Outcome of paediatric portopulmonary hypertension in the modern management era: A case report of 6 patients

JOYE, Raphaël, et al.

Abstract

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Outcome of paediatric portopulmonary hypertension in the modern management era: A case report of 6 patients

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Summary
Portopulmonary hypertension is a rare but serious complication of portal hypertension or portosystemic shunting. Portopulmonary hypertension is an indication for liver transplantation or shunt closure. However, liver transplantation is contraindicated in patients with severe pulmonary arterial hypertension. Reported mortality rates are high in children with portopulmonary hypertension and there are scarce recommendations on its management. Our aim was to report on our real-world experience of managing portopulmonary hypertension in a specialised centre. We describe a series of 6 children with portopulmonary hypertension. Their median age at diagnosis was 13 years (range 10–15). The underlying liver conditions were cirrhosis of unknown origin (1), congenital portocaval shunts (3), biliary atresia (1), and portal vein cavernoma with surgical mesenterico-caval shunt (1). Median mean pulmonary arterial pressure was 47 mmHg (range 32–70), and median pulmonary vascular resistance was 6.6 Wood units (range 4.3–15.4). All patients except one were treated with a combination of pulmonary arterial hypertension-specific therapy (phosphodiesterase type 5 inhibitors and/or endothelin receptor antagonists and/or prostacyclin analogues). Three patients then benefited from shunt closure and the others underwent liver transplantation. Five patients showed improvement or stabilisation of pulmonary arterial hypertension with no deaths after a mean follow-up of 39 months. Based on our limited experience, early and aggressive treatment with a combination of pulmonary arterial hypertension-specific therapy significantly improves patients’ haemodynamic profile and enables the performance of liver transplantation and shunt closure with satisfactory outcomes.

Keywords: Liver transplantation; Portosystemic shunts; Port hypertension; Pulmonary arterial hypertension; Medical treatment; Paediatrics.

Introduction
Portopulmonary hypertension (PoPH) is defined as the combination of portal hypertension or portosystemic shunting and pulmonary arterial hypertension (PAH). According to the new definition, PAH is characterised by the combination of mean pulmonary arterial pressure (mPAP) >20 mmHg at rest, pulmonary capillary wedge pressure (PCWP) <15 mmHg and pulmonary vascular resistance (PVR) >3 Wood units (WU).1 The prevalence of PoPH ranges between 1% and 5.2% in children with portal hypertension2 and around 11% in children with congenital portosystemic shunts (CPSS).3

The main aim of PoPH management is to protect the pulmonary circulation from the putative underlying pathogenic mechanism: exposure to portal blood shunted to the systemic circulation. This is achieved either via shunt closure or in some cases by performing liver transplantation (LT). However, LT is contraindicated in patients with severe haemodynamic impairment. Indeed, perioperative mortality risk depends on the severity of PoPH.4 Patients with an mPAP of >50 mmHg are at a 100% risk of perioperative mortality, obviously contraindicating LT. In these cases, medical treatment with PAH-specific medications should be undertaken as preconditioning therapy to improve haemodynamics. Mortality is low when mPAP is <35 mmHg and PVR is <3 WU, allowing for LT without pretreatment. If mPAP ranges between 35 and 50 mmHg and PVR is >3 WU, perioperative mortality is estimated to be around 50%, and LT should be considered cautiously.4 There is no clear consensus regarding portosystemic shunt closure, but preconditioning is thought to be beneficial.

Most studies on PoPH have been performed in adults. Therefore, the therapeutic approach in children mainly derives from adult guidelines. Small paediatric studies suggest a very poor outcome in children.5 Our aim was to report on our real-world experience of PoPH management in a specialised centre, with the aim of increasing awareness and improving management of these patients.
Patient data were collected via chart review. Full pulmonary hypertension (PH) workup was performed and precapillary PH was confirmed by right heart catheterisation (RHC), as recommended by the Paediatric Task Force of the 6th World Symposium on Pulmonary Hypertension.1

LT was undertaken after medical treatment with PAH-specific medications, when mPAP and PVR neared recommended values for LT.6 Shunt closure was also performed following medical therapy for PH. All patients provided written informed consent for this study.

