

The practical management of fluid retention in adults with right heart failure due to pulmonary arterial hypertension

Simone Stickel^{1*}, Wendy Gin-Sing², Martha Wagenaar³, and J. Simon R. Gibbs⁴

¹University Hospital of Zurich, Department of Pneumology, C HOER 4, Rämistrasse 100, 8091 Zurich, Switzerland;

²National Pulmonary Hypertension Service, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, W12 0HS, UK;

³Amsterdam UMC, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands; and

⁴National Heart & Lung Institute, Imperial College London, Cole Street, London, SW3 6LY, UK

KEYWORDS

Pulmonary arterial hypertension;
Right heart failure;
Fluid retention;
Oedema;
Endothelin receptor antagonists

Our aim with this review is to provide practical advice and management support for nurses and other healthcare practitioners in managing fluid retention in adults with right heart failure (RHF) due to pulmonary arterial hypertension (PAH). Vigilant management of RHF is important for maintaining patient quality of life, as fluid overload can lead to abdominal bloating (ascites) and peripheral oedema, which also has a major impact on patients' morbidity and mortality. Patients with RHF should be assessed regularly for signs of fluid retention. If fluid overload develops, it is important to determine whether it is caused by the progression of PAH, a side effect of PAH-specific treatment, or another drug or comorbid condition, as this affects both the prognosis and the management strategy. Right heart failure can be treated with both pharmacological and non-pharmacological interventions to reduce fluid retention; including altering fluid and salt intake, weight monitoring, and use of diuretics. All patients on diuretics should be regularly monitored for renal dysfunction and electrolyte imbalance and given advice on how to manage the side effects associated with diuretic use. Fluid retention is often assessed and treated in clinical practice by specialist nurses, who act as a key patient contact providing advice and information on symptom management. This review provides an overview of the challenges related to fluid retention, including strategies to help patients manage symptoms and side effects of treatment.

Introduction

Pulmonary arterial hypertension (PAH) is a rare, progressive, chronic condition characterized by increased pulmonary vascular resistance (PVR), which elevates right ventricular (RV) afterload.^{1,2} When the contractility of the RV can no longer compensate to maintain the cardiac output despite raised PVR, RV failure supervenes eventually

leading to death.^{3,4} Right ventricular failure is associated with increased total blood volume (fluid overload), venous congestion, and systemic fluid retention. This leads to hepatic congestion, abdominal bloating (ascites), bowel congestion, and peripheral oedema^{2,5,6} and has a major impact on morbidity and mortality in the PAH population.^{7,8} Despite total circulating volume being increased, renal blood flow is reduced because cardiac output is not sufficient to maintain the integrity of the arterial circulation.⁶ As a result, the kidneys increase salt and water retention via activation of the arterial baroreceptor-mediated renin-angiotensin-aldosterone neuroendocrine system (RAAS).⁶ If

*Corresponding author. Tel: +41 44 255 8681,
Email: Simone.Stickel@usz.ch

left untreated, fluid retention increases demand on an already decompensated RV as indicated by increased jugular venous pressure (JVP) and can lead to increased dyspnoea, reduced mobility, sepsis, increased risk of developing lower limb cellulitis and deep vein thrombosis, and renal, intestinal and hepatic dysfunction.^{9,10}

While there is currently no cure for PAH, the disease can be managed and treated with non-pharmacological measures, alongside disease-specific treatments for PAH and supportive treatments including diuretics for fluid overload.^{2,11-13} Despite improvements in the clinical management of PAH in terms of both targeted therapies and supportive care,¹² fluid retention continues to present significant practical challenges to clinical management. In our experience in practice, this is due partly to a lack of patient awareness of underlying causes of peripheral oedema but also due to under-recognition of the influence of altered salt/fluid balance on body weight by both patients and healthcare professionals (HCPs). Healthcare professionals should always seek to establish the cause of fluid overload as it may result from RV failure due to PAH, complications of PAH or heart failure (e.g. cardiac arrhythmias, sepsis), side effects of PAH medications or other concomitant medications (e.g. non-steroidal anti-inflammatory agents), or comorbid diseases (e.g. hypercapnic respiratory failure).²

This review is intended to provide practical advice from an expert group regarding solutions that HCPs can implement when exercising their clinical judgement in conjunction with patients to improve the management of fluid retention due to RV failure. This content should be of particular interest to specialist pulmonary hypertension (PH) nurses, who co-ordinate the needs of patients with their support systems and other HCPs. Pulmonary hypertension nurses act as the key point contact for advice and information regarding both PAH-specific therapy and treatments for fluid retention.¹⁴⁻¹⁶

The advice contained in this article is based mainly on opinion since much of it lacks evidence. The recommendations do not override the individual responsibility of HCPs to make appropriate decisions individualized to each patient's clinical circumstances or to follow the rules and regulations applicable to drugs and devices.

