

INTRODUCTION

Epidemiology:

Hepatitis C virus is a RNA virus of the Flaviviridae family. HCV accounts for approximately 20% of community-acquired acute virus hepatitis. From 50 to 80% of infected individuals remain serum HCV RNA positive and are considered to be chronic carriers.⁽¹⁾

Hepatitis C virus continues to be a major disease burden on the world. The estimated global prevalence of HCV infection is 2.2 %.(Figure 1)⁽²⁾ According to the World Health Organization (WHO) there are 130-170 million people infected with HCV. There are considerable regional differences.⁽³⁾

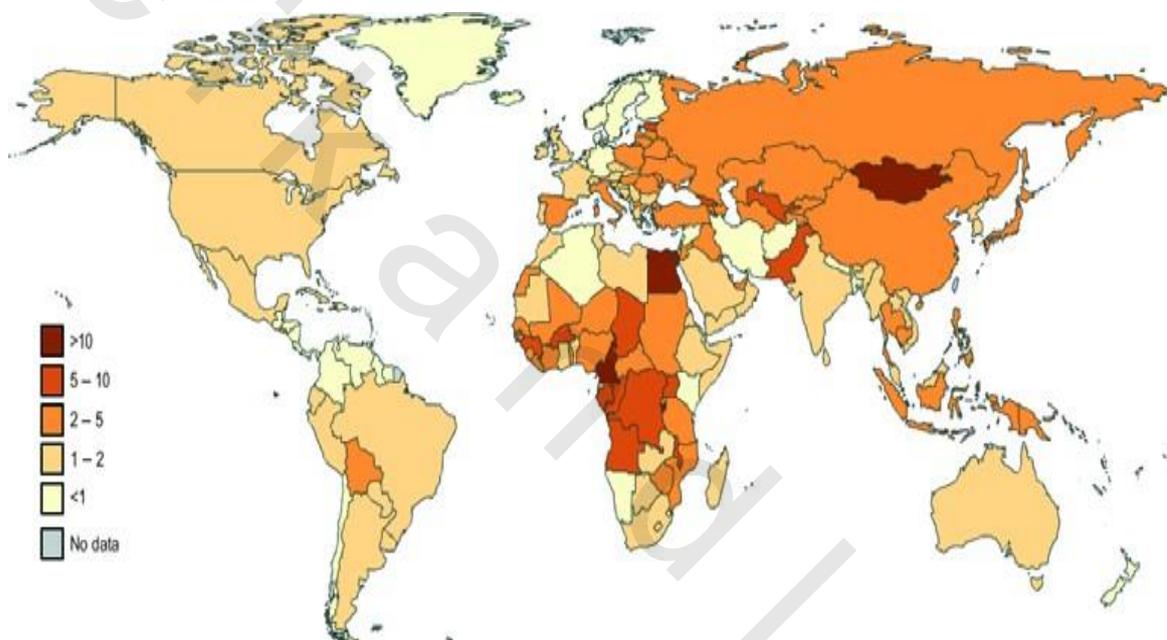


Figure (1): Hepatitis C global prevalence 2010 (%)⁽²⁾

Because many countries lack data, this estimate is based on weighted averages for regions rather than individual countries.⁽⁴⁾ Region-specific estimates range from < 1.0% in Northern Europe to > 2.9% in Northern Africa. The lowest prevalence (0.01-0.1%) has been reported from countries in the United Kingdom and Scandinavia; the highest prevalence (15- 20%) has been reported from Egypt.^(5, 6) An estimated 27% of cirrhosis and 25% of HCC worldwide occur in HCV-infected people. (Table 1)⁽⁷⁾

Table (i): Hepatitis C estimated prevalence and number infected by WHO Region.

WHO Region	Total Population (Millions)	Hepatitis C prevalence Rate %	Infected Population (Millions)	Number-of countries by WHO Region where data are not available
Africa	602	5.3	31.9	12
Americas	785	1.7	13.1	7
Eastern Mediterranean	466	4.6	21.3	7
Europe	858	1.03	8.9	19
South-East Asia	1500	2.15	32.3	3
Western Pacific	1600	3.9	62.2	11
Total	5811	3.1	169.7	57

For more than a decade, Egypt has been widely regarded as having an epidemic, with the highest recorded prevalence of HCV in the world.⁽⁸⁾ The prevalence of infection increases steadily with age, and high rates of infection are observed among persons in all age groups.⁽⁹⁾

Hepatitis C virus is divided among six genotypes with numerous subtypes. These genotypes can differ up to 30% from each other in nucleotide sequence. Depending on the HCV genotype the length of HCV treatment differ.⁽¹⁰⁾

Approximately 90% of Egyptian HCV isolates belong to a single subtype 4a, which responds less successfully to IFN therapy than other subtypes. Furthermore, HCV is less prevalent in countries neighboring Egypt that have similar sociomedical conditions and similar HCV strains.⁽¹¹⁾

Why then is Egypt so seriously affected? Previous research has suggested that the Egyptian HCV epidemic results from the use of unsterile injection equipment during mass treatment of the general population with parenteral antischistosomal therapy (PAT). PAT was extensively practiced in Egypt from the 1920s to the 1980s and was gradually replaced by oral treatment from the 1970s onwards.^(6,11)

