Doctor's Corner - Notes for GP's dealing with Hepatitis C

This document is intended for GP's with very little knowledge of Hepatitis C. I make no apologies for having the cheek to produce this. Training for most GP's on the subject of HCV diagnosis and treatment is poor, and hopefully this will help avoid some of the more major pitfalls. Please note that I am not medically qualified, and although I make every effort to make this as accurate as possible it should not be treated as a reference.

Diagnosis.

Before discussing diagnosis it is worth reviewing the clinical history of hepatitis C. Hepatitis C is a blood borne RNA virus and therefore is transmitted by exposure to infected blood. The virus appears in the blood about two weeks after exposure such that the diagnosis depends on testing for the viral HCVRNA directly. This test is generally not available in primary care and the antibody test (anti HCV antibody) may not become positive until about six weeks post infection, with some not seroconverting for many months (three years is the longest "window period" recorded). Thus a negative antibody test in this phase (Acute hepatitis C is designated to be the first six months of infection) does not exclude hepatitis C infection. About 20% of people develop the symptoms with acute hepatitis C and these symptoms are similar to other causes of acute hepatitis and may easily overlooked if not severe.
On average about 26% clear the virus spontaneously with symptoms, and young females have been associated with higher clearance rates. Thus conversely 70% enter the chronic phase of hepatitis C which may last many decades. The first phase of chronicity is asymptomatic (emphasised in medical texts) but symptoms both specific and non-specific can develop eventually in the second phase (not emphasised in medical texts) before the symptoms and signs of overt chronic liver disease develop in the third phase of the illness, although cirrhosis itself can be asymptomatic.

HCV is probably one of the most difficult diagnostic challenges presented to any GP in the second phase or even later phase of chronic hepatitis C. The list of symptoms, or absence thereof represents a serious challenge. Many patients complain of tiredness (TATT), night sweats, 'brain fade', URQ pain, and non specific muscle and joint pains (without elevated rheumatoid factor) but the list of other symptoms is so extensive and varied that it is almost impossible to obtain a diagnosis on the basis of symptoms alone. There are a few basic pointers that may help. Something like 1.5% of the population carry the virus, and the bulk of these will have contracted it from intravenous drug abuse. This means that the 'average' patient can be quite old, as the teenagers of the 'experiment with drugs' era are the bank managers of today. It will have only taken one injection 30 years ago for you to have a patient in trouble today. Other classic sources of infection include tattoos, particularly those done many years ago and those done abroad. Many have the virus from blood transfusions, and blood products particularly those administered pre-1990 as universal testing and heat treatment of these products was not introduced until the early 1990's and testing for Hep C was not introduced for UK blood donations until September 1991. Note that in some cases gamma globulin, clotting factors and anti-rhesus factor have been the culprits. There are a few cases of needlestick infections from Health Care Workers, and a lot of overseas medical and dental treatment is suspect, particularly patients who have received vaccinations as part of mass innoculation programs abroad. The latter particularly applies to Egypt and Pakistan.
HCV does not generally transfer sexually unless HIV is also present, and in most cases sex can be ruled out as a means of transmission. In long term monogamous relationships it is extremely rare for the virus to transfer, and where it does the culprit is most likely to be shared razors or toothbrushes. The virus can transfer during childbirth in approximately 5% of births where the mother has the virus, and it is worth asking if a patient's mother suffers or suffered from liver problems as in many cases the infection will not have been diagnosed.

Probably the best clue that GP's get to diagnosis is raised ALT and AST when a Liver Function Test is done. Around two thirds of patients with the virus show raised levels, and this should ring alarm bells. (Unfortunately therefore normal LFT do not always exclude chronic hepatitis C.) This and rheumatic pain without raised rheumatoid factor are the main clues. If a patient admits to IV drug experimentation however long ago and has raised ALT then there is around an 85% chance that HCV will be present. Getting a patient to admit to IV drug abuse, however long ago, is often a forlorn hope but the lack of a convincing denial to a carefully worded question may be enough. There is a school of thought in the US that says that no new case of RA should be diagnosed unless HCV has been specifically excluded, and it may well be considered good practice to include an HCV test with the initial blood tests where RA is suspected.

In conclusion "Could this be an unusual presentation of chronic hepatitis C?" is question that needs to be asked more frequently in assessing patients with unexplained chronic symptoms, some of which have been outlined above.

