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Pulmonary hypertension in adults with congenital heart disease: Updated recommendations from the Cologne Consensus Conference 2018

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ABSTRACT

In the summer of 2016, delegates from the German Respiratory Society (DGP), the German Society of Cardiology (DGK) and the German Society of Pediatric Cardiology (DGPK) met in Cologne, Germany, to define consensus-based practice recommendations for the management of patients with pulmonary hypertension (PH). These recommendations were built on the 2015 European Pulmonary Hypertension guidelines, aiming at their practical implementation, considering country-specific issues, and including new evidence, where available. To this end, a number of working groups was initiated, one of which was specifically dedicated to PH in adults associated with congenital heart disease (CHD). As such patients are often complex and require special attention, and the general PAH treatment algorithm in the ESC/ERS guidelines appears too unspecific for CHD, the working group proposes an analogous algorithm for the management of PH-CHD which takes the special features of this patient group into consideration, and includes general measures, supportive therapy, targeted PAH drug therapy as well as interventional and surgical procedures. The detailed results and recommendations of the working group on PH in adults with CHD, which were last updated in the spring of 2018, are summarized in this article.

1. Introduction

Congenital anomalies of the heart and great arteries (congenital heart disease [CHD]) are among the most common congenital anomalies. Every year, approximately 1.5 million children worldwide and about 6500 children in Germany are born with CHD [1–3]. As a result of improved medical care, about 90% of them reach adulthood [4,5]. It is assumed that in Germany currently up to 300,000 adults with adult CHD (ACHD) exist [6]. The overall number of patients who develop pulmonary (PH) or pulmonary arterial (PAH) hypertension in the presence of CHD (P(A)H-CHD) is unknown. PAH in children and ACHD resembles a continuum extending from treatable heart defects to severe pulmonary vascular disease [7] (Fig. 1).

2. Important new aspects of the current European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines

Important changes have been made to the current ESC/ERS guidelines compared with the 2009 guidelines. The PH classification has been updated and is now suitable for adults and children. Typical pediatric diseases, congenital left heart disease with PH but without PAH as well as CHD with segmental PAH have been assigned to the existing groups. Pulmonary vascular resistance (PVR) has been included in the hemodynamic definition of PAH.

A clinical classification of PAH-CHD has been added, which is simpler and more decisive for clinical management than the detailed

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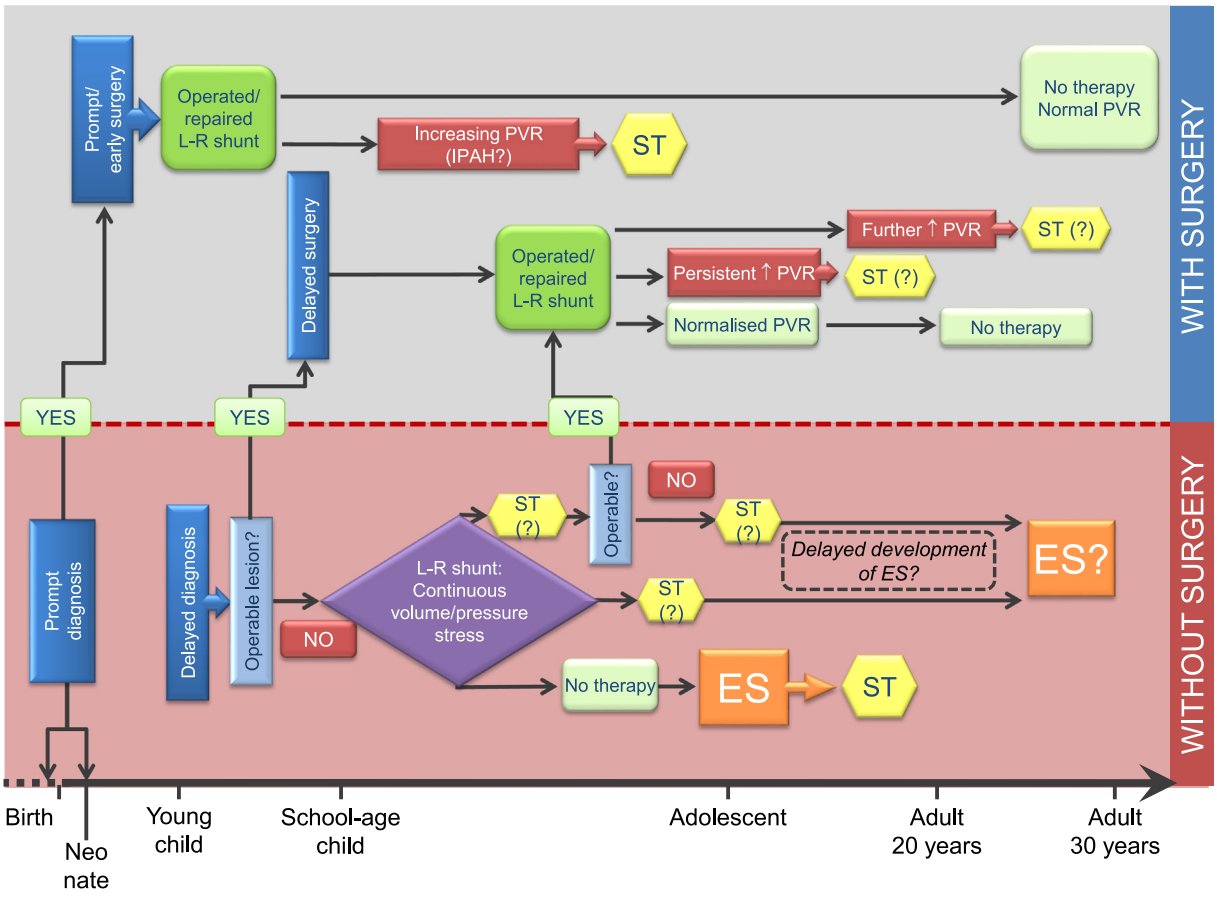

Fig. 1. Pulmonary arterial hypertension in children and adults with congenital heart disease as a continuum ranging from operable heart defects to severe pulmonary vascular disease (Eisenmenger syndrome) [7]. ES = Eisenmenger syndrome, IPAH = idiopathic PAH, L–R shunt = Left-to-right shunt, PAH = pulmonary arterial hypertension, PVR = pulmonary vascular resistance, ST = specific PAH therapy ("advanced/targeted therapy").

anatomical-pathophysiological classification ([8], Web Table II). This also contains information on special disorders and situations such as pulmonary vascular disease in Fontan circulation and in segmental PH.