In Egypt where there has been an ongoing high risk for decades, the high magnitude of the current burden of HCV-related chronic disease is predicted to continue into the future.⁽¹²⁾

Hepatitis C incidence:

Determining the incidence of HCV infection (i.e., the rate of newly acquired infections) is difficult because most acute infections are asymptomatic, available assays do not distinguish acute from chronic or resolved infection, and most countries do not systematically collect data on cases of acute disease. Even in countries with well-established surveillance systems, acute disease reporting systems underestimate the incidence of HCV infection.⁽⁹⁾

Cohort studies in Egypt found incidence rates of 0.8/1000 in an area of Upper Egypt where the background prevalence was 9% and 6.8/1000 in the Nile Delta where the background prevalence was 24%. Sixty-seven percent of infections were in persons < 20 years old.⁽⁹⁾

Hepatitis C Clinical Presentation

Acute hepatitis C (HCV) infection becomes chronic in 70% of patients, which represents a high rate of chronicity for a viral infection. Most patients with chronic hepatitis C infection are asymptomatic or may have nonspecific symptoms such as fatigue or malaise in the absence of hepatic synthetic dysfunction. Patients with decompensated cirrhosis from HCV infection frequently have symptoms typically observed in other patients with decompensated liver disease, such as sleep inversion and pruritus.^(13,14)

Symptoms characteristic of complications from advanced or decompensated liver disease are related to synthetic dysfunction and portal hypertension. These include mental status changes (hepatic encephalopathy), ankle edema and abdominal distention (ascites), and hematemesis or melena (variceal bleeding).^(13,14)

Symptoms often first develop as clinical findings of extrahepatic manifestations of HCV and most commonly involve the joints, muscle, and skin. In a large study of the extrahepatic manifestations of HCV, 74% of medical workers with HCV infection demonstrated extrahepatic manifestations.⁽¹⁵⁾ The most commonly occurring extrahepatic manifestations were as follows:

- Arthralgias (23%)
- Paresthesias (17%)
- Myalgias (15%)
- Pruritus (15%)
- Sicca syndrome (11%)

In addition, sensory neuropathy has been reported as an extrahepatic manifestation in 9% of patients with HCV infection. Risk factors for manifestations of extrahepatic chronic hepatitis C infection include advanced age, female sex, and liver fibrosis.⁽¹³⁾

Patients also present with symptoms that are less specific and are often unaccompanied by discrete dermatologic findings. Pruritus is example of less specific clue to underlying HCV infection in the appropriate setting (eg, posttransfusion, organ transplantation, surgery, intravenous drug use, injury of the nasal mucosa from snorting cocaine through shared straws).⁽¹⁴⁾

Patients with ongoing pathology associated with chronic hepatitis C that eventually results in organ failure can present with symptoms and signs in the skin. Pruritus, dryness, palmar erythema, and yellowing of the eyes and skin are examples of less specific findings in patients with end-stage liver disease with cirrhosis; these findings provide clues that lead to further evaluation of the underlying causes. Chronic hepatitis C has a strong association with pruritus. Indeed, some authorities believe that all patients with unexplained pruritus should be investigated for HCV infection.^(16,17)

DIAGNOSIS OF HCV INFECTION

Acute hepatitis C

Patients with a suspicion of acute hepatitis C should be tested for both anti-HCV antibodies by EIA and HCV RNA with a sensitive technique polymerase chain reaction (PCR), “real-time” PCR, i.e. an HCV RNA assay with a lower limit of detection of 50 IU/ml or less.⁽¹⁸⁾ Four marker profiles can be observed according to the presence or absence of either marker. The presence of HCV RNA in the absence of anti-HCV antibodies is strongly indicative of acute HCV infection, which will be confirmed by seroconversion (i.e. the appearance of anti-HCV antibodies) a few days to weeks later. Acutely infected patients can also have both HCV RNA and anti-HCV antibodies at the time of diagnosis. It is difficult, in this case, to distinguish acute hepatitis C from an acute exacerbation of chronic hepatitis C or an acute hepatitis of another cause in a patient with chronic hepatitis C. Acute hepatitis C is very unlikely if both anti-HCV antibodies and HCV RNA are absent. It is also unlikely if anti-HCV antibodies are present without HCV RNA. These patients should however be retested after a few weeks because HCV RNA can be temporarily undetectable, due to transient, partial control of viral replication by the immune response before replication escapes and chronic infection establishes. Apart from such cases, the presence of anti-HCV antibodies in the absence of HCV RNA is generally seen in patients who have recovered from a past HCV infection. Nevertheless, this pattern cannot be differentiated from a false positive EIA result, the exact prevalence of which is unknown.⁽¹⁹⁾

Chronic hepatitis C

In patients with clinical or biological signs of chronic liver disease, chronic hepatitis C is certain when both anti-HCV antibodies and HCV RNA (sought for with a sensitive technique, detecting 50 IU/ml or less) are present.^(3,20) Detectable HCV replication in the absence of anti-HCV antibodies is exceptional with the current third-generation EIAs, almost exclusively observed in profoundly immunodepressed patients, hemodialysis patients or agammaglobulinemic subjects.⁽²¹⁾

