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Modern Approaches to Hepatitis C Virus Diagnosis and Prevention in Hemodialysis Patients: A Review

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المناهج الحديثة لتشخيص والوقاية من فيروس التهاب الكبد C لدى مرضى غسيل الكلى: مراجعة

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ABSTRACT

Chronic kidney disease (CKD) as well as other organ systems could be impacted by Hepatitis C virus (HCV) infection, a global health issue with a considerable economic and health burden. Furthermore, compared to the general population, the frequency of hepatitis C is still greater in patients who have chronic kidney disease (CKD), such as those receiving chronic hemodialysis and those who have received a kidney transplant. Since Kidney Disease: Improving Global Outcome (KDIGO) released its 2008 guideline for the diagnosis, prevention, and therapy of hepatitis C in CKD, there has been a significant change in the way hepatitis C has been managed. Consequently, KDIGO released an update to such a recommendation in the year 2018. In this review, the suggestion for HCV detection and screening in CKD, HCV treatment prior to and following kidney transplantation, HCV treatment in CKD patients, treatment of kidney disease related to HCV infection, and HCV transmission prevention in hemodialysis units. This review focus on the clinical implications pertaining to direct-acting antivirals in patients undergoing dialysis, individuals afflicted with severe chronic kidney disease, as well as recipients of kidney transplants. This study emphasizes the critical importance of meticulously monitoring potential drug-drug interactions between immunosuppressive therapies and DAAs, discuss the optimal timing for initiating hepatitis C virus treatment in relation to the timing of kidney transplantation. Finally, the study identifies areas of ambiguity that necessitate further research prior to the formulation of definitive recommendation.

Keywords: CKD, Hepatitis C, screening, hemodialysis, prevention

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1. INTRODUCTION

The ongoing rise in the number of patients with CKD has made it a global public health concern. The increasing number of patients with high blood pressure (HBP) as well as diabetes mellitus (DM), the two main risk factors for CKD, is mostly to blame for the disease's increased prevalence. In addition to increasing the risk of CKD, HBP might be a side effect of CKD, manifesting in the majority of patients at some point throughout the disease's progression [1-3]. For advanced-stage chronic kidney disease (CKD), renal replacement heals. In any case of the cause of CKD, the patient's health state is significantly impacted by the increasing loss of kidney functions [4,5]. Patients on hemodialysis are particularly vulnerable to infection because of their compromised immune systems, frequent hospital stays, and surgical procedures.

Furthermore, hemodialysis itself entails prolonged and/or frequent blood exposure through the extracorporeal circuit and vascular access, as well as through other patients' close proximity throughout dialysis, equipment changes, and interactions with medical personnel. Hemodialysis patients are comparatively susceptible to infection with HCV, a specific kind of blood-borne viral infection [6]. Various studies in specialized literature indicate the link between chronic hepatitis and HCV and increased mortality-morbidity among hemodialysis as well as transplant patients. Furthermore, statistical research indicates that the prevalence regarding infection among patients with CKD ranges from 5 to 60% (in industrialized nations), with a particular preponderance among those receiving chronic hemodialysis [7-9]. Furthermore, data up to 2006 substantiate the elevated global prevalence of HCV, 1.47 per 100 patient-years, with a distinct distinction between industrialized and underdeveloped nations [10,11]. Several studies in the particular literature support the prevalence among hemodialysis patients [12,13].

The probability of virus transmission has not significantly decreased, even with the creation of preventative measures. This supports the necessity of educating patients and medical personnel more about the guidelines for preventing HCV transmission in hemodialysis facilities [14-18]. The patients' immunological condition must be known for stopping the infection from spreading. Since the majority of patients do not exhibit clinical symptoms suggestive of HCV infection, it is particularly crucial that patients have routine checkups and screenings [19]. This article aims to provide a comprehensive overview of the most recent advancements and guidelines in managing hepatitis C virus (HCV) infection in patients with chronic kidney disease (CKD). By highlighting the interplay between HCV and CKD, the article seeks to shed light on effective strategies for prevention, diagnosis, and treatment, particularly in high-risk groups such as dialysis patients and kidney transplant recipients.

2- RELATIONSHIP BETWEEN CHRONIC KIDNEY DISEASE AND HEPATITIS C VIRUS

In spite of a decline during the past 20 years, the frequency regarding HCV infection in hemodialysis patients is still greater compared to the general population [20] According to Jadoul et al. [13] utilizing the Dialysis Outcomes and Practice Patterns Study (DOPPS), approximately 10% of hemodialysis patients had an HCV infection between 2012 and 2015, as demonstrated by an antibody seropositivity or recorded diagnosis [21].

