Hepatitis C Clinical Practice Pattern

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Background and Objective of the Survey

Exploring the intricate landscape of Hepatitis C clinical practices, this examination aims to capture the diverse approaches employed by healthcare professionals in the diagnosis and management of this condition. The survey delves into key aspects such as diagnostic methods, treatment modalities, decision-making factors, adoption of novel therapies, challenges faced, and strategies for follow-up care.

Healthcare professionals play a pivotal role in shaping the clinical landscape of Hepatitis C, and their insights provide valuable perspectives on current practices. By understanding the preferences, challenges, and considerations in patient care, we aim to contribute to the ongoing improvement of clinical outcomes.

Participation in this exploration is entirely voluntary, and responses will be anonymized for research purposes. Your expertise and experiences in Hepatitis C management are invaluable, and your contribution to this survey will enhance our collective understanding of clinical practices in this dynamic field. Thank you for your time and valuable insights.

The objective of the survey is:

To study the Hepatitis C clinical practice pattern

Methodology of the Survey

A survey was conducted to study the Hepatitis C clinical practice pattern. A total of 150 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- HCV Epidemiology
- HCV Prevention
- Diagnostic Tools in HCV Infection
- New Therapeutic Era and Its Implications
- Treatment Considerations
- Sustained Virologic Response
- Role of The Primary Care Provider (Pcp) In Treating HCV

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

The history of hepatitis C virus (HCV) has always been characterized by discoveries, challenges, opportunities and difficulties. Starting with the same virus name: a *Lancet* editorial in 1975 suggested the term non-A, non-B hepatitis to describe the hepatitis neither diagnosed as A nor B, underlining that the diagnosis was one of exclusion. Fifteen years after, in 1989, Choo et al successfully cloned a single cDNA clone derived from a new flavi-like virus, by using numerous molecular biological methods: the virus responsible for most post-transfusion hepatitis, also called type C hepatitis, parenterally transmitted non-A non-B hepatitis (PT-NANB), non-B transfusion-associated hepatitis, post-transfusion non-A non-B hepatitis, HC, was finally identified. This discovery paved the way for the development of several diagnostic tests that have been developed over time, starting from the first-generation enzyme-linked immunosorbent assay (EIA-1) for the detection of antibodies to HCV epitopes, with low rates of sensitivity and specificity, until the introduction of molecular methods for the detection of acute infection, HCV RNA and genotyping analysis. Currently used molecular tests allow the detection, quantification and analysis of viral genomes and the identification of viral genotype or subtype, as well as detecting nucleotide or amino acid substitutions associated with resistance to antiviral drugs; new enzyme immunoassays can quantify hepatitis C core antigens, that can be used as alternatives to HCV RNA in patients with chronic HCV infection. Despite the great successes achieved in the fields of virology and diagnostics, several difficulties affect improvements in HCV infection control and eradication. New HCV infections still occur, especially in some of the poorest regions of the world, where HCV is endemic and long-term sequelae such as cirrhosis and hepatocellular carcinoma (HCC) have a growing economic and health burden. In developed countries, the lack of recognition of infection is the main barrier to controlling existing infection and allowing an adequate therapy. The development of an effective primary prevention measure is an unmet need: an HCV vaccine is still no available, despite years of researches and discoveries about the natural history of infection and host-virus interactions. Several HCV vaccine candidates have been developed in the last years, targeting different HCV antigens or using alternative delivery systems, but viral variability and adaption ability constitute major challenges for vaccine development. Many new antiviral drugs for HCV therapy are in preclinical or early clinical development, but different limitations affect

treatment validity, such as comorbidity and risk-conditions, drug-drug interactions, severe adverse effects, alternate genotypes and host immune response. Treatment predictors are important tools, as they provide some guidance for the management of therapy in patients with chronic HCV infection.

In this review we will discuss the most recent data about HCV epidemiology, the new perspectives for the prevention of HCV infection and the most recent evidence regarding HCV diagnosis, therapy and predictors of response to it.

HCV Epidemiology[1]

HCV is a single-stranded RNA member of the Flaviviridae family, packed into a small (50 nm) enveloped viral particle. The single polyprotein precursor of approximately 3100 amino acids, originated by the translation of the single genomic open reading frame, is processed by cellular and viral proteases into 3 structural proteins (core, E1 and E2) and 7 non-structural (NS) polypeptides (p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B). These proteins have different functional roles in the virus life cycle: the core protein constitutes the viral nucleocapsid; E1 and E2 are glycoproteins that form the functional envelope that facilitates viral entry into host cells and induces neutralizing antibody proliferation; the NS proteins are required for the constitution of the replicase complex, assembly, release of infectious particles and viral propagation. The presence of 2 hypervariable regions (HVR) in the E2 envelope glycoprotein, the lack of proofreading ability and the high rate of generating new viral variants during infection allow HCV to continuously evolve, adapt and escape the host immune responses. Moreover, HCV has developed numerous strategies to impair immune responses and evade the host immune system, by delaying and reducing both the intrinsic and adaptive immune response arm. All these immunological determinants partially explain HCV ability to persist in the infected organism and to establish a chronic infection, most often without production of striking symptoms, until the emergence of long-term complications such as hepatic fibrosis, cirrhosis and HCC. Approximately 75%-85% of people infected with HCV will develop chronic hepatitis, 60%-70% will develop hepatic steatosis or fibrosis, 5%-20% will develop cirrhosis and in 1%-5% disease will progress to life-threatening complications and HCC, within 20 years from acute infection.

It has been calculated that 130-170 million people are infected with HCV, with a global prevalence of infection estimated at 2%-3. HCV prevalence is characterized by a high

variability between world's regions, individual countries and between age and risk groups within countries: this can be partially explained by the characteristic of the analysed population and the primary mode of transmission. HCV prevalence is highest in Africa and the Middle East, where Egypt, Cameroon, Saudi Arabia, Iraq and Syria account for the majority of cases and prevalence ranges from 2% to 15%. North America, Australia, Japan and Northern and Western Europe report lower prevalence of HCV infection, with no country showing a rate > 2%. China, India, Egypt, Pakistan and Indonesia account for approximately half of the global HCV-infected subjects. In general, developing countries present the major HCV-related burden but also the major limitations in surveillance: data from most African, Asian and South American countries are lacking. In Egypt, the country with the highest HCV prevalence, there is evidence for an age-related distribution of infection: HCV seroprevalence ranges from 19% in subjects < 18 years old to > 50% in the 30-year-old age group. In this country HCV is endemic and ongoing HCV transmission levels are high, mainly due to unsafe medical procedures and household contacts. The use of improper sterilization procedures during the eradication campaign of schistosomiasis carried out in Egypt from the 1950s to the 1980s has led to an extensive transmission of HCV among persons alive during that campaign, but blood transfusion and needle reuse still remain the principal risk factors. Although lower prevalence rates, other developing countries have a similar epidemiological pattern, with an age-related distribution of cases and a virus transmission linked to unsafe medical procedures and blood transfusions; however, recent data show the increasing role played by injection drug use in the spread of infection, especially in China and Iran. HCV prevalence in the majority of developed countries is classified as low, but marked differences in the epidemiological picture exist among countries, principally related to temporal and transmission factors and resulted in diverse age-specific distribution of HCV cases. Most recent survey on the number of HCV infected people in United States estimated a total of 5-7 million people seropositive, one third of which belonging to high-risk populations, such as incarcerated persons and homeless, and a general HCV prevalence of 1.6%-1.8%, with 75% of cases in subjects born between 1945 and 1965. The expanded consumption of illicit injection drugs, the use of unsafe medical procedures and contaminated blood transfusions are the most likely causes of the creation of the adult cohort of HCV cases, evidence confirmed by the decline in new infections recorded from the mid-1980s, due to improvements of healthcare practices and the more recent introduction of screening of blood and organ donors. HCV prevalence and transmission routes in Australia are similar as in the United States, but age distribution of cases is quite different, with the peak prevalence recorded in people aged 30-39 years, probably related to an increase

of parenteral drug use throughout the 1980s and 1990s. Among developed countries with a low prevalence of HCV infection, Japan shows some distinctive features that differentiate it sharply from other countries: most of HCV cases are recorded in people aged 40-69 years, while HCV prevalence in younger people is very low, so reflecting the occurrence of infection in the distant past, linked to improper sterilization procedures and unsafe medical practice. HCV epidemiological pattern in Europe is heterogeneous: Northern and Western European countries reported very low (< 1%) prevalence rates, while Southern and some Eastern countries reported intermediate-to-high prevalence rates (> 2.5%). Notably, completeness of collected information is limited in many countries of the Mediterranean and the Balkan area, particularly in high-risk groups. The observed differences reflect the variable modes of transmission among countries, strongly related to cultural practices, presence of safe and effective medical and screening procedures and prevalence of specific risk behaviours. In general, iatrogenic spread of HCV infection through blood transfusion occurred in the past is the main cause of the high HCV prevalence in the older population, observed in particular in Southern European countries. Improved blood supply safety from the 1990s limited HCV diffusion among younger cohorts, but sharing of injecting equipment among intravenous drug users has become the predominant route for HCV transmission. The expansion of intravenous drug use is recorded both in Western and in Eastern European countries. Nosocomial infections still occur in European countries, although the advances in medical procedures: 50%-70% of new HCV cases can be attributed to nosocomial exposure, according to recent estimates in Italy and Spain. Another important factor that substantially contributed to HCV epidemic in Europe is immigration from endemic areas, especially during the last 10-15 years in Northern and Western Europe. It is important to highlight that a considerable proportion of HCV positive subjects are unaware of its status and many new infections are not diagnosed or reported: lack of recognition of infection affects epidemiology estimates and treatment opportunities, especially in high-risk groups, so hampering effective control of infection, even with treatments of high efficacy.

Also the genetic diversity of the virus contributes to complicate HCV epidemic picture and constitutes a severe challenge for effective therapy. HCV is characterized by an high genomic variability and is classified into 7 genotypes (1-7), which differ by more than 30% sequence diversity, and at least 67 subtypes, characterized by a about 20% sequence divergence, according to the last update to the previous consensus HCV classification. Moreover, when HCV infects an individual, multiple closely related but distinct viruses, a “quasispecies”

population, can be identified, with sequence variations up to 10%: as already observed, HCV polymerase is characterized by the absence of proofreading capacity, and this leads to an high mutational rate of 10^{-5}-10^{-4} nucleotides per replication cycle. Identification of HCV genotypes and subtypes is a crucial step for the definition of epidemiological patterns and effective treatment. Current commercially available methods allow the detection of nucleotide sequence disparity using direct or indirect approaches and new sequencing technologies can detect minor viral populations in complex quasispecies mixtures; however, improvements in specificity, reading sequence lengths and general clinical significance of generated sequences are required. Global distribution of HCV genotypes is characterized by marked geographical differences, reflecting the evolving pattern of transmission modes and other influencing factors such as immigration and screening diffusion.

Association between HCV genotype and fibrosis progression appears inconclusive, although increasing clinical and experimental data show that infection with genotype 3 is associated with a higher risk of severe hepatic steatosis, accelerated fibrosis progression rate and increased oncogenesis. Conversely, each genotype has different response rates to antiviral therapies. While 80% of HCV genotype 2-and 3-infected patients reach sustained virological response (SVR) under pegylated-interferon with ribavirin (pegIFN/RBV) combination therapy, this regimen leads to a SVR only for about 50% of genotype 1- and 4-infections; genotypes 5 and 6 have intermediate response rates. There is increasing evidence that SVR rates with dual pegIFN/RBV therapy for genotype 3 infected patients appear worse than for genotype 2 infections. The introduction of direct-acting antivirals (DAAs) into combined regimens markedly increased SVR rates for genotype 1 infected patients: the first-generation NS3-NS4A protease inhibitors telaprevir (TVR) and boceprevir (BOC), approved for treatment of only genotype 1, lead to SVR rates of 63%-75%, although with an increase of side effects. New combinations of DAAs have shown a favorable safety profile and an improvement of antiviral activities also against non-genotype 1 HCV, but risks of resistance, treatment failures and the well-known limitations of IFN-based regimens are issues that have still to be overcome.

