
بسم الله الرحمن الرحيم

HCV RELATED GLUMEROLOPATHY

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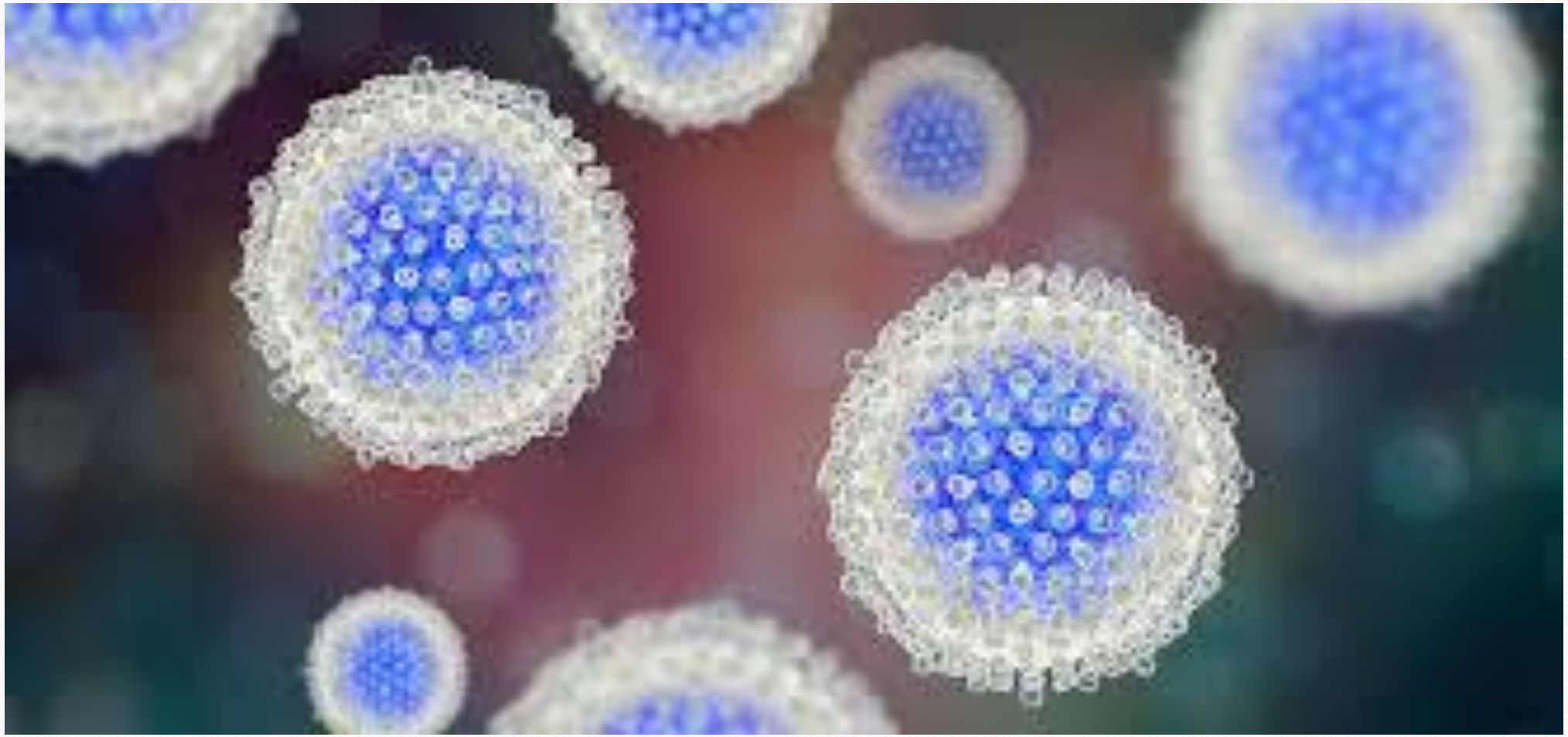