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In Japan, China, Spain, Italy, and Russia, the incidence was intermediate, ranging between 4% in Belgium to up to 20% in Middle East [22]. Between 1996 and 2015, HCV stopped in US section dropped from 11.50% to 6.90%. Nonetheless, data suggests that 31,000 of 448,000 hemodialysis patients in the US by the end of 2016 , have been seropositive for HCV. Typical HCV risk factors (such as remote blood transfusions and intravenous drug use) and nosocomial transmission throughout hemodialysis are among the mechanisms of HCV acquisition among hemodialysis patients. In patients receiving hemodialysis, HCV infection is correlated to lower quality of life ratings as well as the highest risk of hospitalization and mortality [14]. The seropositive status for Hepatitis C is anticipated to be observed in 4.8% of patients undergoing hemodialysis who are on transplant waiting lists. The prevalence regarding HCV positivity at the beginning of hemodialysis (i.e., HCV has been acquired prior to hemodialysis) was examined in the recent DOPPS study. It has been indicated to be around 5%, which has barely changed over the past 20 years and is significantly higher compared to general population in DOPPS countries [18].

3- ENHANCED STRATEGIES FOR DIAGNOSING AND SCREENING HCV IN CHRONIC HEMODIALYSIS PATIENTS

Testing for HCV infection is advised for certain groups of people who are more susceptible to infection, according to the Infectious Diseases Society in America (IDSA) and American Association specialized for Study of Liver Diseases (AASLD) [23-25]. These include intranasal or intravenous drug users, chronic hemodialysis patients, former convicts, transplant recipients before July 1992, and people with a history of HIV infection. For those who are at risk, such as those who have been punctured by needles or other potentially contaminated sharp items, or who were born between 1945 and 1965, testing for HCV infection is advised [26]. The requirement for screening in CKD patients is justified by the increased prevalence regarding HCV infection in those individuals relative to the general population as well as the quick progression to high advanced stages when HCV infection is present [27].

In the case when starting Renal Replacement Therapy, transferring from another dialysis facility, or switching the RRT modality (from hemodialysis to peritoneal dialysis, for example), and on a periodic basis, every 6 months, patients receiving chronic hemodialysis are tested for HCV infection [28]. Two types of laboratory testing are required for diagnosing HCV infection: molecular tests detecting viral particles as well as serological tests for detecting anti-HCV antibodies [29]. In patients receiving chronic hemodialysis, this method is suitable for diagnosing HCV infection figure (1).The "serological window," or the interval of time between blood antibody detection and HCV infection, differs from patient to patient. Anti-HCV antibody detection is possible with the serological assays that are presently available 7–8 weeks following infection. Anti-HCV antibodies might last a lifetime following infection eradication, or their titer could gradually drop until it vanishes over a number of years. The presence of anti-HCV antibodies may persist indefinitely in individuals afflicted with chronic infections [30]. A follow-up test, like the recombinant immunoblot assay (RIBA), is required to establish reactivity against two viral antigens in the case when laboratory tests produce positive results. With the exception of blood banks, confirmation will be less important as screening tests and molecular approaches advance. Polymerase chain reaction (PCR) testing for HCV-RNA verifies diagnosis

and measures the quantity regarding viral copies in blood (viremia). HCV-RNA is detectable in nearly all patients with chronic infections [31].

Testing for liver transaminases, particularly alanine transaminase, as well as anti-HCV antibodies is advised for patients beginning hemodialysis. Anti-HCV antibody detection does not differentiate between past and current infections. Confirming an active HCV infection requires the detection of HCV-RNA [32]. Testing for HCV-RNA could identify infection one week following exposure, while anti-HCV antibodies might be seen in serum about 7–8 weeks following exposure. Treatment varies according to the HCV genotype, which comes in a variety of forms. Genotype identification might not often be necessary for diagnosis and therapy because direct antiviral medicine covers several genotypes [33].

Serum alanine-transaminase (ALT) as well as anti-HCV antibodies levels are commonly assessed in patients receiving chronic hemodialysis. Initial HCV-RNA testing is advised in dialysis facilities where HCV infection is highly prevalent [34-36]. HCV-RNA testing must be performed on patients who have anti-HCV antibodies found. Testing must be done every 6 months for patients whose HCV-RNA levels are undetectable, regardless of whether they were cured naturally or after therapy. A declaration regarding infection and treatment is mandated for individuals exhibiting detectable levels of HCV-RNA [37].