HCV Prevention[1]

The global burden of HCV disease is now fully recognised, thanks to several epidemiological and natural history studies performed during the two decades after virus' discovery. Primary prevention of new infections and management of existing infections (secondary prevention)

are the fundamental approaches to controlling HCV epidemic. Despite the great advances in the treatment of HCV infections, the still heavy public health burden and the limitations of current available therapies highlight the key role of primary prevention strategies to reducing worldwide disease diffusion. Among the different strategies to prevent infections of major public health relevance, vaccination has proved to be the most effective preventive approach to control infectious diseases and interrupt transmission chains. The history of the epidemic sustained by another hepatotropic virus, HBV, is the demonstration of the fundamental importance of the availability of an effective vaccine in preventing viral infections and virus associated disease. The development of a preventive HCV vaccine constitutes an irreplaceable tool to control HCV spread, but several major hurdles hamper the achievement of this important purpose. As already observed, HCV is characterized by an high genetic diversity and variability, because of the lack of proof-reading activity of its polymerase: as such, infection is sustained by a quasispecies of multiple closely related but distinct viruses, with the ability to persist in infected people by escaping immune control of cytotoxic T lymphocytes (CTL) and antibodies against different regions of the viral envelope. Moreover, HCV is able to impair $CD4^+$ T cell response at the beginning of infection and causes a rapid immune exhaustion of $CD8^+$ T cells as the infection endures. Strategies to develop a preventive HCV vaccine should consider these aspects: in particular, an effective HCV vaccine should elicit both a strong humoral immune response, by inducing neutralizing antibodies targeting multiple conserved B and T cell epitopes, and a cellular immune response, by stimulating a rapid activation of T-helper 1 lymphocytes as well as CTL. Moreover, fundamental steps for the development of an HCV vaccine will be the definition of suitable correlates of protection and cross-protection evaluations against the various HCV genotypes. The lack of convenient experimental model systems is another important challenge towards the full understanding of viral pathogenesis and immune response to HCV infection. Only recently the availability of a cell culture-derived HCV model (HCVcc), consisting of human hepatoma cell lines infected with the 2a strain of HCV, and of a cell-culture-based system that allows production of infectious HCV in physiologically relevant human hepatocytes (HCVpc) provide useful tools for the study of HCV interactions with host cell and for testing neutralizing and cross-protective potential of antibodies induced by various HCV vaccine candidates. Nevertheless, these *in vitro* systems do not allow the study of T cell response to HCV infection, and a suitable animal model is still required to study innate and adaptive immune responses *in vivo*. Chimpanzees constitute the only acceptable animal model for HCV analysis, but ethical issues, high costs and scarce supply limit the use of these animals; moreover, chimpanzees have major differences in immunologic

responses to infection from humans, so the results obtained with this model have to be interpreted with caution, especially those regarding protective immunity. Another commonly used animal model for HCV research is a chimeric mouse model, in which engineered mice engrafted with human hepatocytes are able to be infected with HCV either from patient sera or produced *in vitro*: main limitations of this model are high mouse mortality rate and lack of adaptive immune response to HCV. Improved mouse models characterized by a partially reconstituted human immune system and human liver, susceptibility to HCV infection and ability to generate a specific response against the virus have been recently described. Although very useful in viral pathogenesis understanding and vaccine development, animal models cannot substitute accurate evaluations in humans. The design of preventive vaccine trials presents several challenges, especially in the case of HCV: the number of enrolled subjects should be very high to ensure adequate power to the trial, study results may not be applicable to countries other than those where the trial has been performed, factors such as HCV prevalence, exposure frequency, infectivity and chronicity may affect significance of the trial, endpoints and correlates of protective immunity should be clearly defined. Experience achieved in the field of HIV vaccine development, with several recent high-profile failures, highlights the need for accurate studies on HCV vaccine design.

Several approaches have been adopted to develop an effective preventive HCV vaccine: they can be classified on the basis of targeted immunity (humoral immunity, cell-mediated immunity or both) or employed strategy (recombinant protein or viral peptide vaccines, virus-like particles vaccines, DNA/recombinant vaccines, DNA/viral vector vaccines). HCV vaccine candidates combining recombinant envelope E1 and E2 proteins and adjuvants have been demonstrated to elicit humoral responses and production of neutralizing antibodies both in animal model and human phase I trials. A subunit approach combining HCV core protein and ISCOMATRIX® adjuvant has been investigated to promote a broad and strong humoral and cellular immune response to HCV antigens in primates and healthy volunteers, with conflicting results. Formulations combining several highly conserved $CD4^+$ and $CD8^+$ epitopes with different adjuvants, bacterial pore-forming toxoids, heat shock proteins or influenza-based virosomes are promising strategy for the induction of cross-protective humoral and cellular immunity. A virus-like particles approach, based on insect cells infected with a recombinant baculovirus containing the cDNA of HCV structural proteins (core, E1, and E2), has been shown to induce both humoral and cellular immune responses in animal models, but protection against infection after HCV challenge has not been demonstrated. Similar recently described

approaches include the use of engineered HBV S envelope protein, murine leukemia virus and vectored measles viruses. DNA vaccines present the advantage of inducing cytotoxic lymphocyte responses; however, the induced immunity is often brief, weak and unlikely to be effective in infection prevention. Several strategies include a priming with a DNA vaccine followed by a protein-based vaccine to boost $CD4^+$ and $CD8^+$ T cells and humoral immune responses. A potent T cell-mediated immunity can be obtained with the use of a defective or attenuated viral or bacterial vector expressing HCV structural and non-structural antigens: viral vectors include adenoviruses, vaccinia virus, modified vaccinia Ankara (MVA), pox virus and other viruses. Adenoviral vectors have shown the most promising results in inducing strong and broad $CD4^+$ and $CD8^+$ T cell responses. Vaccine strategies based on these vectors reduced peak viremia and induced protection against chronic infection in primates, but did not prevent HCV primary infection. Currently, a phase 1/2 trial, designed to assess safety, immunogenicity and efficacy of a prime-boost vaccine based on an adenoviral vector and a MVA vector in active intravenous drug users aged 18 to 45 years in United States, is ongoing.

Diagnostic Tools In HCV Infection[1]

Background

The diagnosis of hepatitis C infection is usually obtained by detection of anti-HCV antibodies. The anti-HCV reactivity by screening assays can indicate a past, acute or chronic hepatitis and despite the high specificity of the assays (> 99%) false positive results are not rare, especially in some clinical situation such as in pregnant women, in patients with immunologic or hematologic diseases and when testing is performed among population with low risk of infection. In all these circumstances the anti-HCV reactivity must be confirmed with a confirmatory test. Two major guidelines [European Association for the Study of the Liver (EASL) and Centers for Disease Control and Prevention (CDC)] currently recommend the detection of anti-HCV antibodies together with molecular determination of HCV-RNA for the diagnosis of HCV infection. In addition, in the course of infection more and more often it is also advisable to assess the genotype of the virus, as well as its quantitative plasma load, also done by molecular tests. Particularly, these are useful, if not mandatory, in the phases of therapeutic decision, choice of treatment and control of efficacy. Thus, several viral markers, either serological or molecular, can be used in the course of HCV infection both for diagnostic and monitoring purposes.

Serological tests

Detection of anti-HCV antibodies: Several enzyme immunoassays (EIAs), microparticle EIAs and chemiluminescence immunoassays have been developed to detect anti-HCV antibodies. First generation assays can identify as anti-HCV positive about 80% of patients with diagnosis of non-A non-B hepatitis. Only after the characterization of conserved amino-acid sequences, in the NS5 region of the genome, throughout the genotypes, and the detection, within them, of those epitopes that shared T and B cell recognition, have the second and then the third generation of assays been produced. Currently, third generation assays that include, in solid phase, antigens from the core and recombinant antigens from NS3, NS4 and NS5 regions are diffusely used. The evolution from first, to second and finally to third generation has led to a progressive increase in sensitivity and specificity, as well as in a reduction of the window period (8-10 wk after exposure). In fact, this latter purpose has been reached, both in house-made and commercially standardized assays, by simultaneously detect antibody and antigens in the same assays, thus reaching the same sensitivity and specificity of the routinely used assays and also achieving the capability of detecting HCV infection about 21-50 d earlier than simple anti-HCV assays.

In the effort at having an assay capable to discriminate between acute and chronic HCV infection, anti-HCV IgM assays were produced. The attempts, however, have been frustrated by the presence of anti-HCV IgM antibodies both in the acute and in the chronic infection, although in different percentage, so that their significance is often unclear, and the assays are not used in clinical practice.

Avidity assays, used to distinguish primary from chronic or recurrent viral infection in many other diseases, have also been tested in the HCV infection. As reported by some authors, the avidity index has been found significantly lower in primary than in chronic, but also lower in past than in chronic infection. Even if these assays may sometimes be an useful help at assessing the timing of hepatitis C infection after the onset of symptoms, they nevertheless have had poor success in clinical practice as well.

Recently, rapid immuno-chromatographic assays for the detection of anti-HCV antibody, based on recombinant antigens from the core, NS3, NS4 and NS5 regions, were evaluated and shown to possess > 99% specificity and sensitivity ranging from 86% to 99%. As they are able to generate a result within an hour, they can be used as point-of-care testing.

Currently, CDC recommends the use of an approved screening test, either an EIA or a rapid test, and the use of another assay to confirm a positive result as a true positive one.

The recombinant immunoblot assay and other immunoblot assays are commonly used to confirm a reactive result at an anti-HCV screening test. The same antigens as in EIAs are used in these assays, but the antigens are separately coated on a membrane and the result depends on the number of bands present on the membrane. The immunoblot assays, more specific than EIAs, can confirm a true positive anti-HCV result but are unable to confirm an active HCV infection, which only a molecular test can reveal.

Detection of HCV antigen: In addition to the previously described tests that allow the simultaneous detection of antigens and antibodies, assays for the detection of HCV core antigen alone were also developed. It is now available an automated, quantitative chemiluminescence immunoassay which has been shown to have sensitivity and specificity ranging from 80% to 99% and from 96% to 99%, respectively. Several studies demonstrated that the test can similarly detect and quantify all the genotypes and that the quantification of core HCV antigen shows a good correlation with the HCV-RNA levels. On these bases, recently, Ottiger et al proposed a new algorithm to confirm an anti-HCV reactive result and also a mathematical formula to extrapolate HCV-RNA levels by measuring HCV antigen. It must be noted, though, that slight differences across the genotypes and from one patient to another have been reported.

As this is an immunoassay, it is easy to use and less expensive compared to a molecular assay. Moreover, as it is able to detect core antigens it can be used to confirm acute infection and also to monitor HCV response to therapy. The lower limit of detection, varying according to the HCV genotype from 500 to 3000 IU/mL of HCV-RNA, represents the important limitation of the assay. However, even taking this restriction into account, HCV antigen assay can represent a useful diagnostic marker in those laboratories where HCV-RNA molecular tests cannot be performed, pending their hopefully fast conformation to international standards.

Molecular tests

Detection of HCV-RNA: HCV-RNA is detectable in plasma and in serum 1 to 3 wk after infection, about 1 mo before the appearance of anti-HCV antibody, and is a hallmark of ongoing viral replication. Nucleic acid testing (NAT) used for detecting and quantifying HCV-

RNA characterizes the gold standard for HCV diagnosis and can be done by mean of polymerase chain reaction (PCR), branched DNA signal amplification (bDNA) and transcription mediated amplification. Currently, all NATs for detecting and quantifying HCV-RNA levels are standardized by the use of the WHO International Standard and the HCV-RNA results are expressed in Unit International (UI/mL).

The development and the availability of the semi-automated or fully-automated real-time PCR that exhibit excellent sensitivity, specificity and high dynamic range will probably lead to the replacement of the qualitative assays. Several real-time assays are being commercialized which have been demonstrated to be accurate enough in detecting and quantifying HCV-RNA to be suitable for clinical practice. Differences have been reported with regard to the HCV-RNA quantification based on the genetic diversity of the viruses and, probably, due to the mismatching between primers or probes and HCV target sequences.