The practical management of fluid retention

Diagnosis and monitoring

In order to manage and treat fluid retention in patients with right heart failure (RHF) due to PAH, it is important to regularly monitor fluid status and identify fluid overload as quickly as possible. Fluid status can be monitored in the clinic by clinical examination for signs of fluid retention, monitoring serum brain natriuretic peptide, which rises with worsening fluid overload,¹⁷ by cardiac or hepatic ultrasound or, if comprehensive haemodynamic monitoring is required, by right heart catheterization.¹⁸ A full appraisal of the patient's medications and comorbid conditions will help to establish whether fluid retention is due to worsening PAH-related RV dysfunction, PAH-specific drug therapies, other medications, or other comorbidities.⁴

Weight gain is one of the first signs of fluid retention in patients with RV failure, and therefore, weight should be monitored at every patient visit. Alongside monitoring by HCPs, patients should be advised to weigh themselves daily to monitor for rapid weight gain. This should be at the same time each day, ideally first thing in the morning after emptying their bladder and before breakfast. In our experience, we would consider 'rapid weight gain' to be ≥ 2 kg (≥ 4 lbs) gain over 3 days, which may indicate fluid overload. Patients should be told to call their PH specialist nurse or treating physicians if this sudden weight gain is detected.

Clinical signs of fluid retention include raised JVP, hepatic enlargement, ascites, and dependent pitting oedema.^{2,19} Increased JVP after starting PAH therapy can indicate failure to respond adequately to PAH treatment or worsening PAH. If patients who have recently commenced PAH treatment with endothelin receptor antagonists exhibit signs of peripheral oedema (e.g. swollen ankles) but have normal JVP, increased vascular permeability due to PAH-specific drug treatment may be the cause. It is, therefore, important to assess the JVP carefully bearing in mind that in some patients this may prove difficult and may not be possible. There are numerous other causes of fluid retention. Notably, one cause which may be overlooked is a high PaCO₂ in patients who develop respiratory failure. In this case, the fluid balance will be improved once PaCO₂ levels return to normal (e.g., with non-invasive ventilation, if appropriate).

Regular monitoring of patients is strongly encouraged by the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines.² This should include measurement of glomerular filtration rate in all patients requiring diuretic therapy,²⁰ and patients with significantly impaired renal function should be referred to a nephrologist or renal medicine specialist, as they are at high risk of worsening acute renal failure. In follow-up clinical visits, attention should be paid to blood chemistry/electrolytes (especially sodium, potassium, and creatinine) in all PAH patients on diuretic therapy.² Patients with PAH and fluid retention, especially if severe enough to require critical care, should have their C-reactive protein levels monitored for any sign of infection, and prescribed broad-spectrum antibiotics appropriately if infection is suspected.^{21,22}

General/non-pharmacological measures to manage right ventricular failure and fluid overload

There is currently very limited information from clinical trials regarding the practical management of RHF. However, there are a range of non-pharmacological measures based on expert opinion that patients can follow to reduce the likelihood of fluid overload. These are particularly important for patients who may not have access to pharmacological therapies due to differences in healthcare systems or for financial reasons.

Diet and fluid intake

Reduction of both salt and fluid intake is common practice in specialist PH centres to decrease fluid retention.²³ Patients should be encouraged to eat a healthy, well-balanced diet. Dietary salt restriction is important in the management of PAH and chronic RV failure, and patients

are recommended to follow a low-salt diet. Definitions of a 'low-salt diet' vary by country, but we would suggest limiting salt intake to <5 g (2 g sodium) per day.³ As typical salt consumption ranges widely across Europe from 6 to 12 g/day depending on diet,²⁴ some patients may initially struggle with a reduced salt diet. Patients should also be educated on the salt content of foods such as ice-cream, processed juices, or canned vegetables, which they may not be aware, can have high-salt content. It is important that patients are educated in how best to reduce their salt intake,²³ and are reassured that salt cravings will diminish over time.

In general, it is recommended that patients with PAH-related RV failure restrict their fluid intake to between 1.5 and 2.0 L per day.²⁵ Based on our clinical experience, we generally recommend that patients should drink at least 1 L of fluid per day to maintain good renal function although this number should not be taken as absolute since it varies between individuals and according to the weather. Patients should not consume >1 L within a single hour. We also recommend that if patients are already on diuretic therapy without oedema it may be best to suggest 1.5–2 L, reducing to 1.5 L if they gain weight and develop oedema. We have found that in some cases if the patient still has oedema and an increase in diuretics does not improve their condition, it may be advisable to reduce fluid intake further to the minimum of 1 L per day providing renal function is closely monitored and there are no contraindications. Due to the low levels of evidence around salt and fluid intake, this should very much be an individualized management decision, based on the patient's circumstances.

