Barts Health NHS Trust

Imperial College Healthcare NHS Trust

National Pulmonary Hypertension Service Imperial College Healthcare NHS Trust and Barts Healthcare NHS Trust

Pulmonary Hypertension Handbook

June 2018

1. THE SERVICE

The pulmonary hypertension service at Imperial College Healthcare NHS Trust (Hammersmith Hospital) forms part of the National Pulmonary Hypertension Service, which was designated by the National Specialist Commissioning Advisory Group (NSCAG) of the Department of Health in September 2001. NSCAG changed its name to the National Commissioning Group (NCG) in 2008 following the Carter Review of specialised services, and to the Advisory Group for National Specialised Services (AGNES) in 2010. The pulmonary hypertension service adheres to the NHS service specification as required by AGNES. This is over and above the normal requirements of a NHS clinical service and makes this service different.

The clinical service is delivered by a multidisciplinary team and provides advice for patients, carers and staff, diagnostic investigation, treatment, and long-term follow-up of patients with pulmonary hypertension who come mainly from the south of England and Wales.

ICHNT also delivers an outpatient and inpatient service at Barts Healthcare NHS Trust in collaboration with the Adult Congenital Heart Disease team. NHSE standards and protocols are standardised across Imperial and Barts campuses.

It is essential that all patients are managed in close liaison with team members. The team can be really helpful by advising junior staff about patient management, making plans for discharge and answering patients' questions.

The service is committed to evidence-based clinical practice and follows up-to-date guidelines. There are outpatient clinics, inpatient beds, daycase beds and on-call cover. The mission of the pulmonary hypertension team is to improve the quality of

life and the personal experience of illness through the best clinical practice, for every patient and carer(s).

2. STAFF

2.1 Core Imperial Team (for Barts)

Luke Howard	Consultant Pulmonologist and Lead Clinician
Francesco Lo Giudice	Consultant Cardiologist
Wendy Gin-Sing	Clinical Nurse Specialist
Sanjay Gurung	Service Manager
Theresa Browne	Team Secretary
Kamlesh Dhunna	Shared Care Co-ordinator

2.2 Core Barts Team

Bejal Pandya	Consfultant Cardiologist and Barts Lead for PH
Anna Dinsdale	Clinical Nurse Specialist
Sarah Watkins	Clinical Nurse Specialist
Christina Panayiotou	Admin Manager
Fabliah Mashiat	Secretary

3. CONTACTING THE TEAM

Medical advice: Luke Howard, Bejal Pandya, Francesco Lo Giudice
Disease-targeted therapy pumps, doses, and nebulisers: Wendy Gin-Sing

During office hours

Luke Howard:	Mobile via Imperial switchboard (020 3313 1000)
	luke.howard@bartshealth.nhs.uk
	lukehoward@nhs.net
Francesco Lo Giudice	Mobile via Imperial switchboard
	Francesco.logiudice@nhs.net
Wendy Gin-Sing	Mobile via Imperial switchboard
	Wendy.gin-sing@bartshealth.nhs.uk
	wendy.gin-sing@nhs.net

Service Manager:	020 3313 3141
	Sanjay.gurung@nhs.net
Shared care co-ordinator:	020 3313 1316
	kamlesh.dhunna@nhs.net

Out of Hours

Medical: On-call ACHD SpR or Consultant who may decide to contact Dr Luke Howard or Dr Bejal Pandya

4 MANAGEMENT OF ACUTELY UNWELL PATIENTS

4.1 New Patients

Some new patients attend as inter-hospital transfers. These patients require full investigation of pulmonary hypertension to determine the aetiology and severity so that treatment can be planned.

We accept referrals of adults with pulmonary hypertension where a diagnosis of pulmonary arterial hypertension, pulmonary hypertension due to chronic thrombotic and / or embolic disease, pulmonary vasculopathy in interstitial lung disease or miscellaneous causes of pulmonary hypertension are suspected / proven, or the cause of pulmonary hypertension is not certain (see classification in Appendix).

The referring physician should be asked to send a letter/email with the results of a recent electrocardiogram, chest radiograph, echocardiogram, spirometry (where available) and routine blood tests. Copies of all relevant previous imaging investigations should be pushed via IEP. Copies of any other investigations already performed should also be sent.

4.2 Follow-up Patients

Patients under the care of the service may require hospital admission for acute deterioration.