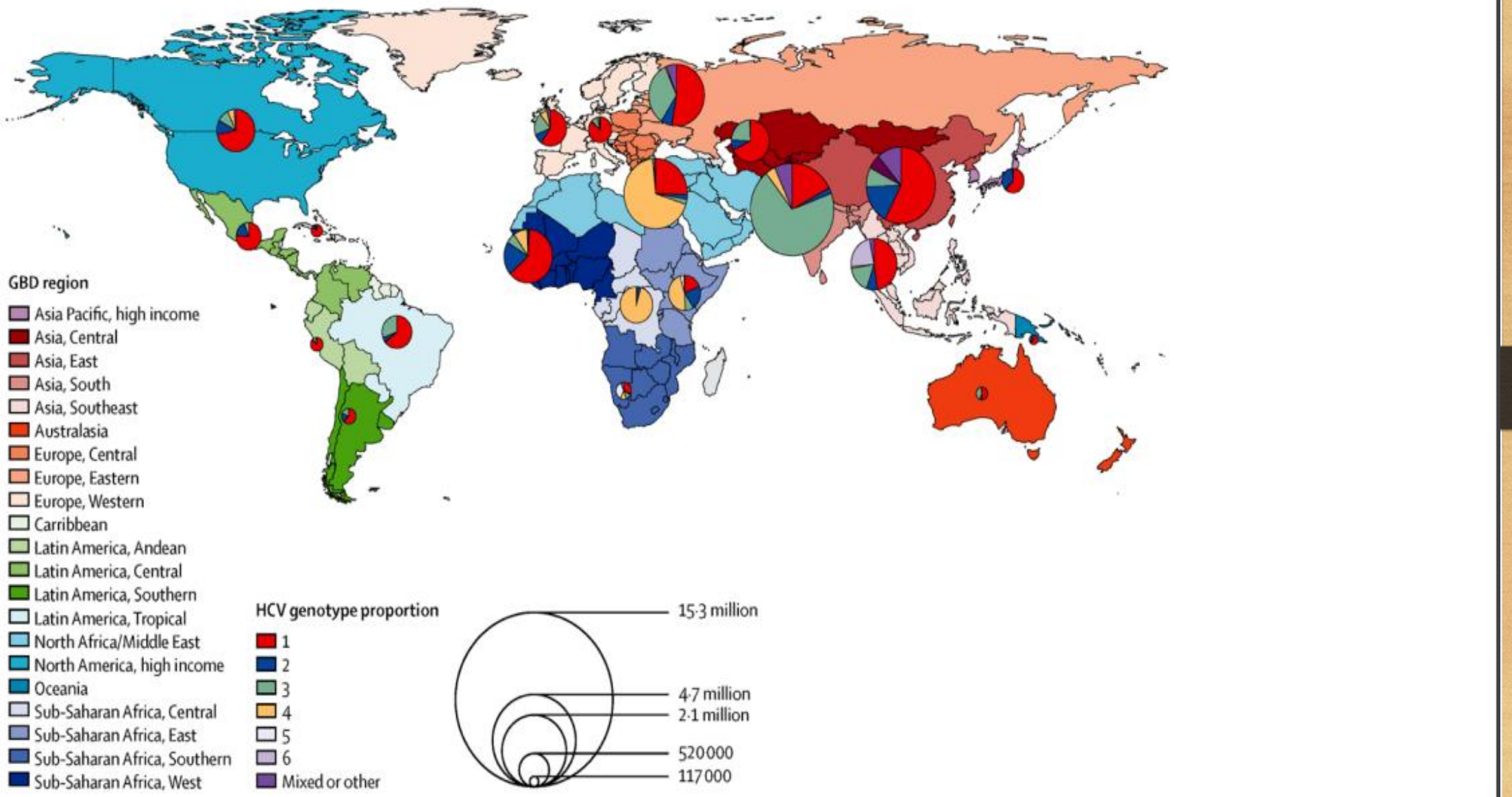
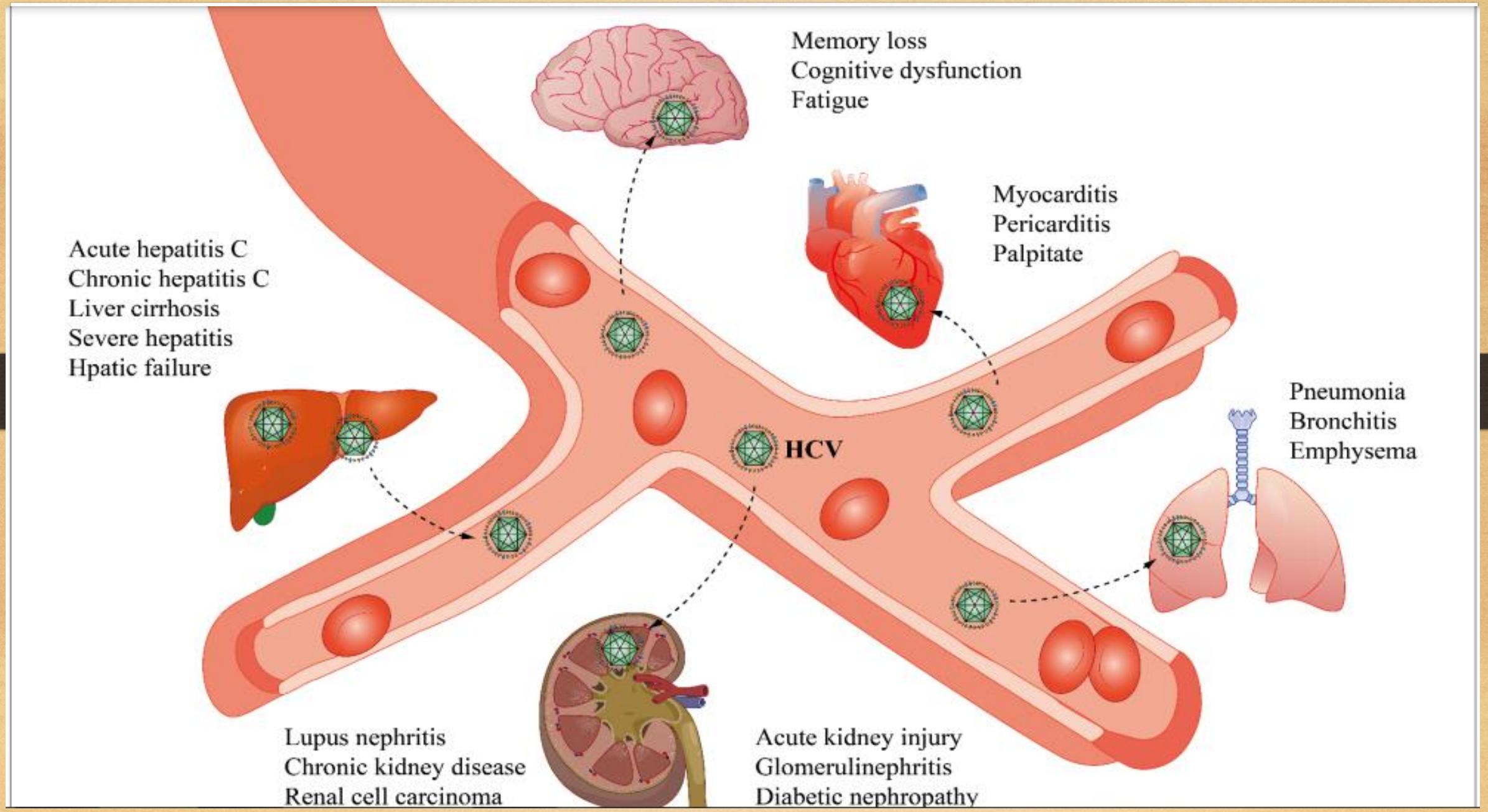
More than 71 million people worldwide have chronic HCV