Detection of HCV genotype: As already said, 7 different HCV genotypes and several subtypes have been characterized so far. The HCV genotype along with HCV-RNA baseline level is considered the major predictor of SVR to antiviral therapies. In clinical practice, HCV genotype can be assessed by commercially available techniques based on real-time PCR with genotype specific probes/primers, semi-automated sequencing and automated reverse hybridization that analyze the 5' NC region of HCV genome, representing the most conserved one. However, analysis of 5' NC region can lead to errors in subtype attribution, because it is not the most appropriate for discrimination among subtypes. For this reason a new version of automated reverse hybridization, the most commonly used method, analyzes both the 5' NC and the core regions. The gold standard of genotyping is the sequencing of NS5B region, able to accurately assign the genotype, with the advantage that the obtained sequence can be used for phylogenetic analysis to epidemiological purposes.

Recently, hybridization on oligonucleotide microarray assay, containing genotype and subtype specific oligonucleotides on the corresponding sequences of the NS5B region, have been successfully developed for identifying HCV genotypes and subtypes.

New Therapeutic Era And Its Implications[1]

To date and for many years, the peg-IFN/RBV combination, able to eradicate the virus in approximately 50% of treated patients, has characterized the standard of care (SOC) for chronic HCV infection. The recent development and availability of new molecules named DAAs are implementing the HCV therapeutic options.

These new DAAs include: NS3/NS4 protease inhibitors, divided into linear and macrocyclic, NS5a phosphoprotein inhibitors, NS5B polymerase nucleoside and non-nucleoside inhibitors and host-targeting antivirals.

Currently, only TVR and BOC, the first two NS3 protease inhibitors, are available and approved for use in Europe, in combination with SOC, in HCV, genotype 1, chronically infected patients. Both are linear ketoamides molecules that target the catalytic site of the NS3/4A protease, blocking the release of HCV NS proteins required to assemble the viral replication complex. Moreover, they also work by stopping the release of immune modulating host proteins, thus promoting the innate immune response to HCV infection.

As HCV is a virus with high genetic heterogeneity, high rate of turnover and no proofreading activity, when used in mono-therapy DAAs cause the rapid emergence of resistant variants, so that they are approved for use in combination with peg-IFN/RBV.

The efficacy of TVR and BOC has been evaluated in phase III clinical trials. In summary, two trials have been performed for each: in naïve chronic HCV patients (advance for TVR and sprint 2 for BOC) and in treatment experienced SOC failed patients (realize for TVR and respond 2 for BOC). All these studies demonstrated significant improvement of SVR in DAAs arms compared to SOC. Several post-marketing studies are currently being performed confirming these favorable preliminary data. However, while representing new therapeutic chances for clinicians and patients, DAAs also entail new challenges and efforts to lab workers.

Detection of HCV-RNA in the new era

As already said, the use of TVR and BOC in HCV treatment leads to a substantial improvement in SVR rates, but the managing and monitoring of the patients in triple therapy has become more complicated than in SOC. Due to the differences in the “stopping rules”, also known as “futility rules”, between SOC and DAAs treatment, and between the two DAAs (TVR and

BOC), HCV-RNA quantitative monitoring faces new challenges. Not only has it to be very accurate for several reasons: for understanding HCV-RNA kinetics, for establishing eligibility for response guided therapy (RGT) and for complying with stopping rules, it also has to be very frequently and rapidly performed (Table 1). In fact, a prompt result from the laboratory is often important not only to avoid unnecessary side effects and the waste of ineffective expensive drug, but also to prevent the occurrence of resistant variants in patients for which it is impossible to achieve SVR. For these reasons, EASL Guidelines recommend the use of a real-time PCR-based assay with a lower limit of detection as low as 10-20 IU/mL for HCV-RNA detection and quantification.

Table 1. Boceprevir and telaprevir response guided therapy and futility rules

End-point	**Boceprevir**	**Telaprevir**
RGT	Non-cirrhotic treatment naïve patients, previously relapsers or partial responders	Non-cirrhotic treatment naïve patients previously relapsers
	HCV-RNA undetectable at weeks 8 and 24	HCV-RNA undetectable at weeks 4 and 24
Futility rules	HCV-RNA > 100 IU/mL at week 12	HCV-RNA > 1000 IU/mL at weeks 4 and 12
	HCV-RNA detectable at week 24	HCV-RNA detectable at week 24

HCV: Hepatitis C virus.

Each real-time assay has its own linear range, with its own upper and lower limit of detection, but the terminology used to interpret the results is the same (Table 2). It is possible to define: (1) lower limit of quantification (LLOQ): the lowest value of HCV-RNA that is possible to accurately quantify, HCV-RNA is detectable and quantifiable; (2) limit of detection (LOD): the lowest value of HCV-RNA that can be detected, always < LLOQ, HCV-RNA is detectable but not quantifiable; (3) < LLOQ: HCV-RNA is detectable but not quantifiable, the interpretation is the same as LOD; and (4) target no detected (TND): no HCV-RNA amplification, HCV-RNA is undetectable or not detected.

Table 2. Qualitative and quantitative hepatitis C virus RNA assays available for clinical use

Assay	**Manufacturer**	**Method**	**LOD, IU/mL (dynamic range, IU/mL)**
Qualitative			
Amplicor HCV v2.0	Roche molecular system	RT-PCR (manual)	50
Cobas Amplicor HCV v2.0	Roche molecular system	Semi-automated RT-PCR	50
Ampliscreen[1]	Roche molecular system	Semi-automated RT-PCR	< 50
Versant HCV RNA	Siemens healthcare diagnostics	Semi-automated TMA	10
Procleix HIV-1/HCV[1]	Chiron corporation	TMA (manual)	< 50
Quantitative			
Amplicor HCV Monitor	Roche molecular system	RT-PCR (manual)	N/A (600-700000)
Cobas Amplicor HCV Monitor v2.0	Roche molecular system	Semi-automated RT-PCR	600 (600-500000)
Versant HCV 1.0 Assay K-PCR	Siemens healthcare diagnostics	Semi-automated RT-PCR	15 (15-100000000)
Abbott RealTime HCV Assay	Abbott diagnostics	Semi-automated RT-PCR	12 (12-100000000)

LCx HCV RNA Quantitative Assay	Abbott diagnostics	Semi-automated RT-PCR	25 (25-2630000)
Cobas Ampliprep/Taqman	Roche molecular system	Semi-automated RT-PCR	15 (15-100000000)

[1]Used for blood screening only. HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; RT-PCR: Reverse transcription-polymerase chain reaction; LOD: Limit of detection.

Timing of sample collection is also assessed by guidelines, depending on the specific futility rules of each drug, as otherwise it happens for SOC. However, HCV-RNA kinetics induced by DAA treatments seems to have a different trend in comparison to that observed by IFN-based therapies (typically biphasic). DAAs determine an initial shorter delay before the beginning of the biphasic decline, in addition the decline observed in each phase is faster. If no fast decrease in the HCV-RNA levels is observed within the first two days, that is at the end of the first phase of decline, resistant variants can be selected. Due to the faster HCV-RNA kinetics induced by current DAAs, which will be at least equaled if not improved by the next generation ones, timing of sampling must be very strict during treatment with DAAs, and is likely to need a further restriction in a future revision of the guidelines.

In summary, for clinical purposes, every piece of information from HCV-RNA testing can be important. A detectable, though not quantifiable HCV-RNA (< LLOQ or LOD) may lead to different therapeutic decisions than undetectable HCV-RNA (TND or < LOD), thus all phases of HCV testing, including timing of sample collection, HCV-RNA measuring and result reporting, must be equally very accurate.

Detection of resistant variants

As already said, due to the virus HCV characteristics (high rate of turnover, no proof-reading activity with production of about 10^{-3}-10^{-5} mutations per nucleotide per genomic replication), HCV exists as a whole of viral variants, called “quasi-species”. In other words, the viral population consists of a prevalent population, typically called “wild type” virus (the virus with the best fitness) and of the minority variants selected during HCV replication and favorable to

the virus. There are also differences in nucleotide sequences within genotype (greater) and subtypes (smaller). It is against this quite heterogeneous viral population that old and new drugs must work.

Resistant viral variants are quickly selected if the new DAAs, that have been shown to have low genetic barrier, are administered in mono-therapy. The combination of the new DAAs with peg-IFN/RBV partially protects against the onset of resistance-associated mutations (RAMs). The function of peg-IFN/RBV is to suppress pre-existing resistant variants, therefore treatment failure occurs more easily in poor IFN responder patients, unfortunately those in greater need of DAAs and for whom DAAs are indicated. Factors associated with IFN response and tests to predict response are discussed elsewhere in this review.

So far, RAMs can be identified only with "in house" assays. Several methods for sequence analysis can be performed: TaqMAMA, hybridization assays, restriction enzyme assays, direct sequencing and next generation sequencing (NGS) techniques. The well standardized and most commonly used in clinical practice direct sequencing can detect the prevalent population of the quasi-species (> 25%), whilst the NGS, used only in research laboratories, can also reveal minority species (> 5%). Currently, the NGS techniques present several problems for a routine use. Although they can produce a significant amount of information, they can generate sequence errors, unreadable sequences, false positive and false negative results for substitutions, insertions and deletions. For that reasons, sophisticated software and trained personnel are needed.

A list of primary RAMs to TVR and BOC has been drawn up and an overlapping of the resistance profile between the two drugs has been found. *In vitro*, a degree of resistance was established for each mutation by phenotypic analysis of the mutated strains and was divided into low, intermediate and high level of resistance (Table 3). If selective drug pressure continues, other compensatory mutations are likely to be induced, with an increase of replicative fitness. However, while a high degree of cross resistance between these linear NS3/4 inhibitors was observed, cross resistance in the class of macrocyclic inhibitors seems to occur more rarely and in far less sites. Nevertheless, whereas mutations at R155 amino acid position were potentially selected by all the NS3/4 protease inhibitors, the mutations at D168 amino acid position were selected only by the new macrocyclic NS3/4 inhibitors. (Table 4)

Table 3. Degree of telaprevir and boceprevir resistance associated mutations

Degree of resistance	**Mutations**	**Fold increase**
Low level	V36A/M/C	3.5-7
	T54A/S	6-12
	R155K/T/Q	8.5-11
Intermediate	V36A/M + R155K/T	57-71
High level	A156V/T	74-410
	V36A/M + A156V/T	> 700

Table 4. Resistance associated mutations and cross-resistance to approved and advanced phase-studied NS3/4 protease inhibitors

Drug	**Molecule**	**V36A/M**	**F43S**	**T54S/A**	**V55A/K**	**Q80R/K**	**S122A/G/R**	**I132V**	**R155K/T/Q**	**A156S/D/T/V**	**V158I**	**D168A/V/T/H**	**I170F/T[1] V170A/T[1]**	**M175L**
Telaprevir	Linear	-[2]		-[2]				-[3]	-[2]	-[2]		-[3]		
Boceprevir	Linear	-[2]		-[2]	-[2]				-[2]	-[2]	-[3]		-[3]	-[3]
Faldaprevir	Linear								-[2]	-[3]		-[2]	-[3]	
Danoprevir	Macrocyclic					-[3]			-[2]			-[2]	-[3]	
Vaniprevir	Macrocyclic		-[3]						-[2]	-[3]		-[2]		

Simeprevir	Macrocyclic					-[2]	-[3]		-[2]	-[3]		-[2]		

[1]The I170F/T and the V170A/T mutations were detected in hepatitis C virus genotype 1a and 1b, respectively, in which I and V represent the consensus amino acid, respectively;

[2]Indicates resistance associated mutations detected in virologically failed patients and confirmed by phenotypic tests;

[3]Indicates mutations detected as additional mutations or still of uncertain significance.

Differences between subtypes have been described both in terms of response to treatment and in terms of selection of resistant variants. Indeed, with both protease inhibitors SVR rates are higher in subtype 1b than in 1a. In fact, not only are the mutations subtype specific, but they also depend on the genetic barrier of the subtype. Typically, when treatment failure occurs R155K/T and V36M mutations are selected in genotype 1a, whereas A156S/T, V36A and T54A in genotype 1b. R155K mutation is selected faster in subtype 1a than in subtype 1b, because the change of a single nucleotide is sufficient to cause an amino-acid substitution in the first, whilst two changes are required in the latter.