A new sub-classification and new parameters have been introduced for the hemodynamic definition of post-capillary PH which replace the term "out of proportion PH". The diagnostic and therapeutic algorithms have been updated. In addition, new strategies for risk assessment and screening have been introduced [8], however the value of these additions remains to be demonstrated in CHD. In Germany, the implications of expert centers for the care of PH patients discussed in the ESC/ERS guidelines has already been broadly taken into account in the field of ACHD [6].

3. Definition of P(A)H

The significance of performing invasive measurements for the diagnosis of P(A)H and for therapeutic management is emphasized by the ESC/ERS guidelines. This also applies, with a few exceptions, to P(A)H-CHD. Thus, the presence of Eisenmenger syndrome (ES) should be assumed in cyanotic adults who have large shunt defects with pressure equalization at the ventricular or arterial level after right ventricular outflow tract and/or pulmonary arterial stenosis have been reliably excluded. The benefit of an invasive investigation should be carefully assessed in these patients, particularly as the risk is higher than in patients with structurally normal hearts.

A post-capillary form of PH should be considered in patients with left-sided valve defects or diastolic dysfunction of the systemic ventricle. This has therapeutic consequences, as targeted PAH therapy is not indicated in patients with isolated post-capillary PH (Ipc-PH) and may be potentially harmful.

In the ESC/ERS guidelines, diastolic pressure gradient (DPG) has assumed the role of transpulmonary pressure gradient (TPG). The rationale for this was that DPG is less dependent on pulmonary blood flow. In the field of CHD, TPG will continue to occupy an important place, because standard values for DPG have not been established for patients with a complex anatomy and those who have undergone a Fontan procedure. It should be noted that pulmonary valve insufficiency that frequently occurs in CHD may lead to an artificially low DPG.

A hemodynamic definition of pulmonary vascular disease in patients with univentricular hearts and Fontan circulation is currently not included in the guidelines. In this context, measurement of TPG – defined as the difference between mean pulmonary arterial pressure (mPAP) and left atrial (LA) pressure – is still favored. The limit values for functional Fontan circulation are given as TPG ≤ 6 mmHg and PVR ≤ 3 Wood units × m^2 [9].

Pulmonary arterial stenoses (see point 4.2.4 of the clinical PH classification) are not considered to be PH in the field of ACHD.

4. Classification

PH is classified into five main groups [1–5] (see article on "Classification and Initial Diagnosis" in this supplement). New entities have been explicitly included in the ESC/ERS guidelines to better account for pediatric diseases and thus the range of CHD. P(A)H in CHD appears in groups 1, 2, 4 and 5 of this classification [10]. PAH in association with congenital shunt lesions is allocated to four clinically defined groups (Table 1) [11]. These include ES, correctable or non-correctable left-to-

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Table 1
Classification by clinical aspects of pulmonary arterial hypertension in congenital shunt defects.

1. Eisenmenger syndrome	▶ All major intra- and extra-cardiac cardiovascular abnormalities with initial systemic pulmonary blood flow (shunt), in which pulmonary vascular resistance (PVR) increases greatly over the course of the disease and in which there is a consecutive bidirectional shunt or a complete shunt reversal (blood flow from the lungs to the systemic circulation). ▶ In clinical terms, there is cyanosis, secondary erythrocytosis and cyanosis-related multiple organ involvement.
2. Left-to-right shunts ▶correctable (by intervention or surgery) ▶ un-correctable	▶ Medium- to large-size defects with mild to moderate systemic-pulmonary blood flow but no cyanosis at rest.
3. Pulmonary arterial hypertension (PAH), associated with an coincidental congenital heart defect (CHD)	▶ PAH is **coincidentally** associated with a congenital heart defect. ▶ Markedly elevated PVR in the presence of SMALL congenital defects that are NOT primarily responsible for the development of elevated PVR (in adults this is typically a ventricular septal defect with an effective diameter < 1 cm or an atrial septal defect with an effective diameter < 2 cm as measured by echocardiography). ▶ The clinical picture strongly resembles idiopathic PAH. Defect closure is contraindicated. (The diameter measured does not always indicate the haemodynamic relevance of the defect! For a more exact assessment of the shunt haemodynamics, pressure gradients, shunt size and direction and the ratio of pulmonary to systemic flow (Qp/Qs) must be taken into consideration)
4. PAH after repair	▶ Persistent PAH that reoccurs within months or years after surgical repair of the CHD, without haemodynamically relevant re- or residual shunts.

right shunts, PAH that is incidentally occurring with CHD, and PAH after CHD repair. In addition, there are exceptional situations such as Fontan circulation or segmental forms of PAH. Further differentiation of P(A)H-CHD can be performed by type, dimension, shunt direction, associated abnormalities and treatment status.

Allocation to defined groups of CHD of PH can be of clinical and prognostic significance in left-to-right shunt defects. The presented classification seems to be adequate for everyday clinical practice, even though it does not accurately reflect the complexity of the disease pattern. A more differentiated classification of P(A)H-CHD can be performed according to the recommendations of the Panama Conference (2011) [12]. Over the course of time, many adults with P(A)H-CHD develop relevant cardiac and non-cardiac comorbidities, which may have critical effects on the development of increased pulmonary vascular disease and thus on the clinical presentation and outcome [13].

