Disease overview – Hepatitis C

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Summary

Several hundred thousand people in the UK are estimated to be infected with hepatitis C virus (HCV), but many individuals are living with the infection without it being diagnosed. This is because the symptoms often take many years, even decades, to develop. Nevertheless, damage to the liver can be severe and hepatitis C is a leading cause of liver disease and liver transplants. The development of pegylated interferons and their use in combination with ribavirin has, for the first time, allowed for the successful treatment of the majority of patients with mild, moderate or severe chronic hepatitis.

Drugs in Context
DOI: http://dx.doi.org/10.7573/dic.212202

Citation: Clark, R. Disease Overview – Hepatitis C. *Drugs in Context*: e212202. doi:10.7573/dic.212202

Date of last literature search: September 2006

NB: This article was originally published by CSF Medical Communications Ltd (CSF) in *Drugs in Context* 2007;3(2):57–64. *Drugs in Context* and all CSF copyrights were acquired by Just Medical Media Ltd in 2009.

Introduction

HCV is a blood-borne virus that is recognised as an important global public health problem, with approximately 170 million people infected globally and about 4 million carriers in Europe alone.[1] Hepatitis (inflammation of the liver) is caused by several mechanisms, including viral infection. As hepatitis A, B, C, D, E and G viruses can cause viral hepatitis, a diagnosis can only be made by testing patients' sera for specific antiviral antibodies or viral RNA. Hepatitis C was previously referred to as parenterally transmitted 'non-A, non-B hepatitis', non-B transfusion-associated hepatitis or post-transfusion non-A, non-B hepatitis until the identification of HCV as the causative agent in 1989.[2] Hepatitis C is caused by an infection with HCV, an enveloped, single stranded, positive-sense RNA virus.[3]

HCV infects hepatic cells, and can cause severe inflammation of the liver with long-term complications.[3] Hepatitis C is one of the main causes of cirrhosis and hepatocellular carcinoma, and HCV-related end-stage liver disease is the leading reason for liver transplantation in Europe and the USA.[4] As yet, a vaccine is not available for hepatitis C, due in the main part to the multiplicity of HCV genotypes and HCV's ability to mutate and evade host defence mechanisms. Thus, preventative measures focus on avoiding contact with HCV and treatment of infected individuals.

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HCV

HCV itself and its life cycle remain largely an enigma because of the lack of *in vitro* systems to study the virion, at least until very recently. Humans are the HCV's reservoir of infection, though it has been transmitted to chimpanzees experimentally.[3] HCV is a very small, even by viral standards, at a diameter of about 50 nm, explaining its comparatively recent detection, and is classified as a separate genus (*Hepacivirus*) within the *Flaviviridae* family.[3] HCV is an enveloped, single stranded, positive-sense RNA virus, and the HCV genome is highly mutable, presumably enabling it to escape host immunological detection and elimination.[3] This may be because HCV lacks efficient genomic 'proofreading' on replication within host cells, and thus it undergoes evolution and persists as a group of virus quasispecies.[3,5]

HCV is classified into six main HCV genotypes: type 1 (40–50% of UK cases), types 2 and 3 (40–50% of UK cases) and types 4, 5 and 6 (about 5% of UK cases).[6] In addition, there are many HCV subtypes (designated a, b, c, etc.) and about 100 different strains (numbered 1, 2, 3, etc.) based on genomic sequence heterogeneity.[3,7] The presence of this heterogeneity hinders the development of vaccines since vaccine antigens from multiple serotypes would be required for global protection. Responsiveness to treatment for hepatitis C also varies considerably according to HCV genotype. Genotype 1 is generally associated with a poorer response to treatment, whereas genotypes 2 and 3 are associated with more favorable responses. Thus, following combination treatment with pegylated interferon plus ribavirin, for example, greater

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sustained virological response rates are obtained with HCV genotype 2 or 3 (about 75–85%) than for genotype 1 (about 40–50%), with an intermediate rate for the less common genotypes (4, 5 and 6).[6] Differences in the prevalence of HCV genotypes are related to geography and mode of acquisition of the virus.[8] HCV genotype 1 infections are most common in Europe or North America, closely followed by genotypes 2 and 3.[9]

