MAGNET CLINICAL PROTOCOLS	Page 1 of
	Supersedes Date: November 14, 2018
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	Policy Section: Patient Care
Hepatitis C Treatment Program	

Providers: Provision of Hepatitis C treatment will be limited to NPs and MDs.

Client Eligibility for Services: All clients who live in the San Francisco Bay Area and have appropriate health insurance will be eligible for the Hepatitis C Treatment Program. The client must be able to return to Magnet/SAS/1035 to receive follow up care.

Healthy Clients: Due to the limited ability to provide comprehensive primary care at Magnet, Clients must be in stable health to be enrolled in the Hep C treatment program. Those with certain health conditions, as determined by the NP/MD, may be referred to a primary care provider if the care and follow up needed is beyond the service capacity of Magnet.

Scope of Care: Clients presenting to the Hepatitis C Treatment Program are not required to have a primary care provider to access treatment. Magnet will provide care and monitoring related to Hepatitis C treatment but will not manage unrelated conditions. The benefits coordinator will assist the clients in enrolling in insurance programs and encourage the client to establish care with a primary care provider. Magnet will provide prescriptions for Hepatitis C treatment and medications used to manage side effects (e.g. promethazine for Nausea).

Screening and Enrollment into the Hepatitis C Treatment Program:
Screening and Enrollment visits into the Hepatitis C Treatment Program occur over multiple visits. All parts of the screening visit must be completed prior to initiation of Hepatitis C treatment. Clients who screen but do not enroll may need to repeat labs depending on the insurance company requirements.

Rapid 2 visit enrollment:

Visit 1: Upon obtaining reactive Hepatitis C antibody test result, all screening labs are collected and benefits navigation is initiated.

Visit 2: Clinician assessment for Hepatitis C Treatment with History and Physical and enrollment is completed.

Screening:
The steps needed in a Hepatitis C Treatment Program screening:

1. Registration
2. Collect Screening labs
3. Confirm Eligibility for Hepatitis C Treatment Program
4. Conduct Clinician Assessment for Hepatitis C Treatment
5. Obtain health history
6. Review current medications and allergies
7. Perform physical exam
8. Provide Hepatitis C treatment counseling
9. Provide Stigma counseling
10. Provide Adherence counseling
11. Refer to Magnet benefits navigation
12. Select Therapy Option
13. Notify client's PCP

Registration: The client will complete the routine registration information, Day of Visit Risk Assessment, HIV Testing Consent, and Hepatitis C Treatment Consent.

Collect Screening Labs:

1. Hepatitis C Viral Load
    a. Reflex to Hepatitis C Genotype
2. Hepatic Function: AST/ALT/ALP/ALB/Total-Bilirubin/Direct-Bilirubin
3. Creatinine/eGFR
4. CBC with differential
5. PT-INR
6. HIV Antibody
7. HBV AB, AG, Total Core AB
8. HAV IgM, Total

*eGFR in Transgender Men and Women***:** Transgender men on testosterone are more likely to have increased muscle mass and Transgender women do not lose muscle mass. As a result, the male reference ranges for eGFR should be used for both Transgender Men and Women.

Confirm Eligibility for Hepatitis C Treatment

Inclusion Criteria

1) Age 18 and Over
2) Lives in the San Francisco Bay Area
3) Chronic Hepatitis C evidenced by detectable HCV viral load

Exclusion Criteria for program-Clients may still be treated but require a referral to a specialist

1) HIV coinfection-Must partner with PCP
2) Hepatitis B coinfection-Must have Hep B treated
3) Failed DAA-May be treated with consultation
4) Decompensated Cirrhosis
5) Renal disease with eGFR <30
6) Active TB
7) Mental Illness impacting likely adherence
8) Life Expectancy less than 12 months
9) Pregnancy
10) Abnormal screening labs not explain by comorbid condition
11) Any other conditions that are deemed contraindicated for treatment by the NP/MD

Conduct Clinician Assessment for Hepatitis C Treatment

*Acute Hepatitis C***:** Hepatitis C may clear on its own 6 months after initial infection. It is difficult to determine if the client will clear the infection on their own. The clinician and client may decide to monitor for spontaneous clearance by repeating a Hepatitis C RNA after 6 months. ALT greater than 200, negative HCV AB with a detectable RNA, flu like symptoms and jaundice may indicate acute hepatitis C that may warrant waiting for spontaneous clearance. The clinician may still elect to treat acute hepatitis C if there is concern for forward infections for Gay/MSM, injection drug use, or women who are attempting to conceive.