Testing

The first stage in the establishment of a diagnosis is an HCV antibody blood test. This in itself is not confirmation of the presence of the virus as approximately 26% of patients clear the virus naturally as mentioned above and will require no medical intervention. Antibodies stay in the patients blood for life, so a patient exposed to the virus will always test positive by the antibody test which somewhat limits its usefulness. It is however, readily available and inexpensive! To diagnose the virus itself requires a test (called in the past a PCR test) which detects virus RNA itself. The newer tests are very sensitive and tend to be regarded as the prerogative of secondary care, Hepatologists, Gastroenterologists and other HCV specialists rather than GP's, but if an antibody test returns a positive result considerable time may be saved by running a Viral Load/HCVRna test at the earliest opportunity. This also prevents the situation where antibody positive patients are referred to specialists when they have already cleared the virus naturally. It should also be remembered that the antibody test is prone to false positives, and may need to be repeated.
It is advisable not to tell a patient that they have HCV until they have had a viral load test as this causes unnecessary worry and may not be accurate. Far better to explain that they have antibodies to it, and further tests need to be done to establish whether the virus is present.
Note that all the above applies to chronic infections. As discussed above, when there is a suspicion that the infection is acute (less than 6 months) the situation is a little different. Standard antibody tests will not give reliable results for the first six weeks post infection. The better viral quantification tests will respond in about two weeks. Acute cases should be processed and treated with all speed as if prompt treatment is given the results are considerably better than if the infection is allowed to become entrenched, in which case the window of opportunity is lost.

Reasons for treatment.

Untreated patients with HCV are at a much greater risk if developing cirrhosis and/or liver cancer. Approximately 20% will get cirrhosis, and 5% liver cancer. The timings are variable, and current thinking is that ALL cases would eventually progress to this point were it not for mortality from other causes. Treatment is expensive, with a course of treatment costing up to £20,000 (at 2007 prices) but effectively this works out at half the price of not treating, as support for patients with failing livers and liver transplants are extremely expensive. This, of course does not take into account quality of life and other issues. NICE guidelines state that ALL patients should be treated where possible. Pediatric treatment is possible, although not generally undertaken before teenage years as for some obscure reason the virus does not seem to inflict much damage before then, and spontaneous clearance can occur. Treatment of elderly patients is possible in many cases, but needs to be assessed by a specialist.

Treatment.

HCV is treated with a combination of pegylated interferon and ribavirin. The treatment usually lasts either 24 or 48 weeks depending on the genotype of the virus. Genotypes 2 and 3 usually being 24 weeks, and the remainder 48 weeks. Genotype 1 is the most common variant and one of the more difficult to cure. Pegylated interferon is usually administered by subcutaneous injection once per week. Patients are usually trained to do their own injections. This is not as bad as it sounds and very few patients have problems doing their own injections. The two most commonly used interferons are supplied in either pre-filled syringes or self-injecting devices. Ribavirin is taken twice daily in tablet form. Success rates vary from 55% to over 90% depending on many factors including genotype of virus, length of infection, age and liver condition. Nearly all treatment is conducted by specialist nurses with the backup of a consultant. It is not unusual for a patient not to see the consultant at all during treatment, and although the system works well in the majority of cases there are situations where the GP becomes the safety net when things start to go wrong.

Treatment and the GP's Role.

Treatment carries with it extensive side effects, and GP's can greatly help patients with the management of these. About 20% of patients will get bad side effects, another 20% virtually none, and the remainder fall in between. Many patients can continue to work during treatment, but for some the side effects become too much and this becomes impossible. If reduced hours or less physical employment options are available these should be encouraged, as this maintains interest and makes treatment more tolerable. Patients, particularly those living alone without family support, tend to struggle if they have to give up work and have no outside interest.
Pre-treatment it is helpful if patients are encouraged to abstain from alcohol completely. It is well known that alcohol increases viral load, further damages the liver, and during treatment it reduces the effectiveness of interferon. Patients should also be encouraged to abstain from the use of Herbal and Traditional Chinese Medicine during treatment as these are known to interact with treatment, and can cause false readings in liver function tests, particularly those relating to liver enzymes. The use of vitamins and other supplements during treatment is also questionable, particularly vitamin C where its associated increase in iron absorption may be unwelcome. Vaccination for hepatitis A and B (and influenza if appropriate) should also be considered before starting therapy. One liver virus at a time is more than sufficient! Patients whose source of infection is likely to have been via NHS treatment or blood products should be made aware of compensation via the Skipton Fund.