In the future, more and more patients with univentricular hearts after Fontan operation will reach adulthood. Even if these patients do not have typical forms of PH corresponding to the established definitions, some of them develop pulmonary vascular disease, have an elevated TPG and may benefit from PAH-targeted therapy [14,15].

5. Diagnosis of P(A)H-CHD

In the absence of specific guidelines for a diagnostic work-up of ACHD, the general diagnostic algorithm for P(A)H is frequently used. In this context, the ESC/ERS guidelines refer explicitly to the need for multidisciplinary co-operation when PAH is suspected [8]. The diagnostic tools available for P(A)H-CHD are similar to those generally used in PH, where modern imaging procedures and cardiac catheterization play a central role. Besides the exact definition of the existing heart defect, the diagnostic approach in P(A)H-CHD includes the functional and hemodynamic grading of P(A)H [16]. Reference is made to current publications with regard to specific symptoms and the clinical assessment [5,10,17–32]. Early diagnosis is important, because in patients with PAH, timely surgical or interventional correction can improve clinical course and prognosis. In addition, concomitant or acquired diseases that may lead to P(A)H must be noted. Because of the complexity of the diagnostic procedures, all patients with P(A)H-CHD should be referred to an experienced ACHD center.

5.1. Echocardiography

The ESC/ERS guidelines provide the upper and lower threshold values for normal heart chamber size and parameters of right ventricular function [8], which cannot per se be applied to CHD patients [8,33]. This is because in CHD typical changes in heart size and function can be present. In addition, because of the variety and complexity of CHD there are no established normal values. Also, the risk stratification for prognosis based on right atrial (RA) size given in the ESC/ERS guidelines (estimated 1-year mortality) cannot be unconditionally applied to CHD patients [8], because a dilated RA may be present as a result of the defect and independently of PAH. Therefore, individual assessment of the parameters is important. Novel, standard echocardiography complementing parameters (tissue Doppler, speckle tracking, 3D features) allow a more exact quantification of global and regional ventricular function in P(A)H-CHD [18]. Because of the frequently limited ultrasound window, practicability and reproducibility, tricuspid annular plane systolic excursion (TAPSE) and fractional area change (FAC) continue to be recommended for analysis of RV function [18,34].

Although echocardiography is the established method for screening and assessment, a multimodal approach of imaging is recommended in CHD with and without PH/PAH. Besides transthoracic echocardiography (TTE), this includes 2D- and 3D-transesophageal echocardiography (3D-TEE), cardiac computerized tomography (CT) and MRI, as well as invasive diagnostics [18,34,35]. 3D-TEE plays an increasingly important role in the exact assessment of defects, in particular of shunts at the atrial and the atrioventricular (AV) valve level, and also in guiding interventional procedures [35,36].

5.2. Genetic studies

The ESC/ERS guidelines recommend diagnostic testing for causative genetic mutations, after appropriate human genetic counselling, only in patients with Group 1 PAH (idiopathic and hereditary PAH, pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis) [8]. There are no specific genetic tests for PAH-CHD which can be used to predict the probability of occurrence of PAH or the effectiveness of targeted therapy. A genetic study to test for genetic changes typical of PAH can be considered in patients with PAH, in whom an intracardiac (small atrial septal defect [ASD], small ventricular septal defect [VSD]) or extracardiac shunt connection (small Patent Ductus Arteriosus) has been incidentally detected, but which does not explain why PAH developed.

5.3. Invasive investigation (cardiac catheterization)

From the perspective of congenital cardiology, in patients with CHD cardiac catheterization with vasoreactivity testing should always be performed at an expert center, because it is technically demanding and may be associated with severe complications. In these patients, an

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ACHD expert should be involved when taking decisions on whether to initiate or change therapy, or clarification of operability or inclusion in studies.

The range of patients that are considered operable has recently been expanded in children with CHD compared with ACHD [9]. Very few data are available in adults and the benchmarks established by the ESC should be used. In shunt defects, generally both right and left heart catheterization should be performed. Coronary angiography is mandatory in ACHD patients aged >40 years, or when risk factors for coronary heart disease are obvious. In ACHD patients with PAH, left heart conditions can aggravate PAH. This requires a robust work-up by means of invasive diagnostics. Important aims of cardiac catheterization in this context are as follows:

- To determine the severity of PH
- To differentiate between flow-related, pulmonary vascular and post-capillary components of PH
- To identify possible causes of group 3 and group 4 of the PH classification
- To identify patients who are still operable

Pulmonary (Qp) and systemic cardiac output (Qs) can be determined by means of oximetry data. Direct measurement of oxygen (O_2) uptake improves the accuracy but is technically challenging. The thermodilution method for assessing cardiac output does not supply useful measurements in shunt defects involving left-to-right or right-to-left shunts.

5.3.1. Vasoreactivity testing

In the context of congenital cardiology, the indication for testing is different from that in idiopathic PAH. There are different capabilities for acute pulmonary vasoreactivity testing like inhaled nitric oxide (10–20 ppm), prostanoids (i.v. epoprostenol or inhaled iloprost), with i.v. adenosine (not recommended in children) or 100% O_2, alone or in combination. It should be noted that, when using high inspiratory O_2 concentrations, during O_2 supply and when pO_2 in the pulmonary veins is >100 mmHg, the simplified shunt calculations based on O_2 saturation alone are flawed. To avoid calculating an inadequately low PVR, a modified calculation formula must be used that takes the O_2 partial pressures into account.

The criteria for positive vasoreactivity (reduction in mPAP ≥10 mmHg and attainment of mPAP ≤40 mmHg with increasing or unchanged cardiac output [37–39]) cannot be meaningfully applied in cases of CHD with shunts. In these cases, aortic O_2 saturation and Qp/Qs ratio must be assessed. The absence of a drop in PAP does not mean that PVR has not decreased, because the left-to-right shunt and thus Qp may have increased. Even if vasoreactivity is absent, patients may be treated with targeted PAH therapies.