Readiness for Hepatitis C Treatment:
Once treatment is started, it must be completed, unless unexpected intolerances or complications arise. Clients who initiate and interrupt their treatment plan risk drug resistance, and their insurance plan may not cover reinitiating treatment. Also, impact of interruptions in treatment are not well studied, and thus effectiveness of therapy cannot be easily predicted for interruptions of varying duration. Assessing readiness is essential in supporting the client to successfully complete treatment. There is no objective measure to determine readiness. Attending visits may be associated with the ability to adhere to the treatment. Readiness will be determined by the client, clinician, and clinic staff. Clients will self-assess their readiness and if the client wants to initiate treatment.

Hepatitis B: Clients with chronic Hep B may be at risk for liver inflammation due to Hep C treatment and should be treated for Hepatitis B.

Serostatus	
Hep B AB positive, AG negative, Total core Negative	Treat Hep C
Hep B AB negative, AG negative, Total core Negative	Vaccinate and treat Hep C
Hep B AB negative, AG positive, Total core positive	Start emtricitabine/tenofovir 200mg/300mg daily per Hepatitis B treatment protocol
Hep B AB negative, AG negative, Total core positive	Repeat Hep B core to rule out false positive, and order Hep B VL, assuming patient is not on HBV therapeutic medications as PEP/PrEP, or ART. If VL is undetectable, okay to treat. If VL is detectable, start emtricitabine/tenofovir 200mg/300mg daily per Hepatitis B treatment protocol

Hepatitis A: Clients with active Hepatitis A should wait until the infection has cleared before starting Hep C treatment.

Serostatus	
Hep A IgM negative, Total negative	Vaccinate and treat Hep C
Hep A IgM negative, Total positive	Treat Hep C
Hep A IgM positive, Total positive	Repeat IgM in 3 months and treat Hep C

Liver Staging: Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. Cirrhosis is definitely diagnosed through liver biopsy, though a variety of serologic and/or radiographic assessments may substitute for pathologic interpretation, with varying degrees of validity. Client with cirrhosis may need a longer course of treatment.

Minimally intensive, serologic liver staging will be conducted using the AST to Platelet Ratio Index (APRI).

Clients with an APRI score less than 1 and no clinical signs of cirrhosis are assumed to not have cirrhosis.

Clients with an APRI score greater than 1 are more likely to have cirrhosis, and signs of decompensation should be evaluated.

APRI scores are not validated during acute Hep C infection and the increase in AST from acute Hep C may lead to an incorrect assumption that the client has cirrhosis leading to overtreatement. Clients who have a APRI greater than 1 with evidence of acute Hep C and no indication of pre existing cirrhosis due to other causes may be assumed to not have cirrhosis.

Evidence of Acute Hep C

1. AST over 200
2. Negative Hep C AB or RNA within the last 6 months
3. Self-reported infection of less than 6 months
4. Prior AST labs within 12 months that are within normal limits

Signs of preexisting cirrhosis

1. Hep B surface AG negative
2. Chronic alcohol use
3. Any medical condition known to cause cirrhosis

$$\text{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

Decompensated Cirrhosis is characterized by the presence of dramatic and life-threatening complications, such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis, or hepatic encephalopathy. Clients with decompensated cirrhosis are referred to a hepatologist for treatment. Decompensated cirrhosis is determined by

1. APRI score greater than 1
2. Ascites
3. Variceal hemorrhage
4. Hepatic encephalopathy
5. Hepatorenal syndrome
6. Spontaneous bacterial peritonitis
7. Physical Exam Findings: Spider angiomata, palmar erythema, gynecomastia, testicular atrophy, abdominal fluid wave, and/or caput medusa.

Obtain Health History: A complete health history will be documented in the client record

Prior Hepatitis C work up
Prior Hepatitis C Treatment
Risk factors for Hepatitis C
- Injection drug use
- Blood transfusion
- Nasal cocaine
- Tattoos/Body Piercing
- Kink Play with blood exposures
- Sexual Exposures

Liver Disease
Psychiatric comorbidities

Review Medications and Allergies: All medications currently prescribed to the client and over the counter (including supplements) will be recorded in the client record.

Hepatitis C treatments have may drug interactions. The medication list should be reviewed for drug interactions and consultations with the clinic pharmacist as needed.
Common drug interactions include:
- Rifampin
- Rifabutin
- Rifapentine
- St. Johns Wort
- Cyclosporine
- Carbamazepine
- Oxcarbazepoine
- Phenytoin
- Phenobarbital
- Statins (Dose dependent)
- Amiodarone
- PPIs and H2 (May be contraindicated or require dosing separation)

Perform Physical Exam: An initial full physical exam will be completed with a targeted assessment for decompensated cirrhosis.