If telephoned by a patient or GP about an acutely sick patient, advise that they go to their local A&E department for assessment. The clinical details should then be discussed with the duty consultant and an inter-hospital transfer may then be arranged.

Patients who take disease-targeted therapy should have a copy of their Patient-Held Record: this contains all recent medical correspondence.

Remember these patients are often well informed about their disease.

4.3 Clinical Presentation

Patients with pulmonary hypertension present with breathlessness, angina, syncope, dry cough and exercise-induced nausea and vomiting. Deterioration is often associated with worse breathlessness, cough, syncope and fluid retention.

Sometimes a low cardiac output state may present with symptoms of diarrhoea and vomiting, which is mistaken for gastro-enteritis; and this is often associated with deranged renal and liver function.

Pulmonary hypertension patients often look deceptively well despite a poor prognosis.

4.4 Prognosis

The prognosis of pulmonary hypertension depends on the aetiology and haemodynamic severity. The prognosis is not as universally terrible as many doctors believe. Prognosis is improved by warfarin, calcium channel blockers (when indicated) and disease-targeted therapies. Each patient tends to follow an individual natural history. For any individual the prognosis is unpredictable. Death may be sudden or from progressive heart failure. A detailed discussion is included in the European Guidelines on Pulmonary Arterial Hypertension.

Communication with patients about prognosis needs to be open and sensitive to what the patient actually wants to know. Team members are experienced at talking to patients about prognosis and will help answer patients' and families' questions.

4.5 Cardiopulmonary Resuscitation

Patients should be resuscitated according to current ALS guidelines.

4.6 What Has Caused Deterioration?

Consider:

- Infection (any source of infection can cause pulmonary hypertension to deteriorate): serious infection may occur without pyrexia
- Arrhythmia (most commonly atrial flutter which may be slow)
- Disease-targeted therapy discontinued
- Bleeding (patients are normally taking warfarin)
- Anaemia, renal or liver failure
- Pulmonary arterial thrombosis +_ infarction
- Psychological and/or social stress
- Extremes of temperature and humidity
- Other co-morbid disease
- Natural history (unprovoked disease progression): diagnose only if above causes excluded. This may occur remarkably rapidly and is also referred to as treatment failure.

In any case of acute deterioration, basic investigations for all patients should include:

- Blood tests: FBC, U&E, Bicarbonate, liver function tests including AST, thyroid function, CRP, troponin
- ECG
- Chest x-ray
- MSU and blood cultures (if infection suspected)
- Arterial blood gases if SpO2 <92% on room air, low venous bicarbonate, lung disease or acutely unwell
- Echocardiogram to estimate progression of pulmonary hypertension

Always document the patient's WHO functional class as below:
Class I – Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.

Class II – Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.

Class III – Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.

Class IV – Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

4.7 Management of Fluid Overload

Fluid overload is a common consequence of haemodynamic deterioration of any cause with worsening right ventricular function, neuroendocrine activation and renal failure.

4.7.1 Initial Assessment

- Identify, investigate and treat the underlying cause

- Investigation as section 5.6

4.7.2 General Measures

- Discontinue drugs which may precipitate fluid retention eg NSAIDs
- Try to avoid the use of sodium-rich antibiotics (eg tazocin)
- Give intravenous drugs in 5% dextrose instead of N-saline whenever possible
- Restrict fluid intake up to 1500 ml/day but relax this in hot weather. If they are still thirsty either allow up to 2000 ml/day and/or ice cubes or sugar-free chewing gum (but causes laxative effect). For a dry mouth check for candida, and administer saliva substitutes such as Oral Balance gel or Saliva Orthana.
- Ensure stable fluid intake: instruct patient not to avoid drinking: this may cause deterioration in renal function.
- Restrict sodium intake to avoid added salt to food (including salted crisps etc) and arrange an opinion from a dietician.

4.7.3 Renal Function & Initiating Diuretic Therapy

Renal function is significantly compromised in the majority of patients as a consequence of low cardiac output even although serum creatinine may appear relatively normal. The estimated glomerular filtration rate should be monitored in all patients.

Patients whose eGFR is <20 ml/min are at high risk of worsening acute renal failure and should be referred routinely to renal medicine. When fluid overloaded they should aim to lose about 0.5 kg/day only. These patients should be made aware of the serious risk of renal failure.

Ankle swelling is usually preceded by liver engorgement and ascites, and disappears before abdominal fluid retention.

