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Eliminating hepatitis C: Part 2. Assessing your patient for antiviral treatment

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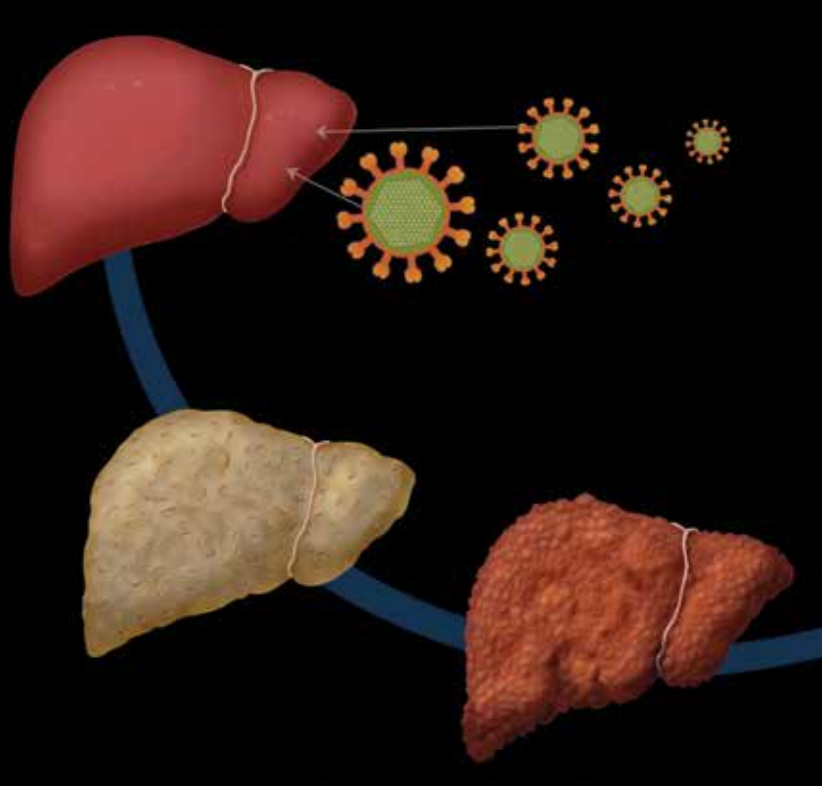
PEER REVIEWED FEATURE 3 CPD POINTS



Eliminating hepatitis C

Part 2. Assessing your patient for antiviral treatment

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As soon as a patient is diagnosed with chronic hepatitis C, preparations can begin for treatment with direct-acting antivirals (DAAs). Most patients can receive DAA therapy in general practice. GPs are ideally placed to assess their patients in preparation for DAA therapy and to identify the minority who require specialist referral.

With the introduction of direct-acting antivirals (DAAs) in Australia in 2016, most people with chronic hepatitis C can be cured of this infection. GPs and suitably qualified nurse practitioners working in all areas of primary care have a key role in identifying, testing and treating their patients with hepatitis C.

The previous article in this series discussed how to identify your patients with hepatitis C. This article provides practical advice on assessing a patient after diagnosis in preparation for DAA therapy. This includes determining whether they can be safely treated in general practice or require specialist referral.

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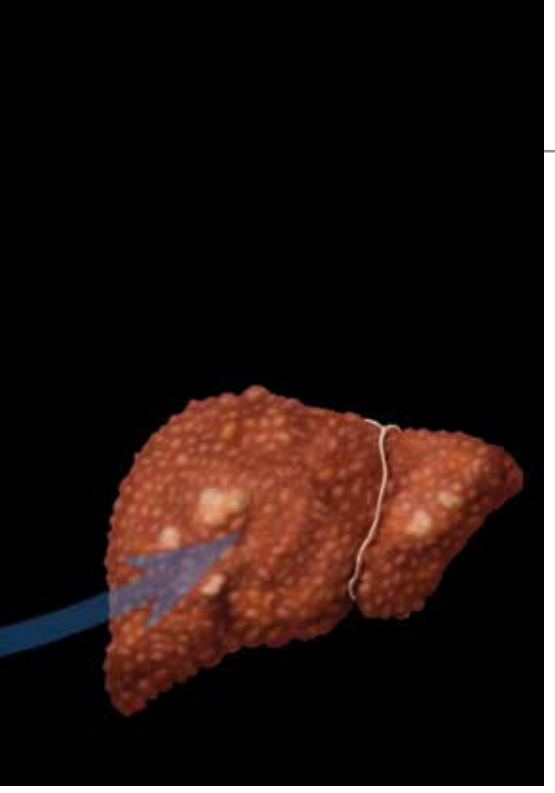
KEY POINTS