6. Risk stratification and follow-up care

The plan for follow-up care in PAH-CHD broadly corresponds to the general recommendations of the ESC/ERS guidelines and includes past medical history, WHO functional class, clinical examination, electrocardiogram, 6-minute walk test (6MWT), cardiopulmonary exercise testing (CPET), echocardiography and laboratory tests. In general, the course of the disease is more stable in CHD and subject to less severe variations, which means that observation intervals can generally be kept longer. An arterial blood gas analysis is usually not necessary because ventilation problems are only rarely present. Pulse oximetry is sufficient.

There is no evidence to support the necessity for repeated cardiac catheterization, which may actually be dangerous in patients with ES. An initial cardiac catheterization is enough to confirm the diagnosis, and catheterization should be repeated if there is diagnostic uncertainty or if clinically relevant changes have occurred.

The **risk assessment** is carried out in a similar manner as in other forms of PAH; however, special aspects should be noted: In large shunt defects, PAP is identical to systemic pressure. Right heart failure occurs less often than in PAH after surgical closure or in idiopathic PAH (IPAH). Severity depends on the Qp/Qs ratio, which can be monitored most easily by pulse oximetry. Quality of life and survival are influenced substantially by concomitant organ damage or complications. Syncope is rare in open shunt connections. If there are neurological symptoms, hyperviscosity symptoms, cerebrovascular accidents or intracranial abscesses must be considered.

The classification proposed for risk stratification in non-congenital forms of PAH and the classification criteria can be applied to PAH-CHD, and in particular to ES, in a modified form. Causes of death are beyond the usual causes in IPAH, especially due to hemoptysis (14%), occasional endocarditis, cerebral abscesses or insults [40–44]. In some studies, complex heart defects and the early occurrence of shunt reversal represented risk factors [42,44]. This also applies to trisomy 21 (Down syndrome) [42,43,45].

Parameters relevant to prognosis in the follow-up of ES include:

- B-type natriuretic peptide (BNP) [43,46]
- Renal function tests [42,43,47]
- Clinical functional class [41–44,46–48]
- Clinical signs of heart failure [42,48]
- Syncope [41,47]
- Cardiac arrhythmias [49,62]
- O_2 saturation at rest [43,47,49,50].
- CPET: blood pressure and increased heart rate [42,50]
- 6MWT: variable but dependent on other parameters [43]
- Cardiac catheterization: PVR/shunt flow [47], vasoreactivity [51]

In two longitudinal studies, improvement in WHO functional class [48] and a drop in BNP levels [43] were rated as favorable in terms of prognosis. As therapeutic targets, these performance variables are the only ones for which survival-related evidence exists both for absolute values and in follow-up assessments.

7. Treatment of PAH in CHD

7.1. Treatment algorithm

As the general PAH treatment algorithm in the ESC/ERS guidelines appears too unspecific for CHD, an analogous algorithm is proposed which takes the special features of this patient group into consideration (Fig. 2). Included are now general measures, supportive therapy, targeted PAH drug therapy as well as interventional and surgical procedures.

7.2. General measures

The guidelines provide general recommendations on lifestyle, particularly concerning pregnancy, immunization, psychological care, physical activity/physical exercise, behavior on air travel and recommendations for elective surgery in PAH, however, they only contain brief advice on P(A)H-CHD management.

- The recommendations for vaccination in CHD are equivalent to the recommendations in the ESC/ERS guidelines for patients with P(A)H (influenza and pneumococcal vaccination).
- Patients with cyanosis need endocarditis prophylaxis if they are at risk [17].
- Physical exercise can have positive effects in CHD and may even improve prognosis [51–56]. To date however, there are only a few

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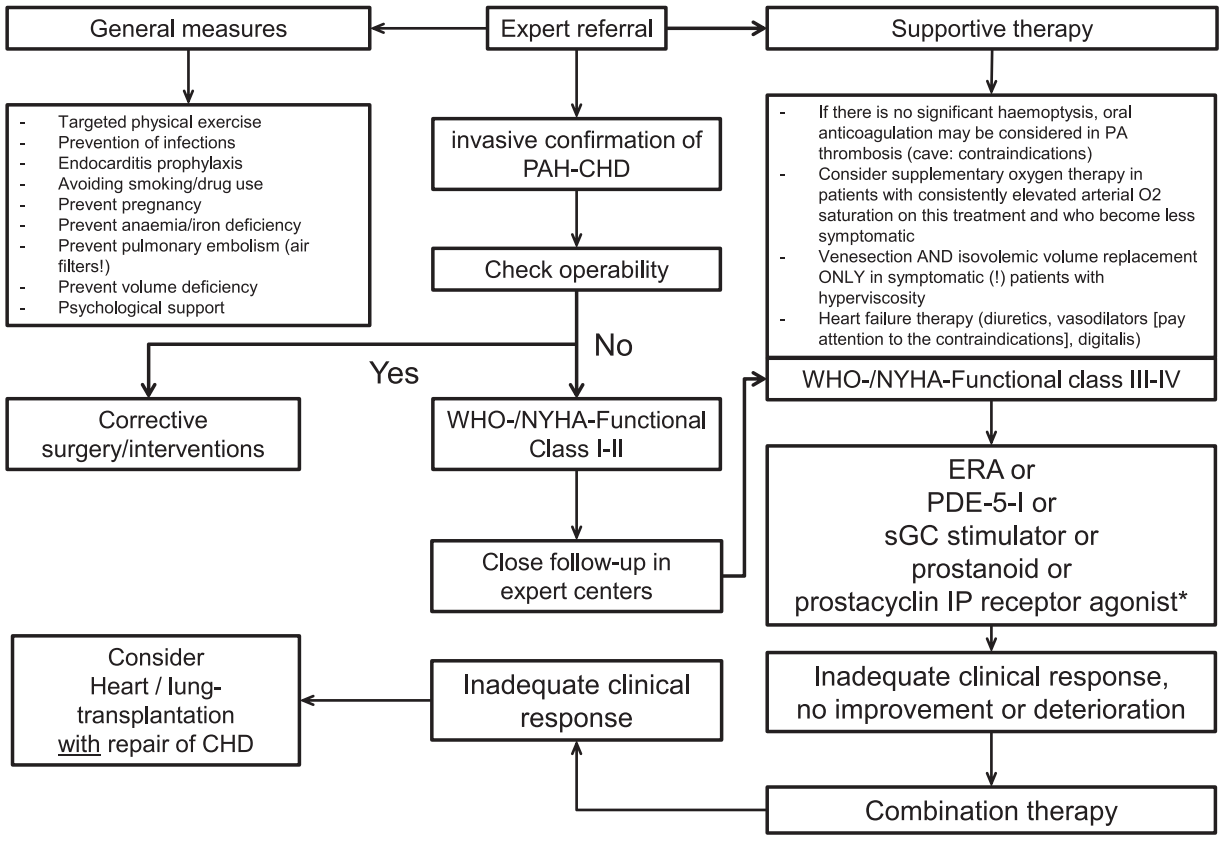