Epidemiology

Hepatitis C is often referred to as a silent epidemic due to its prevalence and long periods without specific or easily recognisable symptoms. The exact scale of the problem is not, however, well defined. The World Health Organization estimates the global prevalence of HCV infection is 3%, or 170 million patients.[1] In the USA, where HCV prevalence has been studied most extensively, about 1.8% of the population were anti-HCV antibody-positive, indicating that a total of 3.9 million had a prior HCV infection and approximately 2.7 million were chronically infected.[10] Seroprevalence is higher in Africa and Asia than in most industrialised regions. Egypt has the highest reported seroprevalence (about 15–20%), which has arisen because many of the country's citizens were exposed to HCV after receiving parenteral therapy for schistosomiasis.[11]

In the UK, there is a lack of good HCV seroprevalence data. The Health Protection Agency (HPA) seroprevalence unit has tested antibodies to HCV in more than 15,000 serum specimens archived from 1986, 1991 and 1996 from a range of ages and both sexes, representing a proxy of the general population in England and Wales.[12] The overall prevalence of anti-HCV was 1% in 1986, 0.6% in 1991 and 0.7% in 1996, and did not vary significantly between these three periods (p=0.14).[13] Based on the age–sex profile of anti-HCV prevalence in the 1996 study, around 300,000 individuals in England and Wales have evidence of exposure to hepatitis C,[14] though the National Institute for Health and Clinical Excellence (NICE) estimate that up to 500,000 people are infected.[6] Moreover, between 1992 and 2004 about 50,000 HCV infections had been reported to the HPA by laboratories in England and Wales, representing only approximately 17% of estimated cases in the population.[14] Based on the aforementioned data, the HPA have estimated a HCV prevalence of 0.5% for England.[12] A cumulative total of 46,398 laboratory-confirmed diagnoses of hepatitis C infection were reported in England between 1992 and 2004 (Figure 1), reflecting increased anti-HCV testing rather than an increase in seroprevalence during this period.[12] Men accounted for 67% of cases, and half of all reports were in people aged 25–39 years (Figure 2).[12] In Scotland, the prevalence of HCV infection is approximately 1%, equating to 37,500 people infected with HCV.[15]

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Natural history

HCV is a member of the *Flaviviridae* family of RNA-containing viruses, and is not integrated into the host genome. Although the liver is the primary target of infection, the natural history

Figure 1. Cumulative laboratory reports of hepatitis C infection in England (1992–2004).[12]