Anti-HCV antibodies must be checked every 6 months and ALT levels must be checked monthly for patients without HCV infection . Immunological testing for HCV infection is advised if ALT levels rise; if not, additional testing is not required [38]. Epidemiological studies must determine if an HCV infection or seroconversion happened outside or within of a dialysis facility when a new case is discovered there. Along with evaluations regarding the viral status of other patients at risk, internal audits of clinical practice should be carried out with accordance to infection prevention and hygiene guidelines. Effective management of infection control depends on identifying and fixing errors [39]

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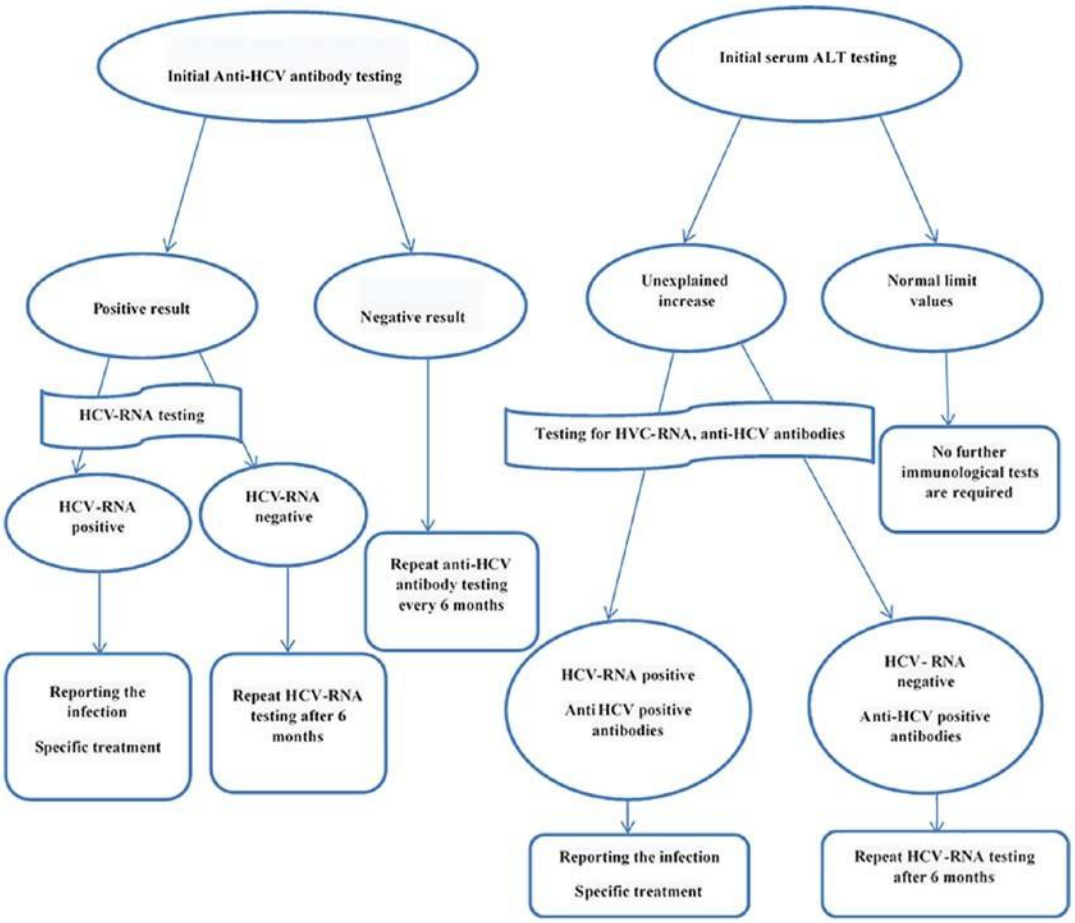

Figure 1. Diagnosis algorithm of HCV infection in hemodialysis patients [31]

4- PREVENTING HCV TRANSMISSION IN HEMODIALYSIS UNITS

It is commonly known that hemodialysis units can limit the spread of HCV [40]. Glove use, hand hygiene, environmental surface disinfection, and injectable medication handling are among the many infection control shortcomings that are commonly seen in the majority of documented HCV outbreaks in hemodialysis facilities. Observational audits must be used to support regular evaluation as well as adherence to evidence-based interventions. Since there is no proof that HCV can spread through the closing inner pathways regarding single-pass dialysis machines, guidelines do not advise the isolation of patients with HCV throughout hemodialysis sessions or using special dialysis equipment for such patients[41].