If not already taking diuretics, give 40 mg oral furosemide and review according to response. If there is an adequate response, give 20-40 mg bd and review and adjust dose daily.

If previously on diuretics or response to oral therapy is inadequate, commence intravenous furosemide infusion with the aim of the patient losing up to 1 kg / day until they reach their dry weight as follows:

- Check electrolytes and renal function prior to starting infusion

- Give current oral dose of furosemide (or equivalent) as infusion dose over 24 h. The minimum starting dose for most patients is 80 mg/day (40 mg if diuretic naïve). Discontinue oral loop diuretics.
- Do not give bolus doses: these cause excessive neuroendocrine activation and reduce urine output.
- Fluid restrict and maintain stable fluid intake up to a maximum of 1.5 litres/day.

4.7.4 Continue Furosemide Infusion as follows:

- Check electrolytes, renal function, fluid intake and output, and weight daily.
- Aim to obtain an average weight loss of 0.5 - 1 kg/day until dry weight reached.
- If inadequate weight loss increase the infusion by 40 mg/day up to a maximum of 320 - 500 mg/day.
- Consider oral torasemide or bumetanide for subsequent chronic therapy as these drugs have better absorption from the gut than furosemide in some patients.

4.7.5 Add an Infusion of Dopamine at 2.5 Mcg/Kg/Min If:

- Creatinine clearance < 35 ml/min
- Sodium <130 mmol/l
- Inadequate weight loss on frusemide 320 – 500 mg/day by infusion
- Note that some patients with recurrent bouts of severe fluid retention only respond to intravenous furosemide if dopamine is given concurrently: dopamine should be started in such patients on admission.

4.7.6 Spironolactone

- Spironolactone may contribute to hyponatraemia
- Continue spironolactone if already prescribed unless sodium <130 or creatinine>140, in which case discontinue.
- Prescribe spironolactone 25 mg/day if the patient is spironolactone naïve providing sodium, potassium and creatinine are within the normal range. Prescribe 12.5 mg/day if creatinine is above the normal range and <140, and sodium and potassium are in the normal range. Women tend to be more sensitive to the hyperkalaemic effects of spironolactone than men.

4.7.7 Thiazide Diuretics

Thiazides may contribute to hyponatraemia.

Bendroflumethazide and metolazone should be used with caution because of the risk of deteriorating renal function. The first choice is usually bendroflumethazide.

4.7.8 Oxygen

- Give continuous humidified oxygen to maintain oxygen saturation >92%.

4.7.9 Uptitrate or Commence Disease-Targeted Therapy

- See section below and initiate only after discussion with the PH team

4.7.10 When Dry Weight Is Reached:

- Stop furosemide infusion and convert to a twice daily (morning and after lunch) oral dose, the total dose of which is the same as the intravenous dose.
- If on a dopamine infusion, continue this for the first 24h of oral therapy and then wean off providing weight loss is maintained.
- Consider the use of oral bumetanide or torasemide instead of furosemide depending on previous response to these drugs. 1mg of bumetanide is equivalent to 40mg frusemide and 50 mg furosemide is about equivalent to 10 mg torasemide.
- Review spironolactone and thiazide therapy.
- Provide clear instructions about the measurement of daily weight after discharge. Patients should contact the team if they gain 2 kg or more in weight.

4.8 Management of Refractory Ascites

Palliative paracentesis may be considered in patients with tense ascites which is unresponsive to diuretic therapy using the management described above, and causing abdominal pain and/or breathlessness (by raising the hemidiaphragms). The main problems with this procedure are the risk of introducing infection to the peritoneal cavity, cardiovascular collapse from too rapid drainage of ascites, protein

loss in patients who are already cachectic and the recurrence of ascites after fluid withdrawal.

- In patients who have not undergone paracentesis in recent months abdominal ultrasound should be undertaken. Some patients who complain of bloating experience abdominal wall oedema without significant ascites.
- Ensure INR 1.5 or less (avoid reversing warfarin: rather wait for INR to fall after stopping warfarin temporarily) OR wait for at least 24 hours following previous DOAC or LMWH dose
- Insert a Banano catheter under local anaesthetic.
- Remove fluid at up to a maximum rate of 2 litres per hour (clamping tube as required) there is a risk of cardiovascular collapse of fluid is removed rapidly in larger volumes, but each patient should be assessed individually and monitored closely during paracentesis.
- When the serum albumin is below the normal range: for every litre of fluid drained replace with intravenous human albumin 8 g.
- Ascitic drains should remain in situ for preferably no more than 4 hours and definitely no more than 6 hours. The risk of infection entering the peritoneum is high.

