

This edition contains articles on:

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Developments in Hepatitis C treatment

The hepatitis C virus (HCV) was first identified in 1989 and is commonly transmitted by contact with blood products. 60–80% of patients infected with the virus become chronic carriers and the majority of carriers will show evidence of mild chronic hepatitis. Approximately 1% of the Scottish population are estimated to have HCV infection; double that of the rest of the UK. Infection is usually indolent and gradually progresses over many years. 20% of patients with chronic hepatitis may progress to cirrhosis over 15-20 years. About 25% of patients with cirrhosis will eventually develop liver failure and 1-2% will develop primary hepatocellular carcinoma annually. HCV in men, older patients and those who take excess alcohol may run a more rapid course.

The goal of HCV therapy is sustained viral response (SVR), where the virus is undetectable six months after the end of treatment. Pegylated alfa interferon and ribavirin are accepted by SMC and are on the *Adult Formulary* as combination therapy. There are a number of subtypes, but in trials, SVR rates for genotype 1 (GT1) patients taking pegylated interferon and ribavirin dual therapy were 38-41%.

The protease inhibitors (PIs) telaprevir and boceprevir directly inhibit viral replication and are a major advance. They are included in the *Total Formulary* for **specialist use only** in adult patients with GT1 infection. Large phase 3 trials in patients chronically infected with GT1 HCV have shown highly significant increases in the proportion of patients who respond. SVR rates of 70% were achieved in patients who received triple therapy (dual therapy plus PI).

Treatment is expensive with additional costs of £20-£30k per person depending on course length. When there is no compelling indication to choose one PI over the other, cost should be considered. Boceprevir will be the preferred agent for some patients including prisoners, those treated via outreach,

patients with significant underlying skin disease, troublesome cutaneous reactions or where the drug interaction profile is preferable.

	Boceprevir	Telaprevir
Treatment duration	24, 32 or 44 weeks	12 weeks
Principal side-effects	Dysgeusia, anaemia, neutropenia.	Pruritus, anaemia, rash, nausea, diarrhoea.
Cautions and contra-indications	<ul style="list-style-type: none"> ▪ Numerous drug interactions; refer to SPC before prescribing. ▪ Benzodiazepines including midazolam are contraindicated. ▪ Patients at risk of QT prolongation should be closely monitored. ▪ Therapeutic monitoring is recommended with methadone. ▪ Two forms of non-hormonal contraception required. 	

PIs present additional cautions and contraindications. They are potent inhibitors of the CYP450 system so reduce the liver's ability to metabolise some other drugs. Of particular importance is the avoidance of oral benzodiazepines, where there is an increased risk of overdose from respiratory depression, especially if taken with alcohol and antidepressants. PIs also increase the available level of methadone, which can result in a prolonged QTc interval and risk of ventricular tachyarrhythmias.

Patient selection is critical to ensure compliance and prevent development of resistance. Patients are supported throughout by specialists, but those thought unlikely to co-operate with follow up are excluded. Many patients have a history of drug use including opiates and benzodiazepines, prescribed or used recreationally. Specialist centres take a detailed drug history and liaise with GPs and Addiction Services to identify any concerns. Patients being considered for PIs undergo baseline ECG and urine screening for drugs of misuse. Regular urine tests and ECGs are part of ongoing monitoring.

The most common side effects, disturbance of taste (boceprevir) and pruritus (telaprevir) usually occur during the first few weeks and are generally mild and manageable. Patients receiving PIs will be monitored for development of anaemia, which is also associated with ribavirin. Telaprevir was associated with development of eczematous skin rash in trials.

Although normally manageable with emollients and antihistamines, there was a risk of this becoming more severe, in <1% of cases resulting in Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome (SJS).

The Viral Hepatitis [Managed Care Network](#) monitors prescribing and will report on activity and outcomes in the annual clinical audit. NHSGGC guidelines on assessment and management of patients with HCV infection are on [Staffnet](#).

Safety update: simvastatin

The MHRA has issued updated [advice](#) on prescribing simvastatin based on information relating to the risk of myopathy and rhabdomyolysis. The changes include some additional medicines with which simvastatin is contraindicated and advice on a maximum recommended dose when simvastatin is taken with other medicines.

Key points are:

- **Simvastatin is now contraindicated with ciclosporin, danazol and gemfibrozil.**
- **The maximum recommended dose for simvastatin in conjunction with amlodipine or diltiazem is 20 mg per day.**

Patients should be reviewed opportunistically at their next scheduled appointment. Clinicians should consider the following in line with the NHSGGC Cholesterol Guideline:

- For patients on contraindicated drugs, review all medicines. Consider:
 - Withholding the statin temporarily, eg for short courses of antimicrobials such as clarithromycin.
 - The ongoing need for a statin.
 - Whether atorvastatin would be a suitable alternative: see the [SPC](#) or drug interactions table on the website for specific advice.
- For patients on diltiazem, amlodipine, verapamil or amiodarone
 - Primary prevention: reduce the dose of simvastatin to 20mg per day.
 - Secondary prevention in patients whose lipids are controlled on simvastatin 40mg per day: reduce the dose of simvastatin to 20mg and recheck lipid levels in a month. If lipids are not within target, switch to atorvastatin 20mg per day and treat in accordance with the guidelines.
 - Secondary prevention in patients whose lipids are not controlled on simvastatin 40mg per day: treat in accordance with the guidelines.