Indeed, neither anti-HCV antibodies nor the HCV RNA load correlate with the severity of liver inflammation or fibrosis nor with their progression. Thus, they cannot be used to predict the natural course of infection or the onset of extrahepatic manifestations. In untreated patients, the severity of liver inflammation and fibrosis must be evaluated every three to five years by means of a liver biopsy or non-invasive serological or ultrasound-based testing.^(22,23)

4. MANAGEMENT OF ANTIVIRAL THERAPY

The current standard treatment for chronic hepatitis C is the combination of pegylated interferon (IFN) alfa and ribavirin.⁽²⁴⁾ The efficacy endpoint of hepatitis C treatment is the “sustained virological response” (SVR), defined by the absence of detectable HCV RNA in serum as assessed by an HCV RNA assay with a lower limit of detection of 50 IU/ml or less 24 weeks after the end of treatment.⁽²⁴⁾

Initiation of therapy

Only patients with detectable HCV RNA should be considered for pegylated IFN alfa and ribavirin combination therapy.⁽²⁵⁾ The decision to treat patients with chronic hepatitis C depends on multiple parameters, including a precise assessment of the severity of liver disease and of its foreseeable outcome, the presence of absolute or relative contra-indications to therapy, and the patient's willingness to be treated.

The HCV genotype should be systematically determined before treatment, as it determines the indication, the duration of treatment, the dose of ribavirin and the virological monitoring procedure.^(26,27)

Prevention

Primary prevention of hepatitis C should target reduction of transmission of the virus. Prevention should target those at risk of acquiring the virus and should involve providing education, risk reduction counseling, HCV screening and substance abuse treatment.⁽⁴⁾

In the United States, the Centers for Disease Control suggest screening for the follow population: 1) Persons who ever injected illegal drugs, including those who injected once or a few times many years ago; 2) Persons who received a blood transfusion or organ transplant before July 1992; 3) Persons who received clotting factor concentrates before 1987; 4) Persons who were ever on long-term dialysis; 5) Children born to HCV-positive women; 6) Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV positive blood; 7) Persons with evidence of chronic liver disease.⁽⁴⁾

Prevention in healthcare setting should also take place by having better sterilization, safer injections, reducing opportunities for percutaneous exposures to blood. In developing countries, better screening for donors and blood screening should take place to reduce the number of transfusion related transmissions.⁽²⁸⁾

Once a patient is found to have hepatitis C, that patient needs to be counseled to reduce the risk of HCV transmission to others. The physician should also offer counseling on treatment, reducing alcohol usage and immunization with hepatitis A, hepatitis B, pneumococcal and influenza vaccines.⁽²⁸⁾

Hepatitis C virus negative persons with ongoing risk factors also require counseling and immunization with hepatitis A and hepatitis B vaccines.⁽²⁸⁾

Modes of Transmission:

The following possible routes of infection have been identified in blood donors (in descending order of transmission risk): Injection drug use, Blood transfusion, Sex with an IV drug user, Having been in jail more than three days, Religious scarification, Having been struck or cut with a bloody object, Pierced ears or body parts, Immunoglobulin injection. Very often in patients with newly diagnosed HCV infection no clear risk factor can be identified. ⁽³⁾

As in other regions of the world, in Egypt some HCV infections are caused by transfusions, injection drug use, and perinatal exposure. However, most appear to be caused by percutaneous medical procedures. ⁽¹⁷⁾

The most efficient transmission of HCV is through large or repeated direct percutaneous exposures to blood (e.g., transfusion or transplantation from infectious donors, injecting drug use). ⁽²⁹⁾ Transfusion of blood products has been a leading cause of transmission of HCV; however, due to improved screening, transmission through transfusions has decreased in most developed countries. ⁽⁴⁾

1. Blood transfusion:

Transfusion-associated HCV infection was a worldwide risk before HCV testing became available. It has been virtually eliminated in those countries that implemented routine HCV testing of donors, but in others, receipt of blood transfusions remains an important source for infection. ⁽²⁹⁾

Recent investigations in Egypt have reported a strikingly high prevalence of antibodies to HCV among blood donors which ranged from 6 to 38% and averaged approximately 15%. ⁽³⁰⁾

2. Intravenous drug users:

The importance of IV drug use cannot be overemphasized. The prevalence of HCV among people who acquired human immunodeficiency virus (HIV) through IV drug use reaches 90%. Co-infection of the two viruses can make treatment all the more difficult. ^(4, 31)

Most countries with a young population of HCV infection must deal with IV drug use as the leading cause for spread of the virus. Many of these IV drug users do not know they are infected. Screening of HCV and treatment of substance abuse are extremely important in this group. ^(4, 31)

3. Hemodialysis:

The rate of seroconversion among hemodialysis patients with no other risk factors has been reported 1.38-1.9% per year. ^(32, 33) These studies generally conclude that the transmission of the virus to hemodialysis patients is generally nosocomial with possible risk factors being failure to disinfect devices between patients, sharing of single-use vials for infusions, poor sterile technique, poor cleaning of dialysis machines, and poor distance between chairs. ⁽³⁴⁾

4. Unsafe injections:

Of even greater importance in the spread of HCV, are unsafe therapeutic injections performed by both professionals and non-professionals.

