Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-127z Riociguat

Stand: Mai 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Riociguat zur Behandlung der pulmonal arteriellen Hypertonie (PAH), ≥ 50kg bis <18 Jahre	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet".*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Als nicht-medikamentöse Behandlungen kommen grundsätzlich infrage: • Lungen- oder Herz-Lungen-Transplantation • physiotherapeutische Maßnahmen i.S. der Heilmittel-RL (Physikalische Therapie z.B. Krankengymnastik, Übungsbehandlung, Atemtherapie)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	keine
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu prüfendes Arzneimittel:	
Riociguat C02KX05 Adempas®	(bereits zugelassen: "Adempas, als Monotherapie oder in Kombination mit Endothelin-Rezeptorantagonisten, ist indiziert für die Behandlung erwachsener Patienten mit pulmonal arterieller Hypertonie (PAH) der WHO-Funktionsklassen (FK) II bis III zur Verbesserung der körperlichen Leistungsfähigkeit. Die Wirksamkeit wurde in einer PAH-Population einschließlich Ätiologien einer idiopathischen oder hereditären PAH oder einer mit einer Bindegewebserkrankung assoziierten PAH nachgewiesen") <u>Anwendungsgebiet laut Positive Opinion:</u> Adempas is indicated for the treatment of PAH in paediatric patients aged less than 18 years of age and body weight ≥ 50 kg with WHO Functional Class (FC) II to III in combination with endothelin receptor antagonists"
Endothelin-Rezeptor-Antagonisten (ERA):	
Bosentan C02KX01 Bosentan Heumann®	Behandlung der pulmonal arteriellen Hypertonie (PAH) zur Verbesserung der körperlichen Belastbarkeit und Symptomen bei Patienten mit der funktionellen WHO-/NYHA-Klasse III. Die Wirksamkeit wurde nachgewiesen bei: – Primärer (idiopathischer und erblicher) pulmonal arterieller Hypertonie – Sekundärer pulmonal arterieller Hypertonie in Assoziation mit Sklerodermie ohne signifikante interstitielle Lungenerkrankung – Pulmonal arterieller Hypertonie in Assoziation mit kongenitalen Herzfehlern und Eisenmenger-Physiologie. Verbesserungen des Krankheitsbildes wurden ebenso bei Patienten mit PAH der funktionellen WHO-Funktionsklasse II gezeigt. (FI Bosentan Heumann® Mai 2020)
Ambrisentan C02KX02 Volibris®	<u>Erwachsene</u> Volibris ist zur Behandlung von erwachsenen Patienten mit pulmonal arterieller Hypertonie (PAH) der WHO-Funktionsklassen II und III indiziert, einschließlich der Anwendung in der Kombinationstherapie (siehe Abschnitt 5.1). Die Wirksamkeit wurde bei idiopathischer PAH (IPAH) und PAH assoziiert mit einer Bindegewebserkrankung nachgewiesen. <u>Kinder und Jugendliche</u> Volibris ist zur Behandlung von Kindern und Jugendlichen (im Alter von 8 bis unter 18 Jahren) mit PAH der WHO-Funktionsklassen II und III indiziert, einschließlich der Anwendung in der Kombinationstherapie. Die Wirksamkeit wurde bei IPAH, familiärer und korrigierter kongenitaler PAH und PAH assoziiert mit einer Bindegewebserkrankung nachgewiesen (siehe Abschnitt 5.1).

Phosphodiesterase-Typ-5 (PDE5)-Inhibitoren:	
Sildenafil G04BE03 Revatio®	Erwachsene Behandlung von erwachsenen Patienten mit pulmonaler arterieller Hypertonie (PAH) der WHO-Funktionsklassen II und III zur Verbesserung der körperlichen Leistungsfähigkeit. Die Wirksamkeit konnte nachgewiesen werden bei primärer PAH und bei pulmonaler Hypertonie in Verbindung mit einer Bindegewebskrankheit. Kinder und Jugendliche Behandlung von pädiatrischen Patienten im Alter von 1 bis 17 Jahren mit pulmonaler arterieller Hypertonie. Die Wirksamkeit konnte anhand der Verbesserung der körperlichen Belastbarkeit oder der pulmonalen Hämodynamik nachgewiesen werden bei primärer pulmonaler arterieller Hypertonie und bei pulmonaler Hypertonie in Verbindung mit angeborenen Herzerkrankungen (FI Revatio® Juni 2020)
Tadalafil G04BE08 Adcirca®	Erwachsene ADCIRCA ist angezeigt zur Behandlung von Erwachsenen mit pulmonaler arterieller Hypertonie (PAH) der WHO-Funktionsklasse II und III zur Verbesserung der körperlichen Leistungsfähigkeit (siehe Abschnitt5.1). Die Wirksamkeit wurde gezeigt bei idiopathischer PAH (IPAH) und bei PAH aufgrund einer Kollagenose. Kinder und Jugendliche ADCIRCA ist angezeigt zur Behandlung von Kindern ab 2 Jahren mit pulmonaler arterieller Hypertonie (PAH) der WHO-Funktionsklasse II und III.
Prostazyklin-Analoga:	
Treprostinil B01AC21 Remodulin®	Behandlung von idiopathischer oder familiärer pulmonal-arterieller Hypertonie (PAH) zur Verbesserung der Belastbarkeit und zur Milderung der Krankheitssymptome bei Patienten mit New York Heart Association(NYHA)-Funktionsklasse III. (FI Remodulin® Januar 2019)
Epoprostenol B01AC09 Epoprostenol-Rotexmedica®	Epoprostenol-Rotexmedica® ist indiziert zur Behandlung pulmonaler arterielle Hypertonie (PAH) (idiopathische oder vererbbare PAH und mit Bindegewebserkrankungen assoziierte PAH) bei Patienten mit Symptomen der WHO Funktionsklasse III – IV zur Verbesserung der körperlichen Belastungsfähigkeit (siehe Abschnitt 5.1). (FI Epoprostenol-Rotexmedica® März 2018)

Quellen: AMIce-Datenbank, Fachinformationen (Stand Mai 2023)

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-388 (Riociguat)

Auftrag von:	Abteilung Arzneimittel
Bearbeitet von:	Abteilung Fachberatung Medizin
Datum:	27. Januar 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

6MWD	6-Minute-Gehstrecke
AAD	Adaptive Aerosol Delivery
AEPC	Association for European Paediatric and Congenital Cardiology
AHA	American Heart Association
ALT	Alanin-Aminotransferase
AS	Atriale Septostomie
ASA	Acetylsalicylsäure
ASD	Atriumseptumdefekt
AST	Aspartat-Aminotransferase
ATS	American Thoracic Society
AVSD	Atrioventrikulärer Septumdefekt
AVT	Testung der akuten pulmonal-vaskulären Gefäßreagibilität
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CCB	Kalziumkanalblocker
CI	Cardiac Index
CLD	Chronische Lungenerkrankung
CHD	Congenital Heart Disease
COR	Class of Recommendation
CPET	Cardiopulmonary Exercise Testing
CTEPH	Chronisch thromboembolische pulmonale Hypertonie
d	Tag
DAO	Descending Aorta
ECRI	ECRI Guidelines Trust
EMA	Europäische Arzneimittel-Agentur
EPPVDN	European Pediatric Pulmonary Vascular Disease Network
ERA	Endothelin-Rezeptor-Antagonisten
ES	Eisenmenger-Syndrom
ESC	European Society of Cardiology
ESPR	European Society for Pediatric Research
ET	Endothelin
FC	Funktionsklasse
FDA	U.S. Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss
GC	Guanylatcyclase