Fig. 2. Therapy algorithm for the diagnosis and treatment of P(A)H-CHD [16]. * Approval status must be considered with pharmacotherapy, because not all substances/drugs are explicitly approved for P(A)H-CHD.

institutions with relevant clinical experience in this field and limited data are available on the methods, intensity and duration of the rehabilitation measures.

- In addition, ACHD with chronic progression of the disease would benefit from psychological care and access to patient organizations.
- On the basis of currently available data, patients with ES do not have to refrain from flying; nor do they need additional O_2-supply during the flight [19,20,57,58].
- Surgery: In patients with ES, even minor non-cardiac surgical procedures are dangerous because these patients are very sensitivity to hemodynamic changes. The increased PVR prevents rapid adjustment to the hemodynamic changes caused by anaesthetics, fluid shifts and/or surgical procedures [59,60]. There is a lack of prospective data on the risk associated with non-cardiac surgery in this patient group. To reduce surgical risk, ES patients should be treated by an expert team during the perioperative period. Patients with ES also have an increased risk of mortality following the acute surgical phase and require a longer period of postoperative monitoring [19,20].

8. Supportive therapy

Beyond the guideline recommendations for supportive therapy, special features must be taken into consideration in patients with P(A)H-CHD:

Heart failure therapy (diuretics, vasodilators, digitalis) should be considered particularly in patients with significant left-to-right shunts and clinical and echocardiographic signs of left ventricular volume overload or in patients with an additional impairment of left ventricular function that potentially contributes to the development/progression of P(A)H.

Diuretics can be used in decompensated right heart failure. In patients with an existing right-to-left shunt and ES, metabolically neutral loop diuretics should be given preferentially. Low-dose hydrochlorothiazide may be added to prevent resistance to loop diuretics. The additional administration of aldosterone antagonists should also be considered. An excessive intravascular volume loss may in turn result in pre-renal acute renal failure. In cyanotic patients with severe erythrocytosis, administration of diuretics may induce hemoconcentration with a further increase in hematocrit and a negative impact on the rheological properties of the blood.

8.1. Anticoagulation

Patients with ES are at increased risk of both bleeding and thrombosis. Hemostatic disorders often exist as a result of changes in platelet function, platelet count and coagulation cascade function [19,61–64]. Oral anticoagulation may be considered in patients without significant hemoptysis in the presence of systemic or peripheral thromboembolism, or pulmonary embolism/thrombosis, particularly when concomitant problems exist such as atrial arrhythmias or artificial valves/conduits. Currently, there are no data indicating that oral anticoagulation has a positive effect on morbidity and mortality in patients with ES. Determining the coagulation parameters is difficult and requires specific skills. For example, the sodium citrate volume in the test tube used for determination must be adjusted to the current hematocrit level [24]. Only scarce data are available currently on the use of direct oral anticoagulants [65].

8.2. O_2 therapy

In a prospective controlled study, nocturnal O_2 therapy had no positive effects on physical resilience, natural disease course and patient

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survival over a follow-up period of 2 years [66]. O_2 therapy may be considered if arterial O_2 saturation rises constantly as patients become less symptomatic as a consequence.

Secondary **erythrocytosis** is of particular importance in ES. Prophylactic or routine phlebotomy to reduce hematocrit or prevent cerebrovascular events is not justified. Depending on O_2 saturation, in patients with ES, even hemoglobin levels above 18 g/dL are adequate. Phlebotomy is indicated only for temporary relief of clinically relevant hyperviscosity in symptomatic secondary erythrocytosis, if volume depletion and iron deficiency have previously been excluded. When performing this procedure, adequate volume replacement has to be ensured.

Relative **iron deficiency anemia** frequently remains undetected in cyanotic patients and concomitant iron deficiency is often overlooked. It is always necessary to check for iron deficiency, which requires complete screening (including ferritin, transferrin, transferrin saturation, soluble transferrin receptor). The determination of peripheral Red Blood Cell Indices alone (MCV, MCH, MCHC) is insufficient. When compensating for iron deficiency, it is important to consider that an excessive increase in hematocrit and hyperviscosity may occur even with low-dose iron supplementation.

The use of **vasodilatory drugs** (e.g. calcium channel blockers [CCBs], angiotensin-converting enzyme inhibitors, angiotensin receptor 1 blockers) in patients with an existing right-to-left shunt can worsen cyanosis and hemodynamics.

9. Targeted pharmacotherapy

The recommendations of the ESC/ERS guidelines on pharmacotherapy in PAH-CHD are focused on patients with ES. The main reason for this may be the currently available evidence, but this also implies that the recommendations do not fully acknowledge the breadth, heterogeneity and complexity of CHD patients with associated PAH.