Eyes: Scleral Icterus, Gross retinopathy
Thyroid: Enlargement or nodules
Lungs: Hydrothorax
Abdomen: Hepatosplenomegaly, Caput Medusae, Ascites
Skin: Spider nevi, Palmar Erythema, Jaundice
Neuro: Tremor, Asterixis

Hepatitis C Treatment Counseling:

- What have you heard about Hep C treatment?
- What do you want Hep C treatment to accomplish?
- What type of supports do you need to successfully complete treatment?

Stigma Counseling: Hepatitis C is often stigmatized. Clients may be living in situation where they are not open about their Hepatitis C status which may be a barrier to adherence. A client-centered plan should be developed with the clinican.

Adherence Counseling: A brief interactive client centered counseling session will be conducted to highlight possible short term side effects of hepatitis C medications. For instance, as relate to Harvoni ® (ledipasvir-sofosbuvir) or Zepatier ® (Elbasvir-grazoprevir), side effects include nausea, abdominal cramping, and headache. The importance of adherence for successful Hepatitis C treatment will be discussed. One adherence strategy will be identified and recorded. Possible strategies to suggest include linking the dose with a daily activity that occurs every day, even when traveling or staying out late, such as brushing teeth or hair, a morning shower, or waking up. Harvoni ® and Zepatier ® can be taken any time during the day, at different times on different days, and with or without food. If people forget a dose, they should take the dose when they remember if the same day. If they do not recall whether they have taken a dose on a given day, they should take a dose.

- The success of your Hepatitis C treatment is directly related to how good you are at taking pills. It can be challenging. Getting into a routine can help you remember to take your pills. What routine do you get into every day that would help you remember to take your pills?

Magnet and SAS will provide medication lockers to support the client for daily adherence. Clients who are marginally housed or are in situation where they cannot keep medications at home may elect to store their medications at these facilities per the Hepatitis C Medication Locker Protocol.

Benefits Navigator: The role of the benefits navigator is to facilitate the enrollment into health insurance programs and patient assistance programs to access Hepatitis C treatment at a reasonable cost. The goal should be to enroll someone in an affordable health insurance program that covers Hepatitis C treatment at an affordable cost. The navigators will enroll clients in insurance and complete prior authorization per the Hepatitis C Benefits Navigation Protocol.

Medication Selection: The selection of the medication for treatment is dependent on the formulary of the client's insurance program. The clinician will prescribe the medication that is accessible to the client. The following is a guide based on genotype. Ultimately, the insurance company will dictate what is available and that treatment may be used if the clinician support the selection. The medication is selected based on the screening labs to allow for the prior authorization process to being before enrollment

Treatment Naïve including Peg/Riba

Genotypes 1-6 with APRI less than 1 and no signs of cirrhosis
Mavyret® (100 mg glecaprevir and 40 mg pibrentasvir) Take 3 pills by mouth daily for 8 weeks

Genotypes 1, 2, 4, 5, 6 with APRI greater than 1 or signs of cirrhois
Mavyret® (100 mg glecaprevir and 40 mg pibrentasvir) Take 3 pills by mouth daily for 8 weeks

Genotypes 3 with APRI greater than 1 or signs of cirrhosis
Mavyret® (100 mg glecaprevir and 40 mg pibrentasvir) Take 3 pills by mouth daily for 12 weeks

Treatment Experienced: Consult with MD and AASLD guidelines for optimum regimen

HIV Co-infection:. HIV co infection does not impact the medication selection or length of treatment but some HIV medications have drug interaction requiring a different Hep C treatment.

Notification of client's PCP: Once a client has been enrolled into the Hepatitis C Treatment Program, a standard letter outlining the client's enrollment into Magnet's Hepatitis C Treatment Program will be sent to the client's primary care provider if there is one. PCP. If a client does not have a PCP or does not want the PCP notified, a generic letter will be provided to the client for future use.

Hepatitis C Treatment Enrollment:
The steps needed in a Hepatitis C Treatment Enrollment:

1. Registration
2. Update current medications
3. Update Health History
4. Review lab results
5. Update Hepatitis C treatment and adherence counseling
6. Provide Prescription
7. Referring to the benefits counselor

Prescription: All clients who are deemed eligible by the NP/MD and have completing the adherence and Hepatitis C Treatment counseling will receive a prescription based on the prior authorization. Insurance companies may require a prescription be sent to a specific pharmacy or require shipping of medications.

3 day check in: On day 3, a phone call or case management visit call will be made to the client to check in about side effects and answer any additional questions.

Follow-up visits: The follow up visits with a clinician will occur at Week 4, Week 8, and SVR 12.