Case 1
A 13-year-old morbidly obese female presented with dyspnoea on exertion (DoE) (functional class (FC) III), hoarse voice (Ortner syndrome) and haematemesis secondary to oesophageal varices. CT scan showed a dilated right ventricle (RV) and pulmonary artery and a dysmorphic liver. Transthoracic echocardiography (TTE) showed moderate right ventricular and severe pulmonary trunk dilatation with signs of elevated pulmonary pressures. A liver biopsy revealed advanced cirrhosis of unclear aetiology. She was diagnosed with portal hypertension and PoPH. Ultimately the patient was identified as carrying a homozygous melanocortin receptor 4 (MC4R) mutation.

RHC confirmed severe PAH with mPAP of 46 mmHg, PVR of 10 WU, CO of 3.5 L/min and PCWP of 11 mmHg. Cardiac MRI showed a decreased RV ejection fraction (RVEF) of 47%. Table 1 summarises the most important clinical, biological and haemodynamic parameters and their course over time. Upfront combination therapy was initiated with tadalafil 40 mg q.d. and macitentan 10 mg q.d. Three months later, clinical symptoms improved (FC II) and RVEF increased to 52% on cardiac MRI.

LT was initially delayed because of the patient’s comorbidities and social context. After 2 years of treatment, haemodynamic parameters significantly improved with mPAP of 39 mmHg, PVR of 4.7 WU, CO of 5.7 L/min, and PCWP of 12 mmHg. RVEF was stable. She then underwent an uneventful LT. Six months after surgery, she showed haemodynamic worsening with mPAP of 62 mmHg, PVR of 7.2 WU, and CO of 6.6 L/min. PCWP was measured at the upper limit, at 14 mmHg. She also presented a pericardial effusion and increased filling pressure. This was partly explained by a postcapillary component added to the initial PAH. Indeed, tacrolimus use and MC4R mutations are both known to negatively impact left ventricular diastolic function. Thus, a glucagon-like peptide-1 analogue was introduced to improve the metabolic profile and to promote weight loss. Fig. 1 displays the changes in mPAP and PVR.

Case 2
A female with biliary atresia underwent a Kasai portoenterostomy at the age of 2 months and subsequently developed secondary biliary cirrhosis with portal hypertension and oesophageal varices. At the age of 15, she presented with DoE, chest pain and syncope (FC IV).

TTE showed moderate RV dilatation and hypertrophy with systolic flattening of the interventricular septum and large pericardial effusion. RHC was then undertaken and PAH was confirmed: mPAP of 48 mmHg, PVR of 5.1 WU, CO of 6.8 L/min and PCWP of 13 mmHg. Cardiac MRI showed a normal RVEF of 61% (Table 1). Initial therapy consisted of sildenafil 20 mg t.i.d. and bosentan 125 mg b.i.d. The patient’s haemodynamic profile had stabilised at 1-year follow-up, but mPAP and PVR values were still too high for LT. Medical therapy was escalated to a triple combination therapy with tadalafil 40 mg q.d., bosentan 125 mg b.i.d., and intravenous epoprostenol (gradually increased to 14 ng/kg/minute).

After 1 year of triple combination therapy, mPAP was 32 mmHg, PVR was 3.8 WU and CO was 6.4 L/min. Cardiac MRI was repeated and showed a stable RVEF. The patient underwent successful LT. Bosentan was replaced by macitentan 10 mg q.d because of potential interactions with immunosuppressants. Epoprostenol was weaned after 6 months resulting in haemodynamic worsening and the introduction of selexipag 600 ug b.i.d., an oral prostacyclin receptor agonist. Three years after LT, clinical symptoms were under control (FC I) and haemodynamic parameters were stable: mPAP of 43 mmHg, PVR of 5.6 WU and CO of 7.2 L/min on triple combination oral therapy with macitentan, tadalafil and selexipag (Fig. 1).

Case 3
A 13-year-old male was brought by his parents for a second opinion following a diagnosis of PAH discovered in the context of a heart murmur and a cardiomegaly on chest x-ray during an assessment for military school. The patient was asymptomatic from a cardiopulmonary standpoint but presented with behavioural problems. Idiopathic PAH was the initial diagnosis, but thorough investigations revealed an extrahepatic CPSS.