Unlike HIV, which integrates the viral genome into host cells and HBV whose viral genome is present in the nucleus of hepatocytes as cccDNA, HCV has no latent reservoir. While warranting the possibility of viral eradication, this implies that the virus is not stored and the RAMs, selected by treatment, tend to be replaced by wild-type virus after the end of drug pressure. Although data from literature indicate an extremely high variability from one patient to another in the time required for the disappearance of the HCV resistant variants, probably depending on the viral fitness of the respective variant, this aspect must be taken into account when sequencing HCV in search for RAMs.

In DAAs failing patients HCV sequencing for individuation of RAMs can yield useful information at an investigative level, but it is unclear its role as a clinical tool and it is not currently recommended in this setting. Likewise, at the moment screening for resistance is not indicated in naïve patients before initiation of treatment with TVR or BOC, mainly because the circulation of mutated strains in the general population has to be very low. However, an entire

new generation of DAAs is currently being developed, some of which with potential use in IFN-free settings and some of which very close to commercial release. One of the emerging aspects in terms of viral susceptibility to these newest drugs is that some polymorphisms, detected in certain viral subtypes, can selectively reduce susceptibility to one or more of them. In fact, for instance, the protease inhibitor simeprevir has most recently been approved by FDA with the mandatory condition that patients harboring a polymorphic Q80K variant strain of genotype 1a-HCV have to be excluded from treatment. Thus, a viral genotype has to be acquired in potential candidates for simeprevir treatment. It is likely that similar limitations will be issued for other new drugs in the nearest future. Therefore, resistance testing in naïve patients, which seemed a mere research exercise so far for the lacking of data indicating a clinical utility, may soon become a pretreatment requirement at least in selected cases.

Treatment Considerations[2]

HCV genotype, prior HCV treatment experience, comorbidities, and degree of liver fibrosis will influence treatment decisions and follow-up care. The goal of treatment for HCV is clearance of infection, thus reducing the progression of liver disease to cirrhosis and its related complications such as end-stage liver disease and HCC, and a reduction in liver-related morbidity and mortality and all-cause mortality. Treatment is recommended for all patients with HCV except those with short life expectancy (less than 12 months).

Genotype and HCV Treatment Regimens

There are six common genotypes of HCV, which vary in geographical distribution, progression of liver disease, and treatment response to medications. Approximately 75% of persons in the United States with HCV have genotype 1 (subtypes 1a or 1b), and 20–25% have genotype 2 or 3, with small numbers of patients infected with genotypes 4, 5, or 6. Genotype 3 is more frequently associated with intravenous drug use and with increased rates of steatosis, faster progression of the disease to cirrhosis, and increased rates of HCC. It is also associated with lower rates of response to DAAs, though this difference may be overcome with most newer regimens.'

Patients with all genotypes can be treated for 8–16 weeks with a daily, all-oral medication regimen of 1–3 pills. Treatment duration is determined by many factors, including HCV genotype, prior treatment with HCV medications, and the presence of cirrhosis. There are

currently ten FDA-approved DAA treatment regimens. Medication regimens comprise DAAs used in combination to inhibit different steps in the HCV life cycle at the NS3/4A, NS5A, and NS5B receptors. Genotype has historically played a major role in determining appropriate medication regimens for individual patients. Currently, however, three regimens can be used across all genotypes, including two drug regimens just approved in July and August 2017 (Table 5). The main adverse effects of DAA medications are fatigue, GI side effects, and headache, with some variation among regimens.

Table 5. Hepatitis C Medications

Generic	**Brand**	**Genotype(s)**	**Drug class**	**Considerations**
Sofosbuvir/velpatasvir	Epclusa	1–6	Sofosbuvir: NS5B polymerase inhibitor Velpatasvir: NS5A inhibitor	Cannot be used in renal disease
Elbasvir/grazoprevir	Zepatier	1, 4	Elbasvir: NS5A inhibitor Grazoprevir: NS3/4A protease inhibitor	Can be used with renal disease Not to be used in decompensated (Child B/C) cirrhosis
Daclatasvir	Daklinza	1, 3	Daclatasvir: NS5A inhibitor Used with sofosbuvir: NS5B	Efficacy reduced in cirrhosis Different dosage pills available for

			polymerase inhibitor	concomitant use of some drugs, including HIV medications
Glecaprevir/pibrentasvir	Mavyret	1–6	Glecaprevir: NS3/4A protease inhibitor Pibrentasvir: NS5A inhibitor	Not recommended in patients with Child B, contraindicated in Child C Can be used in renal patients DAA treatment failures with NS5A or NS3/4A failures
Ombitasvir, paritaprevir, ritonavir	Technivie	4	Ombitasvir: NS5A inhibitor Paritaprevir: NS3/4A protease inhibitor Ritonavir: CYP3A inhibitor	Contraindicated in patients with decompensated (Child B/C) cirrhosis With ribavirin
Ombitasvir, paritaprevir, ritonavir, dasabuvir	Viekira Pak (XR)	1	Ombitasvir: NS5A inhibitor Paritaprevir	Contraindicated in patients with decompensate

			: NS3/4A protease inhibitor Ritonavir: CYP3A inhibitor Dasabuvir: NS5B polymerase inhibitor	d (Child B/C) cirrhosis With ribavirin in 1a patients
Ledipasvir/sofosbuvir	Harvoni	1, 4,5, 6	Sofosbuvir: NS5B polymerase inhibitor Ledipasvir: NS5A inhibitor	Cannot be used in renal disease
Simeprevir	Olysio	1	Simeprevir: NS3/4A protease inhibitor	Used in combination with sofosbuvir Contraindicated in patients with decompensated (Child B/C) cirrhosis
Sofosbuvir	Sovaldi	1–6	Sofosbuvir: NS5B polymerase inhibitor	Used in combination with other medications
Sofosbuvir/velpatasvir/voxilaprevir	Vosevi	1–6 Prior	Sofosbuvir: NS5B	Genotypes 1–6 previously

		treatment experience	polymerase inhibitor Velpatasvir: NS5A inhibitor Voxilaprevir: NS3/4A protease inhibitor	treated with NS5A Genotypes 1, 3 previously treated with sofosbuvir without NS5A

The newest DAA, glecaprevir and pibrentasvir, is the first 8-week treatment approved by the FDA for all genotypes in the treatment-naïve patients without cirrhosis.' Alternatively, ledipasvir/sofosbuvir can be used for 8 weeks in patients with genotype 1 with low levels of viremia (less than 6 million copies) and no cirrhosis. Most other FDA treatment regimens are used for 12 weeks in treatment-naïve patients without cirrhosis. Treatment-naïve patients with genotype 1a and NS5a mutations will require 16 weeks of treatment with elbasvir/grazoprevir, though this mutation is rare. Therefore, NS5a testing should be performed at baseline in genotype 1a patient if the provider intends to treat with elbasvir/grazoprevir therapy.

Treatment-experienced patients and patients with cirrhosis will require 12–24 weeks of treatment. Two new DAAs have specific indications for treatment-experienced patients who have failed prior DAA regimens. Sofosbuvir/velpatasvir/voxilaprevir was approved in July 2017, and is indicated for 12 weeks in all genotypes for patients who have been previously treated. Glecaprevir/pibrentasvir has been approved for patients with genotype 1 who were treated with either an NS5A inhibitor or an NS3/4A protease inhibitor (but not both) for 12 weeks, patients with genotype 1, 2, 4, 5, or 6 previously treated with other non-NS5A or NS3/4A medications for 8 weeks, and genotype 3 treatment-experienced patients for 16 weeks.

Liver Disease Status

Evaluation of the degree of liver fibrosis is essential in this patient population. Many patients with cirrhosis are not diagnosed until they are late in the disease process, which leads to worse outcomes, including complications of portal hypertension (ascites, variceal hemorrhage, hepatic encephalopathy, and HCC). Baseline blood work and ultrasound of the abdomen

should be performed, along with non-invasive tests for liver fibrosis. Biomarkers for evaluating liver fibrosis such as FibroSure or FibroTest are readily available and can be used to estimate the extent of liver fibrosis. Other non-invasive tests for fibrosis, including transient elastography (commonly known as FibroScan), acoustic radiation force impulse (ARFI) imaging, and magnetic resonance elastography (MRE), can also be used with good diagnostic accuracy. These methods should be combined for use in conjunction with other clinical findings to increase the validity of results. Any patient with advanced liver fibrosis or cirrhosis should be referred to a specialist with expertise in liver disease management. Liver biopsy is no longer indicated as a routine test unless there is a concern for other concomitant liver diseases or clinical ambiguity regarding cirrhosis of the liver despite other non-invasive tests.

In patients who are determined to have stage 3 liver fibrosis (pre-cirrhotic state) or cirrhosis, ultrasound of the abdomen is recommended every 6 months to screen for HCC, even post-HCV treatment.[–] However, it is known that these recommendations are not routinely followed, and every-6-month ultrasound surveillance rates are as low as 1.7–17.4%. Patients diagnosed with cirrhosis should also be referred to a gastroenterologist to screen for esophageal varices, as at least two-thirds of patients with cirrhosis will develop varices in their lifetime. Bleeding from varices develops in 30–40% of these patients, with a high rate of mortality associated with first esophageal variceal hemorrhage (20–35%).

The treatment of HCV differs among patients with liver cirrhosis. The NS3/4A protease inhibitors are contraindicated in patients with decompensated cirrhosis (Child B or C). Patients with cirrhosis require a longer course of treatment, and the addition of ribavirin in some regimens. It is recommended that these patients be referred to a specialist for treatment and management of cirrhosis.

Comorbidities

Comorbidities such as renal impairment, advanced liver disease including cirrhosis, HIV disease, and pregnancy add a level of treatment complexity, and collaboration with a hepatologist or infectious disease specialist is recommended unless the health care provider has extensive experience and comfort in treating such patients.

Coinfection with HIV and HCV is common, as the two viruses share a common route of infection. Coinfection is found in 10–30% of all patients with HIV, and up to 90% of patients

with HIV who inject drugs. HIV is also known to accelerate liver fibrosis, so appropriate treatment of patients with HIV coinfection is critical. The major issue in the treatment of such patients, however, is the risk of drug–drug interactions. Adjustments in HIV medications are often needed, so close collaboration with infectious disease providers is recommended.

Treatment of patients with HCV and renal disease also requires specialized care. The prevalence of HCV in patients on hemodialysis is high, ranging from 7.8 to 44%, and concomitant HCV and renal disease is associated with worse outcomes than either disease process alone. Three medications are currently FDA-approved for the treatment of patients with HCV infection and renal disease. Glecaprevir and pibrentasvir attained a sustained viral response (SVR) of 98% across genotypes 1–6, including patients with severe chronic kidney disease (CKD) and on hemodialysis, regardless of previous treatment status or presence of compensated cirrhosis. Glecaprevir/pibrentasvir is the first medication approved for genotypes 2, 3, 5, and 6 in patients with renal disease. For patients with genotypes 1 and 4, two older DAAs are also approved for the treatment of HCV in those with a glomerular filtration rate (GFR) of < 30 mL/min. The C-SURFER trial demonstrated a 94% SVR rate with grazoprevir and elbasvir, with few side effects. The RUBY-1 trial reported an SVR rate of 90% in 20 patients treated with the combination of ombitasvir, paritaprevir, ritonavir, and dasabuvir, with the addition of ribavirin in patients with genotype 1a.

Treatment is indicated for elderly patients with HCV except in the case of short life expectancy. No significant increase in the side effects of HCV medications is seen in the elderly, and no dose adjustment is needed, though there is an increased number of drug–drug interactions. Women of childbearing age should be evaluated for pregnancy, as HCV medications have not been assessed for safety in pregnant women, and ribavirin is teratogenic (category X). New DAAs are pregnancy category B or C, but there are no medications for treatment of HCV that are currently recommended in pregnancy, and so women undergoing HCV treatment should avoid pregnancy.

