern. In order to inherit it, both of the parents of an individual must carry an affected gene. Most have no family history of the condition. People with only one abnormal gene may have mild, but medically insignificant, abnormalities of copper metabolism.

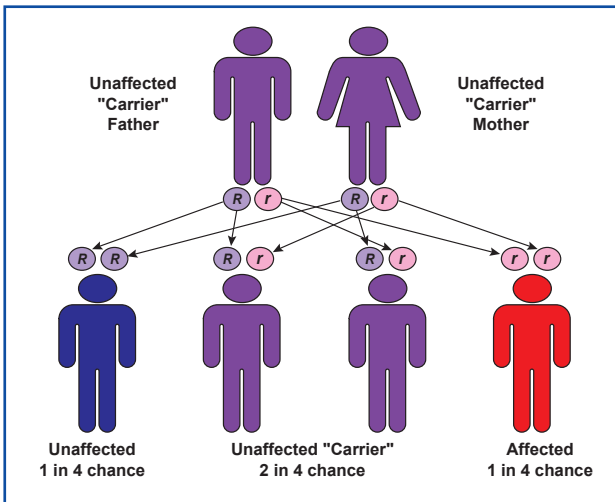


Figure : Wilson disease has an autosomal recessive pattern of inheritance

The Wilson disease gene (ATP7B) has been mapped to chromosome 13 (13q14.3) and is expressed primarily in the liver, kidney, and placenta. The gene codes for a P-type (cation transport enzyme) ATPase that transports copper into bile and incorporates it into ceruloplasmin. Mutations can be detected in 90%. Most (60%) are homozygous for ATP7B mutations and 30% have only one abnormal copy. 10% have no detectable mutation. About 300 mutations of ATP7B have been described.

A normal variation in the PRNP gene can modify the course of the disease by delaying the age of onset and affecting the type of symptoms that develop. This gene produces prion protein, which is active in the brain and other tissues and also appears to be involved in transporting copper. A role for the ApoE gene was initially suspected but could not be confirmed.

Pathophysiology

Copper is needed by the body for a number of functions, predominantly as a cofactor for a number of enzymes such as cytochrome oxidase, dopamine hydroxylase, superoxide dismutase and tyrosinase.

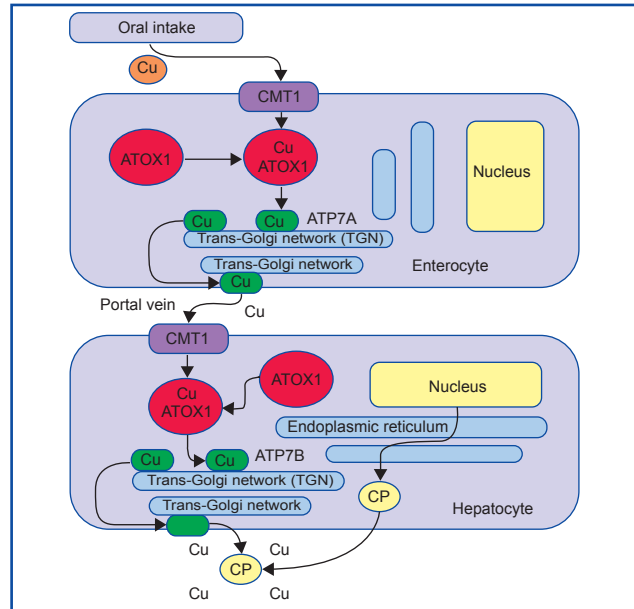


Figure : Normal absorption and distribution of copper. Cu = copper, CP = ceruloplasmin, green = ATP7B carrying copper.

Copper enters the body through the digestive tract. A transporter protein on the cells of the small bowel, copper membrane transporter 1 (CMT1), carries copper inside the cells, where some is bound to metallothionein and part is carried by ATOX1 to an organelle known as the trans-Golgi network. Here, in response to rising concentrations of copper, an enzyme called ATP7A releases copper into the portal vein to the liver. Liver cells also carry the CMT1 protein and metallothionein and ATOX1 bind it inside the cell, but here it is ATP7B that links copper to ceruloplasmin and releases it into the bloodstream, as well as removing excess copper by secreting it into bile. Both functions of ATP7B are impaired in Wilson disease. Copper accumulates in the liver tissue; ceruloplasmin is still secreted, but in a form that lacks copper (termed apoceruloplasmin) and is rapidly degraded in the bloodstream.