It has been estimated that approximately 2 million HCV infections are acquired annually from contaminated health care injections, and may account for up to 40% of all HCV infections worldwide. ^(35, 36)

5. Perinatal transmission:

The rate of perinatal transmission of HCV is 4 to 7% per pregnancy and occurs only when HCV RNA is detectable in maternal serum at delivery. ⁽³⁷⁾

6. Environmental infection:

There is also evidence that the environment can serve as a reservoir for infectious virus. HCV transmission by unapparent percutaneous exposures has been caused by cross-contamination from reused needles and syringes, multiple-use medication vials and infusion bags. ⁽³⁸⁾

Cryoglobulins and cryoglobulinemia

Cryoglobulins are serum proteins that precipitate at low temperatures and then redissolve during incubation at 37°C. ^(39,40) The temperature at which the proteins precipitate is determined by the thermal amplitude. ⁽⁴¹⁾ This in-vitro phenomenon can be observed in a spectrum of hematologic, infectious, and rheumatologic disorders. ⁽⁴²⁾

Different categories of cryoglobulins have been described that refer to their different immunologic compositions, and different clinical syndromes (cryoglobulinemias) have been attributed to their occurrence. Type I cryoglobulins are complexes of a single monoclonal immunoglobulin (Ig), usually IgM. They account for 10–15% of cryoglobulinemia syndromes. ⁽⁴²⁾ Type I cryoglobulinemia is mainly found in patients with hematologic malignancies such as Waldenstrommacroglobulinemia and multiple myeloma. The clinical findings are those of increased serum viscosity, due to the fact that IgM is a relatively large molecule and the formation of large IgM complexes may lead to peripheral vessel occlusion, manifesting as stroke, Raynaud phenomenon, or ischemic limb ulcers. ⁽⁴²⁾

Type II and type III cryoglobulins constitute MC. Type II is composed of polyclonal IgG and monoclonal IgM. Type III is composed of polyclonal IgG and/or polyclonal IgM. Type II accounts for 50–60% of cryoglobulinemias, whereas type III accounts for 30–40%. The IgG component is always polyclonal with both kappa and lambda light chains. The IgM fraction in type II mounts kappa chains and usually possesses rheumatoid factor (RF) activity. The RF activity allows the IgM component to bind intact IgG at both the Fc and Fab fragments, conferring stability of circulating IgG-IgM immune complexes. ^(39,40) The ability to bind the Fc fragment of autologous IgG confers rheumatoid activity. ⁽⁴²⁾

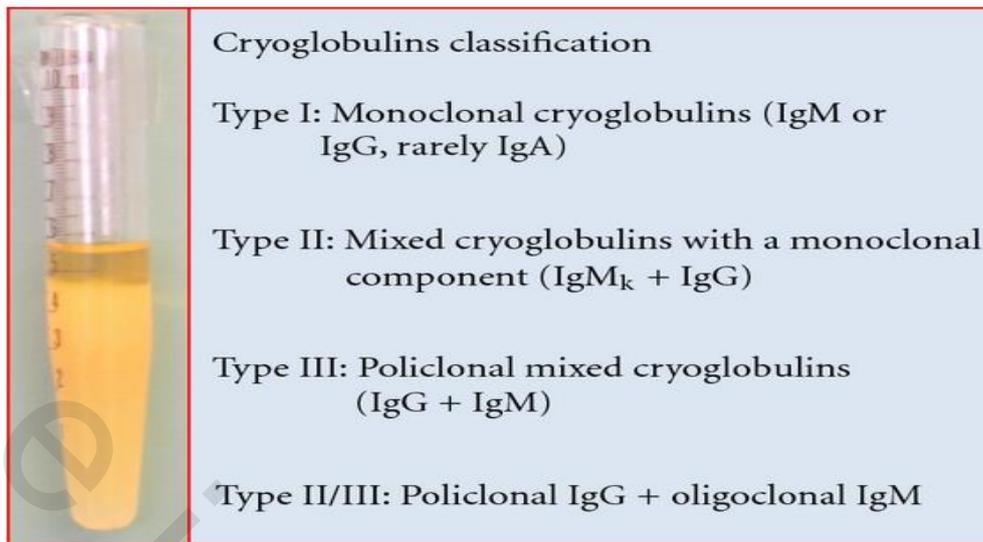


Figure (2): Types of cryoglobulinemia.⁽⁴²⁾

Chronic hepatitis to cirrhosis, and liver failure causes the progression of liver disease to hepatocellular carcinoma. Chronic HCV infection is now the leading indication for liver transplantation in the United States. Although much of the focus in chronic HCV infection has been centered on hepatic sequelae, it is now apparent that clinically significant extrahepatic manifestations are important in some patients.⁽¹⁵⁾