Prior Exposure to Hepatitis B

All DAAs for the treatment of HCV now have a black box warning to check the HBV infection status in patients who are to be treated for HCV. This is due to the risk of reactivation of HBV when patients with HCV infection are undergoing or have just completed treatment. This reactivation of HBV has led to liver failure or death in a small number of patients during

treatment.[7] Patients who are not immune to hepatitis A and B should be immunized and should receive other maintenance immunizations as well, including yearly influenza vaccine, and pneumonia, tetanus, and zoster as applicable. Hepatitis A and B vaccinations can be given as a combined vaccine (Twinrix) at 0, 1, and 6 months or in single antigen injections. Any person with risk factors for hepatitis A or B, or anyone with chronic liver disease including HCV, cirrhosis, fatty liver, or other liver disease, should be given hepatitis A and B immunizations.

Other Considerations

Evaluation of other medical history, medication and herbal use, and illicit drug and alcohol use should be completed per the standard of care. Interactions with antiarrhythmics can occur, particularly amiodarone, which is linked to severe cardiac issues and death when taken with sofosbuvir-containing regimens. Other medications including anticonvulsants, HIV drugs, statins, and proton pump inhibitors (which may require dose adjustments) should be explored. There are no contraindications to the use of statins with DAAs, though some medications require administration of lower-dose statins.

Some insurance carriers require documented evidence of abstinence from illicit drug use in order to approve medications, though treatment of patients with recent or active drug use is no longer seen as an absolute contraindication to treatment. However, it is recommended that patients who are active drug users be treated in a multidisciplinary care setting to reduce the risk of HCV reinfection.

Sustained Virologic Response

Quantitative HCV (HCV RNA) viral load testing is recommended 4 weeks into therapy and at 12, 24, and 48 weeks following completion of therapy. SVR, also known as a virologic cure, is defined as an undetectable viral load at 12 weeks after the completion of therapy. SVR has traditionally been tested at 24 weeks after completion of treatment, and is commonly known as SVR_{24}. However, a 2015 study by Yoshida et al. showed that among 779 patients who achieved SVR at 12 weeks, 777 achieved SVR_{24}, demonstrating 99.7% concordance between these two results. Predictably, many providers now check both SVR_{12} and SVR_{24} to assess for virologic cure. Recent recommendations are to confirm long-term SVR at 48 weeks, given a late relapse rate of ± 0.5%. No further confirmation of SVR post-48 weeks is indicated.

Role Of The Primary Care Provider (Pcp) In Treating HCV

In general, it is our belief that PCPs interested in the treatment of HCV can provide safe and effective treatment. This ability was demonstrated by PCPs and nurse practitioners (NPs) in the ASCEND study, where the outcomes for PCPs and NPs trained in the care of HCV-infected patients were similar to those for specialists in HCV treatment. The use of specialty pharmacies can assist providers with medication authorizations and approval—the most difficult part of the treatment of HCV. Evaluation of patients for HCV treatment also provides PCPs an opportunity for contact with patients that may also have cirrhosis, enabling the evaluation and referral of these patients to specialist expertise in liver disease, including liver transplant evaluation. Furthermore, any PCPs who are comfortable managing complex HCV patients such as those with cirrhosis, HIV coinfection, HCV with CKD/end-stage renal disease (ESRD), or HCV with HCC should be able to treat chronic HCV in these patients. The HCV Guidance web aid is an important tool for guiding the management and treatment of hepatitis C patients, as it is a living document which will continue to provide updated information for clinicians. The time has arrived for PCPs to diagnose, treat, and cure patients with HCV, and interested PCPs should be able to add HCV as a disease that they can successfully manage in a primary care setting.

References:

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2. Guss D, Sherigar J, Rosen P, Mohanty SR. Diagnosis and Management of Hepatitis C Infection in Primary Care Settings. *J Gen Intern Med*. 2018;33(4):551-557.

Survey Form

1) In your clinical practice, how frequently do you encounter cases of Hepatitis C every month?

a. <1 %

b. 1-5%

c. 5-10%

d. 10-20%

e. >20%

2) What is the likelihood of HCV infection becoming chronic?

a. <20%

b. 20-40%

c. 41-50%

d. >50%

3) What are the chances of patient with chronic hepatitis C developing cirrhosis?

a. <5%

b. 5-10%

c. 10-20%

d. >20%

4) Which of the following are common risk factors for developing cirrhosis after becoming infected with HCV?

a. Being male

b. Being age >50 years

c. Consuming alcohol

d. Having nonalcoholic fatty liver disease, hepatitis B, or HIV coinfection

e. Receiving immunosuppressive therapy

5) According to your practice, what % of cirrhosis patients develop hepatic decompensation?

a. <5%

b. 5-10%

c. 10-20%

d. >20%

6) According to your practice, what is the annual risk of developing hepatocellular carcinoma in patients with cirrhosis?

a. <1%

b. 1-5%

c. 5-10%

d. >10%

7) In your practice, which HCV genotypes are commonly encountered in your patients infected with HCV?

a. Genotype 1

b. Genotype 2

c. Genotype 3

d. Genotype 4

e. Genotype 5

f. Genotype 6

8) According to you, what are the major risk factors for hepatitis C infection?

a. People with HIV infection

b. Intravenous drug users

c. Sharing contaminated items

d. Organ & tissue donation

e. Blood transfusion

f. Sexual transmission

9) According to your practice, is hepatitis C a common cause for liver transplantation?

a. Yes

b. No

10) What are the sign and symptoms that you encounter in your patients with acute Hepatitis C?

a. Fever

b. Fatigue

c. Dark urine

d. Abdominal pain

e. Loss of appetite

f. Nausea

g. Jaundice

11) What are the signs and symptoms of chronic HCV infection?

a. Most of these patients are assymptomatic

b. Shows non-specific symptoms such as chronic fatigue and depression

c. Symptoms similar to acute HCV infection

12) In your experience, what is the incubation period for HCV or How soon after exposure to HCV do symptoms appear in most of the cases?

a. 2-12 weeks

b. 2-24 weeks

c. > 24 weeks

13) What are the common extrahepatic manifestations that you encounter in patients of chronic HCV infection?

a. Diabetes mellitus

b. Glomerulonephritis

c. Essential mixed cryoglobulinemia

d. Porphyria cutanea tarda

e. Non-Hodgkin's lymphoma

14) According to you, which of the following patient profiles should be tested for HCV on a routine basis?

a. Diabetes mellitus

b. Glomerulonephritis

c. Essential mixed cryoglobulinemia

d. Porphyria cutanea tarda

e. Non-Hodgkin's lymphoma

f. Patients on maintenance dialysis

15) Which of the following scoring technique or classification do you use for assessing the severity of the disease and deciding the treatment?

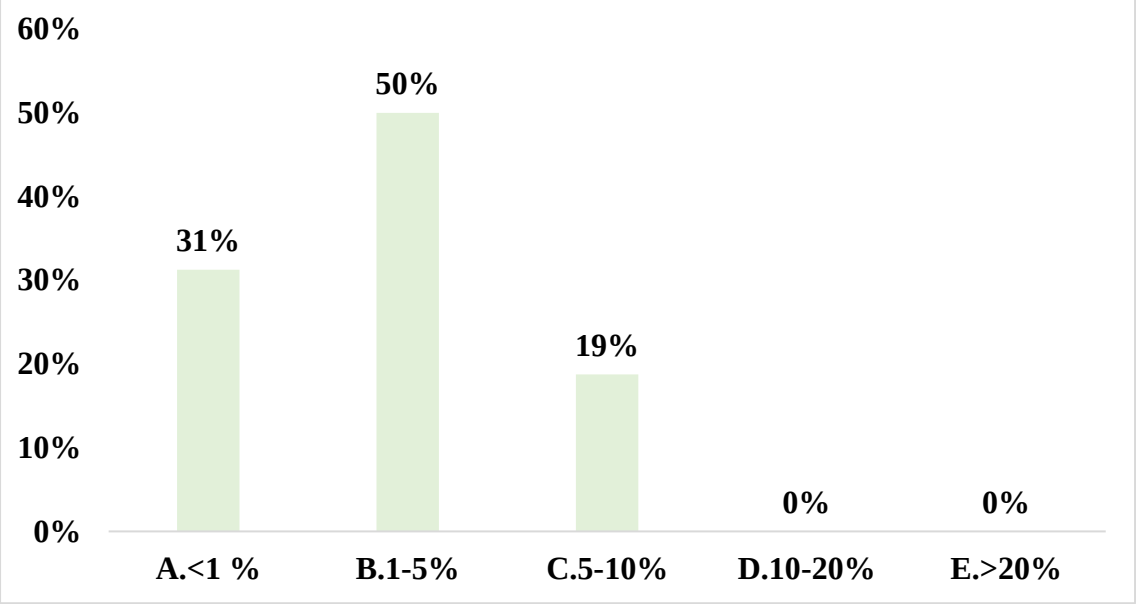
a. Metavir Scoring System

b. The Child-Pugh classification

Survey Findings

1) In your clinical practice, how frequently do you encounter cases of Hepatitis C every month?

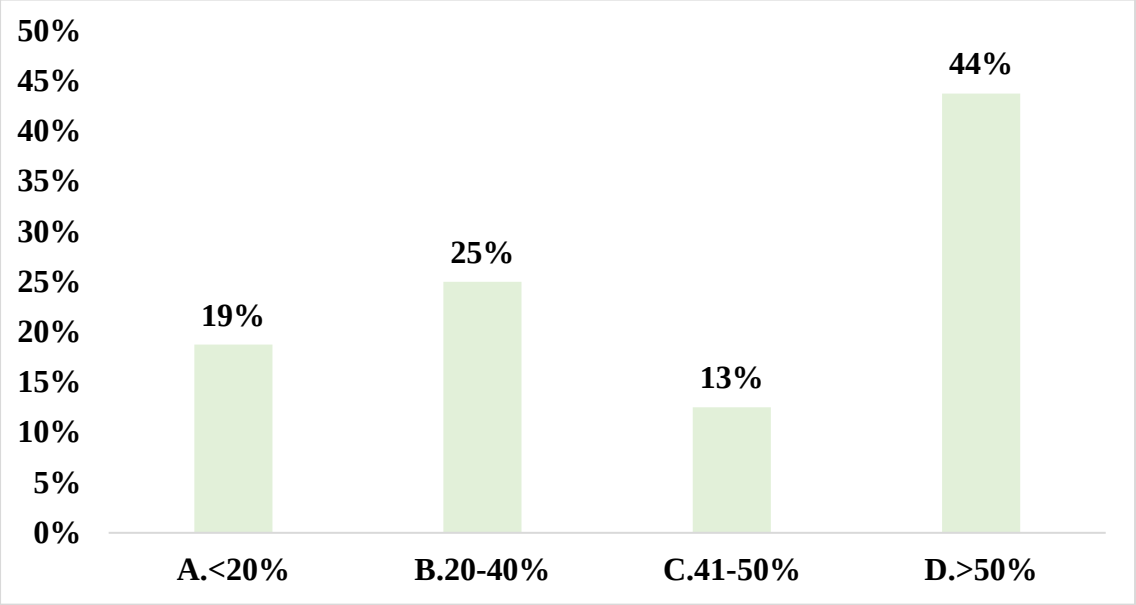
A. <1 %
B. 1-5%
C. 5-10%
D. 10-20%
E. >20%



According to 50% of doctors, 1-5% of times they encounter cases of Hepatitis C every month.

2) What is the likelihood of HCV infection becoming chronic?