9.1. Eisenmenger syndrome

Oral drugs are generally preferred in clinical practice for single-drug therapy of PAH in ES. In Germany, endothelin receptor antagonists (ERAs) currently dominate [67]. For bosentan, efficacy in terms of symptomatic improvement in patients with ES (WHO-FC III) has been demonstrated in a randomized, placebo-controlled study (BREATHE-5) [68]. There are no equivalent robust data based on randomized controlled trials (RCTs) for other compounds. Experts consider, however, that other ERAs or phosphodiesterase-5 (PDE-5) inhibitors can be used instead of bosentan, when bosentan is contraindicated (e.g. in patients with liver function disorders). Retrospective observational studies also point to a potential improvement in the prognosis of patients with ES when treated with targeted drugs [67,69,70]. Overall, there is evidence of symptomatic improvement with drug therapy for PAH in patients with ES categorized as WHO-FC III, both in the short term based on RCT data and in the mid- to long-term under "real-world" conditions [71]. Formally, there is no evidence for patients in WHO-FC II, although in clinical practice a precise determination of WHO-FC is problematic because of frequently fluctuating symptoms.

Limited data are available on **combination therapy** in ES [72–74]. A RCT on the possible benefit of dual therapy with sildenafil added to bosentan in ES showed no significant symptomatic or functional improvement. However, the patients in this study were stable with no obvious indication for escalation of therapy [73]. A non-randomized, prospective study in a limited number of patients, but including a structured assessment, including hemodynamics, demonstrated functional and hemodynamic improvement after therapy escalation in patients who deteriorated clinically on oral monotherapy [72]. This approach corresponds to clinical practice where sequential combination therapy is the rule when deterioration in symptoms occurs or predefined treatment goals are not met (target-oriented therapy). Subcutaneous or intravenous (i.v.) therapies should be reserved for selected patients with advanced, treatment-refractory symptoms on oral combination therapy. Possible side effects should be noted (paradoxical embolism, apoplectic insults, septic complications). The available data on inhaled prostanoid therapy in ES are limited [75] and therapy is restricted by the short half-life of the substance and short administration intervals.

9.2. Shunt defects

Besides patients with ES, CHD patients with PAH and shunt defects, particularly those who have undergone previous shunt closure, present a therapeutic dilemma. These patients show a greatly limited prognosis [74,76]. A proactive approach therefore appears appropriate, and patients with shunt closure (including those with simple defects) need life-long cardiologic follow-up with regular PH screening, even when they currently do not have apparent PH. Drug treatment should be guided by the (more aggressive) principles of drug treatment in IPAH. If CCBs are considered, they should only be used after careful consideration of contraindications. Besides being managed with established ERAs and PDE-5 inhibitors, CHD patients with PAH and previous shunt closure of simple heart defects (ASD, VSD, ductus arteriosus) have also been included in RCTs of novel compounds. In PAH, positive effects have been demonstrated with the ERA Macitentan (in the SERAPHIN study) and the oral prostacyclin receptor agonist Selexipag (in the GRIPHON study) for a combined morbidity/mortality endpoint [77,78]. These studies also included patients with CHD and PAH after simple shunt defect closure. Both compounds are certified for this indication.

A subgroup analysis of the PATENT-1 study showed in CHD patients treated with the soluble guanylate cyclase stimulator riociguat an improvement in 6MWT and hemodynamics [79]. Authorisation is being sought for this indication and can be expected shortly. Based on the poorer prognosis for these patients compared with other PAH-CHD patients, a proactive escalation of therapy should be considered. In cases where clinical symptoms are severe, this may also include parenteral prostanoid therapy.

In patients with systemic-to-pulmonary shunts without cyanosis, who are candidates for defect closure, the benefit of a specific PAH therapy should be considered critically.

Current studies in patients with Fontan physiology indicate that treatment with the ERAs bosentan and ambrisentan in particular can lead to improved exercise capacity [14,80]. If symptoms are suspected of pulmonary vascular origin, Fontan patients should be evaluated in relation to the potential benefit of an ERA therapy (although their use is still off-label at present).

10. Intensive care procedures and interventional treatment

The principles of intensive care have been included for the first time in the ESC/ERS guidelines. The prognosis and general principles of treatment for patients with late corrected CHD and with IPAH are similar. PAH patients in right heart failure and/or those undergoing a surgical procedure require intensive care treatment. Therapy includes treatment of trigger factors (anemia, arrhythmia, infection, comorbidities), optimization of right ventricular preload (diuretics) and afterload (targeted PAH medication), improvement of cardiac output by inotropic agents and maintenance of systemic blood pressure (vasopressors).

Further measures include veno-arterial extracorporeal membrane oxygenation (VA-ECMO, ECLS), balloon atrial septostomy (BAS), surgical creation of Pott's anastomosis or lung/heart-lung transplantation. In cases of previous surgery to the atrial septum (patch material), BAS can be technically more difficult or impossible. The interventional creation of a Pott's anastomosis must be considered to be an experimental procedure at present [81].

In ES, a large number of comorbidities complicate anaesthesia and intensive care management. It is essential to comply with hemoglobin target values adapted to the O_2 saturation. Mortality is high even for

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minor elective surgical procedures and/or anaesthesia (4–7%) [59,82]. Because mechanical circulatory support is, as a rule, excluded in ES, an escalation of treatment (e.g. invasive ventilation, renal replacement therapy) should be carefully considered in the context of the overall prognosis. Veno-arterial ECMO can be used in individual cases of right ventricular failure and/or pulmonary failure as a bridging procedure until recovery or transplantation. In individual patients who have ES due to an ASD, temporary mechanical support with veno-venous ECMO has been described [83]. Because of the multimorbidity of patients with ES, ECLS/ECMO therapy is contraindicated apart from a few exceptions.

11. Transplantation

In patients with ES due to a simple heart defect, it may be possible to perform lung transplantation and correct the CHD at the same operation. Short- and long-term prognosis after transplantation in ES patients is comparable with that of other etiologies. Because of the comparatively slow disease progression in ES, the optimal time for transplant listing is difficult to determine. It is worth discussing the matter early with a transplantation center. Previous chest surgery (in particular lateral thoracotomy), impaired secondary organ function and multiple aortopulmonary collateral vessels worsen prognosis and can also constitute a contraindication to transplantation. Combined heart, lung and kidney or liver transplantation have been performed in individual cases.