If I could make one heartfelt plea to all GP's it would be NOT TO PANIC when presented with a patient on treatment. There is a tendency to overreact when blood tests show alarming figures and the first resort is often to stop the treatment. This can be a disaster as the virus promptly returns and in many cases becomes treatment resistant. Please make it a rule to consult with the patient's treatment centre before stopping their HCV medications, and repeat the test ASAP. Things are often not as bad as they seem!

Side effects.

By far the most common side effect is anaemia. This is haemolytic anaemia caused by the ribavirin component of treatment, and leads to breathlessness and fatigue. In some cases this may cause severe distress. It is not unusual for patients to present with haemoglobin figures below 11, and treatment centres should reduce ribavirin dosing if the haemoglobin drops below 10. Note that **this type of anaemia does not respond to iron supplements** and these can be positively harmfull. The ribavirin destroys red cells, and the liver mops up the debris. This can lead to haemochromatosis where the liver becomes overloaded with iron, and hence iron supplements can make the situation worse. Treatment can rarely involve repeated venesections. The only really effective treatment for haemolytic anaemia is erthyropoetin, which is rarely used due to its high cost.
Ribavirin also tends to induce nausea and diarrhoea. The tablets should be taken with food, ideally in the middle of a meal, not before or after, and the food should contain a small fat content. This reduces the effect on the gut, and increases absorption by up to 65%. Many patients fail to heed warnings about this and suffer accordingly. Diarrhoea may be treated with loperamide, which is effective and safe to use during treatment. Many patients report that probiotic drinks and natural yoghurt are of benefit in reducing gut problems by replacing bacteria destroyed by ribavirin. Most pharmacies mark the tablets 'to be taken with food' but a surprising number ignore the advice. On the subject of gut problems, antacids have been shown to reduce ribavirin absorption and should be avoided if possible. This is not essential, as the effect is relatively small (15%).

Ribavirin is extremely mutanogenic, and contraception during treatment is absolutely essential. The recommendation from the drug manufacturers is for at least two methods of contraception to be employed during treatment and for 6 months afterwards. (Ribavirin is very slow to clear from the body.) This applies to both male and female patients. Interferon side effects are both mental and physical. Many of the effects peak on certain days of the week which coincide with peaks in interferon blood concentrations. There are usually two peaks, at 3-5 hours and 2 - 4 days post-injection. Side effects build up with drug concentrations, and these can take 8 weeks to reach the levels that will persist for the duration of treatment. Many patients complain of headache and flu-like symptoms at these times. These effects can be very successfully managed with paracetamol which is totally safe during treatment provided the maximum daily dosage is not exceeded. The suggested regime for injections is to take 2 paracetamol two hours post injection and go to sleep. Hopefully, the injection peak and the paracetamol peak coincide and the patient sleeps through the effects. During the second peak later in the week regular use of paracetamol usually prevents most of the flu-like effects.

The use of aspirin and members of the aspirin group such as ibuprofen in patients with liver problems can be questionable. Aspirin is well documented to cause bleeding in patients who may also have undiagnosed oesophagal varices due to portal hypertension, and the effect can make the anaemia worse. It is a matter of judgement as to whether this poses a significant risk with any particular patient, but it is generally thought that paracetamol is the safer option for patients undergoing HCV treatment. Unfortunately many NSAIDS are used for arthritis treatment and in these circumstances their use may be unavoidable.
On the subject of pain medication, the opiates are generally regarded as safe to use during treatment, subject to their normal caveats! (It is possible for methadone addicts to receive HCV treatment.)

Interferon causes depression of the immune system and white cell levels, particularly neutrophil levels, may drop to a critical point. Treatment centres should reduce interferon dosage if neutrophils drop below 0.75 but some centres will allow them to drop to 0.5 before dose reduction. Patients can be particularly susceptible to opportunistic infections, particularly chest and urinary tract infections. Minor infections which the body's natural defences would normally deal with can rapidly become major issues, and early use of antibiotics is warranted. Antibiotic treatment does not normally conflict with HCV treatment. Depressed immune system can also lead to skin and scalp problems. The possibility of fungal infections should be born in mind, and clotrimazole cream may get surprising results. Nioxin or Oilatum shampoos will generally control scalp problems, and emollient creams provide some relief for itchy skin. The use of steroid creams can also help, but their use for extended periods particularly on facial areas may lead to unwanted permanent skin thinning and disfiguration. Some patients report hair loss, which does usually recover post-treatment.