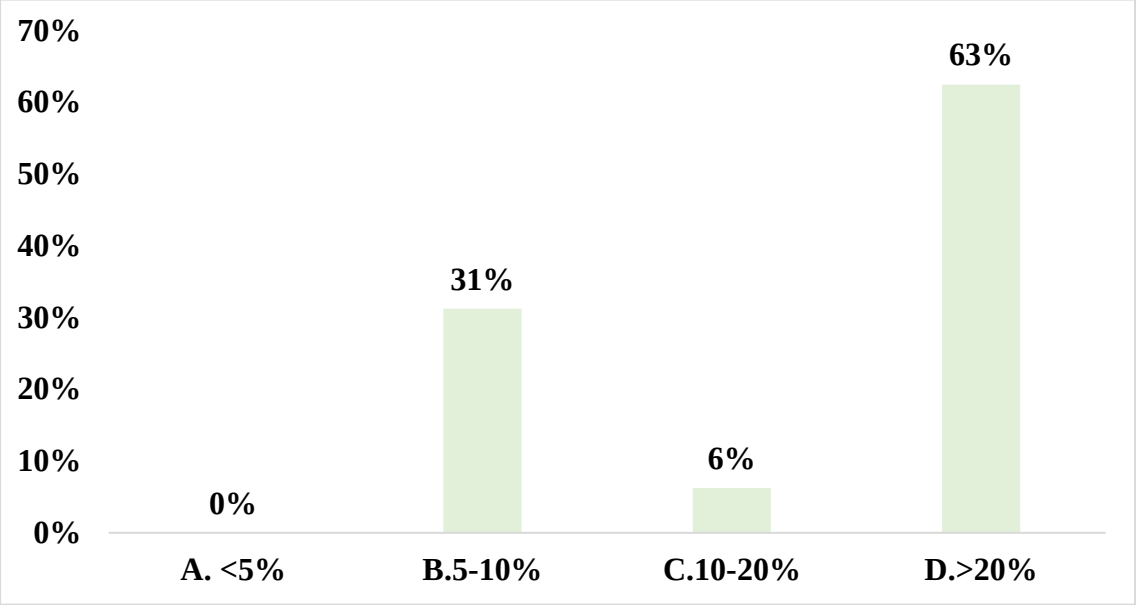
A. <20%
B. 20-40%
C. 41-50%
D. >50%



As per 44% of doctors, >50% is the likelihood of HCV infection becoming chronic.

3) What are the chances of patient with chronic hepatitis C developing cirrhosis?

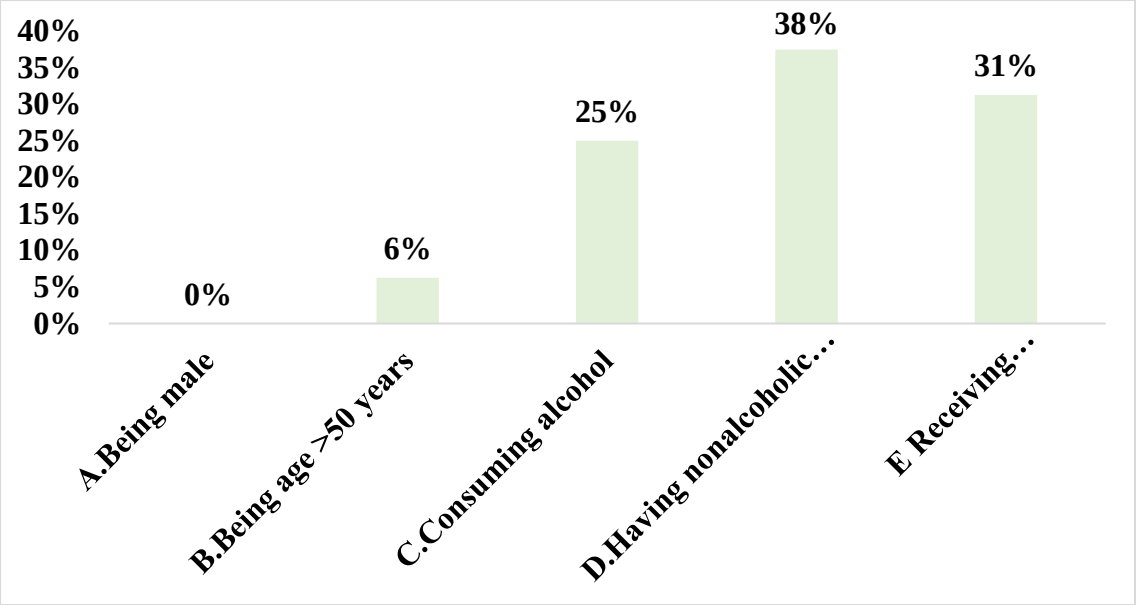
A. <5%
B. 5-10%
C. 10-20%
D. >20%



According to 63% of doctors, >20% are the chances of patient with chronic hepatitis C developing cirrhosis.

4) Which of the following are common risk factors for developing cirrhosis after becoming infected with HCV?

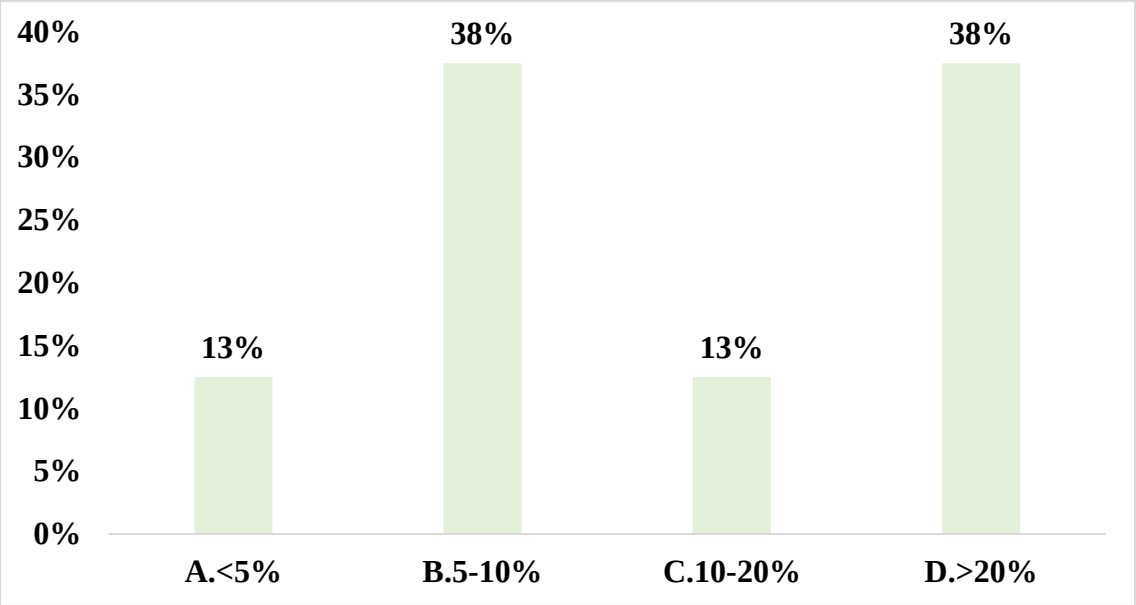
A. Being male
B. Being age >50 years
C. Consuming alcohol
D. Having nonalcoholic fatty liver disease, hepatitis B, or HIV coinfection
E. Receiving immunosuppressive therapy



As per 38% of doctors, having nonalcoholic fatty liver disease, hepatitis B, or HIV coinfection are common risk factors for developing cirrhosis after becoming infected with HCV.

5) According to your practice, what % of cirrhosis patients develop hepatic decompensation?

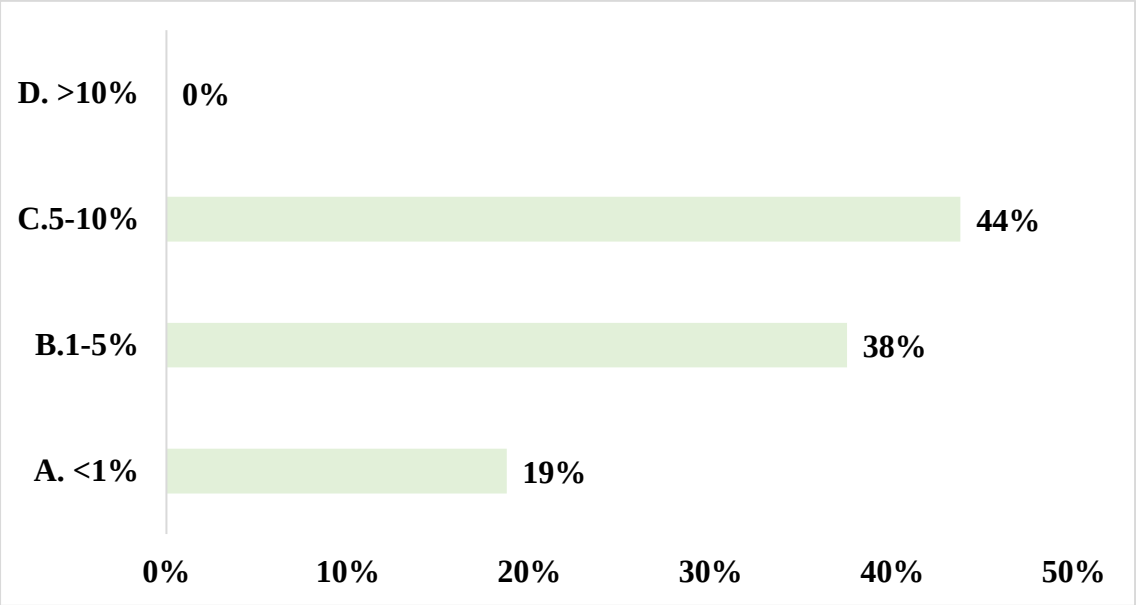
A. <5%
B. 5-10%
C. 10-20%
D. >20%



As per survey, 38% says 5-10% of cirrhosis patients develop hepatic Decompensation, while 38% says >20% of cirrhosis patients develop hepatic Decompensation.

6) According to your practice, what is the annual risk of developing hepatocellular carcinoma in patients with cirrhosis?

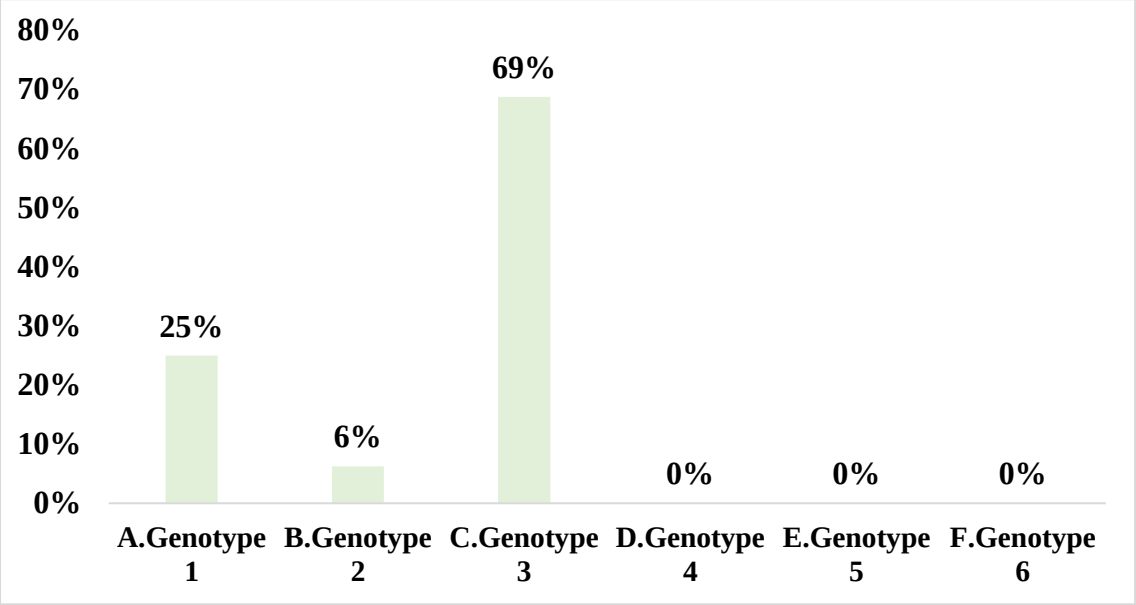
A. <1%
B. 1-5%
C. 5-10%
D. >10%



As per 44% of doctors, 5-10% is the annual risk of developing hepatocellular carcinoma in patients with cirrhosis.

7) In your practice, which HCV genotypes are commonly encountered in your patients infected with HCV?