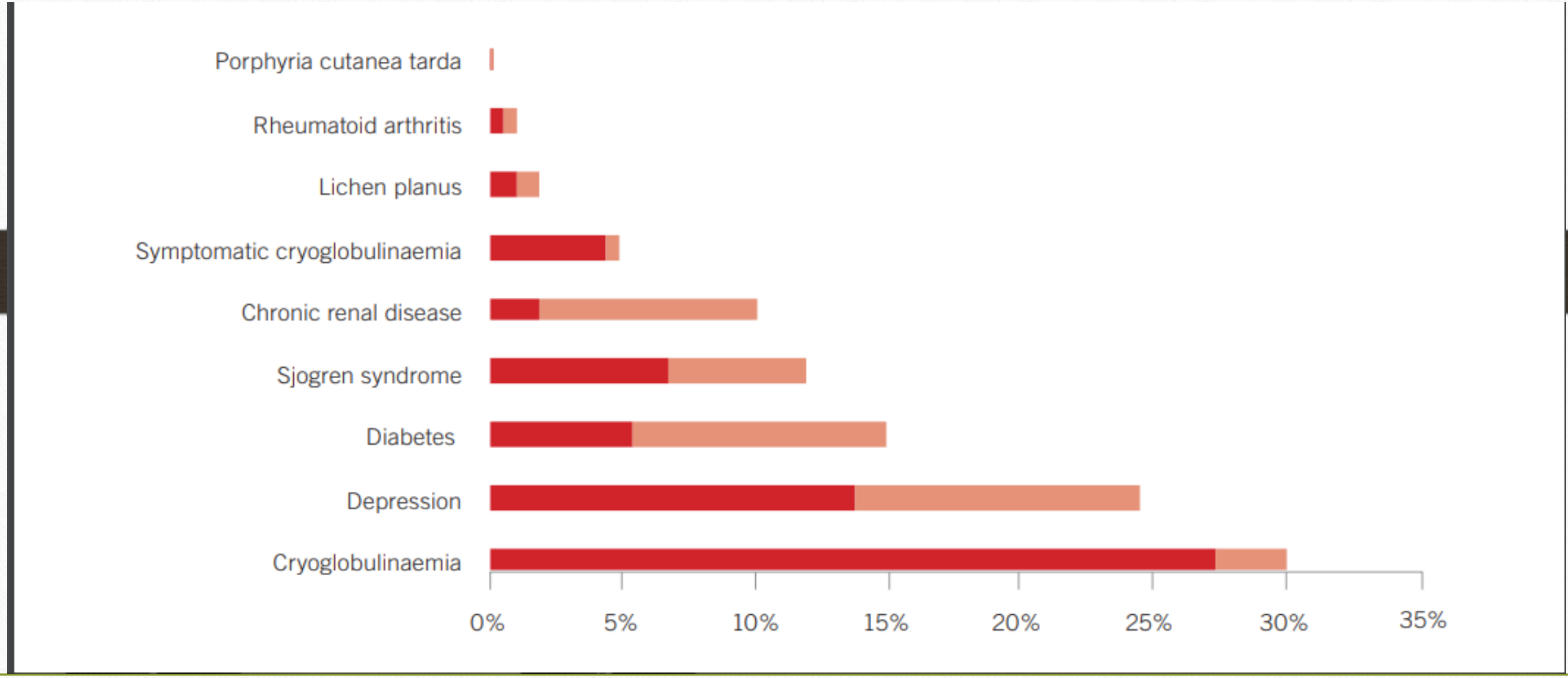

GBD region
Asia Pacific, high income
Asia, Central
Asia, East
Asia, South
Asia, Southeast
Australasia
Europe, Central
Europe, Eastern
Europe, Western
Carribbean
Latin America, Andean
Latin America, Central
Latin America, Southern
Latin America, Tropical
North Africa/Middle East
North America, high income
Oceania
Sub-Saharan Africa, Central
Sub-Saharan Africa, East
Sub-Saharan Africa, Southern
Sub-Saharan Africa, West
HCV genotype proportion
1
2
3
4
5
6
Mixed or other
15·3 million
4·7 million
2·1 million
520 000
117 000

- HCV infection should be considered as a systemic disorder which is often associated with a number of extrahepatic manifestations .

- Almost 40% of patients with HCV develop at least one extrahepatic manifestation during the course of the disease.


Memory loss
Cognitive dysfunction
Fatigue
Myocarditis
Pericarditis
Palpitate
Acute hepatitis C
Chronic hepatitis C
Liver cirrhosis
Severe hepatitis
Hpatic failure
HCV
Pneumonia
Bronchitis
Emphysema
Lupus nephritis
Chronic kidney disease
Renal cell carcinoma
Acute kidney injury
Glomerulinephritis
Diabetic nephropathy

Prevalence of comorbidities among persons with HCV infection



HCV injuries the kidneys by three possible mechanisms:

(a) immune-mediated mechanism

(b) direct virus attacks on nephron tissue

(c) Drug toxicity

Immune-Mediated Kidney Lesions in HCV

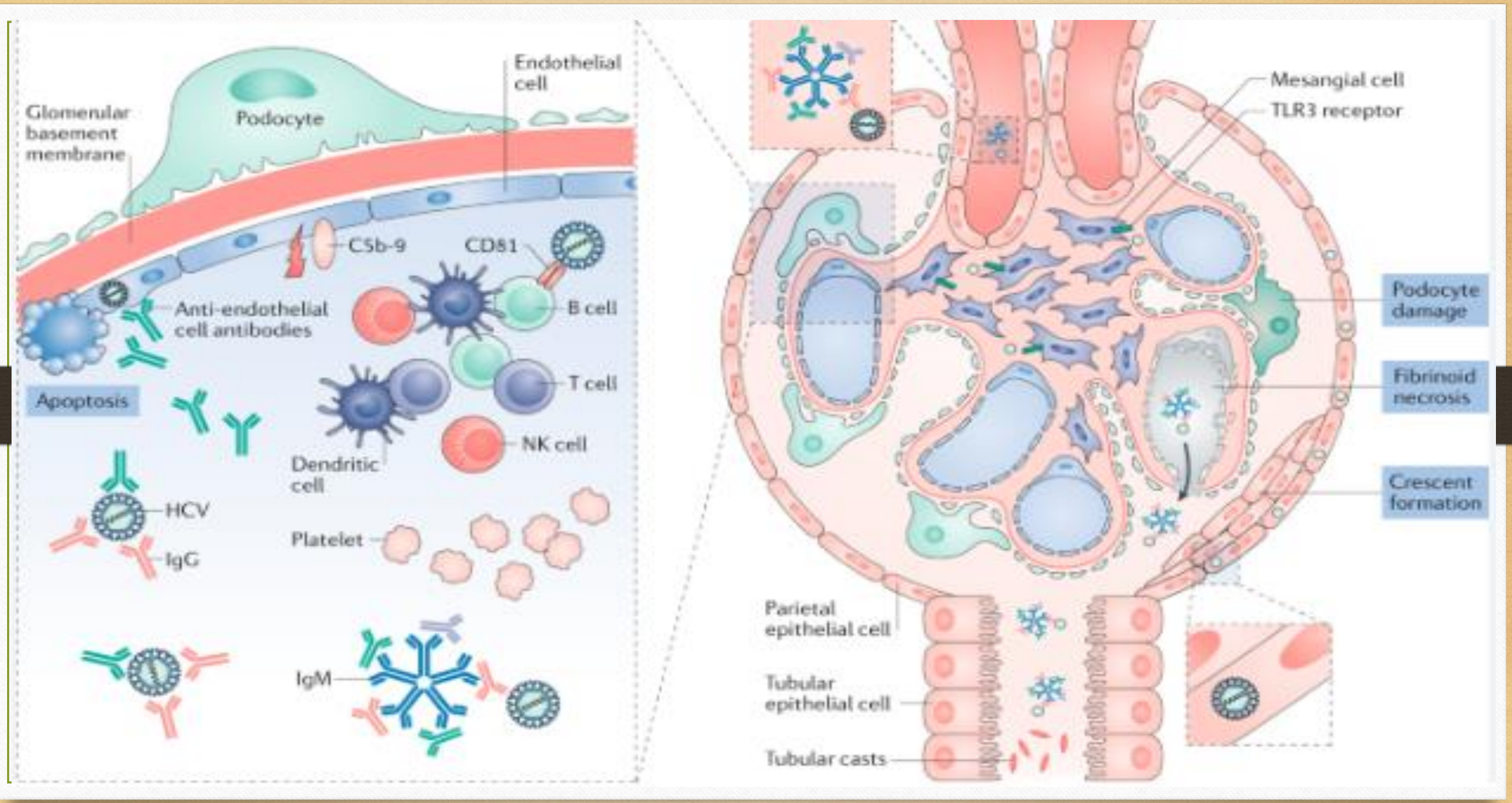
- Kidney tissue express CD81 , which is believed to be the receptor through which HCV infects B lymphocytes and liver cells .
- HCV antigens activate B lymphocytes to produce autoantibodies, immune-mediated cryoprecipitates, and non-cryoprecipitate complexes .
- The formed immune complex contains HCV or its remnants deposit in the nephron tissue, causing glomerular inflammation, initiating anti-HCV-IgG, complement activation, and anti-endothelial antibody production.