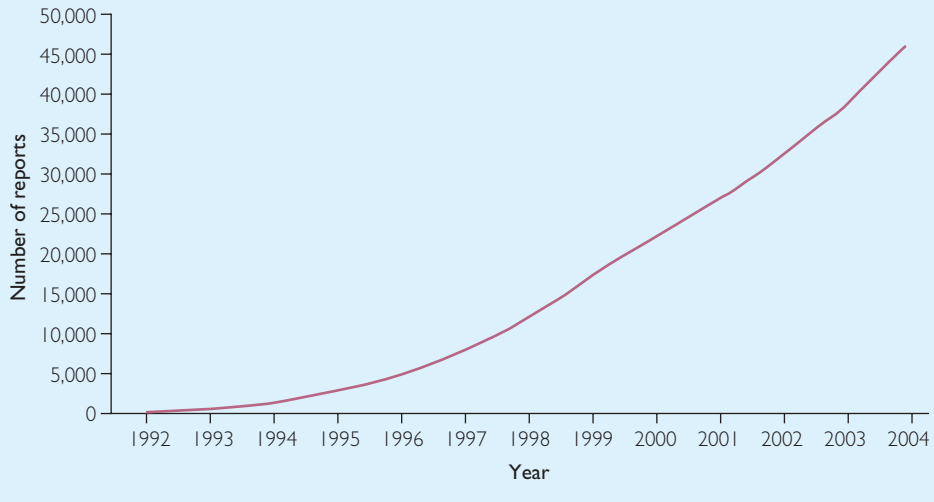
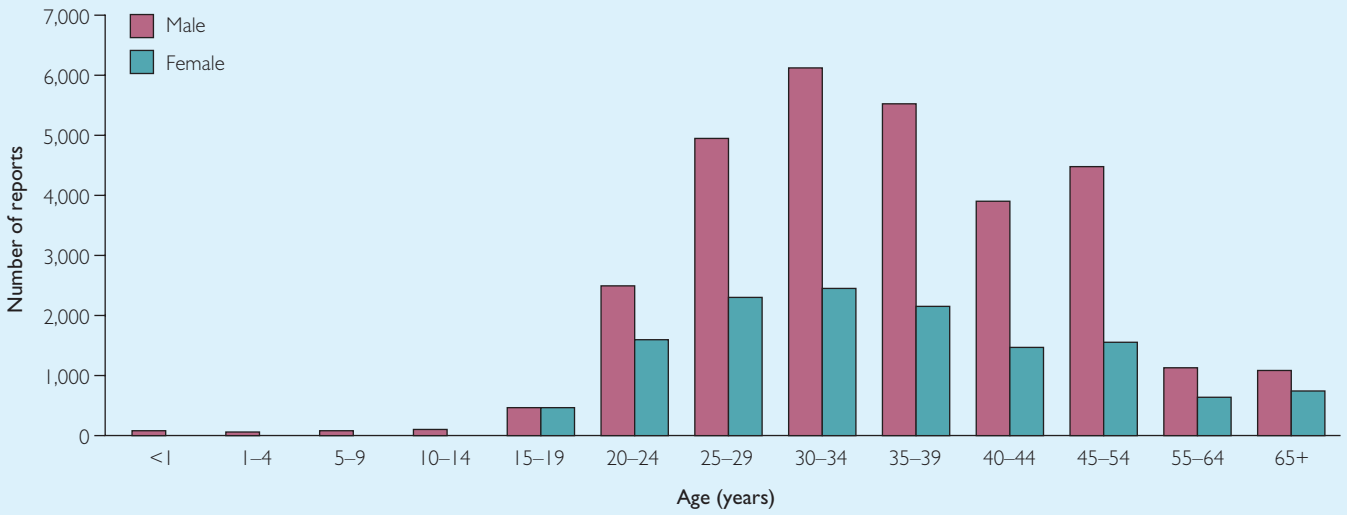


Figure 2. Age and sex distribution of laboratory reports of hepatitis C infection in England (1992–2004).[12]



of HCV infections is still an enigma, with studies hampered by the lack of a suitable animal model and, until recently, a tissue culture system.[16] Several molecules have been implicated in the receptor complex at the surface of target cells, but the exact mode of HCV entry still remains unknown.[17] Systems that support HCV replication and particle formation *in vitro* are starting to emerge only now, 16 years after the discovery of the virus, due to the development of appropriate tissue culture systems, but these are outside the scope of this review.[18]

About 80–85% of those with an acute HCV infection go on to develop chronic hepatitis C, and of these up to 20% will eventually develop cirrhosis, which may lead to hepatic failure and hepatocellular carcinoma.[9] Our understanding of these processes – such as why one in five patients with an acute HCV infection is able to clear the virus – is extremely limited. A strong, multispecific reaction to HCV proteins mounted by cytotoxic T lymphocytes is associated with viral clearance, and both CD4+ and CD8+ lymphocyte functions are important to effect this outcome.[19] Unfortunately, this process fails to eradicate infection in most people; in fact, it may contribute to liver inflammation and, ultimately, tissue necrosis. The ability of HCV to evade the host response occurs through a complex combination of processes that include signalling interference, effector modulation and continual viral genetic variation.[20] HCV is able to persist and spread through these evasion strategies, and a chronic infection develops. In chronic infection, genetic and environmental factors (particularly age, sex, race and alcohol intake) appear to determine disease progression in individual patients.[19] Liver lesions appear to result from locally driven immune responses, which are mainly non-specific, triggering fibrogenesis, with cirrhosis facilitated by external factors such as chronic alcohol consumption and other viral infections.[17] The development of hepatocellular carcinoma is limited mainly to patients with cirrhosis, but the role of HCV proteins in hepatocarcinogenesis is unknown.[17,19] An approximation of the overall progression of hepatitis C is shown in Figure 3.