GIN	Guidelines International Network
GoR	Grade of Recommendations
h	Stunde
HFpEF	Herzinsuffizienz mit erhaltener Ejektionsfraktion
HHT	Hereditäre hämorrhagische Teleangiektasie
HPAH	Hereditäre pulmonal arterielle Hpyertonie
ICU	Intensive Care Unit
iNO	Inhalatives Stickstoffmonoxid
IPAH	Idiopathische pulmonal arterielle Hypertonie
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISHLT	International Society of Heart and Lung Transplantation
IV	intravenös
kg	Kilogramm
LFT	Liver Function Test
LoE	Level of Evidence
LPA	Linke Pulmonalarterie
LV	Linker Ventrikel
LVEF	Linksventrikuläre Ejektionsfraktion
mg	Milligramm
mm Hg	Millimeter Quecksilbersäule
mPAP	mittlerer pulmonal-arterieller Druck
MR	Mineralokortikoidrezeptor
NICE	National Institute for Health and Care Excellence
OP	Operation
PAH	Pulmonal arterielle Hypertonie
PAP	Pulmonal-arterieller Druck
PCA	Prostazyklin-Analoga
PCH	Pulmonale kapilläre Hämangiomatose
PDA	Persistierender Ductus Arteriosus
PDE	Phosphodiesterase
PDE-5i	Phosphodiesterase-5-Inhibitoren
PGI2	Prostazyklin
PH	Pulmonale Hypertonie
PHVD	Pulmonal-hypertensive Gefäßerkrankung
PO	per os

PPHN	Persistierende pulmonale Hypertonie bei Neugeborenen
PPHTN	Portopulmonale Hypertonie
PVD	Pulmonale Gefäßerkrankung
PVOD	Pulmonale Venenverschlusskrankheit
PVR	Pulmonal-vaskulärer Widerstand
PVRi	Index des pulmonal-vaskulären Widerstands
Qp	Pulmonary Flow
Qs	Systemic Flow
RA	Rechtes Atrium
RCT	Randomisierte kontrollierte Studie
RV	Rechter Ventrikel
SC	subkutan
SIGN	Scottish Intercollegiate Guidelines Network
SVR	Systemischer Gefäßwiderstand
TRIP	Turn Research into Practice Database
VSD	Ventrikelseptumdefekt
WHO	World Health Organization
WSPH	World Symposium on Pulmonary Hypertension
WU	Wood Unit

1 Indikation

Behandlung der pulmonalen arteriellen Hypertonie (PAH) bei Kindern und Jugendlichen im Alter von 6 bis unter 18 Jahren.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *pulmonale arterielle Hypertonie (PAH)* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 18.09.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 719 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 3 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA-Beschlüsse/IQWiG-Berichte

Es wurden keine relevanten G-BA-Beschlüsse/IQWiG-Berichte identifiziert.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Es wurden keine relevanten systematischen Reviews identifiziert.

3.4 Leitlinien

Hansmann G et al., 2019 [3].

The European Pediatric Pulmonary Vascular Disease Network (EPPVDN)

2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT

Zielsetzungen

1. To briefly discuss the most recent changes to the classification and definition of PH and its subtypes […];
2. To outline clinical study results and their limitations;
3. To provide graded, evidence-based, and expert-based recommendations for optimal diagnosis and treatment of infants, children, and young adults with PH (including CHD/Eisenmenger and single ventricle physiology/Fontan), according to the grading system provided by the American Heart Association and ESC;
4. To address features of the disease and its management that are specific to pediatric PH;
5. To define the multiple gaps in our knowledge on pediatric PH; and
6. To briefly discuss emerging PH therapies (safety and efficacy).

Methodik

Grundlage der Leitlinie

- Multidisziplinäre Leitliniengruppe, keine Einbeziehung von Patientenvertretungen;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematik der Suche dargelegt, Angaben zur systematischen Auswahl und Bewertung der Evidenz fehlen;
- Konsensfindung erwähnt, aber nicht detailliert beschrieben, externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Weder Gültigkeit noch Verfahren zur Überwachung und Aktualisierung beschrieben.

Recherche/Suchzeitraum:

Searches of the PubMed/MEDLINE bibliographic database were conducted for the time period 1990 – 2018. […] The primary focus of this manuscript is on group 1 PH, according to the WSPH in Nice, 2018.

LoE

Tabelle 1: LOE as currently proposed by the ESC and the AHA

Level of evidence	
Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

GoR

Tabelle 2: COR as currently proposed by the ESC and the AHA

Class of recommendation	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended Is indicated
Class II	Conflicting evidence and/or a divergence opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well, established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is note useful/effective, and in some cases may be harmful.	Is not recommended.

Sonstige methodische Hinweise

Both a new definition and an expanded classification of PH were developed at the World Symposium on PH (WSPH, Nice, 2018)[11,12] […]. (⇨ Anhang Tabelle 1)

11. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53(1):1801913.
12. Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J 2019;53:1801916.

Empfehlungen

Recommendations on the diagnostics, monitoring, and outpatient care in children with PH

Recommendations	COR	LOE
Children with suspected or confirmed PH should be evaluated and treated in specialized pediatric centers.	I	C
In children with end-stage PH, timely referral to a transplant center is beneficial, if lung transplantation represents an option for the individual patient. (S3-21)	I	C
Female adolescents with PH should undergo timely counseling regarding the significant maternal and fetal pregnancy risks and options for secure contraception. (S3-23, S3-24)	I	B
Children with PH in the higher-risk category should not participate in competitive sports. Participation in light exercise is beneficial but should only be undertaken after medial consultation and detailed serial assessment including exercise testing.	I	C
Children with mild to moderate PH should engage in regular light-to-moderate aerobic activity. They should be allowed to self-limit their activities as required but avoid strenuous and isometric exercise, dehydration, and exercise at moderate (1500-2500 meters) or high (> 2500 meters) altitude.	I	C

Referenzen

S3-21 Sweet SC. Pediatric lung transplantation. Respir Care 2017;62:776-798.

S3-23 Bedarf E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J 2009;30:256-265.

S3-24 Brida M, Gatzoulis MA. Pulmonary arterial hypertension in adult congenital heart disease. Heart 2018;104:1568-1574.

Recommendations on the management of PH in children and young adults with CHD (PAH-CHD, PHVD-CHD) (⇨ Anhang Abbildung 1)

Recommendations	COR	LOE
All patients with relevant PAH-CHD should receive and benefit from tertiary care. (S8-1, S8-2)	I	C
Surgery or interventional closure for CHD with simple post-tricuspid shunts (VSD, PDA) and significant left-to-right shunting should be ideally be performed within the first 6 months of life. (S8-12, S8-13)	I	C
Interventional or surgical closure of simple pre-tricuspid shunts (ASD, sinus venosus defect) and significant left-to-right shunting (Qp:QS > 1.5) is semi-elective, requires individual decision-making, and is usually pursued at pre-school or school age (5 years and older). (S8-12, S8-13)	IIa	C
Patients with moderate to large pre- or post-tricuspid shunt lesions and evidence of low-volume left-to-right shunting (i.e., PH out of proportion to the magnitude of cardiovascular shunting), must be considered to have PVD (elevated PVR), and thus should undergo right and left heart catheterization before any intervention/surgery. (S8-3, S8-12, S8-13)	I	C
Children with PAH-CHD and significant left-to-right shunting, congestive heart failure (pulmonary congestion), failure to thrive, and SpO_2 > 95% (lower extremities) can be considered operable for shunt closure in infancy; however, peri-operative PH crisis may occur. (S8-13)	IIa	C
Children with CHD and simple shunt defects (VSD, PDA) beyond the typical timing of surgery (> 6 months old), or those not fulfilling the above criteria (heart failure/pulmonary congestion, failure to thrive, and SpO_2 > 95% at lower extremities), that is, particularly those with shunt(s) and cyanosis, should undergo comprehensive right and left heart catheterization before any intervention/surgery. (S8-13, S8-15, S8-16)	I	C
Children with PAH-CHD, with or without significant left-to-right shunting and uncertainties regarding abnormalities in PVR and/or ventricular compliance, are recommended to undergo comprehensive right and left heart catheterization regardless of the patient's age […]. (S8-1, S8-13 – S8-16)	I	C
Children with PVRi < 6 WU x m² and a PVR/SVR ratio < 0.3, in the absence of additional risk factors, are eligible for standard management/ surgical shunt closure/percutaneous interventional device closure. (S8-13)	I	C
Children with PVRi ≥ 6 WU x m² and a PVR/SVR ratio ≥ 0.3 should be evaluated by AVT. (S8-13, S8-17)	I	C
Individual patient assessment in tertiary pediatric PH centers is particularly needed when PVRi is between 6 and 8 WU x m² (gray zone). (S8-13)	I	C
A treat-to-close (treat-and-repair) approach (defined as PAH-targeted pharmacotherapy with 1-2 medications followed by partial or complete defect closure) might be considered in highly selected patients with pre- or post-tricuspid shunt (ASD, VSD, PDA) from the gray zone (PVRi 6-8 x m²), and potentially even in children with PAH with PVRi > 8 WU x m², with the goal to decrease PVRi < 8 WU x m². After (complete or partial) closure, such patients must stay under long-term tertiary follow-up and be reassessed by cardiac catheterization, in addition to non-invasive measures, to assess for PVR after shunt closure. (S8-13, S8-18)	IIb	C
A partial defect closure (fenestrated patch or device) may be considered in selected patients with PAH-CHD from the gray zone (PVRi 6-8 WU x m²), with or without preceding treat-to-close (treat-and-repair) approach. The impact of PVR numbers	IIb	C