TTE showed moderate right ventricular dilatation and hypertrophy as well as pulmonary trunk dilatation. Doppler identified a pathological pulmonary outflow with a notch. RHC confirmed PAH with mPAP of 32 mmHg, PVR of 4.3 WU, CO of 5.6 L/min and PCWP of 8 mmHg. Cardiac MRI showed a normal RVEF of 57% (Table 1). Initially, upfront PAH-specific combination therapy with tadalafil 40 mg q.d. and macitentan 10 mg q.d. was chosen.

Three months later, mPAP was 22 mmHg, PVR was 1.8 WU, and CO was 8.5 L/min. Cardiac MRI showed a slightly decreased RVEF of 53%. The shunt was surgically closed. Two years later, the patient was still free of any cardiopulmonary symptoms. Haemodynamic parameters were normalised with mPAP of 17 mmHg, PVR of 1.6 WU and CO of 7.6 L/min (Fig. 1). Currently, the patient is stable on macitentan monotherapy.

Case 4
A male with hepatosplenomegaly in infancy presented with a cavernous transformation of the portal vein, probably due to neonatal umbilical vein catheterisation. At the age of 4, he underwent a surgical meso-caval shunt using his internal jugular vein. Six years after the surgery, he presented with DoE and lower limb pitting oedema (FC III).

TTE showed no dilatation or hypertrophy of the right chambers, but minimal tricuspid regurgitation allowed for an estimation of elevated pulmonary pressures. RHC confirmed PAH: mPAP of 32 mmHg, PVR of 4.5 WU, CO of 5.5 L/min and PCWP of
Table 1. Time course of clinical, biochemical and haemodynamic variables of the 6 patients with portopulmonary hypertension.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case 1: At PoPH diagnosis</th>
<th>After treatment</th>
<th>At last follow-up</th>
<th>Case 2: At PoPH diagnosis</th>
<th>After treatment</th>
<th>At last follow-up</th>
<th>Case 3: At PoPH diagnosis</th>
<th>After treatment</th>
<th>At last follow-up</th>
<th>Case 4: At PoPH diagnosis</th>
<th>After treatment</th>
<th>At last follow-up</th>
<th>Case 5: At PoPH diagnosis</th>
<th>After treatment</th>
<th>At last follow-up</th>
<th>Case 6: After treatment</th>
<th>At last follow-up</th>
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<td>Functional class</td>
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<td>II</td>
<td>III</td>
<td>IV</td>
<td>II</td>
<td>I</td>
<td>III</td>
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<td>IV</td>
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<td>Pro-BNP in ng/L (N &lt;300 ng/L)</td>
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<td>31</td>
<td>151</td>
<td>191</td>
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<td>151</td>
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<td>BNP in ng/L (N &lt;107 ng/L)</td>
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<td>13</td>
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<td>Distance in meters (6-MWT) (%) of theoretical distance</td>
<td>392 (58%)</td>
<td>462 (58%)</td>
<td>680 (88%)</td>
<td>500 (70%)</td>
<td>585 (82%)</td>
<td>486 (68%)</td>
<td>525 (65%)</td>
<td>555 (813)</td>
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<tr>
<td>Peak VO2 in ml/min/kg (CPET) (3 of predicted value)</td>
<td>12 (29%)</td>
<td>21 (58%)</td>
<td>16 (40%)</td>
<td>18 (49%)</td>
<td>36.3 (43%)</td>
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<td>VE/VCO2 slope (CPET)</td>
<td>37.9</td>
<td>28.3</td>
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<td>mPAP estimation in mmHg (TTE)</td>
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<td>62</td>
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<td>5.5</td>
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<td>Cardiac output in L/min (RHC)</td>
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<td>PCWP in mmHg (RHC)</td>
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</table>

Functional class, 4 classes that describe the severity of a patient’s pulmonary hypertension symptoms; Mac., macitentan; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PoPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVEF, right ventricle ejection fraction; Sild., sildenafil; sPAP, systolic pulmonary arterial pressure; Tad., tadalafil; TTE, transthoracic echocardiography; VE/VCO2, minute ventilation/carbon dioxide production; VO2, oxygen uptake; WU, Wood units.

*With PAH-specific treatments.
7 mmHg (Table 1). Initial PAH-specific drug monotherapy was started with bosentan 125 mg b.i.d.