The full cholesterol guideline can be found at <http://www.staffnet.ggc.scot.nhs.uk/Info%20Centre/PoliciesProcedures/GGCClinicalGuidelines/Pages/CGDirectoratory.aspx>.

There is a table on our website with advice on managing some common interactions.

Safety update: dabigatran

The MHRA has published further safety [advice](#) on dabigatran related to the risk of serious haemorrhage, clarification on contraindications and a reminder to monitor renal function. Although this advice relates only to dabigatran, similar risks of haemorrhage are likely to exist for other new anticoagulants.

Because of the risk of haemorrhage, dabigatran is contraindicated in a range of clinical conditions where the patient is at significant risk of major bleeding. Healthcare professionals should remember that there is no specific antidote to dabigatran and excessive anticoagulation may require interruption of treatment. The benefits and risks of starting dabigatran should also be considered carefully for patients who may have other conditions that put them at an increased risk of major bleeding.

Dabigatran is now contraindicated with dronedarone, and with the use of other anticoagulant agents, except when switching therapy to or from dabigatran, or with the use of unfractionated heparin for maintenance of venous or arterial catheter patency. Concomitant use of antiplatelet agents increases the risk of major bleeding with dabigatran approximately two-fold; so, as with other anticoagulants, a careful benefit-risk assessment should be made before treatment. Further advice on switching between dabigatran and other anticoagulants is available in the MHRA article and the [SPC](#).

As exposure to dabigatran is substantially increased in patients with renal insufficiency, renal function should be assessed in all patients before starting dabigatran and at least once a year in patients >75 years or with a suspected decline in renal function. Dabigatran is contraindicated in patients with severe renal impairment (CrCl <30ml/min). The [MHRA](#) issued advice on this in December 2011. Although there have not been specific MHRA warnings about rivaroxaban, it is partly renally eliminated and its dose is dependant on renal function (caution if CrCl <30ml/min; contraindicated if CrCl<15ml/min), so annual monitoring of renal function is reasonable.

Clinical information on the use of dabigatran and its place in therapy has been published in [PostScript 66](#), [PostScript 67](#) and [PostScript 69](#).

ADTC decisions summary

See the [website](#) for full details of indications and restrictions.

Some additions to the *Adult Formulary*:

- Azacitidine for intermediate-2 and high risk myelodysplastic syndrome, acute myeloid leukaemia.
- Eplerenone, in addition to standard optimal therapy for chronic heart failure and left ventricular systolic dysfunction restricted to prescribers in specialised heart failure teams only for use in patients intolerant to spironolactone.
- Fidaxomicin, restricted to treatment of adults with proven recurrence of *Clostridium difficile* infection only on advice of a consultant microbiologist or infectious diseases consultant.
- Tadalafil for pulmonary arterial hypertension restricted to initiation and prescribing by specialists in Scottish Pulmonary Vascular Unit or similar.
- Ticagrelor, co-administered with aspirin for prevention of atherothrombotic events in patients allergic or intolerant to or with stent thrombosis on clopidogrel. Restricted to initiation by prescribers in specialised heart failure teams.

The following medicines were among those not added to the *Adult Formulary*

- Azilsartan for essential hypertension.
- Azithromycin eye drops for susceptible strains of purulent bacterial conjunctivitis or conjunctivitis caused by *Chlamydia trachomatis*.
- Rifamixin for traveller's diarrhoea.

Non-Formulary pending protocol / consultation

- (*Adult Formulary*) Abiraterone for metastatic castration resistant prostate cancer.
- (*Paediatric Formulary*) Pegylated interferon alfa-2b for the treatment of hepatitis C.

Other Formulary information

- Methotrexate pre-filled syringes for severe active rheumatoid arthritis. Restricted to specialist initiation but suitable for continuation by GPs.

TOBI Podhaler®

Tobramycin is used to suppress chronic pseudomonas infection in patients with cystic fibrosis (CF). Guidelines recommend nebulised colomycin first-line. Inhaled tobramycin is indicated when a patient cannot tolerate nebulised colomycin, eg due to wheeze, reduced lung function or rash, or where the patient's condition does not improve.

Previously, tobramycin was only available for nebulisation, so this is the first time an antibiotic has been available for delivery via an inhaler. This is

much more convenient for the patient and reduces the need for supply and cleaning of additional nebuliser equipment. It has been added to the *Adult Formulary* as a second-line treatment.