alone for clinical decision making differs between patients at different ages (e.g., infants with VSD vs young adults with ASD). (S8-18 – S8-20)		
Alternatively, PA banding may be considered in selected patients with PAH-CHD with a large post-tricuspid shunt […] as an alternative to partial defect closure, especially when there is complex cardiac anatomy (e.g., straddling AV-valve) in infancy or significant comorbidity (e.g., genetic syndrome).	IIb	C
When a high-risk patient from the gray zone (PVRi 6-8 WU x m²) with an intracardiac shunt (AVSD), and additional small PDA undergoes complete closure of the intracardiac defect, it may be considered to leave the PDA open for optional future RV-decompressing interventions (PDA balloon dilation/stenting). (S8-18)	IIb	C
A cardiovascular shunt defect (ASD, VSD, PDA) generally must not be closed when PVRi > 8 WU x m² in children (PVR > 4.6 WU in adults). (S8-13, S8-21, S8-22)	III harm	C
Patients with Eisenmenger syndrome are usually inoperable irrespective of age with the exception of transplantation. Targeted PAH pharmacotherapy as single drug (ERA or PDE-5i) or combination therapy (sequential or upfront) is safe and can be offered to all patients with established Eisenmenger syndrome, aiming for best possible functional class. If monotherapy is chosen, the currently available data suggests the use of bosentan (ERA) as first-line therapy (COR B for adolescents and young adults). (S8-21 – S8-23, S8-27 – S8-31)	IIa	B
Patients with Eisenmenger syndrome should be routinely screened for iron deficiency and be given supplementary iron (per os, IV) if needed. (S8-23 – S8-34)	I	C
In patients with Eisenmenger syndrome, supplemental oxygen may be considered to reduce symptoms, after careful examination (when PaO_2 < 60 mm Hg). (S8-18, S8-35, S8-36)	IIb	C
In patients with Eisenmenger syndrome and neurological symptoms (minor stroke, stroke), phlebotomy may be considered in severe hyperviscosity syndrome (hematocrit ≥ 70%). (S8-18, S8-24, S8-25) However, iron deficiency from frequent phlebotomies must be avoided. (S8-24)	IIa	C
Phlebotomy should be limited to relieving hyperviscosity symptoms in patients with compensated erythrocytosis. Phlebotomy should not be used to maintain the hematocrit at an arbitrary threshold.	III harm	C
In patients with Eisenmenger syndrome, anti-coagulation may be considered on an individual basis, balancing the risks of thrombosis vs bleeding. Usually only in cases of documented thrombosis, embolism, or atrial fibrillation/atrial flutter is oral-coagulation initiated in this age group. (S8-18, S8-29, S8-30, S8-37, S8-38)	IIb	C

Referenzen

S8-1 Hansmann G. Pulmonary hypertension in infants, children, and young adults. J Am Coll Cardiol 2017;69:2551-2569.

S8-2 Frank BS, Ivy DD. Diagnosis, evaluation and treatment of pulmonary arterial hypertension in children. Children (Basel) 2018;5(4): 44.

S8-3 Koestenberger M, Apitz C, Abdul-Khaliq H, Hansmann G. Transthoracic echocardiography for the evaluation of children and adolescents with suspected or confirmed pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016;102(suppl 2):ii14-22.

S8-12 Lopes AA, Barst RJ, Haworth SG, Rabinovitch M, Al Dabbagh M, Del Cerro MJ, et al. Repair of congenital heart disease with associated pulmonary hypertension in children: what are the minimal investigative procedures? Consensus statement from the Congenital Heart Disease and Paediatric Task Forces, Pulmonary Vascular Research Institute (PVRI). Pulm Circ 2014;4:330-341.

S8-13 Kozlik-Feldmann R, Hansmann G, Bonnet D, Schranz D, Apitz C, Michel-Behnke I. Pulmonary hypertension in children and adolescents with congenital heart disease (PAH-CHD, PPHVD-CHD). Expert consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension – The European Pediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016;102:42-48.

S8-15 Rosenzweig EB, Barst RJ. Congenital heart disease and pulmonary hypertension: pharmacology and feasibility of late surgery. Prog Cardiovasc Dis 2012;55:128-133.

S8-16 Latus H, Wagner I, Ostermayer S, Kerst G, Kreuder J, Schranz D, et al. Hemodynamic evaluation of children with persistent or recurrent pulmonary arterial hypertension following complete repair of congenital heart disease. Pediatr Cardiol 2017;38:1342-1349.

S8-17 Sharma A, Obiagwu C, Mezue K, Garg A, Mukherjee D, Haythe J, et al. Role of vasodilator testing in pulmonary hypertension. Prog Cardiovasc Dis 2016;58:425-433.

S8-18 Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J 2019;53:1801916.

S8-19 Myers PO, Tissot C, Beghetti M. Assessment of operability of patients with pulmonary arterial hypertension associated with congenital heart disease. Circ J 2014;78:4-11.

S8-20 Talwar S, Keshri VK, Choudhary SK, Gupta SK, Ramakrishnan S, Juneja R, et al. Surgical strategies for patients with congenital heart disease and severe pulmonary hypertension in low/middle-income countries. Heart Asia 2015;7:31-37.

S8-21 Galiè N, Beghetti M, Gatzoulis MA, Granton J, Berger RM, Lauer A, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multi-center, double-blind, randomized, placebo-controlled study. Circulation 2006;114:48-54.

S8-22 Brida M, Gatzoulis MA. Pulmonary arterial hypertension in adult congenital heart disease. Heart 2018;104:1568-1574.

S8-23 Kempny A, Hjortshøj CS, Gu H, Li W, Opotowsky AR, Landzberg MJ, et al. Predictors of death in contemporary adult patients with Eisenmenger syndrome: a multicenter study. Circulation 2017;135(15):1432-1440.

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Recommendations on the therapy of acute PH in pediatric ICU – pharmacotherapy and mechanical circulatory support

Recommendations	COR	LOE
Oxygen should be given when the transcutaneous oxygen saturation is < 95% in children with PH and normal cardiac anatomy.	I	C
Intravenous prostanoids should be considered to treat children with severe PH. (S10-1, S10-2)	IIa	B
iNO may be considered for treatment of post-operative PH in mechanically ventilated patients to improve oxygenation and reduce the risk of pulmonary hypertensive crisis. (S10-3, S10-4)	IIb	B
Concomitant sildenafil should be administered to prevent rebound PH in patients who have signs of increased PAP on withdrawal of iNO and require restart of iNO despite preceding gradual weaning of iNO. (S10-5 – S10-8)	I	B
Oral tadalafil can be considered as a therapeutic alternative to oral sildenafil in infants and children with signs of increased PAP. (S10-9)	IIb	B
Intravenous sildenafil may be considered for treatment of PH in critically ill patients, especially in those with an unsatisfactory response to iNO. (S10-8) Intravenous sildenafil reduced PAP and shortened time to extubation and ICU stay in children with post-operative PH. (S10-8)	IIb	C
Inhaled iloprost may be as effective as iNO in children with post-operative PH. (S10-10 – S10-12)	IIb	B

In children who develop signs of low cardiac output or profound pulmonary failure despite optimal medical therapy, extracorporeal life support may be considered as bridge to transplantation or recovery. (S10-13)	IIb	C

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Treatment of pediatric PH (⇨ Anhang Abbildung 2)

PHVD and associated heart failure is complex, and the selection of appropriate therapies remains difficult in children and young adults. The so-called PHA-specific medications currently approved for therapy of adults with PAH target 3 major pathways (endothelin, nitric oxide, and prostacyclin). Moreover, some PH centers may use off-label drugs for compassionate use in selected cases. Pediatric PAH therapy is largely based on expert experience and trial data from adult studies […].

Pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis (PVOD/PCH) is now considered within the spectrum of PAH, characterized by very pronounced venous/capillary involvement, and as such is a condition that is associated with a particularly poor prognosis, very limited response to PAH therapy, and the risk of pulmonary edema with vasodilator therapy […].

Recommendations	COR	LOE
Oxygen therapy is reasonable in hypoxemic PH patients who consistently have oxygen saturations < 92% or PaO_2 < 60 mm Hg (S11-1)	IIa	C
Oxygen can be particularly useful for children with PH and an element of parenchymal/interstitial lung disease (e.g., bronchopulmonary dysplasia/neonatal CLD). (S11-2)	IIa	B
Oxygen may be useful for patients with an intrapulmonary shunt and important for PH patients while at altitude or during air travel.	IIb	C
Based on PAH and heart failure studies in adults, mineralcorticoid receptor blockade with spironolactone or eplerenone may be beneficial in PAH patients by improving RV and LV diastolic function. No data or significant experience on eplenerone in children with PAH are available. (S11-3 – S11-5)	IIb	C

Diuretic therapy may be considered for selected pediatric patients with PH, that is, those with confirmed fluid overload and/or significant left-to-right shunt.	IIb	C
Diuretic therapy should be initiated cautiously because patients with PH and high PVR often are pre-load dependent to maintain an optimal cardiac output. (S11-4)	I	C
The benefit of chronic anticoagulation (warfarin, phenprocoumon) in children with PAH is unclear (so far not studied in children).	IIb	C
Chronic anti-coagulation can be useful in patients with progressive IPAH/HPAH (empirical goal Rs 2.0-INR 2.5), patients with CTEPH, patients in low cardiac output, and those with hypercoagulable states.	IIa	C
Indication for anti-coagulation should be critically reviewed, especially in small children prone to hemorrhagic complications. In these cases, anti-platelet therapy (e.g., ASA) may be an alternative.	IIb	C
Anti-coagulation, but also anti-platelet therapy (e.g., ASA), should be very critically reviewed in those children prone to hemorrhagic complications because of platelet dysfunction, such as congenital or acquired von Willebrand syndrome (flow/shear stressed induced hemostatic defects), or concomitant PCA therapy (IV/SC treprostinil or IV epoprostenol), as anti-coagulation or anti-platelet therapy may cause harm in these settings. (S11-6)	III harm	C
Before starting PAH-targeted therapy for chronic PH, vasodilator responsiveness should be determined by cardiac catheterization; particularly, anatomical obstruction from pulmonary venous disease or from left-sided heart disease should be excluded in this setting (S11-4, S11-7)	I	C
Treatment with CCB (either as monotherapy or in combination with other PAH drugs) should be considered in those patients who have previously been shown to be acutely reactive to iNO ± oxygen during AVT (AVT responders). (S11-7)	IIa	C
For children with a negative acute vascoreactivity response, or in those with a failed or non-sustained response to CCBs, risk stratification should probably determine additional PAH-targeted therapy. (S11-7, S11-8)	IIa	C
CCBs are contraindicated in children who have not undergone AVT, in proven non-responders to acute vasodilator testing, and in those with right heart failure, regardless of AVT response. (S11-7, S11-9 – S11-11)	III harm	C
Children with PAH and a significant intracardiac left-to-right shunt, and those with Eisenmenger syndrome (i.e., suprasystemic PVR and right-to-left shunt), most likely do not benefit from CCB therapy, regardless of acute vasodilatory response or severity of PHVD, and thus, CCBs are not useful in this setting. (S-11-7, S11-9, S11-10).	III no benefit	C
Most children with severe PAH are non-responsive to AVT (iNO ± oxygen) and should receive targeted therapy other than CCBs. (S11-8, S11-9)	I	C
In the child with mild to moderate chronic PH and lower risk, initiation of oral goal-targeted therapy is recommended, regardless of a negative acute vasoreactivity response, and should begin with either a PDE-5i or an ERA, or a combination of PDE-5i and ERA (⇨ Anhang Tabelle 2). (S11-9, S11-12)	I	C
Oral sildenafil can be useful in the setting of iNO weaning in post-operative PH, or in the presence of PH related to parenchymal/interstitial lung disease. (S11-13, S11-14)	IIa	B
High dose oral sildenafil treatment (defined in the STARTS-1/-2 trials), either as monotherapy or add-on drug, was associated with a higher mortality rate in children (>8 kg, >1 year old) with PAH/PHVD, including potentially increased mortality. (S11-9, S11-14, S11-15)	III harm	B
IV sildenafil may be considered in children with CHD and post-operative PAH/intermittent pulmonary hypertensive crisis, on or off iNO. (S11-9, S11-18)	IIa	B
Early combination therapy with two oral PAH-targeted drugs in newly diagnosed (treatment-naïve) children with PAH in WHO functional class II-III is reasonable. (S11-9)	IIa	C
In severe (WHO functional class IV) and/or rapidly progressive PAH (diagnosed by cardiac catheterization and non-invasive imaging), continuous IV PCA therapy (i.e.,	I	C

epoprostenol or treprostinil) should be started without delay (start with prostanoid monotherapy or dual/triple combination therapy including PCAs). (S11-9, S11-19 – S11-21)		
Start of PCA therapy with IV treprostinil or IV iloprost instead of epoprostenol can be considered in certain circumstances. (S11-9, S11-22, S11-23)	IIa	C
SC PCA therapy (SC treprostinil) may be beneficial in children with severe PAH. (S11-24)	IIa	B
Combination of IV (e.g., epoprostenol or treprostinil) or SC PCAs (treprostinil) with 1 or 2 oral PAH-targeted drugs (e.g., sildenafil, bosentan) may result in better long-term survival in patients with severe PAH.	IIb	C
iNO is mainly used in the ICU setting and useful in patients with acute pulmonary vascular crisis and/or acute exacerbation of PH in the setting of an underlying parenchymal lung disease and/or PPHN. (S11-9, S11-25 – S11-27)	I	B
During the weaning phase of iNO, PH rebound may occur that can be prevented through concomitant use of oral or IV sildenafil administration. (S11-28)	I	B
Atrial septostomy (AS), with or without device implantation, preferably resulting in a restrictive interatrial communication, may be considered in patients in functional class III and IV and recurrent syncope under combined medical therapy and as palliative bridge to transplant, increasing the chance for survival while waiting for a donor organ. (S11-29 – S11-32)	IIb	C
Based on the risk factors found in an international (adult) study with high procedure-related mortality, contraindications for AS include (1) a mean right atrial pressure of >20 mm Hg, (2) resting arterial oxygen saturation <90%, (3) severe RV failure, and (4) patients with impending death. (S11-33)	III harm	C
Based on a small series of children with end-stage PAH, a surgical or interventional anastomosis between LPA and DAO (reverse Potts shunt) may be considered as a valuable alternative (destination therapy), or bridge to bilateral lung transplantation, in selected cases. (S11-34 – S11-39)	IIb	C

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Abman SH et al., 2015 [1].

The American Heart Association (AHA), The American Thoracic Society (ATS)

Pediatric pulmonary hypertension

siehe auch: Abman SH et al., 2016 [2].

Zielsetzungen

These guidelines are intended to assist healthcare providers in clinical decision making by describing generally acceptable approaches to the diagnosis and management of children with PAH.

Methodik

Grundlage der Leitlinie

- Multidisziplinäre Leitliniengruppe, keine Einbeziehung von Patientenvertretungen;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematik der Suche dargelegt, Angaben zur systematischen Auswahl und Bewertung der Evidenz fehlen;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig, die Verbindung zu der zugrundeliegenden Evidenz ist indirekt über den Hintergrundtext zu den Empfehlungen möglich;
- Weder Gültigkeit noch Verfahren zur Überwachung und Aktualisierung beschrieben.

Recherche/Suchzeitraum:

Comprehensive literature reviews were performed with PubMed and Ovid Medline […] [Supplement: 10 May 2011]. Additional searches to supplement the primary data review were performed periodically, at least annually, over the time of the project by individual task forces and by the writing group.