- **Most patients with hepatitis C can be treated with direct-acting antivirals (DAAs) in general practice.**
- **GPs are ideally placed to assess patients in preparation for DAA therapy.**
- **Pretreatment assessment includes a comprehensive medical and social history, medication review, physical examination and investigations.**
- **Key questions to determine the safety of DAA therapy in primary care concern the presence of cirrhosis, hepatitis C virus (HCV) genotype, hepatitis B or HIV coinfection, potential drug interactions, previous HCV treatment and renal function.**
- **Patients with cirrhosis, complex comorbidities or who have previously failed DAA therapy should be referred for specialist care.**



After diagnosis, what next?

All people diagnosed with hepatitis C should be considered for DAA therapy. DAAs have the potential to cure most people with hepatitis C and have few contraindications. As soon as a patient is diagnosed with hepatitis C, assessment for treatment can begin, in consultation with the patient.

Pretreatment assessment

Patient assessment in preparation for treatment includes:

- comprehensive medical and social histories
- medication review
- physical examination
- investigations, including a liver fibrosis assessment.

A full list of the required assessments and investigations appears in Box 1.[1]

Six key questions need to be answered to help determine whether the patient can be treated safely in primary care or needs to be referred to a specialist, and the most appropriate treatment option. These questions regard the individual, the hepatitis C virus (HCV) and the liver.

The key questions are:[2]

- Does the patient have cirrhosis?
- What is the genotype of the infecting HCV? (This requirement may be removed in the future owing to the availability of pangenotypic agents.)

1. PRETREATMENT ASSESSMENT OF PEOPLE WITH CHRONIC HEPATITIS C VIRUS (HCV) INFECTION[1]*

History

- Estimated duration of HCV infection
- Previous HCV treatment: date, regimen and response
- Cofactors for liver disease progression: alcohol intake, marijuana use, virological cofactors (HIV, hepatitis B virus), diabetes, obesity
- If ribavirin treatment is planned then note any history of ischaemic heart disease or cardiovascular risk factors
- Vaccinations against hepatitis A and B viruses
- Physical and psychiatric comorbidities
- Ongoing risk factors for viral transmission and reinfection
- Social issues, potential barriers to medication adherence

Medication

- Concomitant medications (prescription, over the counter, illicit)

Physical examination

- Features of cirrhosis: hard liver edge, spider naevi, leukonychia
- Features of decompensation or portal hypertension: jaundice, ascites, oedema, bruising, muscle wasting, encephalopathy
- Body weight and body mass index

Virology

- HCV RNA PCR testing
- HCV genotype†
- Consider HCV RNA level (quantitative)†
- Hepatitis B virus serology (HBsAg, anti-HBc, anti-HBs§), HIV, hepatitis A serology

Investigations

- Full blood examination, liver function tests, urea and electrolytes, eGFR, INR
- Pregnancy test for women with childbearing potential
- Liver fibrosis assessment, for example
  - transient elastography (e.g. FibroScan), shear wave elastography or acoustic radiation force impulse (ARFI) imaging
  - serum biomarker (APRI, Hepascore, ELF test, FibroGENE¶)
- Liver ultrasound examination should be performed in people with cirrhosis to exclude hepatocellular carcinoma (within three months before starting DAAs)
- ECG should be performed if ribavirin therapy is planned and patient is over 50 years of age or has cardiac risk factors

Abbreviations: anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; APRI = aspartate aminotransferase to platelet ratio index; DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; ELF = enhanced liver fibrosis; HBsAg = hepatitis B surface antigen; INR = international normalised ratio.