When the amount of copper in the liver overwhelms the proteins that normally bind it, it causes oxidative damage. This damage eventually leads to chronic active hepatitis, fibrosis and cirrhosis. The liver also releases copper into the bloodstream that is not bound to ceruloplasmin. This free copper precipitates throughout the body but particularly in the kidneys, eyes and brain. In the brain, most copper is deposited in the basal ganglia, particularly in the putamen and globus

participate in the coordination of movement as well as playing a significant role in neurocognitive processes such as the processing of stimuli and mood regulation. Damage to these areas produces the neuropsychiatric symptoms seen in Wilson disease.

It is not clear why Wilson disease causes hemolysis, but various lines of evidence suggest that high levels of free (non-ceruloplasmin bound) copper have a direct effect on either oxidation of hemoglobin, inhibition of energy-supplying enzymes in the red blood cell or direct damage to the cell membrane

Signs and Symptoms

The main sites of copper accumulation are the liver and the brain, and consequently liver disease and neuropsychiatric symptoms are the main features that lead to diagnosis. People with hepatic disease tend to come to medical attention earlier, generally as children or teenagers, than those with neurological and psychiatric symptoms, who tend to be in their twenties or older. Some are identified only because relatives have been diagnosed with Wilson disease.

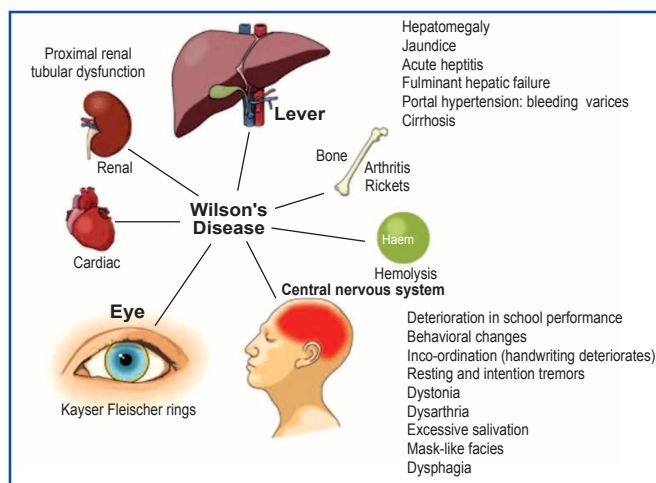


Figure: Organ-system involvement in Wilson diseases

Liver Disease

Liver disease may present itself as tiredness, increased bleeding tendency or confusion (due to hepatic encephalopathy) and portal hypertension. The latter leads to esophageal varices, (may bleed in a life-threatening fashion), as well as enlargement of the spleen and accumulation of fluid in the abdominal cavity.

On examination, signs of chronic liver disease such as spider angiomas (small distended blood vessels, usually on the chest) may be observed. Chronic active hepatitis causing cirrhosis of the liver also develop symptoms. While most people with cirrhosis have an increased risk of hepatocellular carcinoma, this risk is relatively very low in Wilson disease.

About 5% of all people are diagnosed only when they develop fulminant acute liver failure, often in the context of a hemolytic anemia. This leads to abnormalities in protein production (identified by deranged coagulation) and metabolism by the liver. The deranged metabolism leads to the accumulation of waste products such as ammonia in the bloodstream, causing hepatic encephalopathy (confusion, coma, seizures and finally life-threatening swelling of the brain).