As well as being counselled on their overall fluid intake, we recommend that patients should be made aware of unexpected sources of fluids in their diet. These include gelatine, ice, and soup; and we have found that it is sometimes worth advising patients not to eat canned/packaged shop-bought soup at all due to its fluid content and because the salt levels are often higher than ideal. Patients should be made aware of drinking-cup size and may be advised to always drink out of the same sized cup, or use exclusively small cups, and not drink more than one cup of fluid at any one time.

A greater understanding of fluid retention has been shown to improve patients' ability to restrict their daily intake of salt and fluid with the aim of maintaining an appropriate salt/fluid balance.^{12,23} Instructions can be provided by the clinician and/or specialist PH nurse in a brief period of time (5 min), particularly if educational materials are also supplied.²³ Overall, education to reinforce the importance of home practice and adherence to lifestyle and dietary recommendations appears to improve outcomes in RV failure.²⁶

Where patients have experienced rapid weight gain due to fluid overload, the aim should be to reduce their weight back to normal levels, and we would recommend starting treatment as soon as possible to avoid further fluid accumulation and discomfort. Patients with severe fluid overload should aim to be losing 0.5–1.0 kg/day in body weight under the supervision of their HCPs. Patients who are

struggling with the extra weight gained should be counselled on appropriate rest and leg elevation. Support tights or compressive stockings may be used in patients with mild oedema who are receiving diuretics but are contraindicated in severe congestive heart failure with pulmonary and/or massive leg oedema. Healthcare professionals, and in particular nurse practitioners, should also be aware that educating patients on weight control and weight monitoring may, along with the loss of appetite associated with RV failure, lead to patients being discouraged from eating properly and cause them to lose weight, particularly if abdominal oedema is present. In these circumstances, maintained body weight may actually indicate unrecognized fluid retention.

Infections and sudden fluid shifts

Inflammation can lead to increased fluid retention, and therefore, patients should be monitored for any sign of infection and treated immediately if infection is suspected. In patients with PAH and RV failure, the inflammatory response can lead to deterioration of the already compromised RV function.^{2,27} Patients with PAH are also more susceptible to developing pneumonia, which has been shown to be a cause of death in 7% of cases, and it is, therefore, recommended to vaccinate against influenza and pneumococcal pneumonia.^{2,3} Right ventricular failure can also lead to intestinal oedema,²⁸ which can give rise to sepsis.

Patients and HCPs should be aware of any treatments that might lead to a sudden change in the fluid composition of the body. Patients diagnosed with PAH should carry a medical passport stating that intravenous (IV) fluid therapy should not normally be administered without expert consultation. If it is necessary for patients to undergo surgery or any other invasive medical procedure, fluids should be administered either by an anaesthetist experienced with PAH or after consultation with a PAH specialist to provide expert guidance. Where possible, and if the facilities are available, all medical procedures should be carried out at the patient's PH expert centre to ensure that a specialist is on hand.

Hypoxaemia

Many patients with PAH-related RV failure have some degree of resting arterial hypoxaemia,² which should be identified and managed as part of treatment, following the current oxygen guidelines.²⁹ During episodes of decompensated RV failure with marked fluid overload patients should reduce any exercise that provokes symptoms. If patients consistently show arterial blood oxygen saturation of <91% they should be advised to take oxygen until this threshold value is attained.^{2,4,29} In our experience, the exception to this is patients with Eisenmenger syndrome, who do not usually respond to oxygen, and normally have lower resting saturations and haemoglobin levels.

Ambulatory oxygen may be considered where appropriate. Mechanical positive pressure ventilation should generally be avoided as it can have adverse haemodynamic effects, including an increased RV afterload and decreased left ventricular preload.⁴

Pharmacological treatments for patients with right ventricular failure and fluid retention

There are a variety of pharmacological treatments available for patients with PAH, which are often taken in combination.¹³ Alongside optimization of fluid balance (most often using diuretics), drug therapies for patients with PAH and RV failure aim to achieve a reduction in RV afterload, improvement in cardiac output, and maintenance of stable systemic blood pressure.^{4,29,30} Prostanoids or other PAH-specific drugs [e.g. endothelin receptor antagonists (ERAs)] can be used to reduce the RV afterload, while drugs with positive inotropic effects (e.g. dobutamine) can be taken in combination to improve cardiac output. Patients with RHF may also be treated with vasopressors to help stabilize the systemic blood pressure.³¹

For managing the salt/fluid balance, it is important to review medications that may contribute to oedema such as sodium-rich IV antibiotics, some calcium channel blockers (e.g. amlodipine), and corticosteroids. If a patient is taking non-steroidal anti-inflammatory drugs, it may be advisable to move the patient to another medication. It is also important to treat any patient-specific factors that may lead to fluid retention such as anaemia, arrhythmias, or other comorbidities.