Immune-Mediated Kidney Lesions in HCV

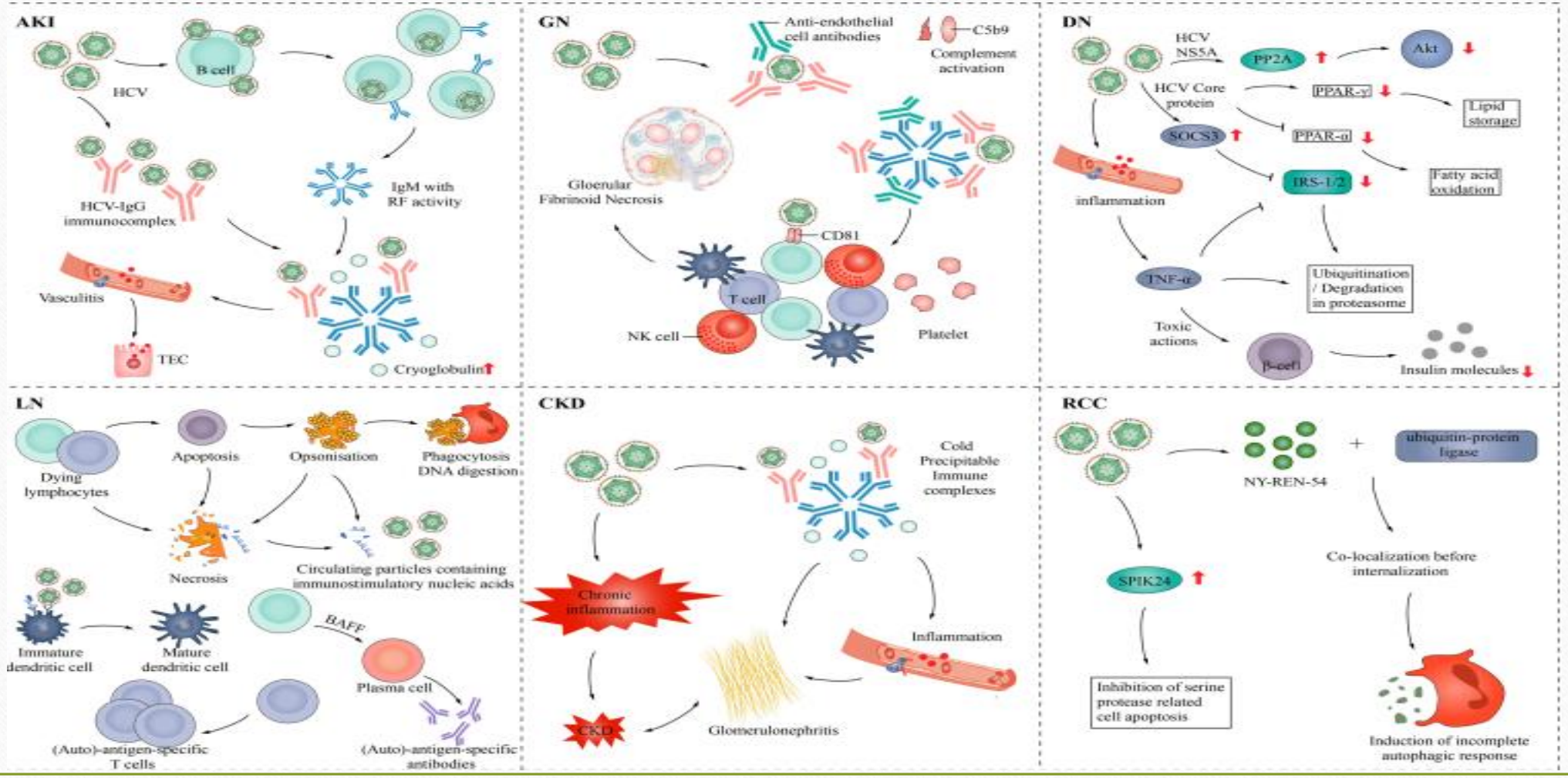
- This process causes adhesion molecule overexpression, recruiting different cell types, such as dendritic cells, natural killer cells, T and B cells lymphocytes, activating the thrombocyte and promoting its aggregation.

Direct Effects of HCV on the Kidneys

- HCV-infected endothelium cells may undergo apoptosis.
- HCV damages Bowman capsule epithelial cells and causes podocyte injury.
- HCV can also induce lysosomal enzyme abnormalities in macrophages.


Glomerular basement membrane
Podocyte
Endothelial cell
C5b-9
CD81
B cell
Anti-endothelial cell antibodies
T cell
Apoptosis
NK cell
Dendritic cell
HCV
IgG
Platelet
IgM
Mesangial cell
TLR3 receptor
Podocyte damage
Fibrinoid necrosis
Crescent formation
Parietal epithelial cell
Tubular epithelial cell
Tubular casts

