



Hepatitis C: Screening, Diagnostic Testing & Pretreatment Evaluation

Doctors' Newsletter

Hepatitis C:

Screening, diagnostic testing & pretreatment evaluation



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Epidemiology:

Acute Hepatitis C virus (HCV) infection progresses to chronic disease in up to 75% of cases and chronic hepatitis C viral infection (CHC) affects about 230,000 individuals (~ 1%) in Australia. These patients with CHC are at risk of progressive liver fibrosis leading to liver cirrhosis, liver failure and hepatocellular carcinoma and other extra-hepatic manifestations. About 20 – 30% with CHC will develop cirrhosis after about 20 – 30 years of chronic hepatitis C infection. Currently the most common indication in Australia for liver transplantation is related to HCV associated liver disease.

In Australia about 80% of people with hepatitis C infection have been diagnosed. However, it is estimated that 40,000 to 50,000 Australians remain unaware that they are chronically infected with hepatitis C virus. Currently only about 11% of people living with chronic HCV infection are currently receiving antiviral treatment. Hepatitis C is now curable and if the virus is eradicated many of the complications are avoidable.

Extra-hepatic manifestations of Hepatitis C viral infection:

The overall course of HCV infection is typically chronic, systemic, and often asymptomatic and usually in non-high-risk patients is diagnosed incidentally by serological screening or diagnosis of liver disease. The Hepatitis C virus, although known as a hepatotropic virus, is also lymphotropic and plays a role in pathogenesis of virus related autoimmune disease including non-organ-specific autoantibody production. **HCV infection therefore can have diverse and obscure disease manifestations and no organ is spared.**

To maximize the number of cases being treated, clinicians need to have a low threshold for screening patients with hepatitis C serology and be aware of both hepatic and extrahepatic manifestations of hepatitis C infection. Note - 30% of patients with chronic HCV infection have normal liver function tests (LFTs) and there may be no other clues that the individual is infected.

Immune related extrahepatic manifestations including:

- ▶ Mixed cryoglobulinaemia & cryoglobulinaemia vasculitis*
- ▶ B-cell lymphoproliferative disorders e.g. B cell NHL and monoclonal gammopathies & MALT syndrome
- ▶ Immune thrombocytopenia
- ▶ Rheumatic diseases including arthralgia, myalgia, arthritis and vasculitis
- ▶ Polyarteritis nodosa*
- ▶ Sicca syndrome including sialadenitis
- ▶ Autoantibody production (i.e. cryoglobulin, RF, antinuclear, antithyroid, anticardiolipin antibodies with potential for antiphospholipid syndrome (potential for severe coagulopathy event))

Cutaneous, including dermatological manifestations of HCV infection, in addition to those previously listed above (See * above)

- ▶ Lichen planus
- ▶ Pruritus including acral necrolytic erythema
- ▶ Mooren corneal ulceration

Inflammatory related extrahepatic manifestations

- ▶ Fatigue
- ▶ Cognitive impairment
- ▶ Depression & impaired quality of life
- ▶ Polyarthrits/fibromyalgia
- ▶ Type 2 diabetes mellitus & insulin resistance
- ▶ Renal insufficiency & glomerulonephritis
- ▶ Cardiovascular disorders



There are possible and anecdotal associations with various other disorders including chronic polyradiculoneuropathy, lung alveolitis, polymyositis, dermatomyositis and psoriasis.

Think Hepatitis C in any patient with a non-descript ill-defined or unexplained illness at any age.

Be aware that > 50% of patients with chronic HCV infection will have an extra hepatic manifestation of this illness.

Screening & Diagnosis:

The most common cause of HCV infection is related to intravenous drug use and this still accounts for about 80% of all cases of CHC in Australia. Less common route of spread is sexual.

Who to screen & test

- At risk behaviour or in high risk group – intravenous drug use, history of or a person in custodial setting, sexual partner with HCV infection. **Note - test annually while seronegative.**
- Pregnant women (now always recommended).
- Children of known mother with HCV infection.
- STD workup & patients with known HIV and/or chronic hepatitis B infection.
- People with tattoos or body piercing.
- Unexplained abnormal LFTs particularly with hepatitis pattern.
- Hepatoma
- Abnormal Iron Studies particularly elevated transferrin saturation ≥ 46
- Fatigue, tiredness, depression, cognitive impairment & impaired quality of life
- People who have had a needle stick injury.
- Migrants from high prevalence regions (Egypt, Pakistan, Mediterranean & Eastern Europe, Africa and Asia).
- Screen all other patients at 40 years old and thereafter in 10 year intervals to 70 years** (see comment below)

The Australian recommendations for the management of hepatitis C virus infection: a consensus statement (August 2017) recommends only screening people who received a blood transfusion or organ transplant before 1990.