In the setting of acute RV failure, it is important to watch out for systemic hypotension, which could lead to myocardial ischaemia,³ and to refer patients to intensive care if presenting with high heart rate, low blood pressure, low urine output, or rising lactate levels.² In intensive care treatment, vasopressors can be used to improve systemic haemodynamics and perfusion of the brain, heart, and other organs without changing PVR.⁴ Inotropes can be used to improve myocardial contractility, increase cardiac output, and maintain systemic arterial pressure and renal perfusion.^{3,4} RV assist devices or extracorporeal membrane oxygenation may also be used in extreme situations in patients for whom lung transplantation is an option.⁴ The position statement from the Heart Failure Association of the ESC addresses the use of diuretics in acute heart failure more thoroughly.³²

Pulmonary arterial hypertension-specific medications

Specific PAH medications can affect fluid retention and HCPs should work with the patient to find the best therapy or therapy combination for patients with RV failure. PAH medications fall into three main groups: ERAs; phosphodiesterase-5 inhibitors and stimulators of soluble guanylate cyclase (sGC); and prostacyclin analogues and prostacyclin receptor agonists.

Fluid retention has been observed during clinical studies with all ERAs, with severity depending on clinical context (e.g. PH aetiology, patient age), dose, and the degree of selectivity to endothelin Type A and endothelin Type B receptors. Natriuresis and diuresis can be induced through endothelin Type B receptors, with blockage of these receptors leading to fluid retention, and blocking endothelin Type A receptors can also modulate renal salt and water excretion.³³ Peripheral oedema has also been observed with endothelin A-selective agents due to activation of the RAAS system secondary to vasodilation, as well as increased

vascular permeability (via endothelin Type B receptor overstimulation).³⁴

Peripheral oedema is listed as a common side effect of ambrisentan, occurring in >10% patients,³⁵ and seen in 23% of ambrisentan-treated patients in Phase III trials vs. 14% of placebo patients.³³ High rates of peripheral oedema were also observed in patients on ambrisentan/tadalafil combination therapy³⁶ and thus optimization of any pre-existing fluid overload is advised before starting ambrisentan.

Oedema and fluid retention during bosentan treatment occurs in 13.2% of patients (vs. 10.9% in placebo patients), with early weight gain (i.e. during initial treatment) and increased incidence of leg oedema reported in Phase III studies.³⁷ It is, therefore, recommended that bosentan-treated patients be monitored for signs of fluid retention (e.g. weight gain), especially in cases with concomitant systolic dysfunction.

The listed incidence of oedema-related adverse events with macitentan 10 mg in PAH is 21.9% (vs. 20.5% with placebo).³⁸ Data from a meta-analysis of 24 randomized control trials indicate that ambrisentan and bosentan significantly increased the risk of peripheral oedema, whereas macitentan did not.³⁹

Phosphodiesterase-5 inhibitors approved for the treatment of PAH include sildenafil and tadalafil. Neither have a listed incidence of peripheral oedema nor have been associated with oedema in clinical trials.⁴⁰ Similarly, peripheral oedema is not a listed adverse event of the sGC stimulator riociguat.⁴¹ A Cochrane review of prostacyclins for the treatment of PAH showed no significant difference in peripheral oedema vs. placebo (odds ratio 1.46, 95% confidence interval 0.98-2.17; $P=0.06$; six trials, 1228 participants).⁴²

Diuretics and diuretic therapy management

Diuretics are recommended as the principal medical treatment in patients with PAH who present with fluid retention.^{3,4,30} Clinical experience has shown clear benefits from diuretic therapy in patients with fluid overload although there are no randomized trials in patients with PAH.^{4,43,44} The choice of drug and dosage is best decided by the treating PAH physician, bearing in mind that rapid and/or excessive diuresis can lead to systemic hypotension, renal insufficiency, and syncope. It is, therefore, vital to monitor serum electrolytes and renal function during diuretic therapy.^{2,29,30}

Diuretic treatment is normally initiated alongside PAH-specific therapy.⁴ There are three main classes of diuretics: (i) loop diuretics (e.g. furosemide, toresamide, bumetanide), which inhibit reabsorption of sodium in the loops of Henle; (ii) thiazide diuretics (e.g. metolazone), which act in the distal nephron convoluted tubules in the kidney; and (iii) potassium-sparing aldosterone antagonists (e.g. spironolactone), which block aldosterone action on mineralocorticoid receptors.⁴⁵ All of these can be used in patients with PAH-related RV failure and the choice, dose, and combination of diuretic employed are dependent on individual patient salt/fluid balance characteristics. Intravenous furosemide treatment is required in some cases, but IV use is not usually suitable for home settings and should be reserved for in-hospital treatment and administered under