Neuropsychiatric Symptoms

About half the people with Wilson disease have neurological or psychiatric symptoms. Most initially have mild cognitive deterioration and clumsiness, as well as changes in behavior. Specific neurological symptoms usually then follow, often in the form of Parkinsonism with or without a typical hand tremor, masked facial expressions, slurred speech, ataxia or dystonia. Seizures and migraine appear to be more common in Wilson disease. It is suggested that cognitive involvements in Wilson disease are related and closely linked to psychiatric manifestations of the disease. Psychiatric problems in Wilson disease may include behavioral changes, depression, anxiety and psychosis. Psychiatric symptoms are commonly seen in conjunction with neurological symptoms and are rarely manifested on their own.

Other Organ Systems

Medical conditions have been linked with copper accumulation in Wilson disease :

- **Eyes :** Kayser–Fleischer rings (KF rings), a pathognomonic sign, may be visible in the cornea of the eyes, either directly or on slit lamp examination as deposits of copper in a ring around the cornea. They do not occur in all people with Wilson disease. Wilson disease is also associated with sunflower cataracts exhibited by brown or green pigmentation of the anterior and posterior lens capsule. Neither cause significant visual loss.
- **Kidneys :** Renal tubular acidosis, a disorder of bicarbonate handling by the proximal tubules leads to nephrocalcinosis (calcium accumulation in the kidneys), a weakening of bones (due to calcium and phosphate loss), and occasionally aminoaciduria (loss of essential amino acids needed for protein synthesis).
- **Heart :** Cardiomyopathy is a rare but recognized problem in Wilson disease; it may lead to heart failure and cardiac arrhythmias.
- **Endocrine :** Hypoparathyroidism infertility and habitual abortion.

Diagnosis

Wilson disease may be suspected on the basis of any of the symptoms mentioned above or when a close relative has been known to have the disease. Most have slightly abnormal liver function tests such as a raised liver enzymes (ALT, AST) and bilirubin level. If the liver damage is significant, albumin may be decreased. The prothrombin time may be prolonged. Alkaline phosphatase levels are relatively low in those with Wilson -related acute liver failure. If there are neurological symptoms, magnetic resonance imaging (MRI) of the brain is usually performed; this shows hyperintensities in the part of the brain called the basal ganglia in the T2 setting. MRI may also demonstrate the characteristic "face of the giant panda" pattern.

There is no totally reliable test for Wilson disease, but levels of ceruloplasmin and copper in the blood, as well of the amount of copper excreted in urine during a 24-hour period, are together used to form an impression of the amount of copper in the body. Both serum ceruloplasmin and copper are reduced but urinary copper excretion is increased in Wilson disease. The gold standard or most ideal test is liver biopsy.

This is assessed microscopically for the degree of steatosis and cirrhosis. Histochemistry and quantification of copper are used to measure the severity of the copper accumulation. A level of 250 µg of copper per gram of dried liver tissue confirms Wilson disease.

In more advanced disease, the changes observed are quite similar to those seen in autoimmune hepatitis, such as infiltration by inflammatory cells, piecemeal necrosis and fibrosis. In advanced disease, finally, cirrhosis is the main finding. In acute liver failure, degeneration of the liver cells and collapse of the liver tissue architecture is seen, typically on a background of cirrhotic changes.

Genetic Testing

Mutation analysis of the ATP7B gene, as well as other genes linked to copper accumulation in the liver, may be performed. Once a mutation is confirmed, it is reasonable to screen family members for the presence of disease as part of clinical genetics family counseling.

Management

Dietary

In general, a diet low in copper-containing foods is recommended with the avoidance of mushrooms, nuts, chocolate, dried fruit, liver, and shellfish.

Medication

Medical treatments are available for Wilson disease. Some increase the removal of copper from the body, while others prevent the absorption of copper from the diet.

Generally, D-penicillamine is the first treatment used. This binds copper (chelation) and leads to excretion of copper in the urine. It is not without problems: about 20% patients experience a side effect or complication of D-penicillamine treatment, such as drug-induced lupus or myasthenia. In those who presented with neurological symptoms, almost half experience a paradoxical worsening of their symptoms. While this phenomenon is observed in other treatments for Wilson diseases, it is usually taken as an indication for discontinuing D-penicillamine and commencing second-line treatment such as trientine hydrochloride, which also has chelating properties. Some clinicians recommend trientine as first-line treatment, but experience with D-penicillamine is more extensive. A further agent with known activity in Wilson disease is tetrathiomolybdate. This is regarded as experimental, though some studies have shown a beneficial effect.