LoE/GoR ⇨ Anhang Abbildung 3

Empfehlungen

Pharmacotherapy (⇨ Anhang Abbildung 4)

1. Supportive care with digitalis and diuretic therapy is reasonable with signs of right heart failure but should be initiated cautiously (Class IIb, Level of Evidence C).
2. Recommendations for long-term anticoagulation with warfarin include the following:
   a. Warfarin may be considered in patients with IPAH/HPAH, patients with low cardiac output, those with a long-term indwelling catheter, and those with hypercoagulable states (Class IIb, Level of Evidence C).
   b. Targeting the therapeutic range for an international normalized ratio between 1.5 and 2.0 is recommended for young children with PAH (Class I, Level of Evidence C).
   c. Anticoagulation should not be used in young children with PAH because of concerns about harm from hemorrhagic complications (Class III, Level of Evidence C).
3. Oxygen therapy is reasonable for hypoxemic PAH patients who have oxygen saturations < 92%, especially with associated respiratory disease (Class IIa, Level of Evidence B).
4. Recommendations for calcium channel blockers (CCBs) include the following:
   a. CCBs should be given only to those patients who are reactive as assessed by AVT and > 1 year of age (Class I, Level of Evidence C).
   b. CCBs are contraindicated in children who have not undergone or are nonresponsive to AVT and in patients with right-sided heart dysfunction owing to the potential for negative inotropic effects of CCB therapy (Class III, Level of Evidence C).
5. Oral PAH-targeted therapy in children with lower-risk PAH is recommended and should include either a phosphodiesterase type 5 (PDE5) inhibitor or an endothelin (ET) receptor antagonist (ERA) (Class I, Level of Evidence B).
6. A goal-targeted therapy approach in which PAH-specific drugs are added progressively to achieve specified therapeutic targets can be useful (Class IIa, Level of Evidence C).

7. Intravenous and subcutaneous PGI_2 or its analogs should be initiated without delay for patients with higher-risk PAH (Class I, Level of Evidence B).
8. Recommendations for the transition from parenteral to oral or inhaled therapy include the following:
   a. This transition may be considered in asymptomatic children with PAH who have demonstrated sustained, near-normal pulmonary hemodynamics (Class IIb, Level of Evidence C).
   b. The transition requires close monitoring in an experienced pediatric PH center (Class I, Level of Evidence B).

Hintergrund

Conventional therapy

[…] Diuretic therapy should be initiated cautiously because patients with PAH are often preload dependent to maintain an optimal cardiac output. Digitalis may be beneficial in patients with overt right-sided cardiac dysfunction and clinical failure, but data are lacking.[297] The benefit of long-term anticoagulation has not been studied in children with PAH, but its use is recommended in patients with IPAH/HPAH, patients in low cardiac output, those with hypercoagulable states, and those with a long-term indwelling intravenous catheter. Even in adults with group 1 PAH, the benefits of warfarin are largely inferred from retrospective analyses in IPAH/HAPH and anorexigen-induced PAH patients, and there are no RCTs. However, retrospective data in adults dying of IPAH/HPAH provide biological plausibility because 57% had thromboemboli.[298] […] the use of other anticoagulant drugs such as aspirin has not been well studied. The risk-to-benefit ratio for anticoagulation should be wisely weighed, especially in small children prone to hemorrhagic complications, and anticoagulation should not be used in those with HHT or PPHTN. In IPAH and HPAH, the aim is to maintain an international normalized ratio between 1.5 and 2.0, although this is an empirical therapeutic target. The use of anticoagulation in patients with Eisenmenger syndrome (ES) is controversial, and the potential risks and benefits of anticoagulation in this setting must be carefully considered because there is a significant risk of pulmonary hemorrhage.[301]

Calcium Channel Blockers

The use of CCBs to evaluate vasoreactivity has significant potential risks because these drugs can cause a decrease in cardiac output or a marked drop in systemic blood pressure.[302] Consequently, elevated RA pressure and low cardiac output are contraindications to short- or long-term CCB. An acute trial of CCB therapy should be performed only in those patients who have previously been shown to be acutely reactive to either iNO or intravenous epoprostenol. Likewise, patients who do not have an acute vasodilator response to short-acting agents and who are then placed on CCB are unlikely to benefit long term and, more important, are at risk of a fatal outcome.[302]

An adaptation of the conventional pediatric definition of a response to AVT for determination of suitability for CCB therapy is a 20% decrease in mPAP, an increase or lack of a decrease in cardiac output, and no change or a decrease in the PVR/SVR ratio.[302]

For acute responders with IPAH treated with CCB, survival was 97%, 97%, and 81% at 1, 5 and 10 years, respectively, and sustained treatment success was 84%, 68%, and 47%, respectively.[296] However, inappropriate use of CCB therapy results in a very poor outcome. IPAH children who were not reactive during AVT but were still treated with CCB had survival rates of 45%, 34%, 29%, and 29% at 1, 2, 3, and 4 years. CCBs are contraindicated in children who have not undergone AVT, are nonresponders, or have RV

failure (ie, WHO functional class IV), regardless of acute response. The last prohibition reflects the potential negative inotropic effect of CCBs, especially in patients with low cardiac output.[302] […] Unfortunately, the majority of children with severe PAH are nonresponsive to AVT, and therapy other than a CCB is usually required.

Long-term CCB therapies recommended for use in acute responders include nifedipine (2-5 $mg \cdot kg^{-1} \cdot d^{-1}$), diltiazem (3-5 $mg \cdot kg^{-1} \cdot d^{-1}$), and amlodipine 2.5-10 mg/d). These agents, particularly diltiazem, may lower heart rate, and diltiazem is used more frequently in young children with higher heart rates […].

PGI_2 Analogs

Long-term use of intravenous epoprostenol improves survival and quality of life in adults and children with IPAH.[302,304-308] Improved survival has been shown in children who were treated with long-term intravenous epoprostenol, with a 4-year survival rate of 94% for treated children[302] and a 10-year treatment success rate (freedom from death, transplantation, or AS) of 37%.[296] A study from the United Kingdom reported IPAH survival rates of 86%, 80%, and 72% at 1, 3, and 5 years, respectively, compared with a survival time of <1 year in historical untreated controls, but this in adults.[309] A combination of intravenous epoprostenol with oral bosentan, oral sildenafil, or both may result in a better survival, but this was reported only in an observational cohort, not a randomized trial.[104,105]

Patients with severe PAH and CHD may also respond favorably to intravenous epoprostenol.[310] […] Complications such as sepsis, local site infection, and catheter dislodgement are common and can be responsible for life-threatening sepsis or rebound PH.[312,313] Recently, the use of specific closed-hub systems has been described in children to decrease the risk of catheter-related infection.[314] Some children have an exceptional clinical response to intravenous epoprostenol, which includes near normalization of PAP. This subset of children may eventually be transitioned from intravenous to oral therapy with close monitoring.[315,316] However, this should be considered only in a pediatric PH center with significant experience in treating children with PAH owing to the potential for significant adverse response in some children who may not be candidates for weaning from intravenous epoprostenol to oral/inhaled drugs. Inhaled epoprostenol has been used in the critical care setting.[317]

[…] Subcutaneous treprostinil allows patients to remain free of central venous catheters, and recent data have shown long-term efficacy in adults with PAH.[319] In its subcutaneous form, discomfort at the infusion site is common and represents a limitation of this route of administration. However, a recent study of subcutaneous treprostinil in young children showed promise with tolerable side effects.[320] Treprostinil in the intravenous form requires central venous access and continuous infusion […]. An increase in catheter-related and Gram-negative bloodstream infections among patients with PAH treated with intravenous treprostinil has been noted, but this risk may be mitigated by using watertight seals throughout the delivery system, using closed-hub systems, and changing the diluent of treprostinil to epoprostenol diluent.[313,314,321,322] Intravenous treprostinil may have fewer side effects than intravenous epoprostenol, but no studies have directly compared both agents.[323] Treprostinil has also been given in an inhaled form,[324] and studies have recently been published in children.[325]

An increase in airway reactivity has been noted in some children receiving inhaled iloprost.[284] The advantage of an inhaled PGI_2 is that it can cause pulmonary vasodilation with minimal effect on systemic blood pressure.[327,328] Inhaled iloprost has also been

studied in combination with bosentan and sildenafil, among others, but definitive studies of efficacy in children are lacking.[329-331] […]