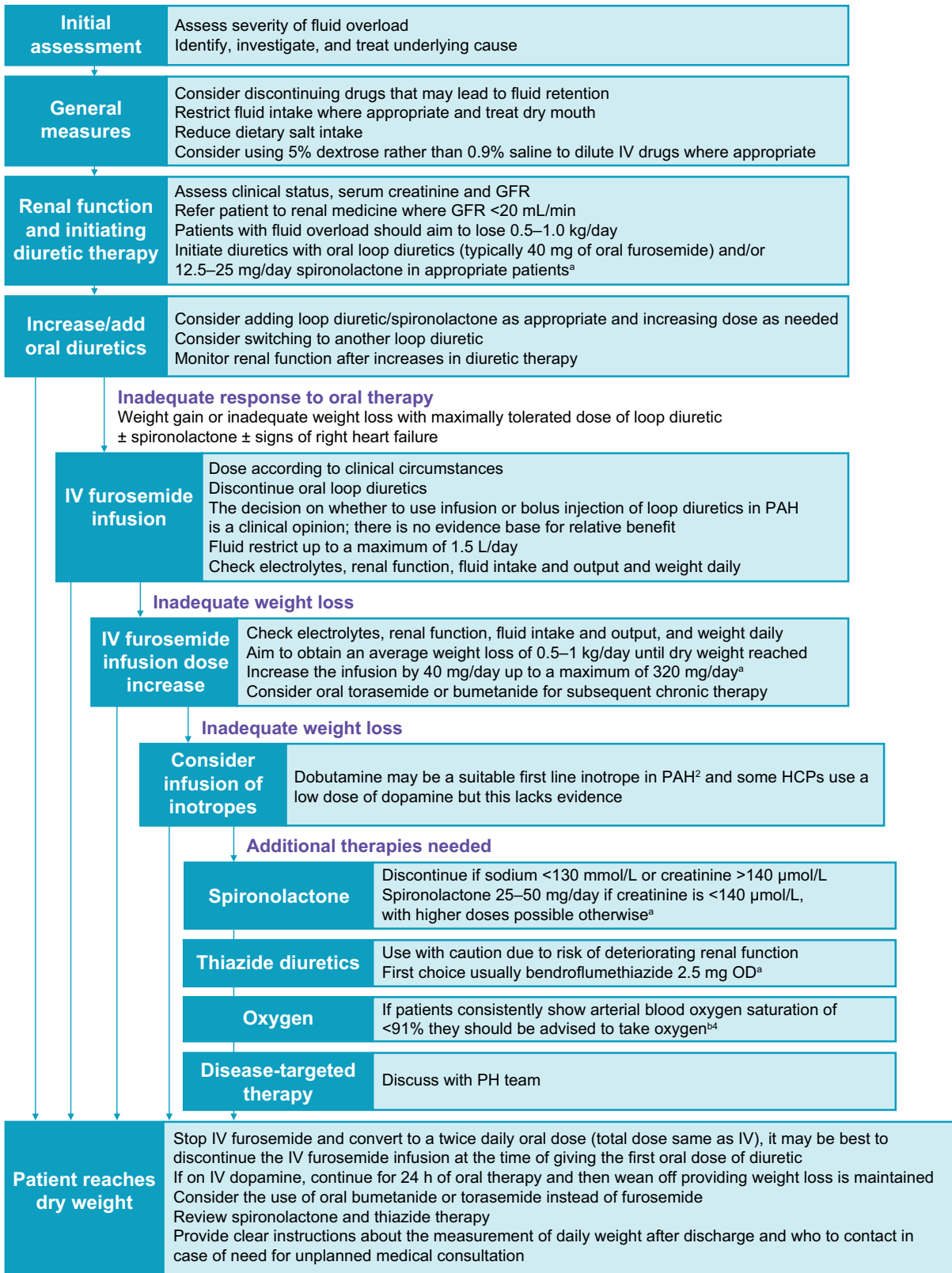


Figure 1 A flowchart for suggested management of fluid overload in haemodynamically stable and uncompromised adults. This flowchart is a recommendation based on the authors clinical experience since there is a lack of published evidence on which to base it. When making clinical decisions on the management of fluid overload for individual patients always take into account their individual clinical situation. When patients require the use of inotropes this should be discussed with the pulmonary hypertension centre. ^aDoses given in this table are for general guidance only and need to be individualized for each patient. ^bThis may not be possible in patients with pulmonary hypertension due to congenital heart disease if they have a right-to-left shunt.