* Adapted from Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018). Melbourne: Gastroenterological Society of Australia; 2018 (www.asid.net.au/documents/item/1208).[1]

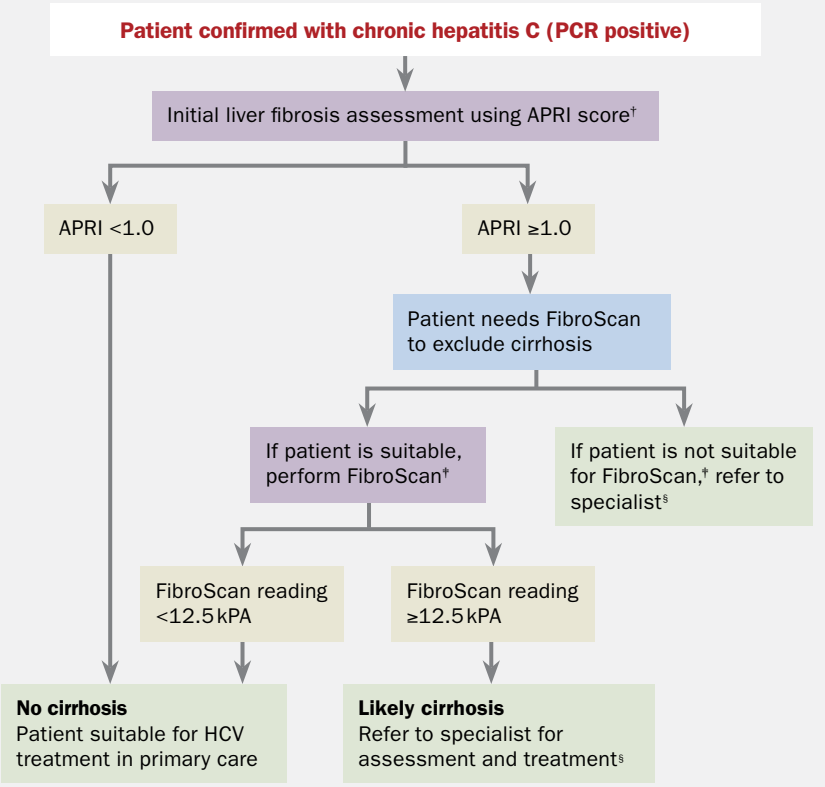
† HCV genotyping is a PBS criterion; it is important before prescribing elbasvir plus grazoprevir or sofosbuvir plus ledipasvir.

‡ HCV RNA level is important for determining eligibility for eight-week treatment duration with sofosbuvir plus ledipasvir.

§ All three tests for hepatitis B virus may be requested if the clinical notes indicate acute or chronic hepatitis.

¶ FibroGENE is a gene-based model for staging liver fibrosis; a FibroGENE calculator is available online (www.fibrogene.com/viral_hepatitis.html).

PATHWAYS TO LIVER FIBROSIS ASSESSMENT IN PRIMARY CARE FOR PATIENTS WITH HEPATITIS C[2*]



Abbreviations: APRI = aspartate aminotransferase to platelet ratio index; PCR = polymerase chain reaction.

* Adapted from Burnet Institute Eliminate Hepatitis C Partnership. Eliminate hepatitis C partnership practice support toolkit. Melbourne: Burnet Institute; 2018 (https://ecpartnership.org.au/toolkit).[2]

† An APRI calculator is available at: www.hepatitisc.uw.edu/page/clinical-calculators/apri

‡ FibroScan is not approved for use in people younger than 18 years, pregnant women, people with ascites and people with a pacemaker or implantable defibrillator. FibroScan and APRI results should be interpreted in conjunction with a full clinical picture by a trained clinician.

§ Appropriate specialists include gastroenterologists, hepatologists and infectious disease physicians, depending on local referral processes.

- Is the patient coinfected with HIV or hepatitis B virus (HBV)?
- Are there any potential drug interactions between the patient's current medication and the DAAs?
- Has the patient previously been treated for hepatitis C?
- What is the patient's renal function?