4.**9 Management of Sepsis**

If sepsis is suspected, then the underlying cause should be identified where possible in the same way as any general medical patient. If the patient has a permanent indwelling intravenous line and there is no other clear cause, then the patient should be investigated and treated for line sepsis (see below). See below in addition for management of chest sepsis and subcutaneous infusion site infection.

4.9.1 Line Sepsis

If the patient has an indwelling permanent line, the infusion should be transferred to a peripheral long-line or central line, preferably internal jugular. The patient is usually anticoagulated and therefore, the subclavian route is contraindicated. Blood cultures should be taken peripherally as the intravenous infusion must not be interrupted. If the patient has a temporary central venous catheter, then it should be removed immediately and replaced with a new one. A new line should NOT be

railroaded over a wire passed down the infected line. An alternative location should be sought.

4.9.2 Subcutaneous Infusion Site Infection

If the site of a subcutaneous infusion appears infected, then the infusion site must be changed. Take blood cultures and treat with Flucloxacillin 1-2g qds iv. If MRSA is likely, on the basis of local risk and/or patient history, treat with Vancomycin according to renal function.

4.9.3 Respiratory Tract Infection

Patients should only be treated for pneumonia if they have signs of new consolidation on chest radiograph. In these cases, they should be treated according to the Hammersmith Hospital pneumonia guidelines (see intranet). For specific pathogens or in cases of allergy, consult intranet or the Infectious Diseases Department for advice. The following samples should be sent:

- Blood cultures; dated serology; sputum for M,C&S, gram stain (discuss with microbiology) and direct immunofluorescence for viruses; urine for Legionella antigen.
- Sputum for AFB if history longer than 4 weeks with a cough

In case of a hospital-acquired pneumonia (HAP), treat as *complicated* HAP, due to severe underlying co-morbidity. Investigate as per community-acquired pneumonia, excluding serology and urine Legionella antigen. Treat according to Trust policy. Further guidance (including advice on treatment of specific organisms) can be found on the intranet or by seeking help from Infectious Diseases.

In the absence of radiological changes and no underlying structural lung disease (other than COPD), but where respiratory tract infection is suspected, Amoxycillin 500mg tds po (or Erythromycin 500mg qds if penicillin-allergic) will suffice. Where structural lung disease is present, other than COPD, consult Infectious Diseases or a Respiratory Physician.

4.10 Management of Haemoptysis

The management of haemoptysis is a medical emergency since it may be or become life-threatening. The most common cause is infection, but it may occur as a consequence of pulmonary arterial thrombosis or ruptured vessels (most commonly the bronchial circulation). Haemoptysis is uncommon in idiopathic pulmonary arterial hypertension but more common in chronic thromboembolic pulmonary hypertension and Eisenmenger's syndrome (where frequent minor (maximum 1 teaspoon) haemoptysis may be benign). In general:

- Resuscitate the patient as required
- Admit to hospital on strict bed rest
- Ensure iv cannula in situ
- Identify and treat the cause (if no obvious cause treat with antibiotics as if a chest infection)
- Send blood for cross-match, FBC, platelets, INR, clotting, renal function, liver function, CRP and blood cultures (x3 if pyrexial).
- Chest x-ray
- ECG
- Discontinue warfarin; only try to reverse warfarin if haemodynamic compromise or massive bleeding.
- If haemoptysis is minor and the patient has a diagnosis of chronic thromboembolic pulmonary hypertension, maintain anticoagulation with intravenous heparin (this is easily reversed if massive bleeding occurs) after INR falls below 2. If the underlying diagnosis is idiopathic pulmonary arterial hypertension anticoagulation should be suspended.
- CT scan of lungs should be considered to search for infection, infarction or thrombosis (usually performed electively).
- In the presence of severe bleeding or recurrent bleeding failing to settle then consider bronchial/intercostals/phrenic/gastric arterial embolisation: should be discussed with Dr James Jackson, Dr Paul Tait or Dr Alison Graham during working hours, or the interventional radiologist on-call (out of hours).
- Normally patients should be started on warfarin in hospital after haemoptysis has been settled and they should be free from haemoptysis with an INR >2 for at least 4 days in hospital prior to discharge.