Box 1 Practical recommendations and considerations for managing the side effects of diuretics in patients with right heart failure due to pulmonary hypertension

- Feelings of dry mouth or thirst can be remedied with frozen pineapple, iced water, or boiled sweets (Considerations: sugary sweets and fruit should not be recommended for patients with diabetes and care should be taken to maintain good dental hygiene).
- Tonic water, topical magnesium oil, or oral magnesium supplements may help to manage cramps (Considerations: quinine can influence myocardial conduction.⁴⁷ Magnesium can cause gastrointestinal symptoms such as nausea, vomiting, and diarrhoea; there are also possible interactions with potassium-sparing diuretics and calcium channel blockers⁴⁸).
- Skin-care regimens can help in cases of cellulitis or cracking of the skin.
- When using loop diuretics, be mindful of the need for increased urination for several hours after a dose and plan the best time to take them, thereby lessening the impact of this drug on a patient's daily commitments.
- Apply what the patient has learned about ways of managing fluid retention before initiating diuretics (e.g. avoiding sources of unexpected fluid and/or salt intakes such as packaged soups, gelatine, or ice; being aware of drinking-cup size).

specialist care to prevent sudden fluid shifts. The utility of bolus injections of loop diuretics should be assessed on a case by case basis and HCPs should be mindful of the fluctuations in intravascular volume associated with bolus doses of diuretics.⁴⁶ We prefer to use a continuous infusion of furosemide rather than bolus doses in most patients.

Patients should be educated about the use of oral diuretics, in particular, the signs of dehydration (e.g. thirst, dry skin/mouth/eyes, rash/itching, fatigue, loss of appetite, orthostatic hypertension, and dizziness) indicating they should discuss reducing their diuretic dose with their HCP.

Dosing ranges should be determined by the HCP and should be adaptive, as PAH patients tend to need greater diuresis over time. Patients should begin therapy on a single diuretic dose of furosemide, with escalation to a combination of treatment with loop diuretics with either thiazide diuretics or spironolactone considered in patients with treatment-refractory peripheral oedema or insufficient symptomatic response.⁴ The addition of a different aldosterone antagonist may also be considered.² In our clinical experience, spironolactone is the preferred add-on therapy to initial furosemide treatment, and a different aldosterone antagonist is only considered when side effects are observed with spironolactone, while initiation of thiazide diuretics is at the discretion of the treating physician. *Figure 1* summarizes a typical therapeutic approach, which we would recommend for the management of fluid overload in a PAH patient with RV failure, based on our clinical experiences with patients.

Management of side effects of diuretic treatment

While diuretic therapies help to maintain fluid levels and prevent oedema, they are associated with side effects including electrolyte imbalance, headache, dizziness, increased blood sugar, increased thirst, muscle cramps, and skin rashes. It is important to monitor renal function and blood biochemistry in patients on diuretics to avoid hypokalaemia and the effects of decreased intravascular

volume that might lead to renal dysfunction.^{2,4} There are also measures that patients can take to reduce the impact of side effects; authors' practical recommendations, based on their experience in the clinic, are summarized in *Box 1*. While these measures are largely concerned with the less severe side effects, it is important to educate patients on what they can do to improve their daily lives, because achieving optimal outcomes with any medication relies on adherence to treatment regimens. There is little evidence on the benefit of these measures, given how dependent their success is on personal circumstances as well as medical history and how difficult this would be to measure. As such, this guidance should be individualized to each patient, but the considerations listed in *Box 1* serve as a starting point for this conversation with patients.

Conclusions

Fluid retention is an important consideration in adults with RV failure due to PAH, and patients should be monitored throughout treatment for signs of oedema. If patients develop fluid overload, it is important to determine whether this is due to progression of the disease, the PAH treatment, or another drug or comorbidity. In particular, ERA treatments can lead to oedema in PAH patients.

There is a range of measures that patients can take to help reduce fluid retention, from changing their diet and fluid intake to diuretic treatments. Healthcare professionals, and particularly nurse practitioners who see the patients regularly, should be aware of these management strategies and work with the patient to educate and inform them of the different approaches. Healthcare professionals should also be aware of other aspects of fluid retention, such as weight management, hypoxaemia, and the increased risk posed by infections. Where diuretic therapies are necessary, patients should be monitored for renal function, and given advice on how to manage and reduce the side effects associated with diuretic use.

Funding

Medical writing and editorial support were provided by Victoria Ates and Richard McDonald of Watermeadow Medical, an Ashfield Company, funded by Actelion Pharmaceuticals Ltd (Allschwil, Switzerland).

Conflict of interest: S.S. has received honoraria for speaking and consultation from Actelion Pharmaceuticals Ltd, Bayer, and MSD. W.G.S. has received honoraria for speaking and consultation from Actelion Pharmaceuticals Ltd, Bayer, MSD, and GSK. M.W. has received personal fees from Actelion Pharmaceuticals Ltd, IQVIA Ltd, Therabel Pharma Netherlands B.V., and Merck Sharpe & Dohme B.V. J.S.R.G. has received grants, personal fees and/or non-financial support from Actelion Pharmaceuticals Ltd, Acceleron, Amco, Arena, Bayer, Bellerophon Therapeutics Inc., Complexa, GlaxoSmithKline, MSD, Pfizer, and United Therapeutics.