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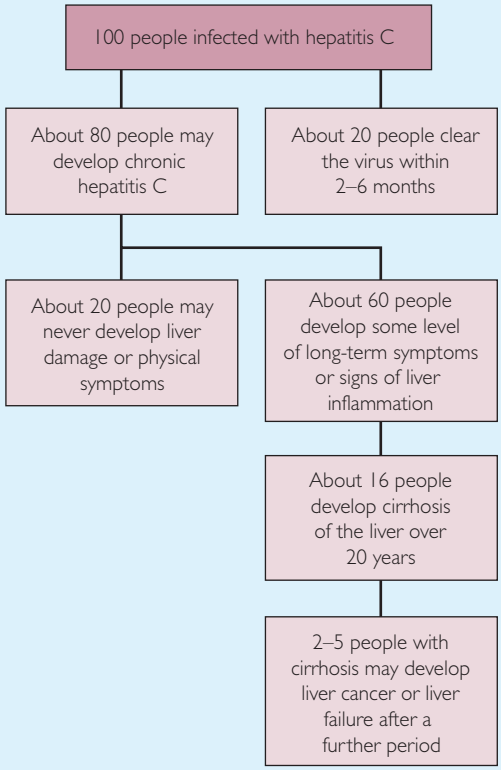
Transmission

HCV is a blood-borne virus, and though it has been detected in other body fluids, blood is the main vehicle of infection. Thus, HCV is transmitted by percutaneous or permucosal exposure to infectious blood or blood-derived body fluids.[21] Risk factors associated with acquiring HCV infection include:

- intravenous drug use (responsible for about ~80% of all cases of HCV in the UK)
- transfusion of blood and blood products (although blood and products have been screened for HCV since 1991 [see below])
- organ transplantation from infected donors
- haemodialysis
- intranasal cocaine use
- occupational exposure to blood (primarily contaminated needles)
- vertical transmission from an infected mother to the neonate

Figure 3. An approximation of the overall progression of hepatitis C.[27]



- sex with an infected person
- fights, human bites, tattooing, body piercing, acupuncture.[21,22]

Transmission from HCV-infected healthcare workers to patients is rare, and transfusions and transplants have now been virtually eliminated as sources for HCV transmission following the introduction of hepatitis C screening for the UK in 1991.[21] As a consequence, at least two-thirds of all newly acquired cases of hepatitis C are related to injecting drug use.[21] Moreover, a review of international studies suggests that 50–95% of intravenous drug user populations are infected with HCV.[23] In contrast, the efficiency of HCV sexual transmission seems to be fairly low, based on studies of heterosexual partners of patients with hepatitis C.[24] Likewise, mother-to-baby transmission of HCV is uncommon, either *in utero*, or at the time of birth, with upper estimates of 4–7% in the UK.[25] Coinfection with HIV, however, increases the rate of mother-to-baby transmission by four- or five-fold.[25]

In about 10% of chronic hepatitis C cases no obvious risk factor for the transmission of the disease can be identified.[22] Unconventional methods of HCV transmission such as infection by tattooing, piercing or nosocomial infection may occur, and there is a low (albeit largely theoretical) risk from sharing household items such as razors or even toothbrushes with an infected individual.[22] Nevertheless, it seems prudent not to share household items that could be contaminated with blood from someone infected with HCV. Intranasal (e.g. snorting cocaine) and oral drug administration (e.g. smoking crack) are also possible routes of HCV transmission, with infected blood particles possibly passed on through shared crack pipes or cocaine straws.[26] There is no risk of HCV transmission from everyday social contact such as holding hands, hugging, kissing, or through sharing toilets, crockery and kitchen utensils.[27] Individuals infected with HCV should not be excluded from work, school, play, childcare or other settings.