An important part of the pretreatment assessment is determining the presence of advanced liver disease. Patients with cirrhosis require specialist referral and may need changes to the standard treatment regimen.

It is also important to address potential psychosocial barriers to treatment during the assessment process. Current active injecting drug use is not a contraindication to hepatitis C treatment. However, some patients may need support to stabilise drug and alcohol use or to establish adherence support services before treatment.

Vaccinations

All susceptible patients with hepatitis C should be offered vaccinations against hepatitis A and B viruses. These vaccinations are subsidised for patients with liver disease and those who are at high risk of infection in some jurisdictions.

Liver fibrosis assessment

Liver fibrosis assessment is important to determine whether the patient has cirrhosis (Flowchart).[2] Although all patients are eligible for treatment, regardless of their cirrhosis status, the presence of cirrhosis determines the need for referral for specialist care and influences treatment regimen and duration in some cases, as well as follow up after treatment.[1] Most patients do not have advanced liver disease and can be treated easily in primary care.

The two most widely used noninvasive methods for assessing liver fibrosis are:

- the aspartate aminotransferase (AST) to platelet ratio index (APRI)
- transient elastography, including FibroScan.

Current active injecting drug use is not a contraindication to hepatitis C treatment

AST to platelet ratio index

The APRI has been developed as a simple serum biomarker for assessing fibrosis using results from a full blood count and liver function test. The APRI is calculated from the AST level and platelet count. APRI calculators are readily available online (e.g. www.hepatitisc.uw.edu/page/clinical-calculators/apri). Alternatively, the APRI can be calculated using the formula shown in the Figure. An APRI result of 1.0 or more indicates possible cirrhosis; the patient should be referred for further assessment including transient elastography. An APRI result less than 1.0 suggests that cirrhosis is unlikely and further evaluation for cirrhosis is usually not necessary unless clinically indicated; the patient can proceed on the treatment pathway.

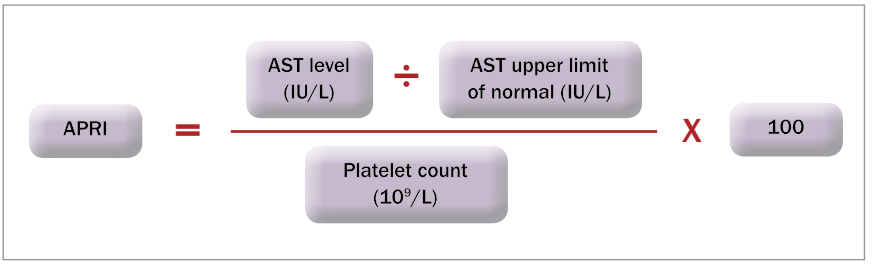


Figure. Formula for the aspartate aminotransferase (AST) to platelet ratio index (APRI).

Transient elastography

Transient elastography measures the stiffness of the liver, which is used to assess liver fibrosis. Threshold levels can determine the presence of cirrhosis. FibroScan is the most extensively validated and widely available method of transient elastography. It uses a series of short, pulsed, low-frequency sound waves and is similar to an abdominal ultrasound examination in terms of patient experience. FibroScan takes a trained operator (usually a nurse or doctor) 10 to 15 minutes to perform. GPs can refer patients to a liver clinic for a FibroScan. In some areas, specialist hepatology nurses offer FibroScan clinics in the community.

A FibroScan reading of 12.5 kPa or higher indicates a high likelihood of cirrhosis.[3] The patient requires referral to a specialist for management and regular monitoring for complications of cirrhosis, including hepatocellular carcinoma. Patients with a FibroScan result of less than 12.5 kPa are generally suitable for DAA therapy in primary care.

A FibroScan reading of 12.5 kPa or higher indicates a high likelihood of cirrhosis. The patient requires referral to a specialist

Alternative methods for evaluating liver stiffness are offered by some radiology services as an add-on to a liver ultrasound examination. They include shear wave elastography and acoustic radiation force impulse (ARFI) imaging. These methods are convenient but less well validated in identifying fibrosis in the presence of chronic hepatitis C.[1]

Risk factors and signs of cirrhosis

Other clinical information should be collected to determine a patient's risk of cirrhosis. This includes their clinical risk factors for cirrhosis and signs of advanced liver disease on physical examination (Box 2). A comprehensive patient assessment is needed because the APRI and FibroScan may not detect cirrhosis in all patients.