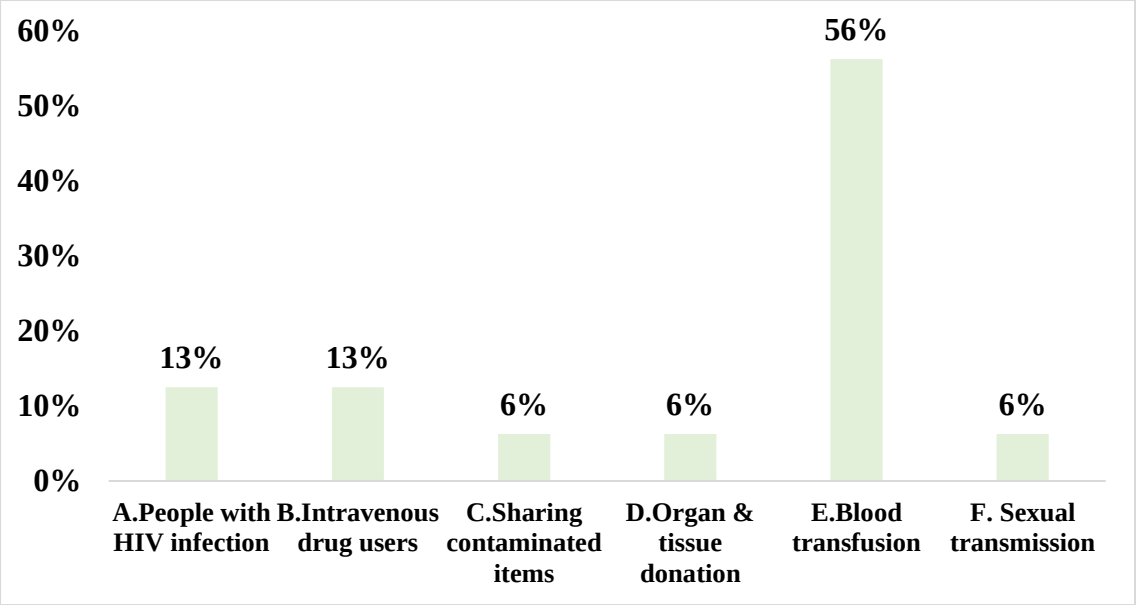
A. Genotype 1
B. Genotype 2
C. Genotype 3
D. Genotype 4
E. Genotype 5
F. Genotype 6



Majority of doctors, 69% believes that Genotype 3 are commonly encountered in your patients infected with HCV.

8) According to you, what are the major risk factors for hepatitis C infection?

A. People with HIV infection
B. Intravenous drug users
C. Sharing contaminated items
A. Organ & tissue donation
B. Blood transfusion
C. Sexual transmission

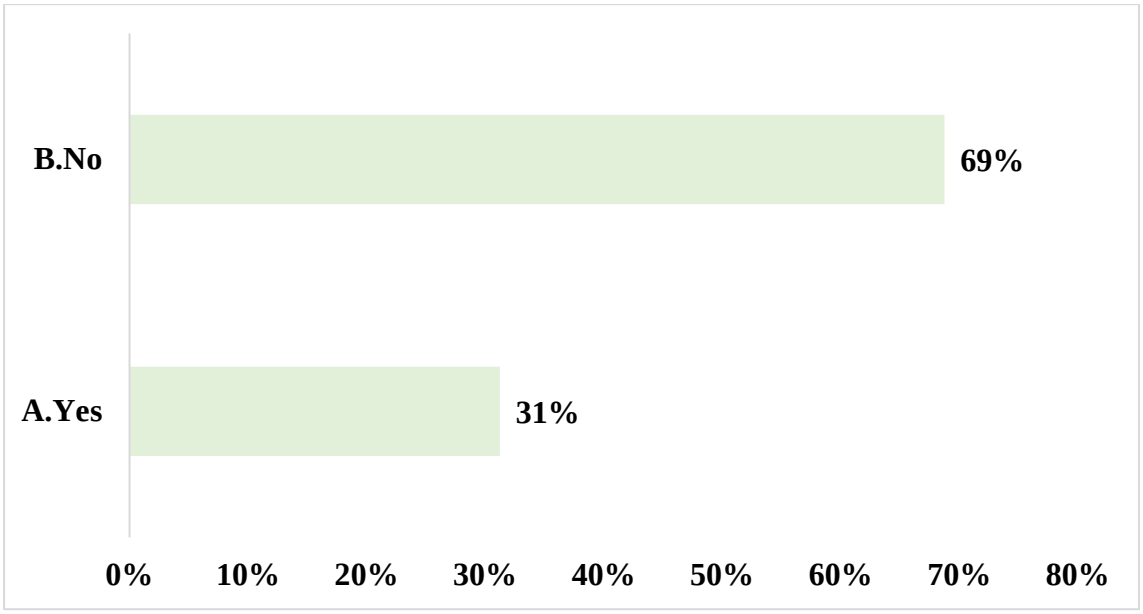


According to 56% of doctors, blood transfusion are the major risk factors for hepatitis C infection.

9) According to your practice, is hepatitis C a common cause for liver transplantation?

A. Yes

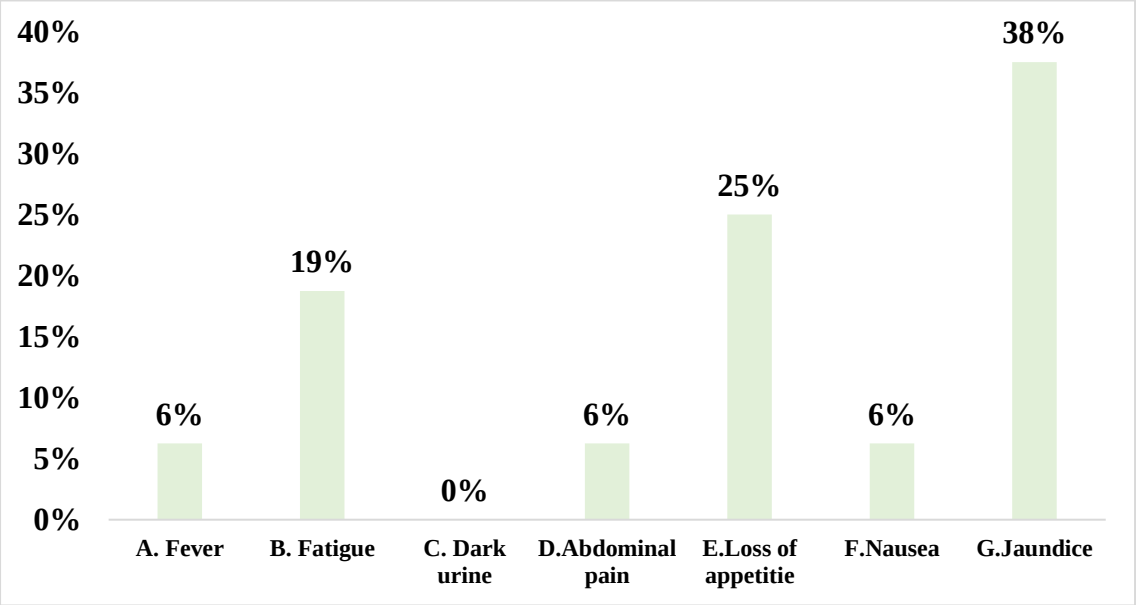
B. No



Majority of doctors, 69% believes that hepatitis C is not a common cause for liver transplantation.

10) What are the sign and symptoms that you encounter in your patients with acute Hepatitis C?

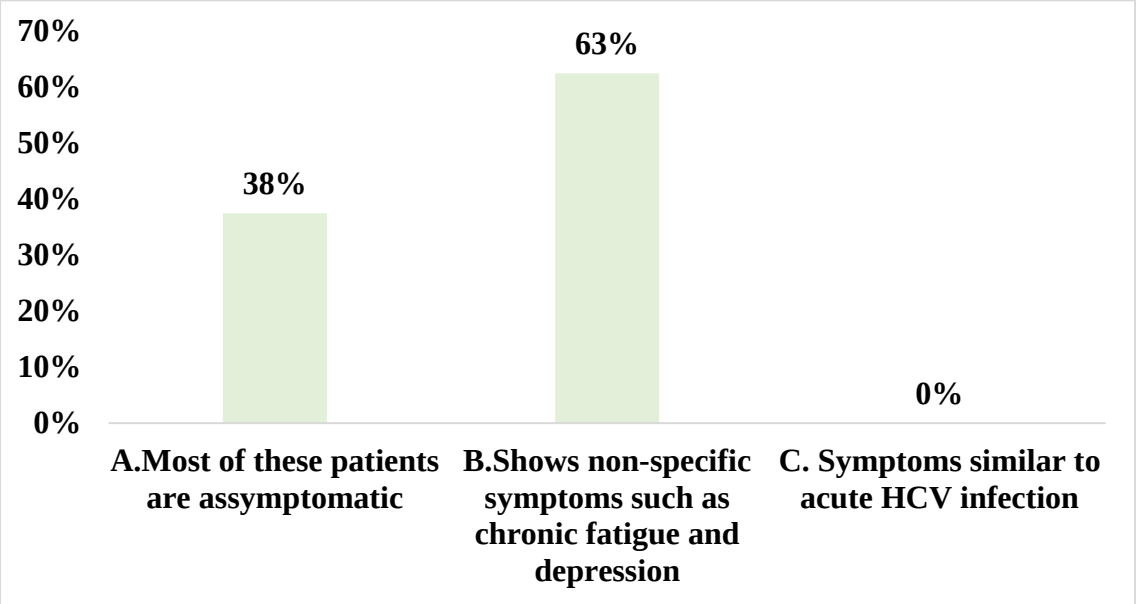
A. Fever
B. Fatigue
C. Dark urine
D. Abdominal pain
E. Loss of appetitie
F. Nausea
G. Jaundice



As per 38% of doctors, Jaundice is the most common sign and symptoms that they encounter in patients with acute Hepatitis C.

11) What are the signs and symptoms of chronic HCV infection?

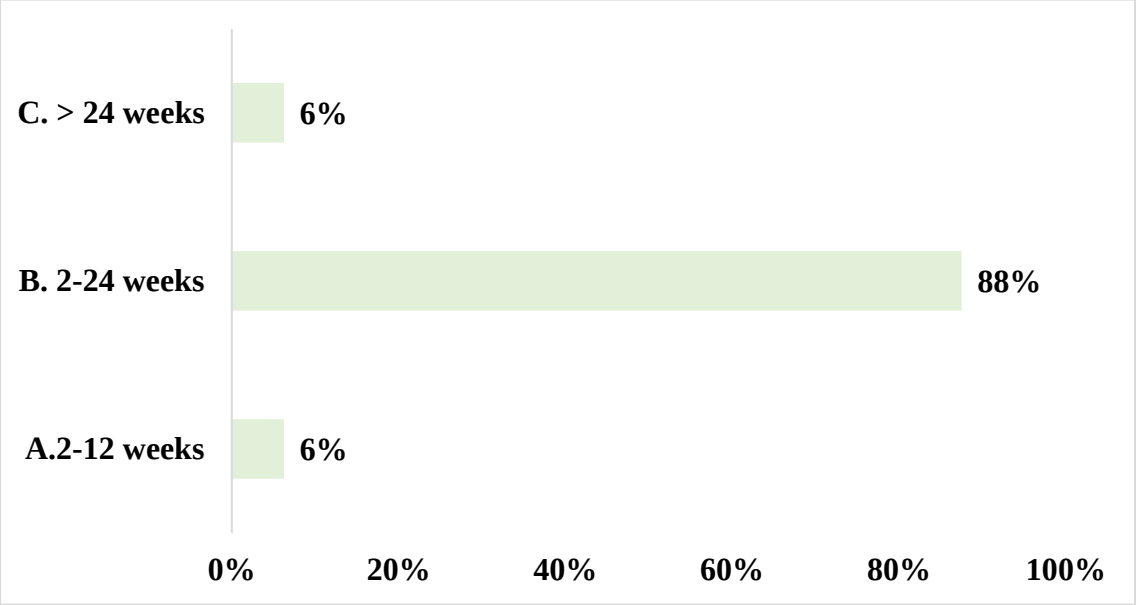
A. Most of these patients are assymptomatic
B. Shows non-specific symptoms such as chronic fatigue and depression
C. Symptoms similar to acute HCV infection



According to 63% of doctors, non-specific symptoms such as chronic fatigue and depression are the signs and symptoms of chronic HCV infection.