Monthly ALT level checks and HCV immunoassays or NAT tests every 6 months are used for screening patients in hemodialysis units with regard to HCV infection. All hemodialysis patients must be checked, the frequency regarding follow-up tests must be raised, and a thorough examination of infection control procedures must be carried out in the case when a newly

acquired HCV infection is found. Public health authorities must be informed of any suspected HCV seroconversion obtained while receiving hemodialysis[41].

Organizing the Treatment Area in Hemodialysis Centers:

The best possible space compartmentalization is required for preventing HCV infection. With regard to hemodialysis session, each one of the patients must have a separate space known as the "patient's area." This area must be regarded as polluted since it contains dialysis machine, the treatment bed or armchair, and the surrounding. By disinfecting and cleaning the area following the patient leaves, bringing sterile materials into the space only following disinfection, and forbidding the movement of sterile materials across patient areas, infection transmission can be prevented[42].

Employment and Isolation of Dialysis Machines for Infected Patients

In addition to strict hygiene guidelines and equipment precautions, isolation and using special equipment and rooms are advised for patients with HBV in order to stop transmission. Yet, investigations have shown that patients infected with HCV do not require these interventions [43]. According to recent studies, strict adherence to general hygiene guidelines is the most efficient way for preventing the spread of infection; isolating HCV-infected patients does not help [44,45]

The chance of the virus penetrating the dialysis-membrane is low in HCV-positive patients. It is not strictly advised to employ specialized dialysis equipment for patients with HCV; instead, these devices could be used in the treatment area for patients with seronegative results. Yet, the risk regarding HCV transmission rises in the case when seronegative patients are dialyzed close to HCV-positive patients without strict hygiene precautions [22].

Considerations for the Hepatitis B Virus

However, because of the significant infectious risk posed by high viral loads as well as the long-term persistence regarding HBV on surfaces (up to seven days), patients infected with HBV need to be isolated in different rooms and treated on specialized machines [37].

Hemodialysis patients in Romania have a significant prevalence of HCV positive . At least four patients are usually under the care of a dialysis nurse [45]. For seropositive patients, a professional dialysis nurse must ideally handle connection as well as blood restitution. Yet, as long as basic hygiene precautions are taken to avoid infection transmission, Seronegative and seropositive patients might be treated at the same time by the same nurse. Furthermore, the nurse must follow specific practice guidelines: seronegative patients must be connected to the hemodialysis machine at the start of the session and seropositive patients must be disconnected at the end of session [46].

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Hand Hygiene

Strict adherence to hygiene guidelines is essential in the hemodialysis facility to stop the spread of HCV infections. Prior to seeing a patient, following a procedure, and following coming into contact with possibly contaminated biological fluids or dialysis machine, medical staff must wash their hands [47]. Medical staff and patients receiving RRT should wash their hands when entering and exiting the dialysis facility and in the treatment room . Patients receiving hemodialysis must properly cleanse their skin area by water with soap at the location of arteriovenous fistula, whether it is prosthetic or native[48].

Dialysis Machine, Surface, and Reusable Material Disinfection

In accordance with best practices, dialysis machine infection, both external and internal, must be cleaned following each treatment. The manufacturer's instructions for internal circuit disinfection should be followed, utilizing the recommended materials for the suggested amount of time. Prior to beginning dialysis, residue testing is required in the case when using chemicals for internal disinfection. If there are no obvious indications of biological fluid (such as blood) contamination, the external surfaces of the dialysis machine must be cleaned and sterilized by low-level disinfectants. at the conclusion of session. Hypochlorite must be utilized as a disinfectant in the case when contamination is present. The patient must often depart the treatment area following completing such procedures [49,50].