After 2 years, haemodynamic parameters had improved (mPAP of 22 mmHg, PVR of 2.3 WU and CO of 7.5 L/min) and LT was performed. Bosentan was replaced by macitentan 10 mg q.d. because of drug interactions then weaned after 18 months of treatment. Cardiac MRI was performed 1 year later and showed a normal RVEF. Two years after the weaning of medical therapy, the patient’s haemodynamic profile had normalised with mPAP of 16 mmHg, PVR of 1.4 WU and CO of 5 L/min (Fig. 1).

**Case 5**

A 13-year-old female presenting with DoE and syncope (FC IV) was initially started on sildenafl and bosentan for idiopathic PAH. The family sought a second opinion in our centre where an extrahepatic portosystemic shunt was identified.

TTE showed severe RV and pulmonary artery dilatation, in addition to systolic flattening of the interventricular septum. RHC confirmed the presence of PAH with mPAP of 54 mmHg, PVR of 8.1 WU, PCWP of 11 mmHg and CO of 5.3 L/min. Cardiac MRI showed a preserved RVEF of 59% (Table 1). The diagnosis of PoPH was confirmed and therapy was switched to tadalafil 40 mg q.d. and macitentan 10 mg q.d.

After 3 months, she reported a resolution of her symptoms. RHC showed haemodynamic improvement with mPAP of 42 mmHg, PVR of 5.5 WU and CO of 5.5 L/min. RVEF was slightly improved at 63% on cardiac MRI. The shunt was surgically closed with an uneventful postoperative course. Four months after surgery, the patient’s haemodynamic profile had normalised with mPAP of 36 mmHg, PVR of 6.8 WU and CO of 4.0 L/min (Fig. 1).

**Discussion**

PoPH in paediatrics is a rare life-threatening complication of portal hypertension and portosystemic shunting. Data in children are scarce but the majority of deaths are heart/lung-related. As reported in the most recent publications, the outcome of PoPH in children remains poor. Tingo et al. reported a case series of 5 children diagnosed with PoPH and treated with PAH-specific medications. Treatment was selected based upon PoPH severity. One of them underwent portosystemic shunt closure whereas none underwent LT. Three of the 5 children died during follow-up. The high mortality rate was partly attributed to diagnostic delay by the authors. Of note, 2 of the 3 patients who died were in fact treated with monotherapy and showed haemodynamic worsening. There was also a diagnostic delay in our patient series. Patients presented with significant clinical symptoms and moderate to severe haemodynamic profile impairment. As discussed below, an “aggressive” treatment with dual oral combination therapy or more seems to improve outcomes.

Because early stages of PAH can be difficult to suspect on clinical evaluation, screening for pulmonary vascular disease is emerging as a key therapeutic determinant in patients with portal hypertension. The age of onset of PoPH seems to be variable, and no predictive factor has been identified. PAH screening should therefore be performed even in cases of stable, compensated underlying liver disease. It should also be cost effective, non-invasive and lead to improved outcomes.

In our series, TTE seems to remain the best tool and is part of the regular follow-up of patients with portal hypertension or portosystemic shunting. We combine biological markers such as brain natriuretic peptide (Table 1) with routine TTE in asymptomatic children with portal hypertension and children listed for LT. Indications for RHC should be based on symptoms, and the presence of direct and indirect signs of elevated pulmonary pressures on TTE. It should be noted that newer imaging techniques, such as MRI, are becoming more widely available and could probably help throughout diagnosis and the follow-up process. In case of CPSS, the closure should be undertaken if the shunt persists beyond the age of two. TTE should be beneficial in patients with CPSS, as it allows for haemodynamic monitoring (mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance).
assessment and the evaluation of indications for RHC prior to shunt closure. If TTE is normal, no further PoPH screening is needed as most shunts are closed anyway. In patients with a surgical portosystemic shunt (inserted to treat portal vein obstruction), we recommend the same screening as for patients with portal hypertension. Further studies are required to support our suggestions.

Treating PoPH with PAH-specific medications is recommended by the International Liver Transplant Society in order to improve haemodynamic profile with the expectation of lowering LT and decreasing perioperative mortality in adults. However, choosing a medical treatment is challenging because patients with PoPH were excluded from most of the randomised studies on PAH. Sildenafil and bosentan have been shown to improve FC and haemodynamic parameters in adult PoPH patients. The use of macitentan led to a 35% reduction in PVR in the first randomised clinical trial on adults with PoPH.