Once all results have returned to normal, zinc may be used instead of chelators to maintain stable copper levels in the body. Zinc stimulates metallothionein, a protein in gut cells that binds copper and prevents their absorption and transport to the liver. Zinc therapy is continued unless symptoms recur or if the urinary excretion of copper increases.

In rare cases where none of the oral treatments are effective, especially in severe neurological disease, dimercaprol (British anti-Lewisite) is occasionally necessary. This treatment is injected intramuscularly (into a muscle) every few weeks and has unpleasant side effects such as pain.

People who are asymptomatic (for instance, those diagnosed through family screening or only as a result of abnormal test results) are generally treated, as the copper accumulation may cause long-term damage in the future. It is unclear whether these people are best treated with D-penicillamine or zinc acetate.

Physical therapy

Physiotherapy is beneficial for patients with the neurologic form of the disease. The copper chelating treatment may take up to six months to start working and physical therapy can assist in coping with ataxia, dystonia and tremors, as well as preventing the development of contractures that can result from dystonia.

Transplantation

Liver transplantation is an effective cure for Wilson disease but is used only in particular cases because of the risks and complications associated with the procedure. It is used mainly in people with fulminant liver failure who fail to respond to medical treatment or in those with advanced chronic liver disease. Liver transplantation is avoided in severe neuropsychiatric illness, in which its benefit has not been demonstrated.

Pregnancy in Wilson Disease

Women with Wilson disease who become pregnant require anti-copper therapy during their pregnancy. The major goal of treatment is to protect the mother from copper toxicity while protecting the fetus from possible teratogenesis due to low copper levels. There is no contra-indication to pregnancy in women with Wilson disease in the maintenance phase of treatment except if liver function is poor. Treatment should not be stopped during pregnancy, although conversion to zinc treatment may be advantageous since D-penicillamine is classified as a teratogen.

Prognosis

Early initiation of treatment usually leads to a normal length and quality of life. Without treatment, Wilson disease is usually fatal, typically before the age of 40. Early treatment gives the best results and so, if there is a family history, screening may allow treatment to start in childhood before the onset of symptoms. Active treatment of early disease, as in children, may lead to some reversal of neurological signs. Both Kayser-Fleischer rings and sunflower cataracts are reversible with treatment. Only limited reversibility occurs with treatment of established hepatic and neurological disease but progression can be arrested. It is essential to educate the patient about the need for lifelong treatment as patients are often relaxed about taking medication when they feel well.

Reference:

1. <http://emedicine.medscape.com>
2. <http://en.wikipedia.org>
3. <http://www.patient.co.uk>

Vaccination is the administration of antigenic material to stimulate an individual's immune system to develop adaptive immunity to a pathogen. Vaccines can prevent or ameliorate morbidity from infections. The effectiveness of vaccination has been widely studied and verified. Widespread immunity due to vaccination is largely responsible for the worldwide eradication of smallpox and the restriction of diseases such as poliomyelitis, measles, and tetanus from much of the world. According to the World Health Organization reports, licensed vaccines are currently available to prevent or contribute to the prevention and control of, 25 vaccine-preventable infections.

History of Vaccine

The fascinating story of vaccination goes back all the way to ancient Greece. As long ago as 429 BC, the Greek historian Thucydides observed that those who survived the smallpox in Athens did not become re-infected with the disease. The Chinese were the first to discover and use a primitive form of vaccination, called variolation. It was carried out as early as the 10th century and particularly between the 14th and 17th centuries. The aim was to prevent smallpox by exposing healthy people to tissue from the scabs caused by the disease. Variolation eventually spread to Turkey and arrived in England in the early 18th century.