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Symptoms

At the time of infection with HCV, and shortly afterwards, few are aware of any symptoms, though patients may feel unwell, have nausea and vomiting and, rarely, jaundice. Even with progression to chronic hepatitis, most patients remain without symptoms for a number of years, making the infection difficult to recognise, particularly during the early disease stages.[28]

Disease progression is highly variable, and patients may not become symptomatic until advanced liver disease occurs.[27] Symptoms, though not common, can include:

- muscle aches
- pyrexia
- mild-to-severe fatigue
- nausea
- loss of appetite/weight loss
- depression or anxiety
- pain or discomfort in the liver
- jaundice
- poor memory or concentration
- alcohol intolerance.[27]

It should also be noted that the severity of symptoms does not necessarily equate to the extent of hepatic damage, with some patients reporting quite severe symptoms without clinical signs of liver damage, whilst cirrhosis can be present without any obvious symptoms.[27] For patients in whom hepatitis C progresses to cirrhosis, serious complications due to hepatic failure may include oesophageal varices and ascites.[27]

Diagnosis

An initial antibody test (for anti-HCV antibodies) will indicate whether a person has ever been infected with HCV. About 15–20% of patients with acute hepatitis C will go on to naturally clear HCV, and thus do not progress to the chronic disease stage, but these patients will still test positive after viral clearance has occurred.[9,27] However, the presence of anti-HCV antibodies cannot be confirmed until 12–27 weeks after exposure, creating a 'window' of seronegativity and potential infectivity.[3] At present, the best tests to diagnose whether circulating HCV is present use the polymerase chain reaction (PCR) to detect HCV RNA and can also diagnose the extent of the infection (viral load) as well as viral genotype(s).[27] Moreover, PCR has become the method of choice for early diagnosis as a positive reaction is obtained within days of inoculation.[3] Early detection and diagnosis can also be obtained using a HCV core antigen enzyme-linked immunosorbent assay.[29]

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About 25% of patients with chronic hepatitis C do not have elevated alanine aminotransferase (ALT) levels, and thus whilst ALT testing can be a useful indicator for prognosis (patients with normal ALT levels tend to have better long-term outcomes), ALT testing is obsolete as a screening tool for blood and blood products.[28,30] Groups that should be offered tests for HCV are shown in Table 1.[31] In addition, some groups should be offered HCV testing as part of their routine healthcare, including patients with renal failure receiving dialysis and those infected with HIV.[31]

On referral to secondary care following a positive PCR test, a liver biopsy may be performed to investigate the degree of liver damage (inflammation, fibrosis and/or cirrhosis, etc.) and is used to distinguish between patients with mild, moderate and severe chronic hepatitis.[3,28] Until recently, only patients with moderate or severe chronic hepatitis C were offered treatment according to UK guidelines, with a watchful waiting strategy adopted for mild cases.[32] Now, guidelines advocate the treatment of mild cases too, and so a biopsy is no longer compulsory before treatment can be started.[6] However, a liver biopsy is still the most accurate way of assessing liver damage in patients with chronic hepatitis C.[31]

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Clinical management

The clinical management of hepatitis C centres on the treatment of patients with chronic hepatitis as effective vaccines are not available, nor are they likely to be in the near future. The current best practice management is for a combination of pegylated interferon (either alfa-2a or alfa-2b) plus the antiviral agent ribavirin. Prior to the development of pegylated interferon, conventional interferon was used, often in combination with ribavirin. However, pegylated interferon has been shown to be more effective than conventional interferon in clearing the HCV infection (no detectable virus in the blood 6 months after treatment has ceased – termed a sustained virological response). This has been acknowledged by NICE, which now recommend pegylated interferon plus the antiviral agent ribavirin as first-line therapy, including those with mild disease, and pegylated interferon for patients for whom ribavirin is contraindicated.[6,32]