Within the past decade, it has been recognized that a majority of patients with essential mixed cryoglobulinemia (MC) are chronically infected with HCV.^(39,40) Although the underlying mechanisms have not been fully elucidated, cryoglobulin formation is clearly linked to the attempt of the host to clear the significant quantities of virions generated daily by the chronic infection.⁽⁴¹⁾

Mixed cryoglobulinemia is marked by a systemic vasculitis that damages small- and medium-sized arteries and veins of many different organs. The immune complexes, composed of different cryoglobulins, deposit in the vessel walls. Through the complement system, they mediate intense activation of the inflammatory response.^(39,40) Clinically, this systemic vasculitis can manifest as myriad symptoms, ranging from mild to severe, including purpuric skin eruptions that may become ischemic ulcers, polyneuropathy, glomerulonephritis, Raynaud phenomenon, and arthralgias. Despite the occasional association of this clinical spectrum with autoimmune, hematologic, or infectious (eg, hepatitis B virus [HBV]) diseases, it has historically arisen without any predisposing disorder and was thus termed “essential MC.” With the discovery of HCV in 1989, it quickly became evident that chronic infection with HCV accounted for at least 90% of cases of MC.⁽⁴⁰⁻⁴²⁾ Supporting the etiologic role of HCV, studies have demonstrated the presence of HCV antibody and HCV RNA in higher concentrations within the immune complexes in the sera of MC patients.⁽⁴¹⁾

Target organ involvement in Hepatitis C Virus-MC

Cutaneous and Joint Involvement

Purpura is the most common clinical manifestation of MC, occurring in at least 90% of cases. Skin lesions often begin in the legs and may progress to deep ulcers in approximately 10% of patients.⁽⁴³⁾ Purpuric lesions can also be found on the buttocks, trunk, and upper extremities, but they rarely involve the face. Itching is rare. Skin eruptions can be intermittent, and repeated episodes can lead to hyperpigmentation of the involved skin. Purpura is often preceded by paresthesiae or a prickling sensation in the involved limb. Progression of skin lesions to frank skin necrosis and gangrene can occur, but is less common.⁽⁴³⁾

Raynaud phenomenon occurs in up to one third of cases and involves hands, feet, lips, ears, and the tip of the nose. Arthralgia without arthritis is commonly experienced, typically affecting the proximal interphalangeal joints of the hands, metacarpophalangeal joints, knees, and hips.⁽⁴³⁾

Neurologic Involvement

The neurologic manifestation of MC is most frequently peripheral neuropathy, commonly polyneuropathy, reportedly occurring in 36–86% of patients.⁽⁴⁴⁾ The pathogenic mechanism of peripheral nerve damage has been postulated to be vasculitis of the vasa nervorum, as well as autoimmune nerve damage, with cases of demonstrated demyelination.^(45,46)

Renal Involvement

Renal impairment in MC is often due to membranoproliferative glomerulonephritis (MPGN) and is clinically evident in 20–30% of MC patients.⁽⁴⁷⁾ Renal biopsy often demonstrates glomerular subendothelial deposits characteristic of type I MPGN; by immunofluorescence, these deposits are typically found to be composed of IgM, IgG, and C3.⁽⁴⁷⁾ These subendothelial deposits are identical to the circulating complexes found in patients with type II MC.⁽⁴¹⁾ Other patterns on biopsy that have been described include subepithelial deposits typical of type III MPGN, membranous nephropathy, renal artery vasculitis, and tubulointerstitial inflammation and scarring.^(48,49)

The clinical symptoms and signs of MC can precede the onset of renal involvement for years. The most common clinical findings from renal disease in MC are proteinuria with microscopic hematuria, moderate renal insufficiency, and hypertension. However, acute onset, marked by a sudden rise in creatinine with severe proteinuria, is the first renal manifestation in approximately 25% of patients.⁽⁴⁹⁾ Oliguria and dialysis requirement occur in a small minority of patients. HCV-associated MPGN can develop following liver and renal transplantation.⁽⁴⁷⁾ A recent report from a large Italian center showed age, serum creatinine, and proteinuria as independent risk factors for the development of progressive renal failure at follow-up. Renal involvement is commonly the greatest cause of morbidity in MC and often justifies more aggressive treatment of the disease.⁽⁴⁸⁾

Endocrine Dysfunction

A variety of endocrine gland dysfunctions have been described to be more common in patients with HCV-related MC than in age- and sex-matched controls. The most well-described disorders are type II diabetes, hypothyroidism with positive antithyroid antibodies, and gonadal dysfunction.⁽⁴⁶⁾

Correlation With Liver Disease Severity

Mixed cryoglobulinemia tends to correlate with duration of HCV infection and older age. However, cryoglobulinemia and/or the presence of detectable cryoglobulins in the serum of HCV patients has been associated with increased risk of advanced fibrosis and cirrhosis in patients with chronic HCV infection, irrespective of age or disease duration.^(39,41) The presence of serum cryoglobulins has been shown to correlate with the severity of hepatic steatosis on liver biopsy.⁽⁴²⁾