The average age a patient first positive HCV Ab test at Southern.IML Pathology is 40 years with male predominance. The only current population HCV Ab screening is pregnant females. Screening of the entire population will be the most effective way of ultimately eliminating HCV infection. Screening all patients 40 years or older where not previously tested has the greatest potential to identify undetected cases and to treat and possibly avoid development of cirrhosis and liver failure.

HCV serology only became available in early 1990s and suboptimal and inadequate medical practice, even in Australia, have resulted in inadvertent HCV infection which may not have been later diagnosed. This is also particularly relevant in migrants from countries such as Italy, Egypt and Pakistan where HCV is nearly endemic due to poor medical practice and procedures.

Screen High Risk groups annually – see list above.

Know serological status of all patients > 40 years old (suggest screen every 10 years).

Hepatitis C Diagnostic Testing

(1) Serological Antibody Assays (HCV Ab)

Initial testing for the diagnosis of HCV infection. HCV Ab is a serological assay that detects antibodies (HCV Ab) generated in response to HCV infection. HCV Ab test becomes reactive about 6 weeks after initial HCV infection and remains positive for life and will also remain positive after successful HCV treatment (achievement of a SVR).

(2) Molecular HCV RNA test

Molecular diagnostic test specifically detects HCV RNA and usually becomes positive approximately 1 to 2 weeks after initial HCV infection.

- **Qualitative HCV RNA (HCV PCR, HCV RNA)** - qualitative HCV RNA test detects if HCV RNA is present in the sample.
- **Quantitative HCV RNA (HCV Viral titer)** - this test detects and measures the HCV RNA as IU/mL of blood (i.e. the viral load). The HCV viral load is not related to the patient's liver severity or HCV prognosis. The HCV Viral load is used for following reasons
 - To measure a patient's viral load prior to starting HCV therapy
 - To monitor a patient's response to therapy
 - To determine whether a patient has achieved a sustained virologic response (SVR)

(3) HCV Genotype

HCV Genotype – there are at least 6 genotypes and 30 subtypes of HCV. Identifying genotype is essential for selecting treatment regimes, duration of treatment and treatment regime.

Interpretation of Test Results for HCV Infection & Further Action			
Test(s)	Result	Interpretation	Further action
HCV Ab	Non-reactive	No HCV Antibody detected	Never exposed to HCV. If acute HCV is suspected HCV PCR should be requested as the HCV Ab result may not be positive yet.
HCV Ab	Reactive (confirmed positive by secondary HCV Ab assay)	Presumptive HCV infection	Indicates exposure to HCV. Recommend HCV PCR to determine if chronic or resolved infection. HCV Ab will remain positive for life
HCV Ab	Indeterminate (see *below)	Probably false positive	Repeat HCV Ab in 4 – 6 weeks and do HCV PCR.
HCV Ab	Reactive	Active HCV infection.	Consider treatment for HCV infection.
HCV RNA	Detected	If infection > 6 months this is chronic HCV infection.	Additional investigations before treatment include HCV viral load & HCV genotype.
HCV Ab	Reactive	No current HCV infection	No further action required in most cases.
HCV RNA	Not Detected (see #below)		Repeat HCV RNA if person suspect of having HCV exposure within past 6 months or still have suspicion for HCV infection.

*HCV Ab – Indeterminate

Screening HCV Ab assay reactive but secondary HCV Ab assay non-reactive. These are mainly false positive and cross-reactivity with other viral antigens or presence of immunological disorders such as lupus or rheumatoid arthritis. There is also increased incidence in pregnancy which usually returns to (non-reactive) negative after pregnancy. Occasional indeterminate reaction can occur in very early HCV infection when levels of antibody may be borderline.