12) In your experience, what is the incubation period for HCV or How soon after exposure to HCV do symptoms appear in most of the cases?

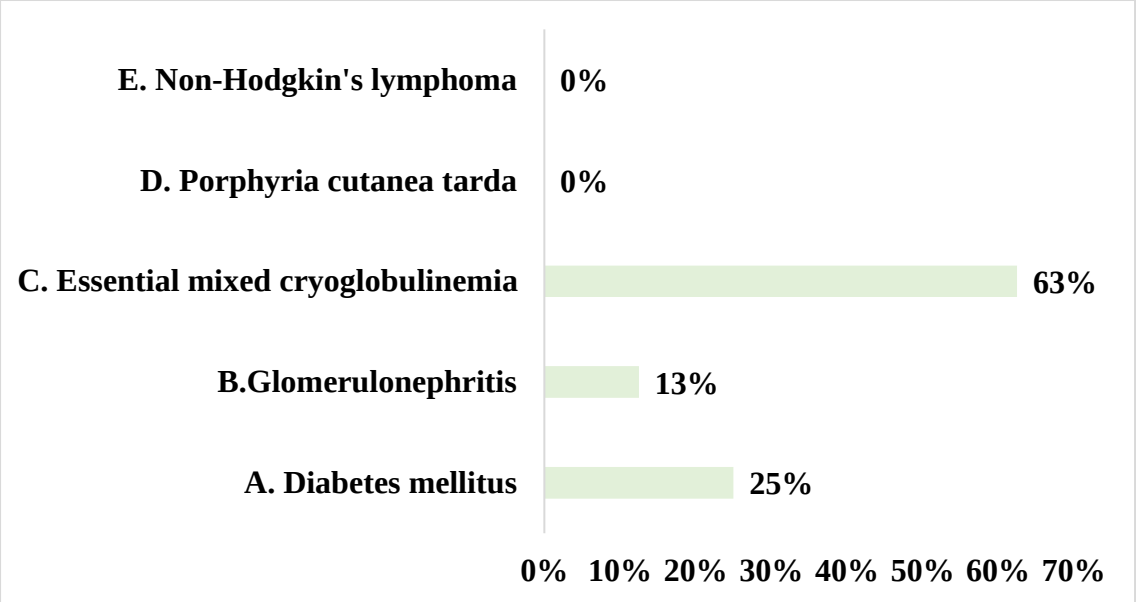
A. 2-12 weeks
B. 2-24 weeks
C. > 24 weeks



According to majority of doctors, 2-24 weeks is the incubation period for HCV.

13) What are the common extrahepatic manifestations that you encounter in patients of chronic HCV infection?

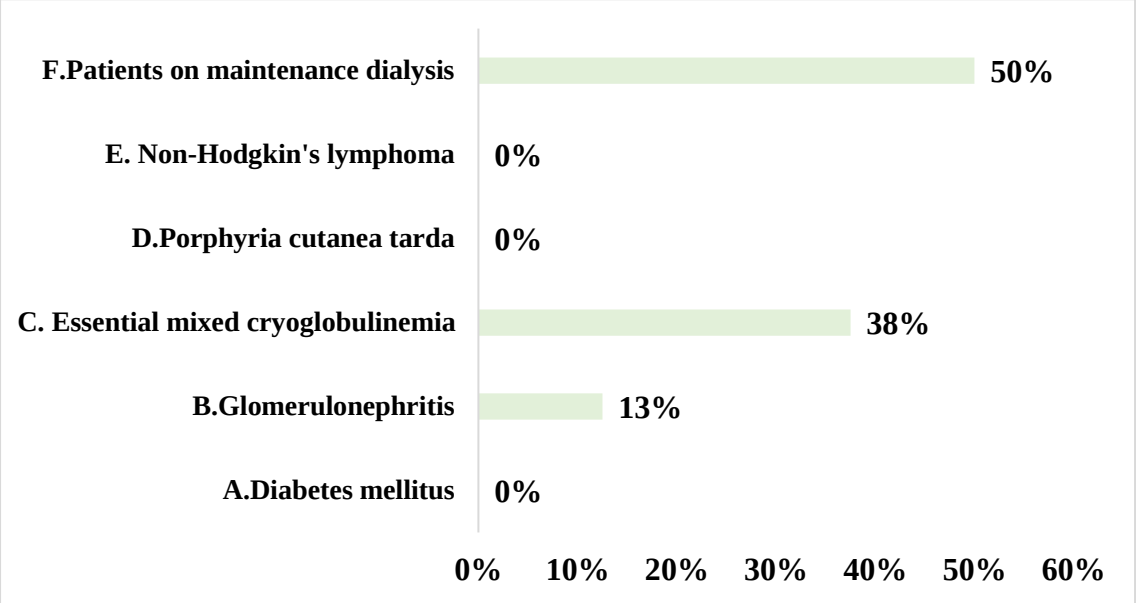
A. Diabetes mellitus
B. Glomerulonephritis
C. Essential mixed cryoglobulinemia
D. Porphyria cutanea tarda
E. Non-Hodgkin's lymphoma



According to 63% of doctors, essential mixed cryoglobulinemia are the common extrahepatic manifestations that is encountered in patients of chronic HCV infection.

14) According to you, which of the following patient profiles should be tested for HCV on a routine basis?

A. Diabetes mellitus
B. Glomerulonephritis
C. Essential mixed cryoglobulinemia
D. Porphyria cutanea tarda
E. Non-Hodgkin's lymphoma
F. Patients on maintenance dialysis

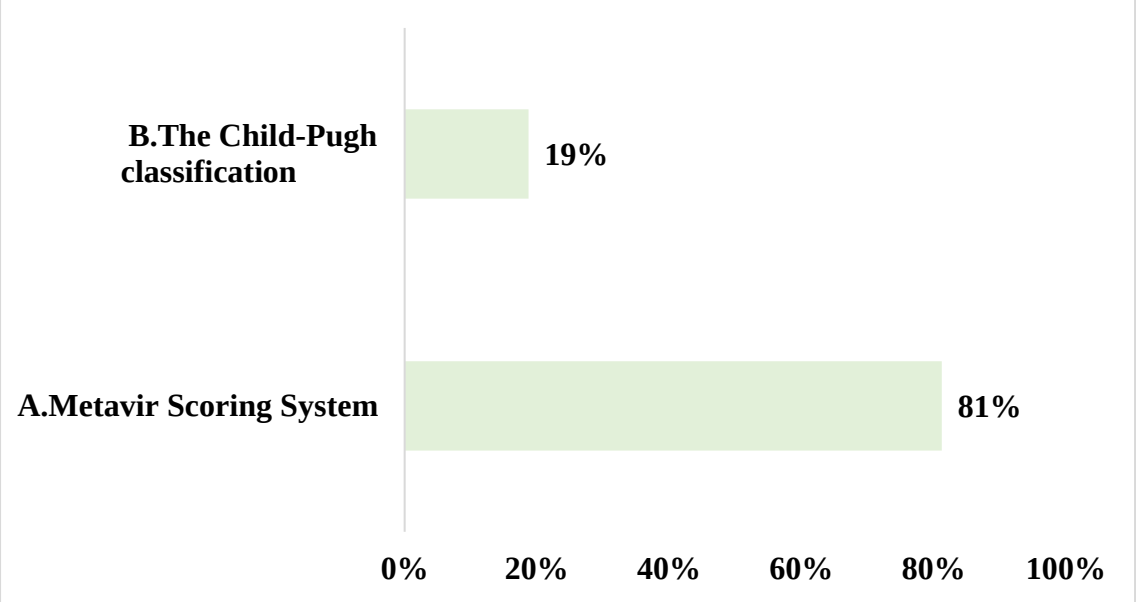


According to 50% of doctors, patients on maintenance dialysis profiles should be tested for HCV on a routine basis.

15) Which of the following scoring technique or classification do you use for assessing the severity of the disease and deciding the treatment?

A. Metavir Scoring System

B. The Child-Pugh classification



As per majority of doctors, 81%, Metavir Scoring System can be used for assessing the severity of the disease and deciding the treatment.

Summary

- According to 50% of doctors, 1-5% of times they encounter cases of Hepatitis C every month.
- As per 44% of doctors, >50% is the likelihood of HCV infection becoming chronic.
- According to 63% of doctors, >20% are the chances of patient with chronic hepatitis C developing cirrhosis.
- As per 38% of doctors, having nonalcoholic fatty liver disease, hepatitis B, or HIV coinfection are common risk factors for developing cirrhosis after becoming infected with HCV.
- As per survey, 38% says 5-10% of cirrhosis patients develop hepatic Decompensation, while 38% says >20% of cirrhosis patients develop hepatic Decompensation.
- As per 44% of doctors, 5-10% is the annual risk of developing hepatocellular carcinoma in patients with cirrhosis.
- Majority of doctors, 69% believes that Genotype 3 are commonly encountered in your
- patients infected with HCV.
- According to 56% of doctors, blood transfusion are the major risk factors for hepatitis C infection.
- Majority of doctors, 69% believes that hepatitis C is not a common cause for liver transplantation.
- As per 38% of doctors, Jaundice is the most common sign and symptoms that they encounter in patients with acute Hepatitis C.
- According to 63% of doctors, non-specific symptoms such as chronic fatigue and depression are the signs and symptoms of chronic HCV infection.
- According to majority of doctors, 2-24 weeks is the incubation period for HCV.
- According to 63% of doctors, essential mixed cryoglobulinemia are the common extrahepatic manifestations that is encountered in patients of chronic HCV infection.
- According to 50% of doctors, patients on maintenance dialysis profiles should be tested for
- HCV on a routine basis.
- As per majority of doctors, 81%, Metavir Scoring System can be used for assessing the severity of the disease and deciding the treatment.

Consultant Opinion

Market Opportunities:

- **Hepatitis C Treatment:** There is a consistent demand for hepatitis C (HCV) treatment, with doctors encountering cases on a regular basis. Pharmaceutical companies have the opportunity to develop and market effective therapies to address this need.

Value for Healthcare Professionals:

- **Metavir Scoring System:** The use of tools like the Metavir Scoring System can provide valuable insights for healthcare professionals in assessing disease severity and guiding treatment decisions. Pharmaceutical companies can support healthcare professionals by providing education and resources on the use of such systems.

Adverse Effect Management:

- **Chronic HCV Symptoms:** Recognizing the non-specific symptoms of chronic HCV infection, such as chronic fatigue and depression, is crucial for healthcare professionals. Pharmaceutical companies can focus on developing therapies that not only target the virus but also alleviate these symptoms to improve patient quality of life.

Withdrawal Management:

- **Risk Factors and Complications:** Addressing common risk factors for HCV infection and potential complications like cirrhosis, hepatic decompensation, and hepatocellular carcinoma requires proactive management strategies. Pharmaceutical companies can support healthcare professionals by developing educational materials and treatment guidelines to aid in early detection and intervention.

Market Positioning:

- **Genotype-Specific Treatment:** With genotype 3 being commonly encountered in patients with HCV, there is an opportunity for pharmaceutical companies to develop genotype-specific treatments tailored to the needs of different patient populations.

Personalized Treatment Decisions:

- **Routine Screening:** Emphasize the importance of routine screening for HCV, particularly in high-risk populations such as patients on maintenance dialysis. Pharmaceutical companies can collaborate with healthcare providers to develop screening programs and initiatives aimed at increasing awareness and early detection.

Improving Patient Outcomes:

- **Early Detection and Treatment:** Early detection of HCV and timely initiation of treatment can significantly improve patient outcomes and reduce the risk of complications like cirrhosis and hepatocellular carcinoma. Pharmaceutical companies can invest in research and development to develop more effective and accessible treatment options, ultimately improving patient outcomes in the long term.

Overall, addressing the challenges and needs identified in the survey, such as early detection, genotype-specific treatment, and symptom management, presents significant opportunities for pharmaceutical companies to innovate and improve patient care in the field of hepatitis C management.

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Developed by:

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