The medicine is given twice daily (doses 12 hours apart if possible and no closer than 6 hours apart) in a schedule of 28 days on treatment then 28 days off treatment. Patients should use TOBI Podhaler after physiotherapy and after any other inhalers or nebulisers due at that time. The main side effect in trials was cough. Patients should try and continue taking the inhaler if they have a cough but to contact their doctor if the cough is persistent or troublesome.

The West of Scotland Adult CF Unit at Gartnavel General Hospital has approximately 240 patients of whom around 40 receive nebulised tobramycin. These patients will be reviewed and eligible patients will have a test-dose at the hospital supervised by the CF team. If the patient tolerates the test-dose, a seven day prescription will be issued from the hospital pharmacy and the patient's GP will be asked to continue prescribing if appropriate.

Safety update: ondansetron

The [new](#) maximum single intravenous dose of ondansetron for the management of chemotherapy-induced nausea and vomiting in adults is 16mg following a study which demonstrated a dose-dependent prolongation of the electrocardiographic-corrected QT interval (QTc). Prolongation of the QTc interval can lead to Torsade de Pointes (TdP), a potentially life-threatening cardiac arrhythmia.

Ondansetron should be avoided in patients with congenital long QT syndrome and caution must be used if patients have risk factors for QT interval prolongation or cardiac arrhythmias or are taking other [drugs that affect the QT interval](#).

There are no changes to the IV dosing for any indication in the paediatric population or for the prevention and treatment of post-operative nausea and vomiting in adults. The dosing for chemotherapy-induced nausea and vomiting using oral or rectal ondansetron in adults or paediatric patients remains unchanged.

PPIs and hypomagnesaemia

NHSGGC Biochemistry would like to clarify the advice provided in the last edition. If a patient is on a PPI, measuring magnesium is recommended only for patients who:

- have symptoms of hypomagnesaemia,
- have hypokalaemia or hypocalcaemia,
- are taking digoxin,
- have other causes of magnesium deficiency, eg prescribed diuretics, malabsorption syndromes, stoma losses.

Antibiotic Update

Acute Care Adult Guideline Updates

See [PostScript Acute 7](#) for a summary of the major changes included in the updated *Therapeutics – a Handbook for Prescribing in Adults 2012*. There are changes to treatment of endocarditis, urinary tract infections, pneumonia and upper respiratory tract infections among others.

Gentamicin

- A new NHSGGC [Gentamicin Prescribing, Administration and Monitoring Chart](#) has been launched for **all adult patients in the acute setting who are receiving treatment dose gentamicin**. This aims to standardise practice across NHSGGC, minimise the duration of gentamicin therapy and assist in the early detection of renal toxicity or potentially irreversible oto or vestibular toxicity. Each dose should be individualised and not normally prescribed more than 24 hours in advance based on the changing status of the patient. For a detailed article on gentamicin-induced ototoxicity see [PostScript Safety 12](#).

The chart incorporates the following key prescribing [messages](#):

- A reminder to ensure prompt administration – within one hour of recognition of sepsis.
- How to calculate the first dose, monitor and interpret gentamicin results.
- A requirement to carry out toxicity assessments before prescribing each dose. Signs of gentamicin renal and oto / vestibular toxicity are highlighted.
- The need to complete and document an action plan regarding further doses.
- The need to discuss with an infection specialist and document in the notes if treatment continues beyond three to four days. Risks of prolonged treatment must be considered and treatment options discussed with microbiology or an infection specialist.
- A requirement to refer to audiology for assessment if treatment continues beyond seven days.

Gentamicin should now be prescribed “as charted” on the Kardex and all dosage information including time and frequency of dosing is recorded on the new chart. The new chart will be managed as controlled stationery and will be available to order via Cedar (order code 97907).

There is currently no change to the prescribing arrangements for vancomycin.

Primary Care Guidance

Quinolone prescribing in primary care has increased and GPs are advised to reserve ciprofloxacin for upper urinary tract infections, prostatitis or on the advice of microbiology for resistant infections (excluding pregnancy). Quinolones should not be used in the treatment of respiratory tract infections. Ofloxacin is the antibiotic of choice for epididymitis (see primary care [guidelines](#)).

GP practices with higher quinolones prescribing are encouraged to adopt the quinolone prescribing indicator ([PostScript Primary Care](#) April/May 2012) and to audit and review this area of prescribing.

The new gentamicin chart aims to standardise practice across NHSGGC and minimise the duration of therapy. Each dose should be individualised and not normally prescribed more than 24 hours in advance based on the changing status of the patient.

GPs are advised to reserve ciprofloxacin for upper urinary tract infections, prostatitis or on the advice of microbiology for resistant infections. Quinolones should not be used in the treatment of respiratory tract infections.

www.ggcprescribing.org.uk

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