British physician, Dr Edward Jenner, discovered vaccination in 1796 in its modern form and proved to the scientific community that it worked. He is called the "Father of Immunology". Although vaccination was taken up enthusiastically by many, there was some violent opposition as it became more widespread in the 1870s. Louis Pasteur improved vaccination even more and developed a rabies vaccine in 1880s. As the science of immunology developed and scientists began to understand more about how diseases worked, other vaccines were created. German scientist Emil von Behring was awarded the first Nobel Prize in Medicine. Japanese physician and bacteriologist Shibasaburo Kitasato discovered the antitoxins of diphtheria and tetanus.

By the end of the 1920s, vaccines for diphtheria, tetanus, whooping cough and tuberculosis were all available. Vaccination spread across the globe and although these early vaccines were crude, they worked. The first vaccination program dramatically reduced the number of deaths from disease and they were crucial in establishing the concept of preventive public health measures. Polio vaccination was introduced in the UK in 1955 and it dramatically reduced the number of cases. Now-a-days, poliomyelitis is extremely rare and is close to being completely eliminated from the planet.

The first attempt to use the smallpox vaccine on a global scale began when the World Health Organization decided to try and eradicate smallpox across the world in 1956. Smallpox was declared as being eradicated in 1980. It was one of the most remarkable achievements in the history of medicine.

Professor Harald zur Hausen discovered that cervical cancer was caused by a virus, making it possible to develop a vaccine for the disease. This discovery led to the development of the HPV vaccine, which protects against cervical cancer and is available since 2008.

Mechanism of Action of Vaccine

Vaccines consist of microbial antigens and work by priming the immune system. After the administration of vaccines, the foreign antigens evoke immune response. The antigens that evoke this response are called immunogens. Immunogens can be administered in various ways such as, by intramuscular injections, subcutaneous injections, intra-dermal injection or by oral route. Stimulating immune response with an infectious agent is known as immunization. The immune response generated after vaccination or immunization is adaptive, highly specific and has memory. It protects the host from subsequent attack by organisms against which vaccination or immunization has been carried out. Thus, the vaccinated person becomes immunized. Immunization may be active i.e. administering immunogen to a person's body before the disease occurs. Passive immunization refers to administration of pre-formed antibodies to a person usually after contracting the infectious agents e.g., rabies immune globulin or hepatitis B immune globulin. The antibodies may be collected from hyper-immune human or animal sera.

Adjuvants and Preservatives

Vaccines typically contain one or more adjuvants, used to boost the immune response. Tetanus toxoid, for instance, is usually adsorbed onto alum. This presents the antigen in such a way as to produce a greater action than the simple aqueous tetanus toxoid. People who get an excessive reaction to adsorbed tetanus toxoid may be given the simple vaccine when time for a booster occurs.

In the preparation for the 1990 Gulf campaign, Pertussis vaccine (not acellular) was used as an adjuvant for Anthrax vaccine. This produces a more rapid immune response than giving only the Anthrax vaccine which is of some benefit if exposure might be imminent.

Vaccines may also contain preservatives to prevent contamination with bacteria or fungi. Until recent years, the preservative thimerosal was used in many vaccines that did not contain live virus. As of 2005, the only childhood vaccine in the U.S. that contains thimerosal in greater than trace amounts is the influenza vaccine, which is currently recommended only for children with certain risk factors. Single-dose Influenza vaccines supplied in the UK do not list Thiomersal (its UK name) in the ingredients. Preservatives may be used at various stages of production of vaccines, and the most sophisticated methods of measurement might detect traces of them in the finished product, as they may in the environment and population.

Types of Vaccines

Four main types are currently in clinical use :

1. *Inactivated vaccines :*

An inactivated vaccine consists of virus or bacteria that are grown in culture and then killed using a method such as heat or formaldehyde. Although the virus or bacteria particles are destroyed and cannot replicate, the virus capsid proteins or bacterial wall are intact enough to be recognized and remembered by the immune system to evoke a response. When manufactured correctly, the vaccine is not infectious, but improper inactivation can result in intact and infectious particles. Since the properly produced vaccine does not reproduce, booster doses are required periodically to reinforce the immune response.