The mental effects of interferon are probably the most difficult aspect of treatment. Many patients suffer 'riba rage' as it is colloquially known. In mild cases this is just moodiness and irritability, but in more severe cases it results in severe irrational anger and/or depression. There have been suicides during HCV treatment. SSRI anti-depressants often ease these symptoms to manageable levels. One suggested start point is citalopram at 20mg daily. Although excessive use of antidepressants is frowned upon in many circumstances, and most doctors are cautious of their use, in this particular case it is unually unnecessary to conduct extensive investigation into the mental condition of the patient as depression induced by treatment is well recognised and likely to worsen before SSRI's reach their full effect. Early intervention is very much the preferred course of action. Some treatment centres will not start interferon/ribavirin treatment until a patient is stabilised on SSRI anti-depressants, particularly if there is any history of depression. A previous history of significant depression should normally entail assessment before starting therapy as ongoing depression is is contraindication to therapy at that time. Counselling or referral to a psyschitarist may help, and attendance of support groups is also beneficial. There are many web-based forums which provide support and their use should be encouraged.

Thyroid functions are often disrupted by treatment, and although this area is primarily the territory of endocrinologists it may fall within a GP's remit. Both high and low extremes may be encountered. It is generally thought that the minimum of treatment in this area is generally best, particularly after the end of HCV treatment when thyroid values tend to fluctuate as the ribavirin/interferon decays away. Some specialists believe that thyroid treatment at this point delays the return of the body's normal thyroid control mechanism, and are inclined not to intervene unless absolutely necessary.
Many patients report substantial weight loss during treatment. This is mostly due to loss of appetite, and in some cases nausea often aggravated by failure to take ribavirin with food. Many patients report continuous thirst due to the interferon's flu-like effects, and although adequate hydration is to be encouraged, excessive fluid intake may lead to oedema and reduced interferon levels.
It should be born in mind that there is an association between gall stones and Hepatitis C, and URQ pain may be from that source rather than an inflamed liver, however **URQ pain can occur in hep C per se, contraindicating the widely held belief that liver inflammation is painless and indeed this may be specific to hepatitis C both before and during therapy.** Subject to blood clotting functions being checked, patients with gallstones and appendicitis may be operated on successfully during HCV treatment.
The incidence of type 2 diabetes in HCV patients is considerably above the average, and many patients report symptoms of hypoglycaemia.
Eyesight deterioration is occasionally reported, but this is usually reversed post-treatment.
Opthalmologists occasionally report 'cotton wool spots' which usually clear without intervention, but more serious events have been known and referral to a specialist may be the best course of action if there is any doubt. Many patients report difficulty in sleeping at night. Some of this may be due to lack of exercise and daytime napping due to general anaemic malaise but the therapy alone can cause this and be very distressing for some. The use of a mild hypnotic or antihistame with hypnotic properties may be beneficial.

Many GP's are reluctant to prescribe many drugs to patients on treatment due to warnings relating to liver function. It should be born in mind that in many HCV patients the liver function is normal or close to it, and the presence of the virus in itself does not necessarily preclude the use of these drugs, particularly if their duration of use is brief. However, in cases of impaired liver function drug doses may be effectively magnified by the liver's inability to metabolise the drugs.
It should be born in mind that anaemia increases cardiac symptoms in those with significant heart disease /decompensation. Although the incidence of heart problems is low, and patients should be screened for heart problems prior to treatment there is always a small chance of an adverse cardiac event.

Post treatment.

Post treatment recovery is usually reasonably quick, with patients losing the interferon side-effects within three weeks. Ribavirin persists for an extended period, and is still detectable six months after the last dose. Recovery from treatment anaemia may take some time and although most patients are back to normal health in a few weeks, this may extend to six months or more in rare cases.
The protocol is to test for the presence of the virus six months after treatment end. If it is absent, the likelyhood of the virus returning is less than 1%, and this is referred to as SVR (Sustained Viral Response). Patients who acheive SVR can be expected to have normal lifespans and no further hepatic complications. Those with damaged livers may achieve a significant improvement with time, as cirrhosis appears to recover slowly in many cases. They may still require specialist follow up with 6 monthly AFP blood tests and ultrasound to detect early hepatoma/hepatocellular carcinoma whose risk is considerably reduced by successful therapy but unfortunately not to zero.

Footnotes

Please regard the above as a starting point. I very much appreciate all comments, criticisms, and suggestions for improvements. I am sure that there are many omissions, and probably as many errors, so feel free to let me know!

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