Source of Hepatitis C Virus-related Mixed Cryoglobulins

1. The Role of Sustained Antigenic Stimulation:

A common hypothesis for HCV-related cryoglobulinemia is chronic antigenic stimulation of the humoral immune system, which facilitates clonal B-lymphocyte expansion. However, other chronic viral infections, including HBV, are not associated with the same high prevalence.⁽⁵⁰⁾ Furthermore, the B lymphocytes that accumulate in peripheral blood in patients with HCV-related cryoglobulinemia consist of a naive, resting phenotype without evidence of activation. Nevertheless, global B-cell stimulation may still prove to be fundamental to HCV-related cryoglobulinemia.⁽⁵⁰⁻⁵¹⁾

It has also been suggested that the HCV E2 envelope protein binds to the cell surface glycoprotein CD81 that is present on B cells as well as on hepatocytes. Interaction with HCV E2 reduces the threshold for B-cell activation and might increase the frequency of VDJ rearrangement in antigen-reactive B cells.^(52,53)

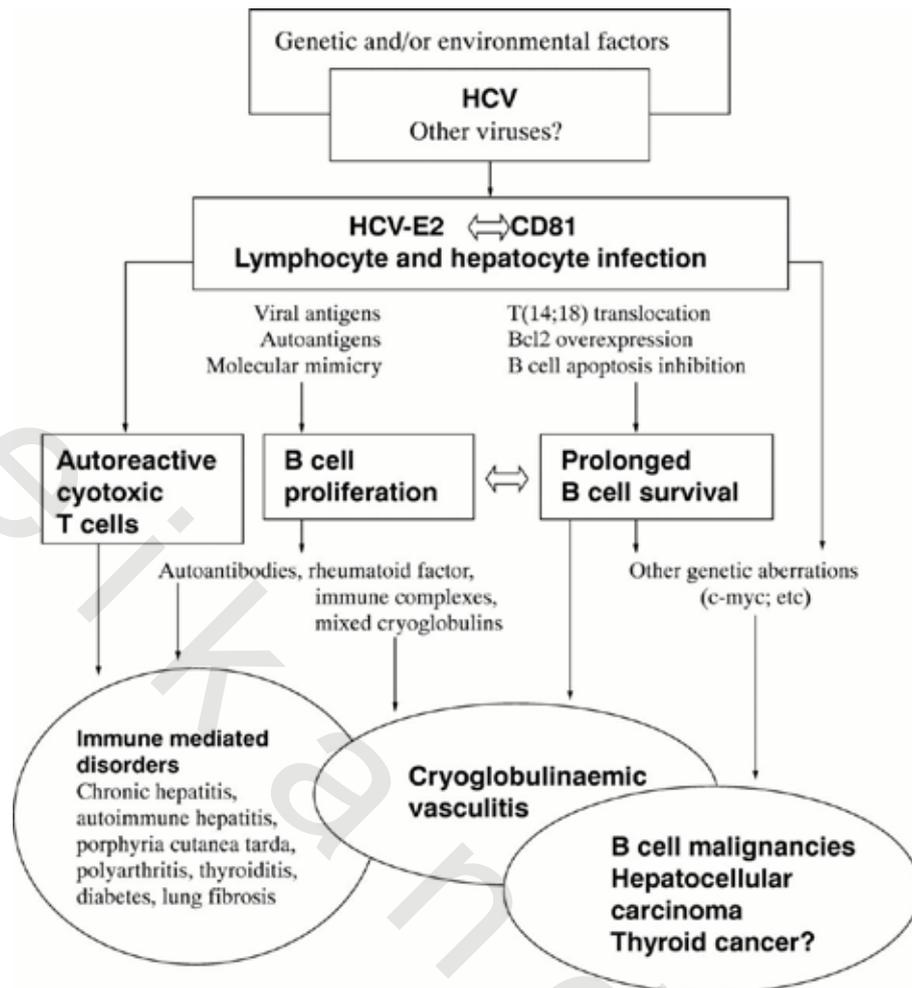


Figure (3):Pathogenesis of HCV-related cryoglobulinaemia. ^(52,53)

Expansion of RF-synthesizing B cells also appears to be a hallmark of HCV-MC. RFs are tolerance-resistant autoantibodies directed against the Fc regions of IgG molecules. ⁽⁵⁴⁾

The interaction between HCV and B and T cells is essential for the clearance of the more than 1 trillion copies of virus produced daily and is likely to generate significant amounts of immune complexes that could lead to stimulation of high-affinity RF, as previously described. Polyclonal activation of CD5-positive cells are regarded as the major source of the IgM-RF molecule in type III MC. Emergence of a single dominant clone could explain type II. ⁽⁵⁵⁾

2. Chromosomal Aberrations:

A number of other possibilities have been proposed to explain the effects of chronic HCV infection on B cells. Peripheral blood mononuclear cells in patients chronically infected with HCV, and especially in those with cryoglobulinemic vasculitis, show a t(14;18) translocation that is responsible for *Bcl-2* activation. ⁽⁵⁶⁾ This proto-oncogene increases B-cell survival by inhibiting apoptosis and could lead to increased B-cell quantities. The consequent expansion of B lymphocytes could explain the increased production of autoantibodies and cryoglobulins. ⁽⁵⁰⁾