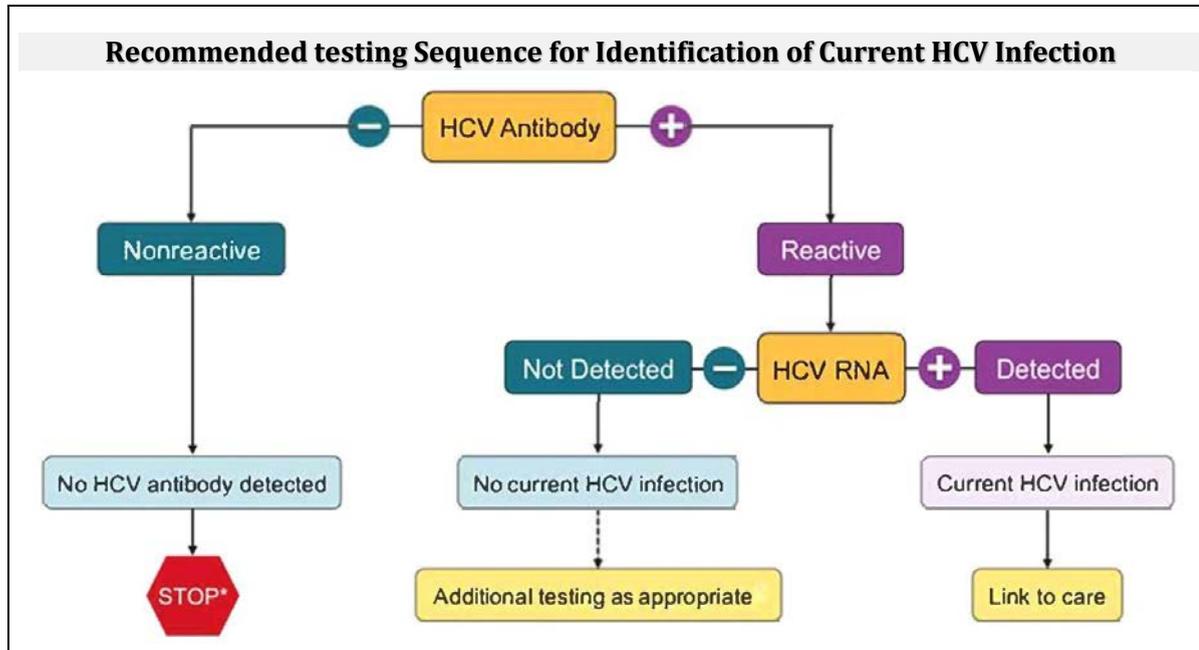
#HCV Ab – Reactive & RNA test – Not Detected.

Note:

- (1) Patient spontaneously cleared HCV and did not become chronically infected, or
- (2) If previously had documented chronic HCV infection, then these results suggest successfully treated and achieved sustained virologic response (SVR)

Any patient with HCV Antibodies (HCV Ab – reactive) should have HCV RNA Test to determine if patient has chronic hepatitis C infection.

Patients with chronic Hepatitis C should be offered treatment.



Pre-Treatment Evaluation

The following laboratory tests are recommended during pre-treatment assessment of people with chronic hepatitis C virus (HCV) infection. See reference (1).

Virology

- HCV genotype and subtype & Quantitative HCV RNA (HCV Viral Load)
- HBV (HBsAg, anti-HBc & anti-HBs), HIV Ab & HAV Ab

Other Pathology Investigations

- Full Blood Examination (FBE)
- Liver Function Tests (LFT)
- Urea & Electrolytes (E&U) including eGFR
- INR
- Pregnancy test (women of childbearing potential)
- Liver Fibrosis Assessment
- Elastography (Fibroscan, ARFI, SWE) (%see below)
- Serum biomarkers (APRI, Hepascore, ELF test, FibroGENE) (*see below)

%Check with laboratory before ordering for availability & cost.

*Southern.IML Pathology can provide a serum biomarker APRI & ELF Test estimate of liver fibrosis. Order testcode "Liver Fibrosis Index".

References

1. The Australian recommendations for the management of hepatitis C virus infection: a consensus statement (August 2017)
2. Australian Family Physician. Hepatitis C An update. AFP 42 (2013) 452-456.
3. Cutaneous Manifestations of Hepatitis C Clinical Presentation. <http://emedicine.medscape.com/article/1134161-clinical>.
4. Extrahepatic Manifestation of chronic hepatitis C virus infection. P. Cacoub et al. Digestive and Liver Disease 46 (2014) S165-S173
5. Hepatitis C Online. <https://www.hepatitisc.uw.edu>