References

- Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR, Dupuis J, Long CS, Rubin LJ, Smart FW, Suzuki YJ, Gladwin M, Denholm EM, Gail DB; National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. *Circulation* 2006;114:1883-1891.
- Galiè N, Humbert M, Vachiéry JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;37:119.
- Skhiri M, Hunt SA, Denault AY, Haddad F. [Evidence-based management of right heart failure: a systematic review of an empiric field]. *Rev Esp Cardiol* 2010;63:451-471.
- Harjola V-P, Mebazaa A, Celutkienė J, Bettex D, Bueno H, Chioncel O, Crespo-Leiro MG, Falk V, Filippatos G, Gibbs S, Leite-Moreira A, Lassus J, Masip J, Mueller C, Mullens W, Naeije R, Nordegraaf AV, Parissis J, Riley JP, Ristic A, Rosano G, Rudiger A, Ruschitzka F, Seferovic P, Sztrymf B, Vieillard-Baron A, Yilmaz MB, Konstantinides S. Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. *Eur J Heart Fail* 2016;18:226-241.
- Piazza G, Goldhaber SZ. The acutely decompensated right ventricle: pathways for diagnosis and management. *Chest* 2005;128:1836-1852.
- Schrier RW, Bansal S. Pulmonary hypertension, right ventricular failure, and kidney: different from left ventricular failure? *Clin J Am Soc Nephrol* 2008;3:1232-1237.
- James KB, Stelmach K, Armstrong R, Young JB, Fouad-Tarazi F. Plasma volume and outcome in pulmonary hypertension. *Tex Heart Inst J* 2003;30:305-307.
- Chin KM, Kim NH, Rubin LJ. The right ventricle in pulmonary hypertension. *Coron Artery Dis* 2005;16:13-18.
- Abou Dagher G, Hajjar K, Khoury C, El Hajj N, Kanso M, Makki M, Mailhac A, Bou Chebl R. Outcomes of patients with systolic heart failure presenting with sepsis to the emergency department of a tertiary hospital: a retrospective chart review study from Lebanon. *BMJ Open* 2018;8:e022185.
- Verbrugge FH, Dupont M, Steels P, Grieten L, Malbrain M, Tang WH, Mullens W. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. *J Am Coll Cardiol* 2013;62:485-495.
- Grunig E, Eichstaedt C, Barbera JA, Benjamin N, Blanco I, Bossone E, Cittadini A, Coghlan G, Corris P, D'Alto M, D'Andrea A, Delcroix M, de Man F, Gaine S, Ghio S, Gibbs S, Gumbiene L, Howard LS, Johnson M, Jureviciene E, Kiely DG, Kovacs G, MacKenzie A, Marra AM, McCaffrey N, McCaughey P, Naeije R, Olschewski H, Pepke-Zaba J, Reis A, Santos M, Saxer S, Tulloh RM, Ulrich S, Noordegraaf AV, Peacock AJ. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. *Eur Respir J* 2019;53:1800332.
- Gin-Sing W. Palliative care in pulmonary arterial hypertension. *Curr Opin Support Palliat Care* 2017;11:7-11.
- Burks M, Stickel S, Galiè N. Pulmonary arterial hypertension: combination therapy in practice. *Am J Cardiovasc Drugs* 2018;18:249-257.
- Gin-Sing W. Pulmonary arterial hypertension: a multidisciplinary approach to care. *Nurs Stand* 2010;24:40-47.
- Kingman MS, Lombardi S. Management of the patient with pulmonary arterial hypertension receiving intravenous prostacyclin: an expert nurse practical guide. *J Infus Nurs* 2014;37:442-451.
- Housten-Harris T. The nurse specialist and practical issues in the care of pulmonary arterial hypertension patients. *Int J Clin Pract Suppl* 2007;61:10-18.
- Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Kakishita M, Fukushima K, Okano Y, Nakanishi N, Miyatake K, Kangawa K. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000;102:865-870.
- Lillian H, Marsha B, Martha K, Traci S. Volume management in pulmonary arterial hypertension patients: an expert pulmonary hypertension clinician perspective. *Pulm Ther* 2018;4:13-27.
- Chua Chiao JMS, Parikh NI, Fergusson DJ. The jugular venous pressure revisited. *Cleve Clin J Med* 2013;80:638-644.
- Khan YH, Sarriif A, Adnan AS, Khan AH, Mallhi TH. Chronic kidney disease, fluid overload and diuretics: a complicated triangle. *PLoS One* 2016;11:e0159335.
- Condliffe R, Kiely D. Critical care management of pulmonary hypertension. *BJA Education* 2017;17:228-234.
- Quarck R, Nawrot T, Meyns B, Delcroix M. C-reactive protein: a new predictor of adverse outcome in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;53:1211-1218.
- Zeiger T, Cobo GC, Dillingham C, Burger CD. Prevalence of sodium and fluid restriction recommendations for patients with pulmonary hypertension. *Healthcare (Basel)* 2015;3:630-636.
- European Commission. *Survey on Members States' Implementation of the EU Salt Reduction Framework*. https://ec.europa.eu/health/sites/health/files/nutrition_physical_activity/docs/salt_report1_en.pdf (Accessed 15 May 2019).
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129-2200.
- van der Wal MH, Jaarsma T, Moser DK, Veeger NJ, van Gilst WH, van Veldhuisen DJ. Compliance in heart failure patients: the importance of knowledge and beliefs. *Eur Heart J* 2006;27:434-440.
- Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;107:216-223.
- McGoon MD, Kane GC. Pulmonary hypertension: diagnosis and management. *Mayo Clinic Proc* 2009;84:191-207.
- McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J; American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association; American College of Chest Physicians; American Thoracic Society, Inc; Pulmonary Hypertension Association. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert

- Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009;**53**:1573-1619.
30. Badesch DB, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, McLaughlin VV. American College of Chest P. Medical therapy for pulmonary arterial hypertension: aCCP evidence-based clinical practice guidelines. *Chest* 2004;**126**:355-625.
 31. Ventetuolo CE, Klinger JR. Management of acute right ventricular failure in the intensive care unit. *Ann Am Thorac Soc* 2014;**11**: 811-822.
 32. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WHW, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion—a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:137-155.
 33. Shapiro S, Pollock DM, Gillies H, Henig N, Allard M, Blair C, Anglen C, Kohan DE. Frequency of edema in patients with pulmonary arterial hypertension receiving ambrisentan. *Am J Cardiol* 2012;**110**:1373-1377.
 34. Vercauteren M, Trens F, Pasquali A, Cattaneo C, Strasser DS, Hess P, Iglarz M, Clozel M. Endothelin ETA receptor blockade, by activating ETB receptors, increases vascular permeability and induces exaggerated fluid retention. *J Pharmacol Exp Ther* 2017;**361**:322-333.
 35. GlaxoSmithKline. *Volibris 5 mg Film Coated Tablets—Summary of Product Characteristics*. <https://www.medicines.org.uk/emc/product/6258/smpc/> (Accessed 15 May 2019).
 36. Galiè N, Barbera JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiéry JL, Grunig E, Oudiz RJ, Vonk-Noordegraaf A, White RJ, Blair C, Gillies H, Miller KL, Harris JH, Langley J, Rubin LJ; AMBITION Investigators. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015;**373**:834-844.
 37. Janssen-Cilag Ltd. *Tracleer® (Bosentan). Summary of Product Characteristics*. <https://www.medicines.org.uk/emc/product/6162/smpc> (Accessed 15 May 2019).
 38. Janssen-Cilag Ltd. *Opsumit (Macitentan) 10 mg Summary of Product Characteristics*. <https://www.medicines.org.uk/emc/product/5223/smpc> (Accessed 15 May 2019).
 39. Wei A, Gu Z, Li J, Liu X, Wu X, Han Y, Pu J. Clinical adverse effects of endothelin receptor antagonists: insights from the meta-analysis of 4894 patients from 24 randomized double-blind placebo-controlled clinical trials. *J Am Heart Assoc* 2016;**5**:e003896.
 40. Buckley MS, Staib RL, Wicks LM, Feldman JP. Phosphodiesterase-5 inhibitors in management of pulmonary hypertension: safety, tolerability, and efficacy. *Drug, Healthc Patient Saf* 2010;**2**: 151-161.
 41. Das Gupta A, Bowman L, D'Arsigny CL, Archer SL. Soluble guanylate cyclase: a new therapeutic target for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Clin Pharmacol Ther* 2015;**97**:88-102.
 42. Barnes H, Yeoh HL, Fothergill T, Burns A, Humbert M, Williams T. Prostacyclin for pulmonary arterial hypertension. *Cochrane Database Syst Rev* 2019;**5**:CD012785.
 43. Cho S, Atwood JE. Peripheral edema. *Am J Med* 2002;**113**:580-586.
 44. Schroth BE. Evaluation and management of peripheral edema. *JAAAPA* 2005;**18**:29-34.
 45. Roush GC, Sica DA. Diuretics for hypertension: a review and update. *Am J Hypertens* 2016;**29**:1130-1137.
 46. Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. *Cochrane Database Syst Rev* 2004;**1**:CD003178.
 47. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart* 2003;**89**:1363-1372.
 48. Guerrero MP, Volpe SL, Mao JJ. Therapeutic uses of magnesium. *Am Fam Physician* 2009;**80**:157-162.