2. Attenuated vaccine :

In an attenuated vaccine, live virus or bacteria with very low virulence are administered. They will replicate, but locally or very slowly. Since they do reproduce and continue to present antigen to the immune system beyond the initial vaccination, boosters may be required less often. These vaccines may be produced by passaging, for example, adapting a virus into different host cell cultures, such as in animals or at suboptimal temperatures, allowing selection of less virulent strains, or by mutagenesis or targeted deletions in genes required for virulence. There is a small risk of reversion to virulence, which is smaller in vaccines with deletions. Attenuated vaccines also cannot be used by immunocompromised individuals.



Figure: Vaccination in intramuscular route

3. Virus-like particle vaccines :

Virus-like particle vaccines consist of viral protein(s) derived from the structural proteins of a virus. These proteins can self-assemble into particles that resemble the virus from which they were derived but lack viral nucleic acid, meaning that they are not infectious. Because of their highly repetitive, multivalent structure, virus-like particles are typically more immunogenic than subunit vaccines. The human papillomavirus and Hepatitis B virus vaccines are two virus-like particle-based vaccines currently in clinical use.

4. Subunit vaccines :

A subunit vaccine presents an antigen to the immune system without introducing microbial agents whole or otherwise. One method of production involves isolation of a specific protein from a virus or bacterium (such as a bacterial toxin) and administering this. A weakness of this technique is that isolated proteins may have a different three-dimensional structure than the protein in its normal context, and will induce antibodies that may not recognize the infectious organism. In addition, subunit vaccines often elicit weaker antibody responses than the other classes of vaccines.

Vaccine-Preventable Diseases

A vaccine-preventable disease is an infectious disease for which an effective preventive vaccine exists. If a person acquires a vaccine-preventable disease and dies from it, the death is considered a vaccine-preventable death.

The most common and serious vaccine-preventable diseases tracked by the World Health Organization (WHO) are: diphtheria, *Haemophilus influenzae* serotype b (Hib) infection, hepatitis B, measles, meningitis, mumps, pertussis, poliomyelitis, rubella, tetanus, tuberculosis, and yellow fever.

List of Vaccine-Preventable Diseases

The WHO lists 25 diseases for which vaccines are available:

1. Anthrax	14. Pneumococcal disease
2. Measles	15. Typhoid fever
3. Rubella	16. Hepatitis E
4. Cholera	17. Poliomyelitis
5. Meningococcal disease	18. Tick-born encephalitis
6. Influenza	19. <i>Haemophilus influenzae</i> type b
7. Diphtheria	20. Rabies
8. Mumps	21. Varicella and herpes zoster (shingles)
9. Tetanus	22. Human papilloma-virus
10. Hepatitis A	23. Rotavirus gastroenteritis
11. Pertussis	24. Yellow fever
12. Tuberculosis	25. Japanese encephalitis
13. Hepatitis B	

Efficacy of Vaccines

In 2012, the World Health Organization estimated that vaccination prevents 2.5 million deaths each year. With 100% immunization, and 100% efficacy of the vaccines, one out of seven deaths among young children could be prevented, mostly in developing countries, making this an important global health issue. Four diseases were responsible for 98% of vaccine-preventable deaths: measles, meningitis by Hib, pertussis, and neonatal tetanus. The Immunization Surveillance, Assessment and Monitoring program of the WHO monitors and assesses the safety and effectiveness of program and efficacy of vaccines at reducing illness and deaths from diseases that could be prevented by vaccines.

Vaccine-preventable deaths are usually caused by a failure to obtain the vaccine in a timely manner. This may be due to financial constraints or to lack of access to the vaccine. A vaccine that is generally recommended may be medically inappropriate for a small number of people due to severe allergies or a damaged immune system. In addition, a vaccine against a given disease may not be recommended for general use in a given country, or may be recommended only to certain populations, such as young children or older adults. Every country makes its own immunization recommendations, based on the diseases that are common in its area and its healthcare priorities. If a vaccine-preventable disease is uncommon in a country, then residents of that country are unlikely to receive a vaccine against it. For example, residents of Canada and the United States do not routinely receive vaccines against yellow fever, which leaves them vulnerable to infection if travelling to areas where risk of yellow fever is highest (endemic or transitional regions). Vaccines work really well. Of course, no medicine is perfect but most childhood vaccines produce immunity about 90 - 100% of the time. Certainly, better hygiene and sanitation can help prevent the spread of disease. All vaccines must be licensed by the Food and Drug Administration (FDA) before being used in the United States.