Aside from the danger of biological fluid contamination, proper disinfection regarding surfaces and reusable items utilized throughout treatment is indispensable. The right disinfecting agents at the right dilution must be used, depending on whether a low, middle, or high level of disinfection is needed [51-54]. Figure (2) show The fundamental guidelines for avoiding HCV infection in hemodialysis section

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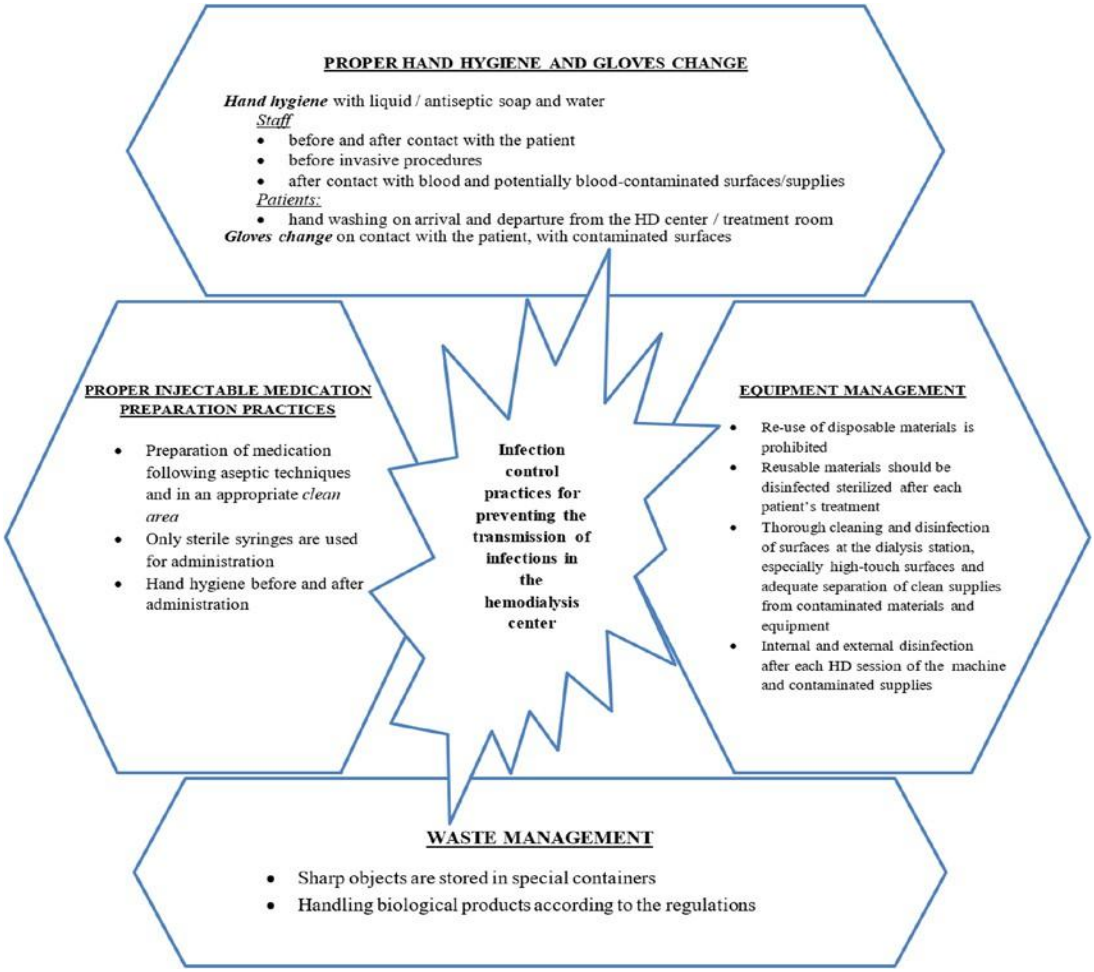

Figure 2. The fundamental guidelines for avoiding HCV infection in hemodialysis section [49].

Treatment for HCV Infection in Patients with CKD

Benefits of Treatment: A number of research's had linked a sustained viral response (SVR) to a decrease in overall population mortality .In patients with CKD, achieving SVR with HCV treatment improves cryoglobulinemic vasculitis , decreases vascular events [35] and reduces extrahepatic symptoms. In comparison with patients who do not get treatment, SVR lowers the risk regarding kidney parameter's function decline and End stage kidney disease related mortality. Achieving SVR was linked to an 88% reduced risk of CKD and an 86% lower risk of ESKD in a study that included 204 recipients of liver transplant who had HCV [54], [60]

Options for Therapy: Because of ribavirin's anemia-inducing effects and worries regarding graft rejection in kidney transplant recipients (KTRs), interferon-based treatments have been infrequently utilized in CKD patients because of their poor tolerability and low efficacy. Direct acting antivirals (DAAs), such as NS5A replication inhibitors as well as nonnucleoside NS5B polymerase inhibitors, were on the market since the year 2011 and provide good efficacy for CKD stages G4–G5 without the need for dose modifications. Yet, patients with an estimated

glomerular filtration rate of no more than 30mL/min/1.73m² are not advised to take sofosbuvir[61]- [63].