ET Receptor Antagonists

Bosentan, a dual ERA, lowers PAP and PVR and improves exercise capacity in adults with PAH,[286] and similar results have been reported in children.[315,340-346] Bosentan lowers PAP and PVR and is well tolerated in children with IPAH or PAH associated with CHD.[343,344,347] Elevated hepatic aminotransferase levels occur in ≈ 11% of adults and 3% of children treated with bosentan. In a 12-week study, bosentan was well tolerated and lowered the PAP and PVR [in] children with IPAH or PAH related to CHD.[343] A retrospective study of 86 children on bosentan for a median exposure of 14 months, with and without concomitant therapy, reported that bosentan caused sustained clinical and hemodynamic improvement and was well tolerated, with 2-year survival estimates of 91%.[342] Follow-up of these patients at 4 years revealed that the Kaplan-Meier estimate of disease progression in patients on bosentan was high (54%), with a survival estimate of 82%.[348] Bosentan therapy provided short-term improvement in WHO functional class and 6MWD test in children and adults with PAH and systemic-to-pulmonary shunt.[349] This beneficial response progressively declined after 1 year, with a more rapid decline observed in children, who tended to have more severe disease at baseline than adults.[349]

The safety of bosentan therapy in children with PAH has recently been reviewed.[350] Elevated transaminase levels were reported in 2.7% of children compared with 7.8% of patients ≥ 12 years of age, and the overall discontinuation rate from bosentan was 14% in children compared with 28% in patients ≥ 12 years of age. Importantly, bosentan pharmacokinetics were not altered by concurrent sildenafil therapy.[346] Bosentan has been studied in adult patients with ES in a placebo-controlled trial, showing few adverse events and improved exercise capacity and hemodynamics.[288] Other studies have further demonstrated beneficial effects of bosentan in patients with ES.[351,352]

[…] Adults had improvements in 6MWD and delays in clinical worsening on ambrisentan.[354] The incidence of elevated liver function tests was 2.8%, which was similar to that of the placebo group.[290] Short-term use of ambrisentan improved 6MWD in 17 patients with ES.[355] In a retrospective study, 38 pediatric PAH patients were treated with ambrisentan as add-on therapy or as replacement therapy for bosentan.[356] In both groups, mPAP and functional class improved during the follow-up, but 1 patients required an AS because of disease progression.[356] […].

PDE Inhibitors

[…] Early evaluation of sildenafil in 14 children with PAH showed an increase in 6MWD from 278 ± 114 to 443 ± 107 m over 6 months (P=0.02); at 12 months, the distance walked was 432 ± 156 m (P=0.005) and was associated with a decrease in mPAP and PVR.[364] In several small studies of children with PPHN, IPAH, and PH associated with CHD, sildenafil has been shown to improve exercise capacity and hemodynamics.[105,113,215,257,258,362,363,365-368] […] In a 16-week randomized, double-blind, placebo-controlled study of treatment naïve children [STARTS-1], the effects of oral sildenafil in pediatric PAH were studied.[292] Children (n=235) with IPAH or PAH associated with CHD (age, 1-17 years; weight ≥ 8 kg) received low-, medium-, or high-dose sildenafil or placebo 3 times daily. […] The percentage change in peak oxygen consumption for the treatment group versus the placebo group was 7.7 ± 4.0% (95% confidence interval, -0.2 to 15.6; P=0.056). Peak oxygen consumption, functional capacity, mPAP, and PVR improved with the medium- and high-dose groups compared with placebo, whereas the low dose was ineffective.

The dose-extension study [STARTS-2] was blinded until all patients completed STARTS-1. After study patients completed 3 years of treatment, an increased risk of mortality was found in patients who were originally randomized to high dose at the beginning of the 16-week study or former placebo patients who were later randomized to the high dose at the beginning of the extension study. After 3 years, the incidence of mortality was 9% (5 of 55), 14% (10 of 74), and 20% (20 of 100) in the groups receiving low-, medium-, and high-dose sildenafil, respectively. Overall, the risk for mortality was greatest in older patients with IPAH who had higher mPAP and PVRI at enrolment. Children weighing < 20 kg and those with PAH associated with CHD did not have the same mortality risk as other subgroups in the study. Although the causality of this observed increased mortality at 3 years is not known, high-dose sildenafil carries an unfavorable risk-to-benefit ratio when used as monotherapy.[292] […] A recent study showed that intravenous sildenafil improves oxygenation index in PPHN in patients treated with or without iNO.[215] However, sildenafil infusion can increase intrapulmonary shunting and worsen hypoxemia in the postoperative CHD patient.[114,374]

[…] A placebo-controlled study demonstrated that tadalafil improved exercise capacity, time to clinical worsening, and health-related quality of life in adult patients with IPAH or associated PAH.[289] Open-label use of tadalafil has suggested benefit in ES and in combination with PGI_2.[289,375-378] A recent retrospective study demonstrated the safety and potential efficacy of tadalafil therapy in 33 pediatric patients with PAH.[378] In this study, 29 of 33 patients were switched from sildenafil to tadalafil. […] In 14 of 29 children transitioned from sildenafil to tadalafil, repeat cardiac catheterization showed significant improvements in mPAP and PVRI.

Combination therapy

[…] few studies have been performed that specifically examined combination therapies […]. A therapeutic approach using the combination of bosentan, sildenafil, and inhaled iloprost may improve survival and reduce the need for lung transplantation in adult patients with severe PAH.[381] Whether combination therapy should be used as a first step through concurrent initiation of ≥ 2 drugs or as add-on therapy is still not known, and more studies are clearly needed.

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Isolated PAH

1. Lung biopsy may be considered for children with PAH suspected of having PVOD, pulmonary capillary hemangiomatosis, or vasculitis (Class IIb, Level of Evidence C).
2. Referral to lung transplantation centers for evaluation is recommended for patients who are in World Health Organization (WHO) (functional class III or IV on optimized medical therapy or who have rapidly progressive disease (Class I, Level of Evidence A).
3. Referral to a lung transplantation center for evaluation is recommended for patients who have confirmed pulmonary capillary hemangiomatosis or PVOD (Class I, Level of Evidence B).

Hintergrund

Isolated PAH includes IPAH and HPAH […]. These diseases are included in the group 1 WHO classification of PAH.[5] Isolated PAH is characterized by progressive obliteration of the pulmonary vascular bed, leading to right-sided heart failure and death if left untreated. […]. PAH resulting from PVOD and pulmonary capillary hemangiomatosis is also included in this classification.

PVOD is a rare disorder that is often initially misdiagnosed as IPAH […]. When the patient fails to respond or worsens in response to targeted PAH therapies, the diagnosis is often uncovered. […] The only definitive way to make this diagnosis is by lung biopsy, which is not without risk for this patient population. […] The only long-term treatment for PVOD is lung transplantation, and early referral to an experienced transplantation center is critical for long-term survival.

[…] The pathogenesis of pulmonary capillary hemangiomatosis is unknown, and there are no effective medical therapies. Lung transplantation is curative, however, because of the lack of awareness and the difficulty in making this diagnosis, the majority of reported cases have been discovered postmortem.[386] If pulmonary capillary hemangiomatosis is suspected by radiographic imaging or failure to respond to targeted PAH therapy, one should consider performing a lung biopsy because the only definitive treatment is lung transplantation.[387,388] Novel treatments, including interferon-α2a, may be considered while bridging to transplantation.[389]

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Pediatric Heart Disease (⇨ Anhang Abbildung 5)

1. In children with significant structural heart disease (ie, atrial septal defect [ASD], ventricular septal defect [VSD], and patent ductus arteriosus [PDA]) who have not undergone early repair (as generally defined as by 1 to 2 years of age, depending on the lesions and overall clinical status), the following are recommend:
   a. Cardiac catheterization should be considered to measure PVR index (PVRI) and to determine operability (Class II, Level of Evidence B).

   b. Repair should be considered if PVRI is < 6 Wood units (WU) · m² or PVR/SVR < 0.3 at baseline (Class I, Level of Evidence B).
2. In children with evidence of right-to-left shunting and cardiac catheterization revealing a PVRI ≥ 6 WU · m² or PVR/SVR ≥ 0.3, repair can be beneficial if AVT reveals reversibility of PAH (absolute PVRI < 6 WU · m² and PVR/SVR < 0.3 (Class IIa, Level of Evidence C).
3. If cardiac catheterization reveals a PVRI ≥ 6 WU · m² or PVR/SVR ≥ 0.3 and minimal responsiveness to AVT, the following are recommended:
   a. Repair is not indicated (Class III, Level of Evidence A).
   b. It is reasonable to implement PAH-targeted therapy followed by repeat catheterization with AVT after 4 to 6 months and to consider repair if the PVRI is < 6 WU (Class IIb, Level of Evidence C).