12. Complications in PH-CHD

In the contemporary literature hemoptysis does not appear to be a leading cause of death [67]. According to the applicable guidelines, a chest radiograph followed by a chest CT scan if necessary, should be performed when hemoptysis occurs. Existing anticoagulation or antiplatelet therapy should be temporarily discontinued [17]. If necessary, antitussive agents should be administered and anemia treated by blood replacement therapy. In therapy-refractory cases, interventional selective bronchial arterial embolization may also be necessary.

Patients with cyanosis or prosthetic material need endocarditis prophylaxis during procedures involving risk [84].

In case of fever with an unclear origin or oligosymptomatic course (weight loss, reduced performance etc.), endocarditis and cerebral abscesses should be excluded [24].

13. Pregnancy in PH-CHD

Patients with PAH-CHD, and with ES in particular, should be advised against pregnancy. Because systemic vascular resistance drops during pregnancy, the right-to-left shunt increases and arterial O_2 saturation decreases. Women in WHO-FC III or IV are at particularly high risk. With ES, maternal mortality is given as 30–60% and is associated timely and causally with syncope, thromboembolism, hypovolemia, hemoptysis or preeclampsia [85]. Most fatalities occur during delivery or in the first weeks afterwards [85]. Furthermore, the number of abortive and small-for-date births are high. For contraception see “General and supportive therapy of PAH”. It should be noted in patients with ES that the insertion of intrauterine contraceptive coils may lead to vasovagal reactions, which can be life-threatening in these patients. The ERA bosentan reduces the efficacy of hormonal contraceptives by enzymatic induction.

Although interruption of pregnancy is not free of risk, it is indicated because of the substantial maternal risk. If interruption of pregnancy is refused during an existing pregnancy, interdisciplinary care by experienced cardiologists, gynaecologists/obstetricians, anaesthetists, intensive care physicians and neonatologists is necessary. Taking the risk spectrum and possible contraindications into account, thrombosis prophylaxis can be performed with vitamin K antagonists (VKA) or with low-molecular weight heparin. Administration of non-VKA anticoagulants is not recommended [86]. PAH therapy must be optimized appropriately for the prevailing circumstances. ERAs and riociguat are contraindicated, however. In contrast, treatment with PDE-5 inhibitors is possible, the most extensive experience having been acquired with sildenafil. Combination therapy with parenteral or inhaled prostanoids is possible. Intravenous epoprostenol is recommended in patients in WHO-FC IV or those with severe right heart failure [86].

Delivery should take place at a center of maximal care where ECMO and transplantation procedures are available. In principle, both spontaneous delivery and caesarean section are possible. In the case of vaginal delivery, the expulsion phase should be kept as short as possible by assisted vaginal delivery (ventouse cap, forceps). Generally, arterial hypotension should be treated immediately, using parenteral volume replacement and vasopressor agents if necessary. Treatment with intravenous prostanoids may be considered during delivery [86].

13.1. Pulmonary hypertension in left heart disease (group 2)

Group 2 of the PH classification explicitly includes congenital causes in subgroups 2.4 and 2.5. All patients with suspected PH and left heart disease (LHD) caused by a congenital defect should be referred to a specialist center.

13.2. Groups 2.1 and 2.2

A high proportion of patients with CHD have diastolic or systolic LV dysfunction. Heart failure with preserved ejection fraction (HFpEF) may occur in Shone's Complex, restrictive right ventricle in pulmonary atresia with VSD, and large aortopulmonary collaterals.

13.3. Group 2.4

LV dysfunction may be caused by congenital inflow obstruction of the LV (mitral valve stenosis), LV outflow tract stenosis (e.g. subvalvular, valvular, or supravalvular aortic stenoses, Shone's Complex) or congenital cardiomyopathies (e.g. HOCM).

13.4. Group 2.5

This includes congenital or post-operative pulmonary venous stenosis (e.g. cor triatriatum sinistrum, previous pulmonary vein diversion, and pulmonary venous baffle stenosis after atrial switch).

PH due to left-heart disease (PH-LHD) can also occur in univentricular hearts with Fontan circulation, particularly if there is diastolic dysfunction and AV valve insufficiency.

Aortic disease can also underlie PH-LHD.

14. Recommendations on the closure of a left-to-right shunt in PH-CHD

According to the guidelines, defect closure can be considered in patients with systemic-to-pulmonary shunt defects with predominant left-to-right shunt [8]. The criteria for shunt closure are based primarily on the calculation of PVR, especially the to the body surface indexed PVR (PVRI, PVR Wood units × m^2). Other criteria are the type of heart defect, patient age as well as PVR:SVR and Qp:Qs ratios.

Invasive diagnosis is indicated to identify patients who are suitable for defect closure. There are no prospective data on the benefit of vasoreactivity testing, test occlusions or lung biopsies to clarify the question of whether defect closure can be tolerated hemodynamically. With regard to hemodynamic parameters, different criteria apply to

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children and adults with CHD. In children, the following criteria are used to determine operability (all must apply) [9]:

- Qp:Qs > 1.5:1
- Reduction of PVRI by >20% to <6 Wood units × m^2 during vasoreactivity testing
- PVRI/SVRI <0.3

No valid data exist for ACHD. The recommendation on operability for patients >17 years old is therefore more conservatively based on a PVRI of <4 Wood units × m^2. There are also no data on whether the indication for closure can be made more generous in younger adults (in the 2nd decade of life). An algorithm has been proposed for ACHD as an aid to decision-making (Fig. 3). Furthermore, operability depends on the type of heart defect, the duration of the course of the disease and probably on ethnic differences as well. In patients who show vasoreactivity during testing and who reach the grey area of 4–8 Wood units × m^2, specific PAH therapy may be considered in order to reassess after six months whether the range of operability has been reached [9]. Diastolic pulmonary pressure and TPG should also be taken into account during vasoreactivity testing. A "treat-to-close" concept and/or fenestrated closure of the defect may be considered in younger patients [87]. Finally, it has not been clarified whether shunt closure is associated with a risk of transforming the disease into a form of PAH, resembling IPAH, with a poorer prognosis and thus causing long-term harm [74].