Prior to starting therapy, all potential patients must have their HBV infection levels evaluated. To avoid reactivation throughout DAA treatment, antiviral therapy for HBV must be taken into consideration in the case when hepatitis B surface antigen is found. HBV DNA as well as liver function tests must be used for the purpose of monitoring patients for reactivation in the case when there is evidence of a previous HBV infection [64]-[67].

Options for Treating Patients with G1–G5 and G5D CKD:

The European Association for the Study of Liver and KDIGO advise utilizing any existing DAA regimens without modifying the dosage for CKD Depending on local availability, regimens like glecaprevir-pibrentasvir and sofosbuvir-velpatasvir might be taken into consideration. For HCV genotypes GT1 and GT4, a combination of grazoprevir and elbasvir is advised for CKD G4–G5, such as dialysis patients (G5D). Research such as the CSURFER study showed that such regimen had a 99% SVR and good tolerability. Drug interactions with CYP3A4 inducers or inhibitors and medications that impact OATP1B1/3 transporters must be carefully avoided [68]- In spite of fibrosis or prior treatment, pangenotypic glecaprevir-pibrentasvir regimens could treat HCV GT1–GT6 in CKD G4–G5D patients. This regimen demonstrated significant efficacy even in dialysis patients, as seen by its 98% SVR in EXPEDITION-4 study figure (3).

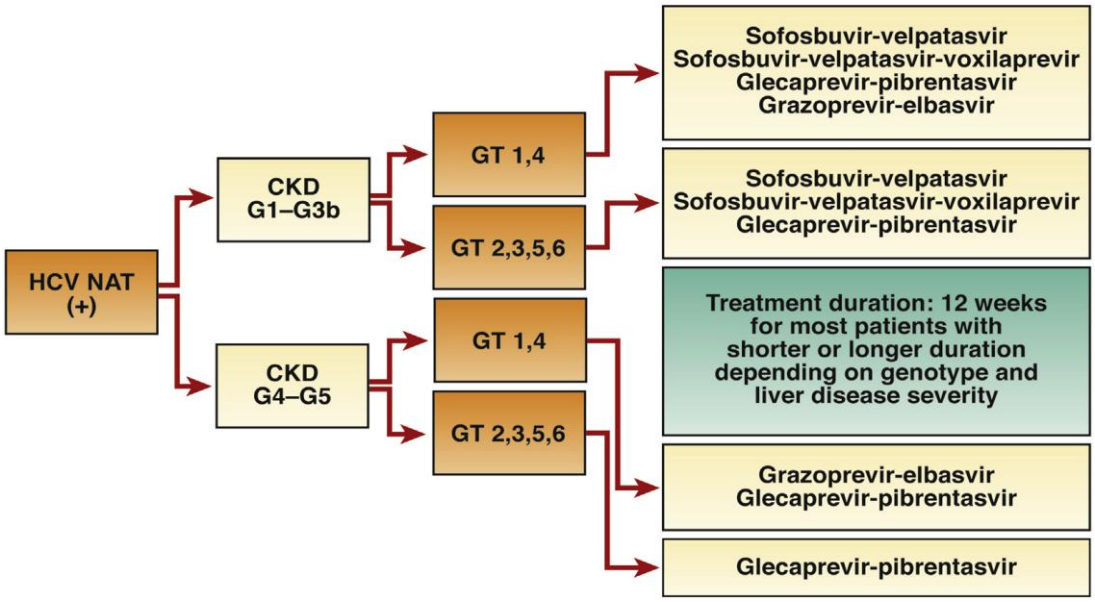

Figure (3):Options for Treating Patients with G1–G5 and G5D CKD

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5. CONCLUSIONS

Because HCV infection is linked to higher mortality rates in chronic hemodialysis patients, it is imperative that hemodialysis facilities limit the spread of the disease. It is crucial to put into practice the infection prevention strategies suggested by worldwide recommendations in hemodialysis facilities. To create customized good practice procedures, more research is necessary to assess how these general guidelines might be adjusted to the unique geographic circumstances of each hemodialysis facility.

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Conflict of interests.

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