HCV in renal diseases



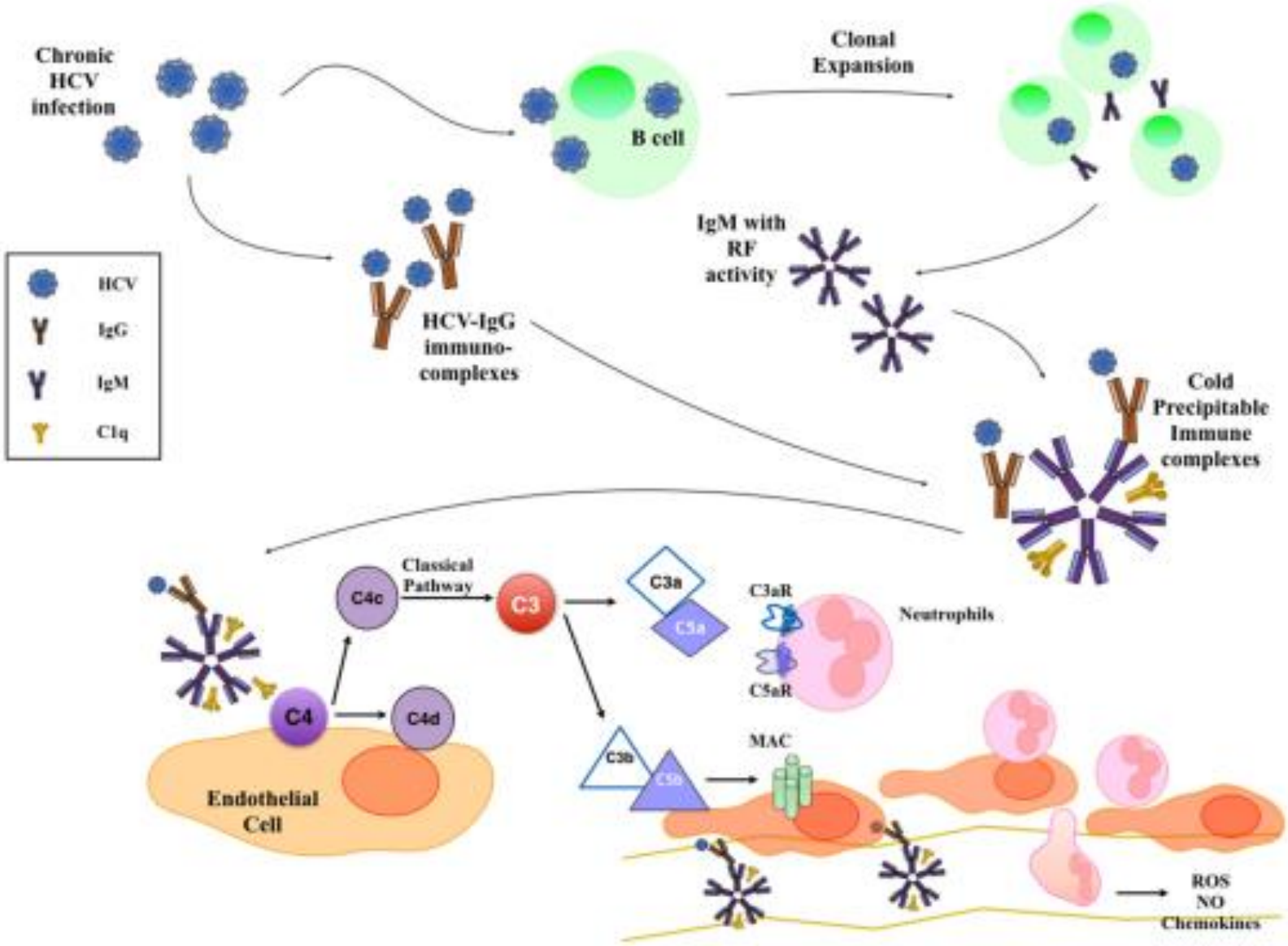
HCV & MPGN

- The most prevalent type of HCV-associated GN is TypeIMPGN, with type II cryoglobulinaemia.
- HCV is the primary cause of mixed cryoglobulinaemia, which leads to cryoglobulinaemic vasculitis and cryoglobulinaemic glomerulonephritis.
- HCV RNA has been reported to be present in 80% of cases of cryoglobulinemia-related MPGN but only in 25% of MPGN cases without cryoglobulinemia.

Common types	Less common types
MPGN, with cryoglobulinemia	• MPGN without cryoglobulinemia • IgA nephropathy • Postinfectious glomerulonephritis • Membranous nephropathy • Thrombotic microangiopathies • Focal and segmental glomerulosclerosis • Fibrillary or immunotactoid glomerulopathy.

pathophysiological mechanism of HCV-related MC

- The pathophysiological mechanism of HCV-related MC probably involves E2-CD81 interaction.
- CD81 is expressed on B lymphocytes and the E2-CD81 interaction leads to monoclonal proliferation of B lymphocytes and eventually HCV-related MC.
- Persistently stimulated B-lymphocytes produce immunoglobulin G (IgG)-HCV complexes, resulting in the generation of rheumatoid factor-IgM and cryoglobulins.


Chronic HCV infection
B cell
Clonal Expansion
HCV
IgG
IgM
C1q
HCV-IgG immuno-complexes
IgM with RF activity
Cold Precipitable Immune complexes
Classical Pathway
C4c
C3
C3a
C5a
C3aR
C5aR
Neutrophils
C4
C4d
Endothelial Cell
C3b
C5b
MAC
ROS
NO
Chemokines

pathophysiological mechanism of HCV-related MC

- Cryoglobulins may also induce endothelitis via anti-endothelial activity and complement activation leading to increased expression of VCAM-1 and platelet aggregation.

pathophysiological mechanism of HCV-related MC

- Toll-like receptors (TLR) may also have a role in HCV-associated renal injury.
- TLR3 expression was found to be increased in the mesangial cells of patients with HCV-related MPGN.
- Glomerular expressions of TLR4 and fibronectin were found to be upregulated in a murine model of cryoglobulinemic glomerulonephritis.

Clinical presentations of patients with Cryoglobulinemic vasculitis:

- Cryoglubulinemic vasculitis is seen in 2-3 % patients,
  The triad of purpura, asthenia, and arthralgia is in 30% of these case.
- Most of the patients (80%) have severe hypertension.
- The serum levels of C4 and C1q are usually very.
- The majority of such patients are RF-positive.
- It is rarely associated with "occult" HCV infection that can be only unveiled by nucleic acid testing in liver or bone marrow biopsy.

Clinical presentations of patients with Cryoglobulinemic nephritis (CN):

Isolated proteinuria (<3 g/24 h), usually with microscopic hematuria (30%).

Nephrotic syndrome (20%)

Acute nephritic syndrome (15%). Some patients present with a mixed nephrotic and nephritic syndrome

Macroscopic hematuria (10%)

Chronic renal insufficiency (10%)

Acute kidney injury with oligoanuria (5%)

HCV & MN

- The clinical presentation and the histological findings of HCV-associated MN are similar to idiopathic MN.
- Usually serum complement levels are normal.
- cryoglobulins and RF are absent in the serum.
- HCV RNA was detectable in all of these patients.

SCREENING

SCREENING

- HCV-positive patients should be screened annually for microalbuminuria, microscopic hematuria, RF, cryoglobulinemia, complement factors and hypertension.