Drug interactions

DAAs can interact with many medications. Common examples include proton pump inhibitors, statins, ethinylestradiol and antiepileptic medications such as carbamazepine and phenytoin. The potential for interactions depends on the specific DAA. The University of Liverpool in the UK has developed a comprehensive tool for checking potential drug interactions (available online at: www.hep-druginteractions.org).

When to refer

Most patients with hepatitis C can receive DAA therapy safely in primary care (see the case study in Box 3 and the Table). Patients with cirrhosis, complex comorbidities or who have received previous failed DAA therapy should be referred for specialist care (Box 4).[1,2]

Appropriate specialists are those who have expertise in treating patients with viral hepatitis. This includes gastroenterologists, hepatologists, infectious diseases physicians and sexual health physicians, depending on the indication for the referral and local pathway (including telehealth or other videoconferencing consultations for GPs and patients in rural or remote areas who have limited access to specialist care).

Psychosocial assessment

When determining patient readiness for DAA therapy, GPs must take account of comorbidities, lifestyle and social issues. Major psychiatric disorders such as schizophrenia or ongoing drug use (including injecting drug use) and alcohol use or being homeless can pose challenges to adherence for patients but are not contraindications to treatment. It is important to optimise the patient's health when they are considering treatment.

2. RISK FACTORS FOR CIRRHOSIS AND SIGNS OF ADVANCED LIVER DISEASE

Clinical risk factors for cirrhosis[1]

- Male sex
- Older age when infected
- More than 20 years of HCV infection
- Comorbidities including:
  - diabetes
  - metabolic syndrome
  - coinfection with hepatitis B virus or HIV
  - obesity
  - excessive alcohol consumption

Physical signs of advanced liver disease

- Leukonychia
- Spider naevi
- Palmar erythema
- Gynaecomastia
- Hepatic flap
- Foetor
- Splenomegaly or hepatomegaly
- Oedema
- Ascites
- Jaundice
- Encephalopathy

3. CASE STUDY: A NEW PATIENT WITH A HEPATITIS C RISK FACTOR

Michelle is a fit and active woman aged 49 years who recently transferred to your practice because her previous GP retired. In your initial consultation, you take a medical history, including Michelle's current medications. She has asthma and mild gastric reflux. Her current medications include budesonide/formoterol fumarate dihydrate 200/6 two inhalations twice daily, salbutamol as required and methadone 40 mg daily.

You start a conversation with Michelle about her methadone treatment. She reports that she injected heroin between the ages of 14 and 35 years. She commenced methadone treatment when she was 35 and has not injected drugs for the past 10 years. She has no current or past history of significant alcohol use. You ask if she has ever been tested for hepatitis C and she reports that a previous GP told her she had been exposed to the virus but she is unsure if she has a current infection. She has not previously received antiviral therapy.

You order a comprehensive set of pathology investigations. The results show that Michelle has current hepatitis C with elevated aspartate aminotransferase (AST) and alanine aminotransferase levels (Table).

You calculate Michelle's AST to platelet ratio index (APRI) score using her AST and platelet levels:

$$APRI = [(53/40)/255] \times 100 = 0.52.$$

An APRI of 0.52 indicates a low likelihood of cirrhosis. Michelle has evidence of past cleared hepatitis B virus (HBV) infection but is not currently coinfected with HBV or HIV. She has normal renal function and has not been previously treated for hepatitis C. You decide that it is appropriate for Michelle to receive antiviral treatment in primary care.

Treatment and monitoring will be covered in the next article in this series.