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Table 1. Those for whom hepatitis C testing should be offered.[31] ALT, alanine amisotiansterase

- People who have ever injected drugs in the past.
- Currently injecting drug users.
- People who have received transfused blood in the UK prior to September 1991, or blood products prior to 1986.
- Recipients of organ and tissue transplants in the UK before 1992 or abroad in countries where hepatitis C is common and donors may not have been screened.
- Babies born to mothers known to be infected with HCV.
- Children of mothers found to be infected with HCV.
- Regular sexual partners of patients infected with HCV.
- Healthcare workers accidentally exposed to blood where there is a risk of HCV transmission.
- Anyone who has received medical or dental treatment in countries where HCV is common and infection control may be poor (this will include blood transfusions and blood products where donations are not screened for HCV).
- People who have had tattoos, body piercing and other forms of skin piercing where infection control procedures are poor.
- In individuals whose ALT is elevated in the absence of no obvious cause.

Moreover, these recent guidelines also advocate the treatment of patients who are current intravenous drug abusers.[6]

Treatment with pegylated interferon monotherapy plus ribavirin is effective in 84% of genotype 2 or 3 infections and 52% of genotype 1 infections.[33] However, this still leaves considerable room for improvement.[34] Novel treatments are being developed and tested, and focus on hepatitis C protease inhibitors or HCV-RNA polymerase inhibition, though these are not currently indicated for the treatment of hepatitis C.

In addition, patients should be advised:

- to stop or reduce alcohol consumption (continued alcohol consumption is associated with more rapid progression of liver disease) – patients may need to be referred for specialist alcohol support and counselling
- not to share any injecting equipment (where appropriate)
- to avoid sharing razors or toothbrushes, and to cover cuts and skin lesions with waterproof dressings
- to consider that, although uncommon, sexual transmission can occur, and that the use of condoms will reduce this risk
- to consider advising any regular sexual partners that they may wish to consider being tested for hepatitis C.[27]

Socioeconomics

The presence of up to 500,000 individuals in the UK infected with (mostly undiagnosed) chronic hepatitis C represents a huge potential future cost to healthcare services. In particular, high costs associated with liver failure and transplantation could be reduced if these patients were diagnosed and treated.[35] Studies of the economic effects of individual drug regimens are considered in the next section. However, one UK-based study looked at the effect of pegylated interferon alfa-2a or 2b plus ribavirin in the UK.[36] This found that the incremental cost per quality-adjusted life year (QALY) for pegylated dual therapy remained under £30,000 for most patient subgroups, and thus these regimens represent good value for money.

Key points

- HCV was discovered comparatively recently, and due to a lack of suitable hosts/model systems, at least until recently, has largely remained an enigma.
- HCV is classified into six main HCV genotypes: types 1, 2 and 3 are the most common in the UK.
- HCV genotype 1 is more difficult to treat than genotypes 2 or 3.
- In the UK, the estimated prevalence of hepatitis C is between 0.5% (England and Wales) and 1% (Scotland).
- About 80–85% of those with an acute HCV infection go on to develop chronic hepatitis C, and of these up to 20% will eventually develop cirrhosis, which may lead to hepatic failure and hepatocellular carcinoma.
- Blood has been identified as the main vehicle of HCV infection, and intravenous drug abuse is by far the most common method of transmission in the UK.
- Infection with HCV produces a variety of symptoms, but many patients may appear asymptomatic, particularly until an advanced stage of chronic hepatitis C.
- The clinical management of hepatitis C centres on the treatment of patients with chronic hepatitis as effective vaccines are not available.
- A combination of pegylated interferon (either alfa-2a or alfa-2b) plus the antiviral agent ribavirin is currently the best available treatment for most patients with chronic hepatitis C.
- NICE now recommend that pegylated interfon plus ribavirin should be used for all patients with chronic hepatitis C where appropriate, including those with mild disease.

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Acknowledgements

Figures 1 and 2 are adapted from the Health Protection Agency, 2005.[12]
Figure 3 is adapted from the Scottish Executive. [27]