A vaccine must go through extensive testing to show that it works and that it is safe before the FDA will approve it. These tests, usually include clinical trials, compare groups of people who get a vaccine with the groups of people who get a "control" (e.g. either a different vaccine or placebo).



Figure :A child being immunized against polio

Community Immunity (Herd Immunity)

When a critical portion of a community is immunized against a contagious disease, most members of the community are protected against that disease because there is little opportunity for an outbreak. Even those who are not eligible for certain vaccines (such as infants, pregnant women or immunocompromised individuals) get some protection because the spread of contagious disease is contained. This is known as "community immunity."

The principle of community immunity applies to control of a variety of contagious diseases, including influenza, measles, mumps, rotavirus, and pneumococcal disease.

Expanded Program on Immunization (EPI)

EPI has been launched on 07 April 1979 in Bangladesh and made available to all target groups by 1990. Supplementation of vitamin-A capsule has been started in 1990. Five doses of tetanus toxoid for women of child bearing age started in 1993. In 2003, hepatitis B vaccine has been added in the routine schedule. Pentavalent vaccine containing DPT-Hib-HepB has been introduced in 2009 in exchange of the previous trivalent DPT. MR and measles second dose have been introduced in 2012.

EPI is successful in Bangladesh. It has reduced the death by the vaccine preventable diseases. It resulted in reduction in infant and neonatal mortality and pushed Bangladesh towards better health. It has significant achievement in comparison with other South Asian

countries. Bangladesh is considerably better positioned than India, Pakistan and other countries. But it is not enough which is clearly indicated by the data of Sri Lanka and Maldives. There is a lot of room for improvement. Through the delivery system of immunization the government is implementing other projects like health education, arsenicosis control program, control of non-communicable diseases etc.

Immunization Schedule in Bangladesh, 2012

Vaccine	Age of Administration
BCG	At birth
DPT-Hib-HepB	6 weeks, 10 weeks, 14 weeks
OPV	6 weeks, 10 weeks, 14 weeks
MCV	MR-38 weeks and +15 years female, Measles-15 months
TT	Females 15 to 49 years (5 doses with an interval of + 1 month, + 6 months, + 1 year and + 1 year with preceding dose)

*Vitamin-A capsule has been included along with this schedule for the age group 6-59 months. Moreover, special campaigns have successfully conducted for OPV vaccination.

It is estimated that a total of 1.2 million deaths have been prevented from 1987-2000 through EPI services. More than 95% of infants receive BCG vaccine on first contact. However, the coverage gradually falls with subsequent doses. Nationally, 63% of infants receive all antigens at the right time and at appropriate intervals.

The elimination of neonatal tetanus is progressing well. Pregnant women and women of childbearing age are provided with tetanus vaccine through EPI. A survey conducted in 1986 found neonatal deaths due to tetanus were 41 per 1,000 live births. By 2000 this number had fallen to 2.3 per 1,000 live births. It is also estimated that some of the districts have reached the elimination goal, however, this needs to be validated through survey. In March 27, 2014, Bangladesh in one of the 11 South Asian countries declared polio-free by the World Health Organisation.

Conclusion

In common speech, 'vaccination' and 'immunization' have a similar meaning. This distinguishes it from inoculation, which uses unweakened live pathogens. Vaccination efforts have been met with some controversy on scientific, ethical, political, medical safety, and religious grounds. In rare cases, vaccinations can injure people and in the United States, they may receive compensation for those injuries under the National Vaccine Injury Compensation Program. Early success and compulsion brought widespread acceptance and mass vaccination campaigns have greatly reduced the incidence of many diseases in numerous geographic regions.

References :

- www.vaccines.gov; www.nhs.uk,
- www.unicef.org; www.searo.who.int

Test Yourself - 34

Correct Answers :

1. b 2. d 3. a 4. c 5. b 6. a

CONGRATULATIONS!