TABLE. MICHELLE'S TEST RESULTS

Test	Result (reference range)
AST (U/L)	53 (<40)
ALT (U/L)	60 (<40)
Bilirubin (mcmol/L)	20 (4 to 20)
Platelets (x 10^9 cells/L)	255 (150 to 400)
eGFR (mL/min/1.7 m^2)	97 (>90)
HCV RNA	Viral load 3,100,000 IU/mL, genotype 3
Hepatitis B serology	Anti-HBs and anti-HBc positive, HBsAg negative
HIV	Negative
Hepatitis A total antibody	Negative
Pregnancy test	Negative
Full blood count, urea and electrolytes, INR, fasting glucose level, body mass index	Within reference range

Abbreviations: ALT = alanine aminotransferase; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; INR = international normalised ratio.

4. PATIENT CIRCUMSTANCES THAT REQUIRE REFERRAL TO A SPECIALIST[2]

Liver related

- Advanced fibrosis or cirrhosis (FibroScan liver stiffness score ≥12.5 kPa)
- Persistently abnormal liver function test results after treatment

Coinfections and comorbidities

- HCV-HIV coinfection
- HCV-HBV coinfection
- Complex comorbidities
- Renal impairment (eGFR less than 50 mL/min/1.73 m^2)

Treatment related

- Failed first-line DAA therapy
- Complex drug-drug interactions
- Experienced major adverse events during treatment

Abbreviations: DAA = direct-acting antiviral; HBV = hepatitis B virus; HCV = hepatitis C virus; eGFR = estimated glomerular filtration rate.

5. RESOURCES ON HEPATITIS C MANAGEMENT FOR HEALTHCARE PROVIDERS AND PATIENTS

Gastroenterological Society of Australia (GESA)
Hepatitis C treatment resources for medical practitioners (www.gesa.org.au/resources/hepatitis-c-treatment/):

- **Consensus statement:** *Australian recommendations for the management of hepatitis C virus infection* (September 2018)
- **Wallchart for GPs:** *Clinical guidance for treating hepatitis C virus infection: a summary* (also at: http://cart.gesa.org.au/membes/files/Resources/Hepatitis%20C/GP_algorithm_Sep_Oct_edit2018.pdf); this summarises the clinical guidance for treating hepatitis C, including a pre-treatment assessment form
- **Request form:** *Remote consultation request for initiation of hepatitis C treatment*
- **Video:** *A practical guide to prescribing the new hepatitis C antiviral drugs in general practice*

Hepatitis Australia
A range of hepatitis C resources and information (www.hepatitisaustralia.com/Pages/Category/hepatitis-c)

Eliminate Hepatitis C (EC) Partnership
Resources for primary care providers:

- **EC Practice Support Toolkit** (https://ecpartnership.org.au/toolkit): includes resources to promote hepatitis C testing, treatment and follow up developed specifically for GPs and other primary care providers
- **Other resources** (https://ecpartnership.org.au/resources)

Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)

- **Links to hepatitis C training, information and resources** (www.ashm.org.au/HCV)
- **REACH-C checklist** (www.reach-c.ashm.org.au)

This may include initiating opioid substitution therapy before starting treatment and referral to support services as required.

More intensive adherence support may need to be organised before treatment. This will be covered in more detail in the next article in the series.

Conclusion

The role of GPs in managing patients with hepatitis C and preparing them for DAA treatment is crucial to the hepatitis C elimination effort in Australia. Resources on hepatitis C management for healthcare providers and patients are shown in Box 5. If left untreated, people with hepatitis C will be at increased risk of developing cirrhosis and associated complications, including liver failure and hepatocellular carcinoma. Preparation for hepatitis C treatment involves a few straightforward steps. Most people diagnosed with hepatitis C can be assessed and treated in primary care, giving GPs an exciting opportunity to offer their patients a cure. MT

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1. Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018). Melbourne: Gastroenterological Society of Australia; 2018. Available online at: www.asid.net.au/documents/item/1208 (accessed July 2019).
2. Burnet Institute Eliminate Hepatitis C Partnership. Eliminate hepatitis C partnership practice support toolkit. Melbourne: Burnet Institute; 2018. Available online at: https://ecpartnership.org.au/toolkit (accessed July 2019).
3. Hepatitis C Virus Infection Consensus Statement Working Group. Clinical guidance for treating hepatitis C virus infection: a summary. (September 2018). Melbourne: Gastroenterological Society of Australia; 2018.

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