Weekly Engagement to Hepatitis C Treatment: Clients at SAS will be engaged on a weekly basis to assess adherence, Hep C counseling, and appointment reminders per the Hepatitis C Treatment Engagement Protocol.

Follow up Events

*Adherence Measur*e: Adherence will be measured using by asking "How many doses have you missed within the last 7 days?" with responses of 0, 1, 2, 3, 4, 5, 6, 7. Any reported missed doses should be addresses in the adherence counseling.

Nausea or vomiting or headaches: Gastrointestinal side effects and headaches have been reported with hepatitis C treatments. These side effects are generally self-limiting and resolve. If a client reports nausea or vomiting the client will be encouraged to take the medication at night and/or with non-spicy food. Persistent symptoms should be supported

*Pregnancy***:** Clients of child bearing potential will be given a urine pregnancy test at baseline and at all follow-up visits. If the urine pregnancy test is positive, the client should be referred to an OB/GYN. Hepatitis C Treatments are contraindicated during pregnancy medication and should be reported to the ARV Pregnancy Registrar at 1-800-258-4263

Extended stops of Hepatitis C treatment: It is not known how treatment stops may impact Hepatitis C treatment. If the client stopped for less than 30 days, they should resume treatment where it was left off. Breaks of longer than 30 days should get consultation for how to proceed.

Approach to Patients with Detectable HCV RNA at Treatment Week 4: The role of week 4 HCV RNA testing with the use of DAA-based therapy is not completely clear at this time. Phase 3 trials with direct-acting antivirals have demonstrated that nearly all non-cirrhotic patients had a week 4 HCV RNA level that was undetectable (or less than the LLOQ); in contrast, a significant proportion of cirrhotic patients will have a detectable HCV RNA level at week 4. For patients who have low-level detectable HCV RNA at treatment week 4, the AASLD/IDSA guidance recommends performing a repeat quantitative HCV RNA level 2 weeks later (at treatment week 6) and if the HCV RNA has increased by more than 10-fold (1 $\log_{10}$ IU/mL) then HCV therapy should be stopped. (https://www.hepatitisc.uw.edu)

On-Treatment Persistent Low-Level Viremia: The significance of on-treatment persistent low-level viremia (that does not increase) is not known and there is no clear indication this represents lack of adherence or likelihood of virologic relapse. Indeed, recent data from Sidharthan and coworkers involving patients receiving DAA sofosbuvir-containing therapy has shown that low-level quantifiable HCV RNA levels at week 4 was not clinically useful in predicting SVR12; these findings contrast sharply with prior studies using interferon-based regimens.[9] The AASLD/IDSA guidelines do not provide a recommendation regarding stopping or extending therapy in the setting of stable low-level viremia. In contrast with the AASLD/IDSA strategy, some experts do not routinely recheck the HCV RNA after a detectable level at week 4 in patients believed to have good adherence, since the vast majority of these patients go on to clear HCV. If, however, adherence is a concern, it is advised to recheck the HCV RNA in 2 weeks,

and if there is a greater than 10-fold increase, then obtain expert consultation and consider stopping therapy. (https://www.hepatitisc.uw.edu)

Management of Abnormal ALT at Week 4 of Therapy: For clients who have increases in ALT levels at week 4, the AASLD/IDSA guidance provides the recommendations outlined below. On October 22, 2015 the US FDA issued a Drug Safety Warning that treatment with ombitasvir-paritaprevir-ritonavir, with or without dasabuvir, can cause serious liver injury, mostly in patients with underlying advanced liver disease. In most of the reported cases, the liver injury occurred within 1 to 4 weeks of starting treatment. Until this recent announcement, the currently available DAAs had not associated with hepatotoxicity with the rare exception of paritaprevir-ritonavir-ombitasvir and dasabuvir when used in conjunction with medications containing ethinyl estradiol; this combination should not be used together.