4.11 Management of Disease-Targeted Therapies

The NHS Policy for prescribing these drugs governs their use. This policy is revised annually and published by Specialised Commissioners. These drugs (with the exception of calcium channel blockers) can only be prescribed by designated pulmonary hypertension centres in the UK. Disease-targeted therapies are divided in to four categories:

a) Calcium channel blockers. These are given in high-dose to a small subset of patients with a proven positive vasodilator response, as tested by the inhalation of nitric oxide, at right and left heart catheterisation. Calcium channel blockers may be hazardous in the absence of a positive vasodilator study. No pulmonary hypertension patient should receive these therapies unless specifically indicated by the team and they should not be started for standard indications, such as ischaemic heart disease, without advice.

Uptitration of calcium channel blockers will normally only take place on day case review, since to be used effectively to treat pulmonary hypertension they must be administered at high doses which are only achieved by gentle uptitration.

b) Endothelin-receptor antagonists (Ambrisentan, Bosentan, Macitentan).

These block the vasoconstrictive and proliferative effects of endothelin-1. They may cause liver damage (specific elevations in ALT and AST not ALP) and anaemia (usually only mild). All patients must have monthly blood tests for liver function including AST and ALT, and under the license women of child bearing age must have a pregnancy test. Haemaglobin is checked at least 3 monthly. If ALT or AST >3 times the upper limit of normal, repeat the blood test urgently and seek advice from the team. Sitaxsentan was withdrawn in 2010 because of serious liver toxicity.

c) Phosphodiesterase type 5 inhibitors (Sildenafil (Viagra, Revatio), Tadalafil).

These drugs inhibit the breakdown of cGMP, a signalling molecule of Nitric Oxide. Viagra and Revatio are both preparations of Sildenafil and have exactly the same properties, but are branded and licensed for erectile dysfunction and pulmonary hypertension, respectively.

Common side effects include, nausea, headache, hypotension, muscle pain and visual disturbance, including raised intraocular pressure. In the event of visual problems, refer to an ophthalmologist for an urgent opinion.

d) Soluble guanylate cyclase stimulator (Riociguat)

Riociguat acts on the nitric oxide pathway by directly stimulating the end receptor, gyanulate cyclase. It has been licenced for use in patients with non-operable chronic thromboembolic pulmonary hypertension and patients with idiopathic pulmonary arterial hypertension. The NHS England commissioning policy permits its use as a second line therapy in IPAH when patients have failed treatment with a phosphodiesterase inhibitor.

e) Prostacyclin analogues (Epoprostenol, Iloprost, Treprostinil). Prostacyclin is an endogenous vasodilator and anti-proliferative agent. Currently, Epoprostenol can be given intravenously and Iloprost via nebuliser. Treprostinil is administered subcutaneously but is no longer available to be started on new patients under the NHS England commissioning policy. It is prescribed to a handful of patients who were commenced on this therapy several years ago. The most important difference between these drugs is their half-life (Epoprostenol, 6 min; Iloprost, 20-25 min; Treprostinil, 3h). Thus, great care must be taken to ensure that an intravenous infusion of Epoprostenol is not disconnected even for a minute.

The side effects of prostacyclin analogues include headache, flushing, nausea, vomiting, diarrhoea, jaw pain, myalgia, joint pain and a 'flu-like syndrome. They occur following initiation and uptitration of these drugs. Patients should be written up for prn paracetamol, loperamide, metoclopramide (1st line antiemetic).

Nebulised Iloprost is started at a dose of 2.5 mcg and is administered 6-7 times-a-day. The dose is uptitrated according to patient side effects to a maximum dose of 5 mcg. Blood pressure should be monitored hourly for 3 hours after starting or uptitrating therapy.

Commencement and early uptitration of intravenous prostacyclins must be started on CCU, whereas subcutaneous infusions can be managed on A9. The units for

infusion rate are in ng/kg/min, typically start at 1-2ng/kg/min and increase by 1-2 ng/kg/min every 6-12 hours depending on tolerance of side-effects.

Full details of the management of disease-targeted therapies are given in the protocols which are available on each cardiology ward.