Hintergrund

In the child with CHD and PVD, determination of baseline hemodynamics and reactivity to vasodilators is crucial for selecting surgical candidates who will likely have successful short-term and long-term outcome.[84,117,411] One of the most important factors in long-term survival and freedom from PVD is the age at which surgery is performed.[412]

[…] In general, surgery in the child with CHD is recommended before 2 years of age,[393,414] but most centers will perform complete repair of lesions within the first months of life.

Cardiac catheterization provides an assessment of PVR, PVR-to-SVR ratio, and pulmonary-to-systemic blood flow. […] The first Natural History Study of VSD concluded that no child repaired before 2 years of age, regardless of the initial PVR-to-SVR-ratio, had an elevated PVR-to-SVR ratio 4 to 8 years after surgery.[414] […] Children with PVR > 6 WU · m² have a poor prognosis regardless of their lung morphology […].[116] Studies of children and young adults with VSD reported successful surgical outcomes in patients with preoperative PVR < 8 WU · m².[108,417] A positive AVT response with short-term exposure to iNO in children with higher baseline PVR may predict beneficial outcomes after surgery.[111,418] Six of 7 children with CHD and baseline PVR > 6 WU · m² and PVR-to-SVR ratio > 0.3 who responded to brief iNO inhalation with a decrease in PVR and PVR-to-SVR ratio > 10% and an absolute PVR-to-SVR ratio < 0.3 survived surgical intervention.[418] Several studies suggest that a PVRI < 7 to 8 WU · m² in response to vasodilator challenge predicts a good outcome,[108,411,417,419] although good surgical outcomes can occur with higher PVR in some settings.

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Outpatient Care of Children with PH

1. Children should be evaluated and treated in comprehensive, multidisciplinary clinics at specialized pediatric centers (Class I, Level of Evidence C) […].
6. As a result of significant maternal and fetal mortality associated with pregnancy in patients with PH, it is recommended that female adolescents with PH be provided with age-appropriate counseling about pregnancy risks and options for contraception (Class I, Level of Evidence C).
7. Because of the risks of syncope or sudden death with exertion, it is recommended that a thorough evaluation, including cardiopulmonary exercise testing (CPET) and treatment, be performed before the patient engages in athletic (symptom-limited) activities (Class I, Level of Evidence C).
8. Pediatric patients with severe PH (WHO functional class III or IV) or recent history of syncope should not participate in competitive sports (Class III, Level of Evidence C).
9. During exercise, it is recommended that pediatric patients with PH engage in light to moderate aerobic activity, avoid strenuous and isometric exertion, remain well hydrated, and be allowed to self-limit as required (Class I, Level of Evidence C) […].

Hintergrund

Many aspects of care that affect the long-term course of children with PH involve clinical issues beyond PAH-specific diagnostics and therapies alone. […] improving outcomes of the child with PH requires establishing experienced, knowledgeable, and multidisciplinary pediatric PH programs […]. Recommendations concerning the potential harm of pregnancy in young women with PH,[633] [and] caution with intense exercise[134,634] […] are also highlighted.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 9 of 12, September 2020) am 15.09.2020

#	Suchfrage
1	MeSH descriptor: [Pulmonary Arterial Hypertension] explode all trees
2	MeSH descriptor: [Hypertension, Pulmonary] this term only
3	(pulmonary NEAR/6 hypertension):ti,ab,kw
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from Sep 2015 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 15.09.2020

#	Suchfrage
1	"pulmonary arterial hypertension"[MeSH Terms]
2	"hypertension, pulmonary"[MeSH Terms:noexp]
3	"pulmonary hypertension"[Title/Abstract] OR "pulmonary arterial hypertension"[Title/Abstract]
4	#1 OR #2 OR #3
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR

#	Suchfrage
	treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
6	(#5) AND ("2015/09/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 15.09.2020

#	Suchfrage
1	"pulmonary arterial hypertension"[MeSH Terms]
2	"hypertension, pulmonary"[MeSH Terms:noexp]
3	"pulmonary hypertension"[Title/Abstract] OR "pulmonary arterial hypertension"[Title/Abstract]
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(#5) AND ("2015/09/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

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Anhang

Tabelle 1: Classification of Pulmonary Hypertension (6th World Symposium on Pulmonary Hypertension, Nice 2018) (Hansmann G et al., 2019 [3].)

1 Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug- and toxin-induced PAH
1.4 PAH associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease (CHD)
1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillary (PVOD/PCH) involvement
1.7 Persistent PH of the newborn syndrome
2 PH due to left heart disease
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH
3 PH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders
4 PH due to pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
5 PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

Abbildung 1: Algorithm for the management of patients with CHD associated with PAH/PHVD and congenital shunt lesions (Hansmann G et al., 2019 [3].)

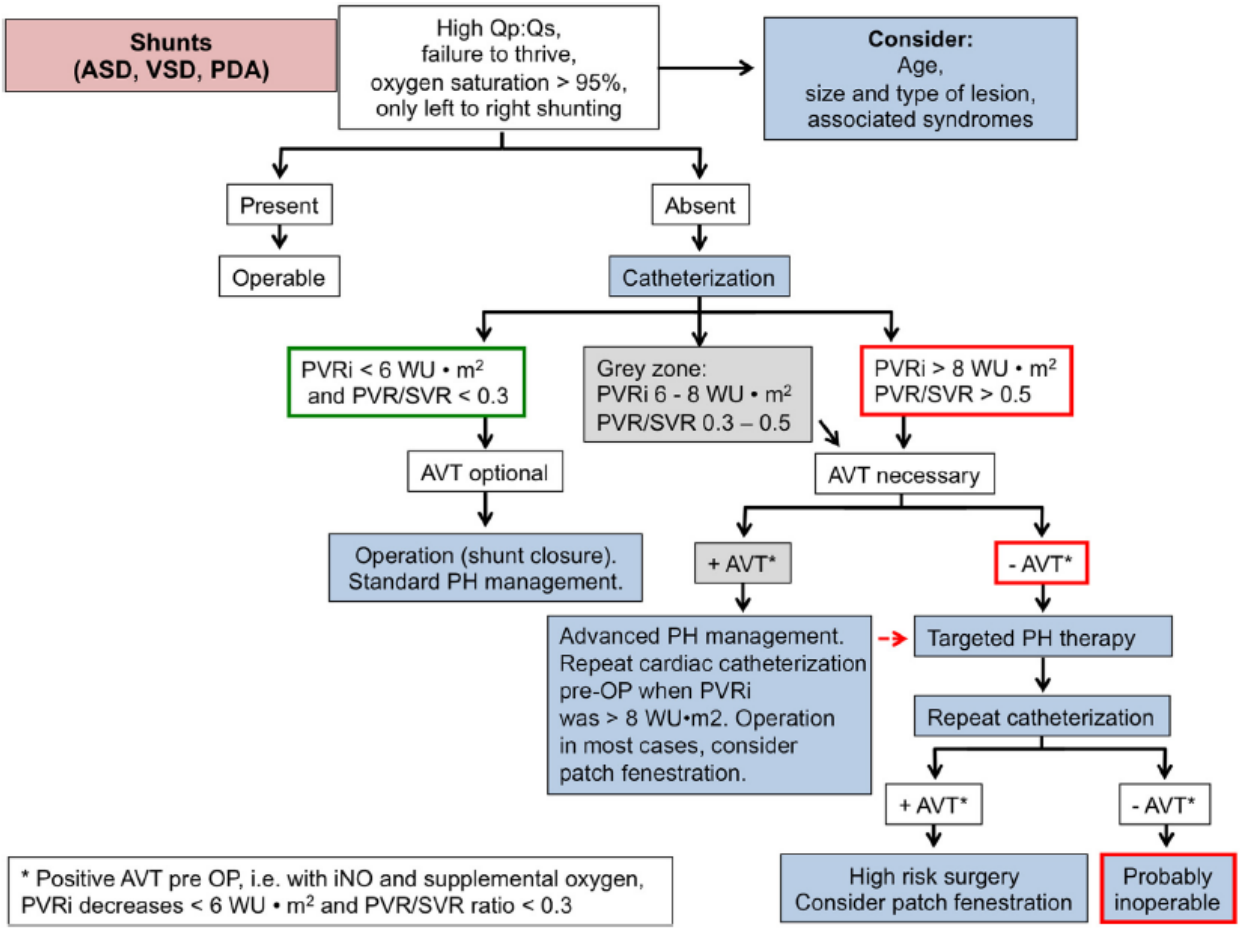


Abbildung 2: Treatment algorithm for pediatric PAH (Hansmann G et al., 2019 [3].)