- **A 10-fold or Greater Increase in ALT Levels**: Patients that have a 10-fold or greater increase in ALT levels, regardless of the presence of clinical symptoms, should have HCV therapy discontinued promptly and undergo close monitoring for liver toxicity.
- **Symptomatic Increase in ALT Levels of Less than 10-Fold**: If a patient has any increase in ALT levels less than 10-fold that is accompanied either by symptoms suggestive of acute hepatitis (weakness, nausea, vomiting, or jaundice) or increases in other hepatic function panel labs (bilirubin, alkaline phosphatase, or international ionized ratio), HCV therapy should promptly be discontinued and the patient should undergo close monitoring for liver toxicity. The guidelines do not specify what degree of change in bilirubin, alkaline phosphatase, or international ionized ratio would realistically be considered significant enough to warrant discontinuation of therapy. Most experts would use clinical judgment with this recommendation and not discontinue therapy with a very low level increase in ALT accompanied by a low-level increase in bilirubin or alkaline phosphatase.
- **Asymptomatic Increases in ALT Levels Less than 10-Fold**: Patients with an increase in ALT levels that is less than 10-fold, but without symptoms suggestive of acute hepatitis, should have close monitoring and repeat ALT levels checked at treatment week 6 and 8. If the ALT levels remain consistently elevated, discontinuation of therapy should be considered. Most experts in this situation would follow this general AASLD/IDSA recommendation but make a decision on a case-by-case basis, taking into account the degree of ALT elevation, the trend in ALT levels, and the presence or absence of underlying cirrhosis or acute hepatitis symptoms. (https://www.hepatitisc.uw.edu)

Missed Appointments: It is important for clients to attend follow up appointments to ensure optimal health. Clients who miss appointments should be rescheduled to the next available appointment. At SAS, the treatment navigators may assist in finding clients and supporting them to attend their visit.

Terminating Treatment Counseling: Unless there is a medical indication, clients should be encouraged to complete the course of their treatment. Efforts should be made to support side effects and adherence issues. If a client terminates early, they should be informed that they may not be able to access treatment again.

Week 4
Labs

1. HCV RNA
2. Hepatic Function: AST/ALT/ALP/ALB/Total-Bilirubin/Direct-Bilirubin
3. Creatinine/eGFR
4. CBC with differential
5. Urine Pregnancy, if needed

Update Medical History

Update Adherence and Hep C Counseling

Week 8
Labs

1. Urine Pregnancy, if needed

Update Medical History

Updated Hep C Counseling

SVR12: A Hepatitis C RNA is obtained 12 weeks after completion of treatment. A Sustained Viral Response at SVR12 is strongly associated with Hepatitis C cure but only reduces the risk of hepatocellular carcinoma. The lab will be reflexed to an RNA to help determine if the client was reinfected versus had a treatment failure. It is difficult to determine a treatment failure vesus a refinfection. A change in genotype would be an indicator of a reinfection.

SVR 12 Achieved:

- Metavir Fibrosis Score F0-F2: Treatment completion counseling. No medical follow up indicated.
- Metavir Fibrosis Score F3-F4: Treatment completion counseling. Refer to PCP for every 6 month liver ultrasound.

SVR 12 Not Achieved:

- All clients: Obtain consult for next steps.

Treatment Support: Clients enrolled in the Hep C case management program will receive intensive support during their treatment and do not need additional visits unless indicated by the clinician. Clients who are not part of the case management program should receive additional check ins either in person or by phone depending on client and clinician preference at week 2 and week 8. The check ins should include adherence and side effect monitoring.

Treatment Completion Counseling: Upon completion of treatment, clients should be encouraged and supported for completing the treatment. SVR 12 should be discussed. Risk for

reinfection are discussed and a harm reduction plan should be developed. Refer to SAS/Stonewall as needed for ongoing support.

Hepatitis C Consultation: Nurse Practitioners will obtain a consult for any situations that they consider out of their scope of practice. In addition, the Nurse Practitioner will obtain a consult for any of the following situaitons:

1. Treatment requiring ribavirin
2. Elevated LFTs greater than 2X the upper limit of normal during treatment
3. Lack of viral suppression at week 4 or SVR
4. Grade III side effects or intolerances not commonly reported with treatment

Time and Events:

	Screen	Enrollment	Day 3	Week 2	Week 4	Week 8	SVR 12	Early Termination	Treatment Completion
Age	X								
Gender at Birth	X								
Identified Gender	X								
Contact info	X	X			X	X	X		
Hep C Consent	X								
Treatment Readiness	X	X							
Physical Exam	X								
Health History	X	X			X	X	X		
RX Provided		X							
Hep C and Adherence Counseling	X	X			X	X			
HIV AB/RNA	X								
HBV AB/AG/Total Core	X								
HBV VL if needed	X								
HAV IgM, Total	X								
HCV AB	X								
HCV RNA	X				X		X		
HCV Genotype	X						X		
NS5A Resistance testing	X								
GFR/Creatinine	X				X				
CBC/Diff	X				X				
AST/ALT/ALP/ ALB/T –Bili/D-Bili	X				X				
PT-INR	X								
Urine Pregnancy (if applicable)		X			X	X			
Adherence Measure					X	X			
Stigma Counseling	X				X	X			
Benefits Navigation	X	X	X		X				
Treatment Support			X	X					
Termination Counseling								X	
Completion Counseling									X