Before using these therapies be aware:

- Disease-targeted therapies should normally be used according to NHS Commissioning Policy. In an emergency it may be necessary to treat outside this policy.
- Emergency therapy consists of intravenous Epoprostenol and should be used when immediate treatment is required.
- Except in LIFE-THREATENING situations (e.g., unconsciousness, collapse with sweating, severe dyspnoea, etc.), doses should be adjusted only on the advice of the Pulmonary Hypertension Team. However, should a LIFE-THREATENING experience occur, the dose may be changed without their advice.
- On occasion, patients with pulmonary hypertension receiving continuous infusion of Epoprostenol, Iloprost or Treprostinil have suffered cardiovascular collapse. In the great majority of such emergency situations, symptoms result from too little, rather that too much Epoprostenol, Iloprost or Treprostinil. In such cases, patients were cool, pale, and cyanotic. When cardiovascular collapse has occurred and patients are cool, pale, and cyanotic, immediate consideration should be given to increasing the dose.
- On the other hand, overdoses of potent vasodilators may cause hypotension, loss of consciousness and cardiovascular collapse. Patients receiving excesses of these dilators are warm and flushed, although in massive overdose the patient may appear more as if they are under treated. If the physician judges that an excess of Epoprostenol may be responsible for the patient's symptoms, infusion of Epoprostenol may be reduced or discontinued. If excess vasodilator is suspected, it is best to withdraw the Epoprostenol slowly, if possible. However, Epoprostenol may be withdrawn immediately if clinical conditions warrant.

- Never stop or reduce the dose of disease-targeted therapy without discussion with a team member. Such alterations of dose are rarely needed and it is normally dangerous to discontinue such medication (risk of death). Although prostacyclin analogues are prescribed in ng/kg/min, if a patient loses weight it is not necessary to reduce the dose to allow for the new weight.
- Discuss initiation or elective dose increases with a team member.
- These drugs can fail: oral therapies have a ceiling dose, but prostacyclin analogues have no upper dose limit although dose increases are limited by side-effects.

4.12 Management of High Dependency Patients: CCU and ITU

Patients who may require management on ITU: seek an ITU consultation before the patient requires ITU admission if possible.

4.13. Management of hypoxaemia

Patients who are acutely ill, fluid overloaded or unstable should be treated with oxygen to maintain oxygen saturation in a (near)-normal range

Patients who are well, do not have lung disease and are stable do not require continuous oxygen simply because their oxygen saturation is low. Nocturnal oxygen is recommended if needed in patients to maintain an oxygen saturation >92%.

The clinical team will arrange home oxygen when this is required.

5. MANAGEMENT OF ANTICOAGULATION

Pulmonary thrombosis is an important cause of disease progression. A few patients with pulmonary arterial hypertension and all chronic thromboembolic pulmonary hypertension require long-term anticoagulation. Anticoagulation may be contraindicated because of bleeding diathesis such as varices in hepatic cirrhosis and patients with connective tissue disease.

- Warfarin should be commenced without using a loading dose: if restarting warfarin give the patient their usual dose, if new to warfarin use 5 mg daily for three days.
- Pulmonary arterial hypertension target INR 2.0 – 3.0

- Chronic thromboembolic pulmonary hypertension target INR 2.0 – 3.0
- In hospital sick patients should be anticoagulated with warfarin or treatment dose low molecular weight heparin, formulation according to Trust policy. Patients admitted electively for investigation who are not thromboembolic or fluid overloaded do not require routine anticoagulation, but the Trust prophylaxis protocol should be followed.
- Direct oral anticoagulants are second line therapy to warfarin in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. In chronic thromboembolic pulmonary hypertension the full dose of DOAC should usually be used.
- Thromboembolic patients should be anticoagulated at all times except for invasive procedures (in which case discontinue warfarin and manage with enoxaparin).
- Patients with pulmonary arterial hypertension may normally discontinue warfarin for invasive procedures without heparin cover.
- Take care to adjust warfarin dose and monitor INR when using antibiotics or other drugs which interact with warfarin (eg erythromycin)
- The SpR/SHO will contact the GP of patients starting warfarin for the first time to find out arrangements for anticoagulation and refer patient as appropriate for anticoagulation monitoring.