When a shunt defect is present, invasive diagnostics including hemodynamic assessment is useful. A combination of pre- and post-capillary PH may be present, particularly from the 4th decade of life onwards. Therefore, in adults with chronic PH, decision making can be difficult regarding conservative treatment prior to surgery. Defect closure is contraindicated in patients with ES and is useless (as well as potentially dangerous) in patients with small/coincidental defects.

15. Recommendations on PAH in univentricular hearts

In patients with Fontan physiology, determination of TPG and PVRI are crucial for the assessment of hemodynamics. A TPG ≤6 mmHg with PVRI ≤3 Wood units × m^2 is considered to be the upper limit of favorable hemodynamics. Currently there is no evidence to demonstrate whether treatment with pulmonary vasodilators (PDE-5 inhibitors, ERAs) is useful in patients who exceed these limits. Sildenafil, ambrisentan and bosentan have been shown to exert a favorable effect on symptomatic Fontan patients. Exercise tolerance and O_2 saturation have improved on Bosentan and Ambrisentan. Maximum O_2 uptake (VO_2max) and lung perfusion were improved on sildenafil. Another randomized crossover study showed that sildenafil improves exercise tolerance and ventilatory efficiency in Fontan patients [14,15,80,88,89].

16. Importance of qualified ACHD centers

According to ACHD-quality guidelines, existing in Germany since 2004, as of 04/2018 there are 17 certified national ACHD centers, 10 certified specialist departments and/or practices and about 300 certified ACHD cardiologists. According to the ESC guidelines, national ACHD centers are obliged to undertake clinical research, participate in clinical studies and registries and to ensure the training and continuing education of ACHD physicians and aspiring physicians. Certified ACHD specialist departments and practices must take part in the training and continuing education programs offered at the national ACHD centers. In contrast to the proposed minimum numbers for the treatment of PH/PAH patients in the ESC/ERS guidelines, the numbers for CHD patients have not yet been firmly established. A request has been made at the federal and regional medical associations to incorporate the additional title "ACHD cardiologist" in the Further Medical Education.

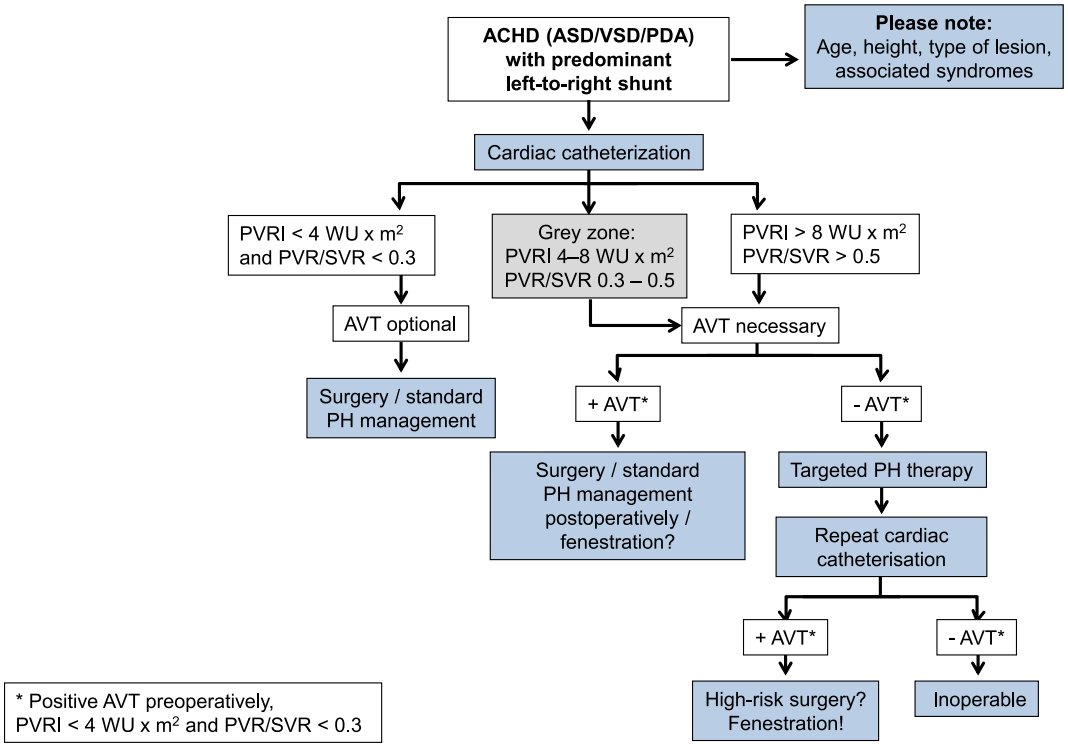

Fig. 3. Algorithm for the repair of congenital heart defects with prevalent systemico-pulmonary shunts in adulthood (ACHD). Evaluation of the option for closure of a predominantly left-to-right shunt depending on pulmonary vascular resistance [9]. AVT = acute vasoreactivity testing, PVRI = pulmonary vascular resistance index, PVR/SVR = ratio of pulmonary/systemic vascular resistance.

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Conflicts of interest/author declarations

HK: received support for research and/or conference participation and/or fees for lectures and/or consulting from Actelion, Pfizer, Bayer.

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KB: none reported.

AE: none reported.

MG: received support for research and/or conference participation and/or fees for lectures and/or consulting from Actelion, Bayer-Schering.

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FdH: none reported.

MH: received support for research and/or conference participation and/or fees for lectures and/or consulting from Actelion, Bayer.

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OM: none reported.

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