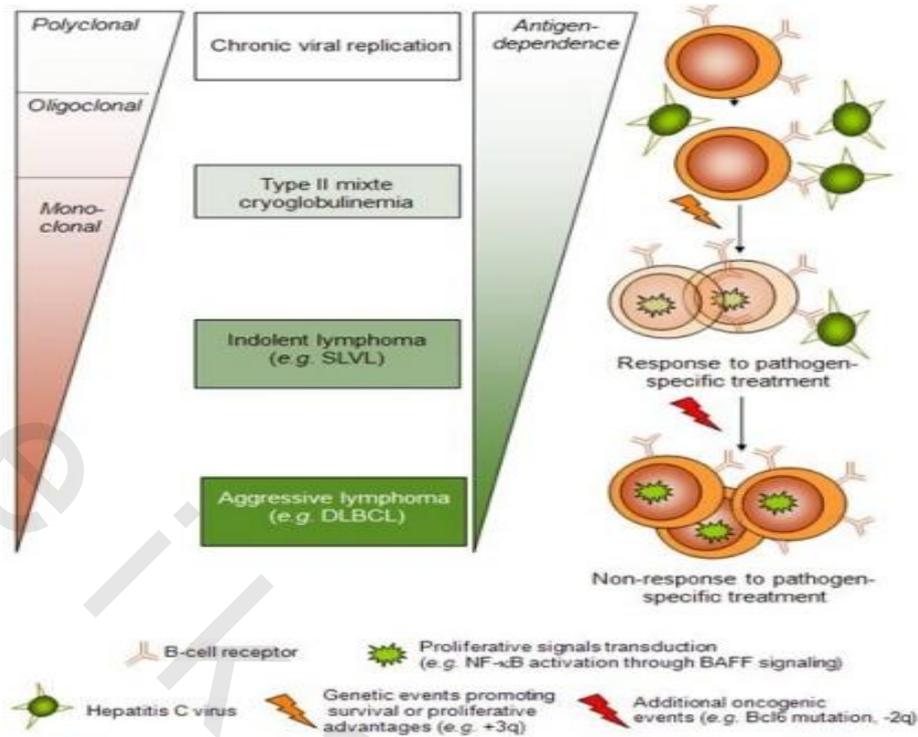
3. Cytokines, Chemokines, and HCV-Related cryoglobulinemia:

Effector signals that enhance survival of immunocompetent cells are the subject of current research. A newly described cytokine, B-cell activating factor of the tumor necrosis factor family (BAFF)-also known as B-lymphocyte stimulator (BLyS) .⁽⁵⁷⁾ may be important in HCV-related cryoglobulinemia, as well as in several systemic autoimmune diseases, including rheumatoid arthritis (RA), primary Sjogren's syndrome (pSS), and systemic lupus erythematosus (SLE). BAFF mRNA is present mainly in lymphoid tissue and is expressed by monocytes, macrophages, dendritic cells, and growth factor-stimulated neutrophils on exposure to interferons or CD40 ligand.⁽⁵¹⁾ BAFF mRNA, however, is absent from B cells.⁽⁵⁷⁾ BAFF binds to three receptors selectively expressed by B cells: B-cell maturation antigen; transmembrane activator, calcium modulator, and cyclophilin ligand interactor; and BAFF receptor. BAFF has several effects on B cells: it plays a critical role in B-cell maturation in long-lived bone marrow plasma cell survival in the promotion of humoral immune response and in CD40-independent immunoglobulin class-switch recombination.^(52, 58)

Autoreactive B cells are more dependent on BAFF for survival than alloreactive B cells.⁽⁵⁹⁾ Because autoreactive B cells are associated with the development of autoimmune disorders such as SLE, RA, and pSS, as well as cryoglobulinemia, BAFF levels may be significant in the pathogenesis of these disorders.⁽⁶⁰⁾ The recent demonstration of increased serum BAFF levels in SLE, RA, and pSS and elevated serum levels in chronic HCV patients compared to controls and patients with chronic HBV infection strongly suggests that BAFF plays a role in HCV-related cryoglobulinemia.^(60,61) Interestingly, serum BAFF levels were even higher in those patients with chronic HCV infection and symptoms indicative of systemic vasculitis or mixed cryoglobulinemia, HCV-MC. Levels were also higher in type II than type III HCV-MC.⁽⁶²⁻⁶³⁾

Association with Non-Hodgkin Lymphoma

Chronic HCV infection has profound impact on B-cell stimulation and survival. Chronic HCV infection and HCV-associated MC have been closely associated with the development of non-Hodgkin lymphoma (NHL).⁽⁶⁴⁾ NHL that arises in cryoglobulinemic patients is often a low-grade lymphoma with bone marrow involvement, but can develop into a high-grade lymphoma phenotype.⁽⁶⁵⁾ Extranodal involvement is common in the liver, salivary glands, and spleen. Regression following successful antiviral therapy of HCV with interferon has served to further strengthen the association.^(66,67) Although the driving force behind lymphoproliferation in chronic HCV infection is unclear, increased levels of BAFF may play a role. Mice transgenic for BAFF develop lymphocytic disorders, including lymphomas.⁽⁶⁸⁾