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Test Yourself - 35

- The followings are true for "Acute Abdomen" except:**
 - The usual organisms in the inflamed appendix are colon bacilli and streptococci.
 - The majority of cases of peritonitis involve organisms found in the normal flora of gastrointestinal tract.
 - The onset of pancreatitis is more sudden in nature.
 - Many episodes of PID go unrecognized.
- All the followings are correct for "Hepatitis C" except:**
 - It is one of the main causes of chronic liver diseases, liver cirrhosis and hepatocellular carcinoma.
 - Genotype 1 is highly prevalent in people who inject drugs.
 - Until 1990's, the major routes of HCV infection were blood transfusion.
 - The risk of acquiring HCV by needle sticks is about 6 times higher than that of HIV.
- All the below are true for "Wilson Disease" except:**
 - The condition is due to mutations in the Wilson disease protein gene.
 - It is inherited in an autosomal recessive pattern.
 - The Wilson disease gene has been mapped to chromosome 14.
 - In this condition, the main sites of copper accumulation are the liver and the brain.
- All the followings are correct for "Vaccine Preventable Diseases" except:**
 - The Chinese were the first to discover and use a primitive form of vaccination.
 - Vaccines consists of microbial antigens and work by priming the immune system.
 - Vaccines typically contain one or more adjuvants, used to boost the immune response.
 - In an inactivated vaccine, live virus or bacteria with very low virulence are administered.
- The followings are right for "Hepatitis C" except:**
 - Acute HCV infection is asymptomatic in most cases.
 - Chronic hepatitis C does not proceed towards cirrhosis.
 - The primary goal of Anti - HCV therapy is to cure the infection in order to halt disease progression, prevent complications.
 - Efficacy of Anti - HCV therapy should be monitored based on repeated measurement of HCV RNA levels.
- All the followings are correct for "Vaccine Preventable Diseases" except :**
 - In 2012 the WHO estimated that vaccination prevents about 3.5 million deaths each year.
 - Most childhood vaccines produce immunity about 90 - 100 percent of the time.
 - EPI has been launched in Bangladesh in 1979.
 - Through EPI services about 1.2 million deaths have been prevented from the year 1987 to 2000.

Soon our officials will be visiting you with a token of our appreciation

The Director General of World Trade Organization, Mr. Roberto Azevedo visited *SQUARE* Pharmaceuticals' state-of-the-art manufacturing plants at Kaliakoir, Gazipur on 4th of June, 2014. Commerce Minister Mr. Tofail Ahmed & Commerce Secretary Mr. Mahbub Ahmed accompanied the WTO chief. Our Honorable Managing Director Mr. Tapan Chowdhury, received the guests upon arrival. Ambassador of Brazil to Bangladesh - Her Excellency Ms. Wanja Nobrega was also present on the occasion.







A delegation of nineteen personnel from the National Defence College (NDC) of Tanzania visited *SQUARE* Pharmaceuticals' state-of-the-art manufacturing plants at Kaliakoir, Gazipur on 07 June 2014. The delegation was headed by Major General Festo Ndewiro Ulomi (Rtd.). As a part their Efficient Industrial Management, the delegation visited *SQUARE* Pharmaceuticals manufacturing plant.

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Normalizes visceral spasm


-  Shows excellent antispasmodic action on abdominal and pelvic (urogenital) pain
-  Offers an effective approach to relieve visceral pain
-  Exhibits superior antispasmodic action

Since 1958



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CamlosartTM $\frac{5/20 \text{ mg}}{5/40 \text{ mg}}$

Amlodipine + Olmesartan Medoxomil Tablet

*The most powerful CCB / ARB combination
for adequate BP control*



- Higher success rate with AML/OLM combination than monotherapy
- Ensures double-digit BP reduction
- Significantly reduces SeSBP
- Shows powerful efficacy in hypertensive patients with diabetes
- Controls Blood Pressure round-the-clock
- Ensures lower incidences of edema


 Heart for LifeTM

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