- kidney biopsy be performed in HCV-infected patients with clinical evidence of glomerular disease .

TREATMENT

Three approaches may be suggested for the treatment

- (1) antiviral therapy to prevent the further direct damage of HCV on kidneys and synthesis of immune-complexes.
- (2) B-cell depletion therapy to prevent formation of immune-complexes and cryoglobulins.
- (3) nonspecific immunosuppressive therapy to prevent the synthesis of immune-complexes and cryoglobulin associated vasculitis.

Treatment of HCV Infection

- The choice of specific regimen be based on HCV genotyp (and subtype), viral load, prior treatment history, drug–drug interactions, (GFR), stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities.

- The definitive cure of HCV infection is commonly reflected by the sustained virologic response (SVR), defined as no-viremia for 24 weeks after ending antiviral therapy.

Treatment of HCV Infection

- Prior iterations of these guidelines had recommended initiation of both interferon/ribavirin and immunosuppression for cryoglobulinemic glomerulonephritis.

- This important paradigm shift occurred because data suggests that approximately 70% of patients with cryoglobulinemic glomerulonephritis will go into either a partial or complete remission with DAAs (Direct-acting antivirals) alone.

RIBAVIRIN

- Ribavirin is rarely warranted, but if indicated, it is dose reduced in CKD.
- Patients with GFR < 30 ml/min per 1.73 m2 (CKD G4–G5D) should be treated with a ribavirin-free DAA.
- Patients with GFR≤50 but ≥30 per 1.73 m2 , ribavirin given orally at alternating doses of 200 and 400 mg every other day
- Ribavirin may cause hemolytic anemia especially in patients with reduced renal functions.

- Taribavirin, a prodrug of ribavirin, does not significantly accumulate in erythrocytes, and has shown an antiviral efficacy similar to that of ribavirin, with a lower occurrence of anemia.

IFN-α

- IFN-α has been reported to exacerbate proteinuria and vasculitis in some patients with glomerulopathies.

- One of the immunologic effects of IFN is the alteration of the balance of (Th1) and (Th2) , IFN-induced Th1-dominant immune response may be involved in the exacerbation of underlying glomerulonephritis.

DAA(UP TO DATE)

- patients with HCV-related glomerular disease showing stable kidney function and/or non-nephrotic proteinuria be treated initially with DAA.
- For all patients with chronic HCV infection , including those with sevser renal impairment , who have accsess to DAA therapies.
- For patients with MC suggest antiviral treatment even if life expectancy is limited to improve ranal function and symptom,DAA is warranted.
- No dose adjustment are warranted for DAA agents in patients with sever renal impairment or on dialysis.

Direct-acting antivirals (DAAs) according to class

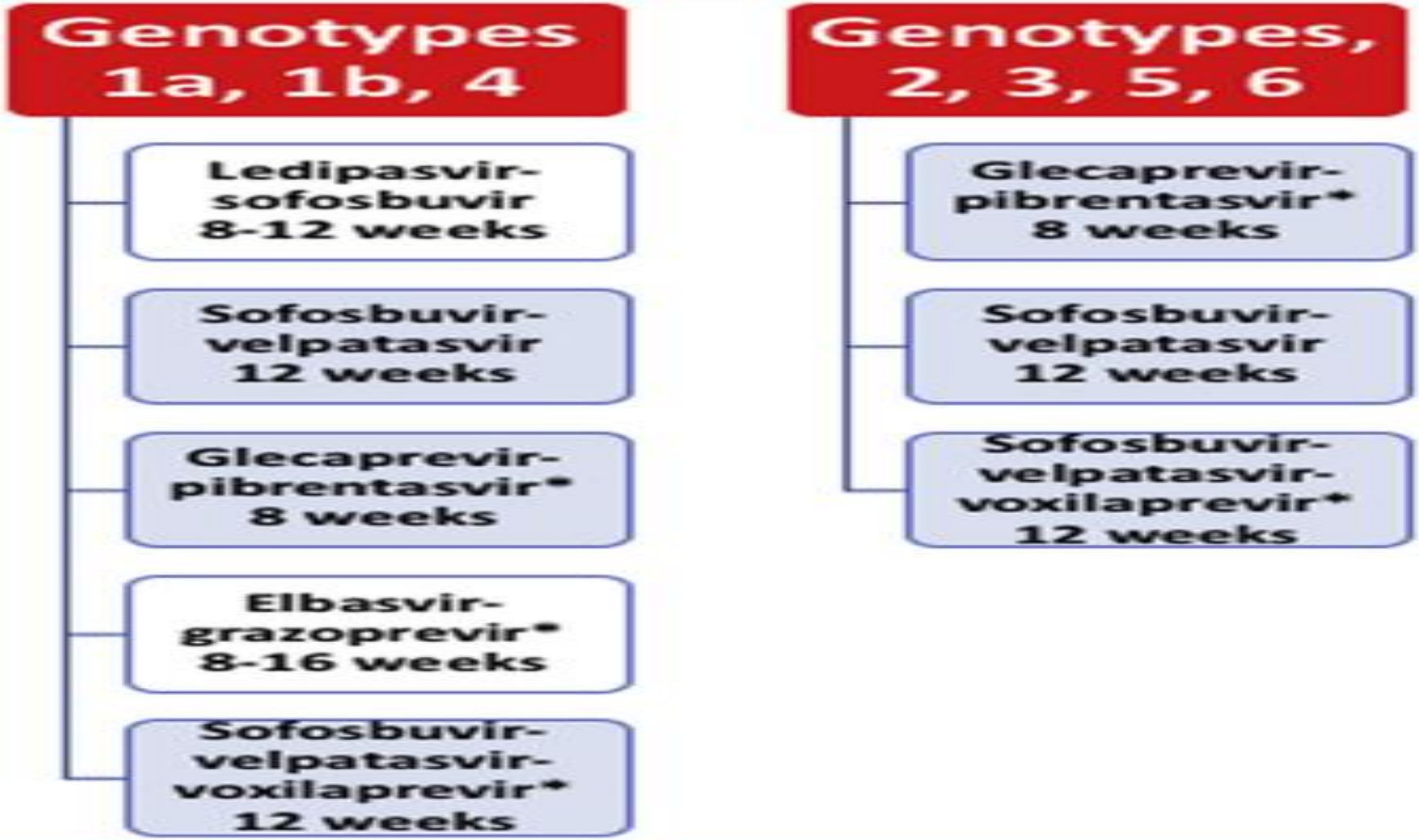
NS3/4A (protease) inhibitors	NS5A inhibitors	NS5B polymerase inhibitor (nucleotide analogue)	NS5B polymerase inhibitor (non-nucleoside analogue)
Glecaprevir	Daclatasvir	Sofosbuvir	Dasabuvir
Voxilaprevir	Velpatasvir		
Grazoprevir	Ledipasvir		
Paritaprevir	Ombitasvir		
Simeprevir	Pibrentasvir		
	Elbasvir		