In children, PAH-specific drug therapy studies are scarce and mostly recognised for idiopathic PAH, heritable PAH or PAH associated with congenital heart diseases. PoPH is a rare form of a rare disease, and PAH-specific medications are therefore used off-label with the treatment algorithm based on adult recommendations. Our experience suggests that an early and aggressive approach with medical treatment allows for a successful bridge to LT when needed and improves the survival rate compared to published results. Our strategy also allows for haemodynamic improvement in portosystemic shunt patients and may facilitate postoperative care. We suggest initiating treatment with a combination of a phosphodiesterase type 5 inhibitor (i.e. sildenafil, tadalafil) and an endothelin receptor antagonist (i.e. bosentan, macitentan). Prostacyclin analogues can be introduced upfront in the most severe cases, or as an additional therapy if haemodynamic response is unsatisfactory for LT consideration.

Current recommendations suggest to lower mPAP to <35 mmHg and PVR to <3 WU before LT in order to decrease perioperative mortality. One should keep in mind that these values are only validated for LT in adults. Further studies are needed to better understand the influence of haemodynamic parameters on CPSS closure, something which the International Registry for Congenital Portosystemic Shunts (ircpss.com) aims to address.

After LT, early complications can arise during surgery and for a few days postoperatively. RV function seems to be a good determinant of postoperative outcomes. RV pressure and function might therefore be the best prognostic factors and should be considered in addition to the mPAP and PVR threshold. In our centre, we combine RHC with cardiac MRI to assess RV function before and after medical treatment and before surgery. All 6 of our patients had a normal RVEF on MRI before LT or shunt closure, and there was no perioperative haemodynamic instability. We thus strongly recommend adding cardiac MRI to haemodynamic values in the preoperative decision algorithm.

Long term outcomes after LT or shunt closure for PoPH are variable, with either a decrease, a stabilisation or an increase in mPAP and PVR. In our series, 2 patients showed haemodynamic improvement and were partly or fully weaned off treatment. Of note, the haemodynamic profile of these patients was also the least severe at diagnosis. Three patients showed haemodynamic stabilisation rendering treatment de-escalation impossible thus far. One patient showed a slight deterioration with signs of postcapillary PH. This highlights the importance of an optimal screening strategy to diagnose PoPH at an early stage. More studies are needed to identify factors able to predict late postoperative outcome.

To conclude, PoPH is a progressive disease with significant mortality in children with portal hypertension or portosystemic shunts. Early PoPH diagnosis through screening programmes may be an option to improve outcomes. The methodology of screening should be cost effective and adapted to the type of liver disease.

Based on our experience, aggressive therapy with a combination of PAH-specific drug therapy significantly improves the haemodynamic profile and allows for LT with symptom-free survival in the medium term. Based on the present series, performing surgery in patients with preserved RV function seems to be the best approach.

Multicentre studies in children with liver disease or CPSS are required to establish guidelines for screening and treatment of PoPH.

### Abbreviations
6-MWT, 6-minute walking test; CO, cardiac output; CPET, cardiopulmonary exercise testing; CPSS, congenital portosystemic shunts; DoE, dyspnoea on exertion; FC, functional class; LT, liver transplantation; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PoPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterisation; RV, right ventricle; RVEF, RV EF, ejection fraction; sPAP, systolic pulmonary arterial pressure; TTE, transthoracic echocardiography; WU, Wood units.

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### Conflict of interest
Frédéric Lador reports grants, personal fees and non-financial support from Actelion, personal fees from MSD, grants and personal fees from Bayer, outside the submitted work. Maurice Beghetti has received grants from Actelion and Bayer, contracted as consultant and participate to steering committee for Actelion, Bayer, GSK, Eli Lilly and Acceleron, outside the submitted work.

Please refer to the accompanying ICMJE disclosure forms for further details.

### Authors’ contributions
RJ, FL, VAM and MB were involved in the interpretation of the data, the conception and the drafting of the manuscript and participated to the revisions. YA, NF, JW, BEW, JPV and ALH were involved in the acquisition and interpretation of the data and the conception of the manuscript.

All the authors approved the final version of the manuscript.

### Data availability statement
The authors confirm that the data supporting the findings of this article are available within the manuscript. They are also included in patients’ charts and are available from the corresponding author on request.
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Supplementary data
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