6. CONTRAINDICATED DRUGS

6.1 Contraindicated Drugs: Completely Avoid:

- Non-steroidal anti-inflammatory agents (follow WHO pain ladder)
- Oestrogens (may worsen progression of pulmonary hypertension: use Fosamax and calcium for osteoporosis, refer to Mr Panay, Consultant Gynaecologist for contraceptive advice). Transdermal oestrogen patches are used for post-menopausal symptoms
- Cyclizine (use metaclopramide)

6.2 Contraindicated Drugs which should be avoided if possible:

- Flecainide, mexilitene, propafenone, disopyramide (amiodarone is permitted)

- Beta-blockers (may be used at low dose as with oesophageal varices and significant arrhythmias but can result in severe deterioration: caution!)
- Steroids (worsen oedema but necessary in connective tissue disease)
- Tricyclic antidepressants (SSRIs preferred: sertraline is licensed for use in cardiovascular disease)
- Ondansetron (Ondansetron may increase the risk of developing abnormal changes in the electrical activity of the heart, which can result in a potentially fatal abnormal heart rhythm. Prolongation of the QT interval can lead to an abnormal and potentially fatal heart rhythm (including Torsade de Pointes). Patients at particular risk for developing Torsade include those with underlying heart conditions, such as congenital long QT syndrome, those who are predisposed to low levels of potassium and magnesium in the blood, and those taking other medications that lead to QT prolongation.

7. SPECIAL DRUG INTERACTIONS

A full list of interactions is to be found in the BNF Appendix 1 and the UK and ESC Guidelines. These special circumstances are drawn to your attention:

7.1 Bosentan

- must not be given with glibenclamide, cyclosporin, ritonavir, fluconazole, itraconazole and ketoconazole
- partially inactivates hormonal contraceptives: refer to gynaecology
- may interfere with warfarin and INR: check INR one week after starting bosentan
- reduces plasma levels of simvastatin
- plasma levels are increased by erythromycin and ketoconazole

7.2 Sildenafil

- must not be given with nitrates, GTN spray, nicorandil, cimetidine, itraconazole, ketoconazole, ritonavir (and other antivirals)

- patients are strongly advised to avoid eating grapefruit or drinking grapefruit juice
- plasma levels are increased by erythromycin and ketoconazole

7.3 Bosentan + Sildenafil

- Plasma sildenafil levels are decreased
- Plasma bosentan levels are increased (increased risk of deranged liver function)
- There are no studies to guide optimal dosing
- When adding sildenafil to bosentan, sildenafil should be commenced at 12.5 mg tds and subsequently uptitrated to 25 mg tds.

7.4 Prostacyclin Analogues

- Sildenafil and bosentan may enhance systemic hypotension

8. OUTPATIENTS AND DAY CASES

Outpatients are seen on Monday morning in Clinic 5. A maximum of 3 new patients and 6 follow-ups will be seen. No overbookings are acceptable.
Day cases are seen on the XXX Unit. Day case visits are best for patients travelling long-distances and/or requiring several investigations. They are also used for starting and uptitrating disease-targeted therapies. Day cases are clerked by the Clinical Nurse Specialist and are then reviewed by the consultant on duty for that week.

9. OBSTETRICS & GYNAECOLOGY

Pregnancy carries a very high mortality in pulmonary hypertension and all patients are advised to avoid getting pregnant. Mr Nick Panay at Quuen Charlotte's and Chelsea Hospital (QCCH) sees patients for family planning advice in his outpatient clinic following appropriate referral.

All women of childbearing age should be offered an appointment if:

- They want contraceptive advice
- They are starting on bosentan, even if they already use contraception

Patients wishing to discuss pregnancy / surrogacy should be referred to the high risk pregnancy service at QCCH to see Prof Catherine Nelson-Piercy.

10. PULMONARY ENDARTERECTOMY (PEA)

Patients with chronic thromboembolic pulmonary hypertension are normally worked up for PEA surgery. They are referred to Mr David Jenkins at Papworth Hospital on completion of all of their investigations for surgery and subsequently followed up at Hammersmith. Papworth Hospital do not arrange to see patients who are deemed inoperable, but will do so if asked.
Note that referral on completion of pulmonary hypertension investigations is urgent and must not be delayed.

11. LUNG TRANSPLANTATION

Lung transplantation is carried out at Harefield Hospital. Patients may be seen by arrangement in the joint transplant clinic on some Tuesday afternoons. Referral is made by completing a transplant booklet. The team will speak to Dr Reed or Dr Carby directly about urgent referrals.

12. PATIENT DISCHARGE FROM WARDS

- Discharge planning should commence on the day of admission.
- Inpatient transfers who are 65 years or older should normally be discharged back to their local hospital.
- Arrange follow-up at Barts (outpatient or daycase)
- SpR to inform local physician and GP of discharge

13. PRIVATE AND OVERSEAS PATIENTS

The service currently only accepts patients who are entitled to NHS care.