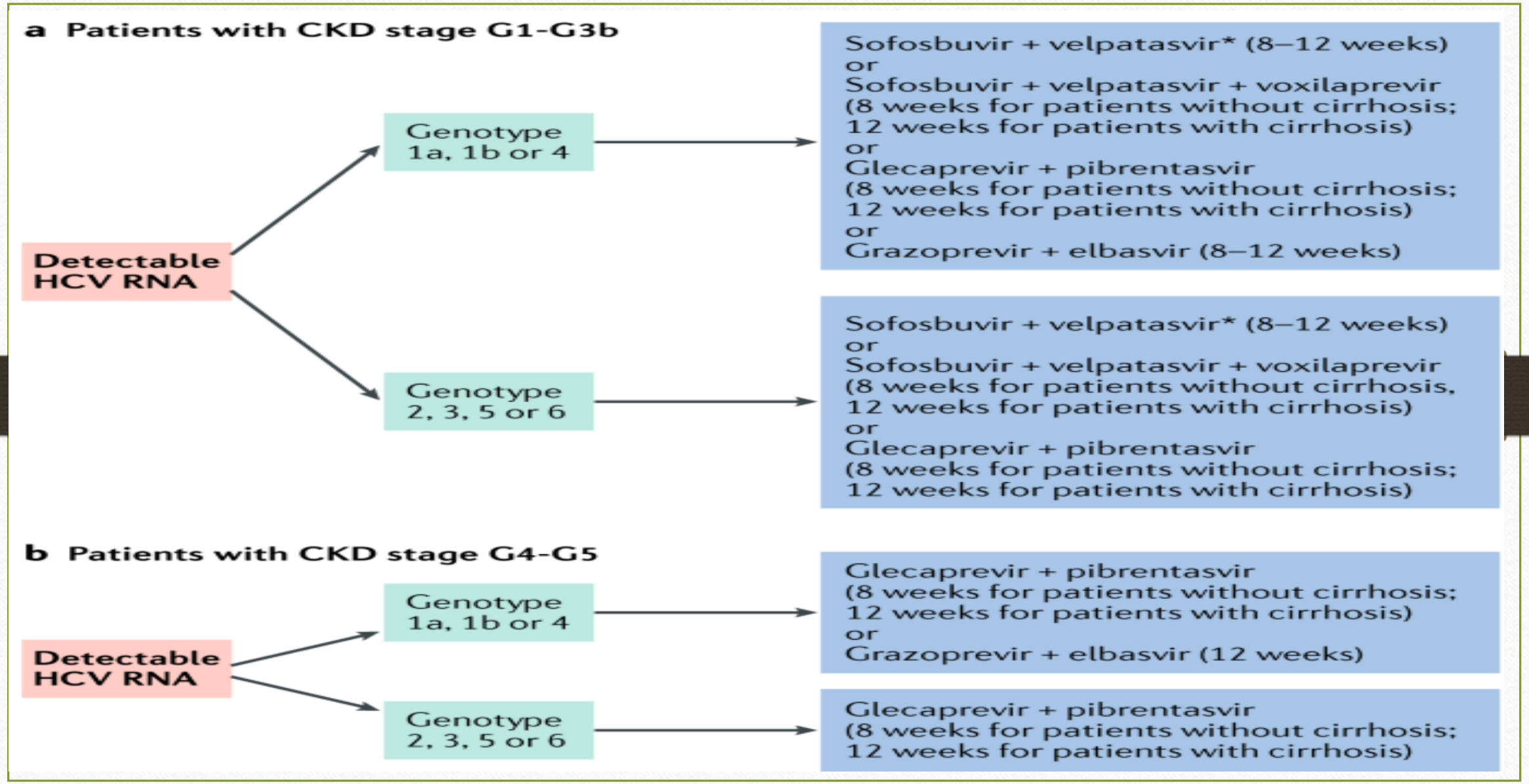
sofosbuvir

- Although sofosbuvir, the first novel DAA approved in 2013, and its active metabolite are renally eliminated, numerous studies have suggested sofosbuvir is safe in patients with kidney disease.

- multiple real-world studies showed that sofosbuvir-based DAAs were effective and well-tolerated in the dialysis populations, and other analyses showed extremely low rates of kidney injury in patients receiving sofosbuvir-based DAAs.

HCV –CKD (AGKD)


Genotypes 1a, 1b, 4
Ledipasvir-sofosbuvir 8-12 weeks
Sofosbuvir-velpatasvir 12 weeks
Glecaprevir-pibrentasvir* 8 weeks
Elbasvir-grazoprevir* 8-16 weeks
Sofosbuvir-velpatasvir-voxilaprevir* 12 weeks
Genotypes, 2, 3, 5, 6
Glecaprevir-pibrentasvir* 8 weeks
Sofosbuvir-velpatasvir 12 weeks
Sofosbuvir-velpatasvir-voxilaprevir* 12 weeks


a Patients with CKD stage G1-G3b
Detectable HCV RNA
Genotype 1a, 1b or 4
Sofosbuvir + velpatasvir* (8–12 weeks)
or
Sofosbuvir + velpatasvir + voxilaprevir
(8 weeks for patients without cirrhosis;
12 weeks for patients with cirrhosis)
or
Glecaprevir + pibrentasvir
(8 weeks for patients without cirrhosis;
12 weeks for patients with cirrhosis)
or
Grazoprevir + elbasvir (8–12 weeks)
Genotype 2, 3, 5 or 6
Sofosbuvir + velpatasvir* (8–12 weeks)
or
Sofosbuvir + velpatasvir + voxilaprevir
(8 weeks for patients without cirrhosis,
12 weeks for patients with cirrhosis)
or
Glecaprevir + pibrentasvir
(8 weeks for patients without cirrhosis;
12 weeks for patients with cirrhosis)
b Patients with CKD stage G4-G5
Detectable HCV RNA
Genotype 1a, 1b or 4
Glecaprevir + pibrentasvir
(8 weeks for patients without cirrhosis;
12 weeks for patients with cirrhosis)
or
Grazoprevir + elbasvir (12 weeks)
Genotype 2, 3, 5 or 6
Glecaprevir + pibrentasvir
(8 weeks for patients without cirrhosis;
12 weeks for patients with cirrhosis)

Indication of immunosuppressive:

- There are two groups of patients with cryoglobulinemic glomerulonephritis that need immunosuppression in addition to DAAs.