Figure(4):Hypothetical model of progression from mixed cryoglobulinemia to lymphoma.⁽⁶⁸⁾

The same hypothesis of chronic antigenic stimulation, chromosomal aberrations and cytokines that involved in the pathogenesis of HCV related mixed cryoglobulinemia could explain also the progression to lymphoma.⁽⁶⁹⁾

BAFF promoter polymorphisms

B lymphocyte stimulator (BLyS, also known as BAFF, TALL-1, zTNF4, TNFSF13B) is identified as a member of the tumor necrosis factor superfamily, expressed in monocytes, macrophages, and dendritic cells.⁽⁷⁰⁻⁷³⁾ BLyS is a potent B cell co-stimulator, and promotes B cell differentiation, proliferation and survival.^(74, 75) In BLyS deficient mice, the number of B cells, serum IgG and IgM levels were decreased, and B cell development was blocked at the transitional T1 stage.⁽⁷⁶⁻⁸¹⁾ BLyS and a proliferation-inducing ligand (APRIL) bind to B cell maturation antigen (BCMA) and transmembrane activator and CAML-interactor (TACI) which belong to the tumor necrosis factor receptor superfamily and are mainly expressed in B cells.^(61,62) The intracellular domains of BCMA and TACI associate with TNF-receptor-associated factors (TRAFs), leading to activation of NF-κB.^(61,62) Recently, another receptor for BLyS, BAFF-R (also called BR3) was identified, which does not bind to APRIL.⁽⁸²⁾

Several lines of evidence indicate that these receptor–ligand systems crucially contribute to the pathogenesis of the autoimmune diseases. Transgenic mice overexpressing BLyS develop symptoms characteristic of SLE.⁽⁸³⁻⁸⁵⁾ Recently, increase of BLyS level was also reported in the serum or synovial fluid of human SLE, RA and Sjögren's syndrome.⁽⁸⁶⁾ Serum BLyS level was shown to be correlated with those of anti-dsDNA antibody and RF.⁽⁸⁷⁻⁹⁰⁾

On the basis of these observations, it was considered that BLYS, APRIL, BCMA, TACI and BAFF-R are strong candidates for the susceptibility gene to human autoimmune disease.⁽⁹¹⁻⁹⁴⁾

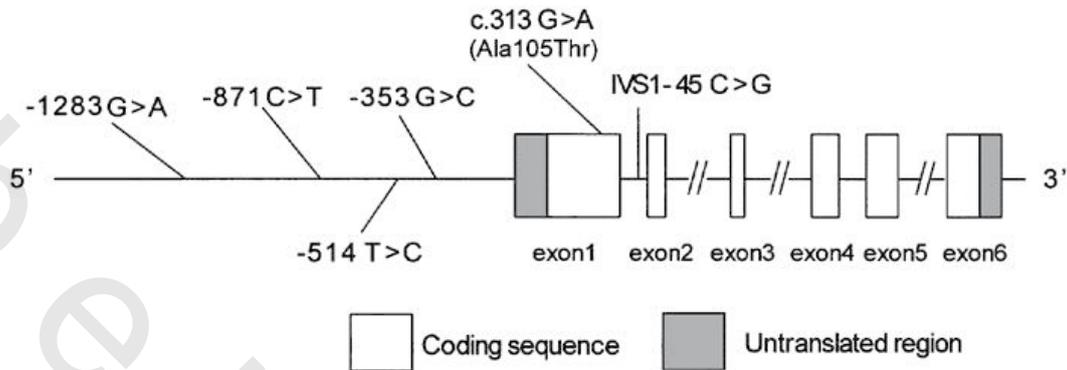


Figure (5): Genomic configuration of human BLYS gene.⁽⁹⁵⁾

Four SNPs in the BAFF promoter region, -1283G>A, -871C>T, -514T>C, and -353G>C, and one SNP in intron 1, IVS1-45C>G, were also detected. Significant association of BLYS SNPs with susceptibility to SLE and RA was not observed.⁽⁹⁶⁻⁹⁹⁾ But a tendency for increase of the -871T/T genotype was observed in SLE patients with anti-Sm antibody and mRNA levels were significantly increased in individuals carrying -871T allele compared with those not carrying -871T allele.⁽¹⁰⁰⁻¹⁰²⁾

Although human BLYS was found to be conserved in the coding region, several SNPs in the promoter with potential functional significance were identified.⁽¹⁰³⁾ One of the promoter SNPs was shown to be associated with elevated BLYS mRNA level in the monocytes, the homozygotes of which were found more frequently in SLE patients with anti-Sm antibody. These results suggested that BLYS polymorphism may be involved in the genetic susceptibility to some of the phenotypes of autoimmune diseases.⁽¹⁰⁴⁾

BAFF Promotor polymorphism can be a host predisposing factor to develop mixed cryoglobulinemia in chronic HCV patients.