Indication of immunosuppressive:

- First, patients with aggressive, organ-threatening manifestations, including rapidly progressive glomerulonephritis, severe systemic vasculitis (central nervous system involvement or pulmonary hemorrhage), or symptomatic nephrotic syndrome.

- second group that may need immunosuppression are patients who receive DAAs and achieved SVR, yet continue to display signs and symptoms of active glomerulonephritis .

Indication of immunosuppressive:

- Rituximab as the first-line immunosuppressive treatment.
- Rituximab does not decrease the effectiveness of DAAs, nor is it associated with flares of clinical hepatitis when used with DAAs .
- DAA treatment should be concurrent, there is no reason to delay DAA initiation in patients who also require immunosuppression. (delay antiviral therapy for one to four months (UPTO DATE)

Non-specific Immunosuppressive Therapy

- Cyclophosphamide has also been used to suppress B cell function and cryoglobulins production, but this treatment should be used with caution because it can induce flare-ups of HCV infection
- mycophenolate mofetil is a more selective treatment to inhibit lymphocyte proliferation and function and represents a safer alternative to induce remission in cryoglobulinemic vasculitis .
- Steroid pulses or low doses of steroids have been used to treat glomerular infiltration .

Rituximab VS cyclophosphamide

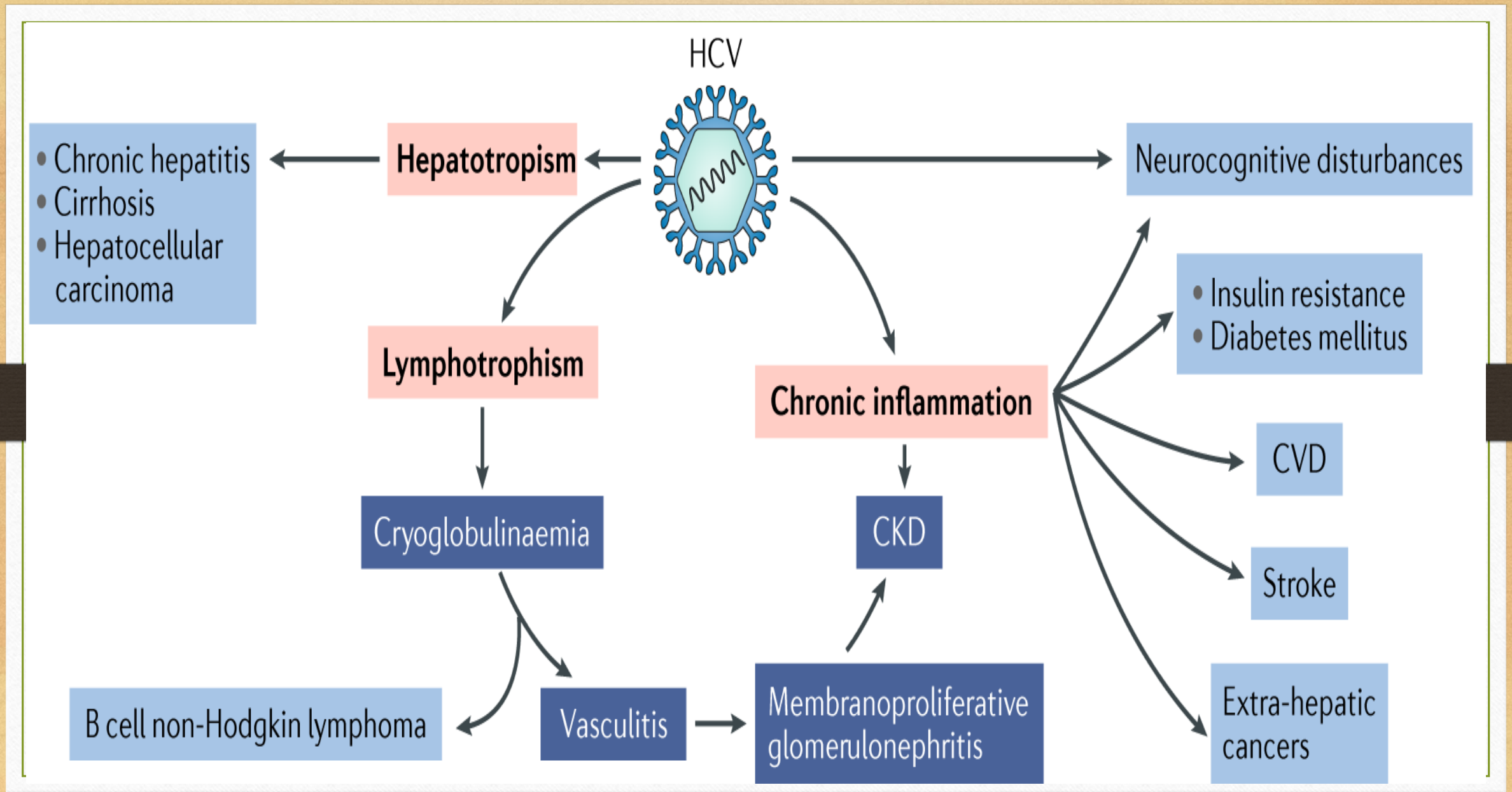
- When compared to cyclophosphamide, rituximab may be suggested to be the prefered agent in the treatment of HCV-associated glomerulopathies because it is at least as efficient as cyclophosphamide in inhibiton of the synthesis of immunecomplexes and cryoglobulins, and it does not seem to cause flare of HCV infection

Plasmapheresis

- Plasma exchange therapies are performed in the acute phase of the disease to remove circulating immunecomplexes and cryoglobulins from the plasma.
- The usual dose of plasmapheresis in the treatment of HCV-associated glomerulopathies is the exchange of 3 L of plasma 3 times/ wk.
- It should be combined with immunosuppressive therapies to prevent the re-accumulation of immune-complexes and cryoglobulins.

IL-2

- Low-dose interleukin 2 (IL-2) has been recently suggested as an alternative treatment for HCV-associated mixed cryoglobulinemic vaculitis.
- IL-2 is hypothesized to promote regulatory T cell (Treg) survival and function.
- Reduction in cryoglobulinemia and improvement of vasculitis were observed and it led to a prominent inhibition of inflammation and oxidative stress mediators.


HCV
Hepatotropism
• Chronic hepatitis
• Cirrhosis
• Hepatocellular carcinoma
Neurocognitive disturbances
Lymphotrophism
Cryoglobulinaemia
B cell non-Hodgkin lymphoma
Vasculitis
Membranoproliferative glomerulonephritis
Chronic inflammation
CKD
• Insulin resistance
• Diabetes mellitus
CVD
Stroke
Extra-hepatic cancers

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Thank
you!