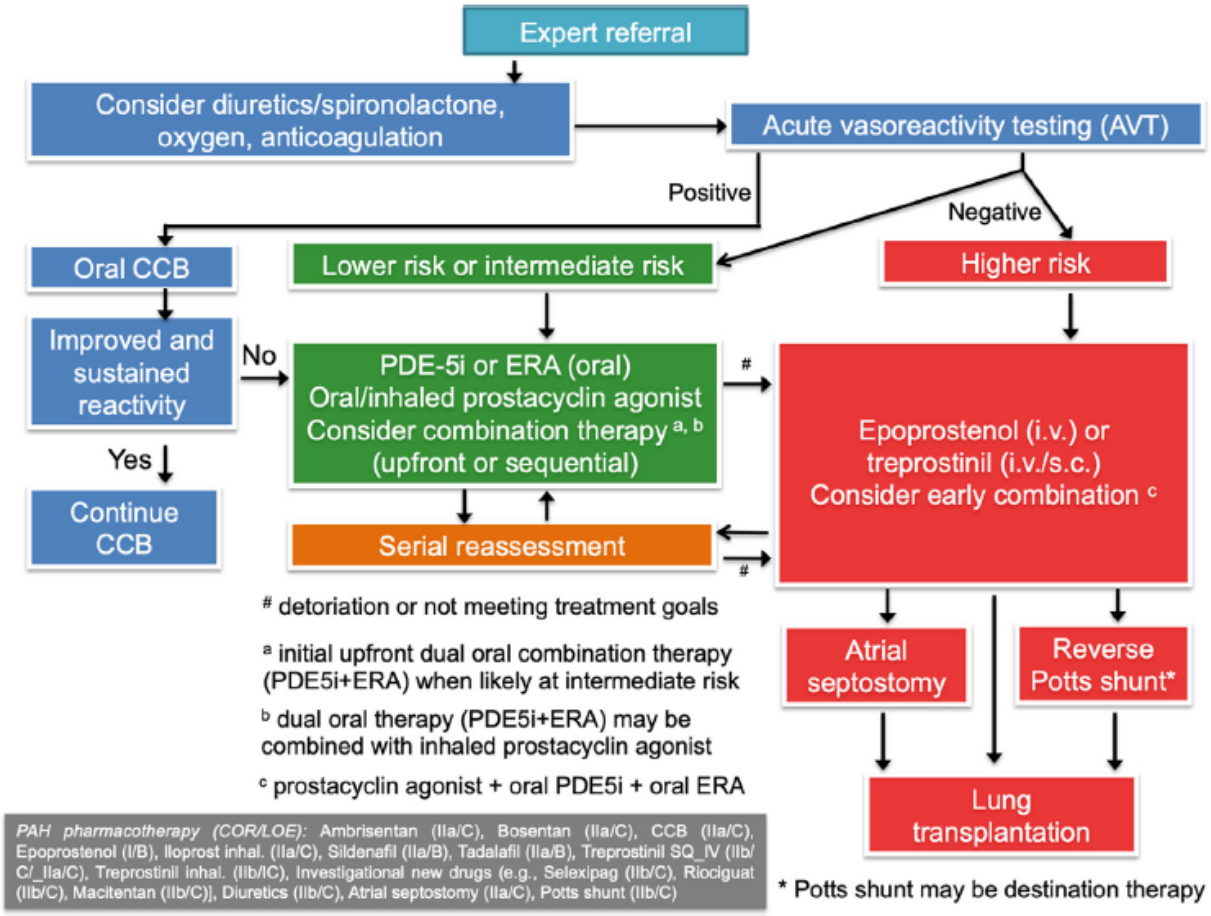


Tabelle 2: Oral and parenteral pharmacotherapy for pediatric pulmonary arterial hypertension (Hansmann G et al., 2019 [3].) (modifiziert)

Agent	Indication	Expected benefit	Possible side effects	COR/LOE Comments
Calcium Chanel Blockers				
Amlodipine	• Only if reactive to vasodilator testing. • Do not use in patients with high right atrial pressure or low cardiac output.	Decrease in PVR	• Bradycardia • Decreased cardiac output • Peripheral edema • Rash • Gum hyperplasia • Constipation	COR IIa / LOE C • Duration of benefit may be limited even with initial favorable response. • Efficacy in Eisenmenger syndrome is rare.
Nidedipine	• Only if reactive to vasodilator testing. • Do not use in patients with high right atrial pressure or low cardiac output.	Decrease in PVR	• Bradycardia • Decreased cardiac output • Peripheral edema • Rash • Gum hyperplasia • Constipation	COR IIa / LOE C • Duration of benefit may be limited even with initial favorable response. • Efficacy in Eisenmenger syndrome is rare.
Phosphodiesterase type 5 Inhibitors				
Sildenafil	• Approved for adult PH Group 1 • EMA approved for pediatric PH Group 1 (age > 1 year). • FDA warning (2012) and subsequent clarification (2014)	• Duration of benefit may be limited even with initial favorable response. • Efficacy in Eisenmenger syndrome is rare.	• Flushing • Agitation • Hypotension • Vision and hearing loss are concerning findings in premature infants • Priapism	COR IIa / LOE B COR III / LOE B for high dose • One pediatric RCT (STARTS-1/-2) • A greater mortality was noted in the STARTS-2 extension study in treatment-naïve children treated with high dose sildenafil monotherapy. • STARTS-1/-2 medium dosing regimen with best effect on VO_2 max was: (a) 8-20 kg, >1 year old: 10 mg/dose three times daily PO, (b) 20,1-45 kg: 20 mg/dose three times daily PO and (c) > 45 kg: 40 mg/dose PO three times daily • FDA warning (2012) and subsequent clarification (2014) of chronic use in children aged 1 – 17 years • Concomitant use of CYP3A4 inhibitors decreases clearance of sildenafil. • Co-administration of bosentan leads to decreased sildenafil concentrations and

				increased bosentan concentrations (clinical relevance is unclear though). • Use in premature neonates not well studied.
Tadalafil	Approved for adult PH Group 1 by EMA and FDA in 2009.	• Increase in CI • Decrease in PVR	• Side effects similar to sildenafil • Probably no significant effect on vision.	COR IIa / LOE C • Once a day dosing • Safety and efficacy data in children are limited.
Guanylate Cyclase (GC) Stimulators				
Riociguat	Approved by EMA and FDA for adult PH Group 1 in 2014: (IPAH/HPAH only) and Group 4 PH (CTEPH) for monotherapy or combination therapy with ERA.	• Increase in CI • Decrease in PVR	• Systemic arterial hypotension • Headache, dizziness and dyspepsia • Not to use together with PDE5-inhibitors (sildenafil, tadalafil).	COR IIb / LOE C • Safety and efficacy data in children not available in 2018. • COR I / LOE A for adult PH group 1 and 4
Endothelin receptor antagonists (ERA)				
Bosentan (dual ET_A and ET_B receptor antagonist)	• Approved by EMA and FDA for adult PH Group 1. • Approved by FDA and EMA for use in children > 1 years old. • For patients > 12 years old, a benefit also shown for FC II.	• Increase in CI • Decrease in PVR	• Abdominal pain, vomiting, extremity pain, fatigue, flushing, headache, edema, nasal congestion, anemia • Not recommended in patients with moderate or severe hepatic impairment. • Monthly LFTs required. • Incidence of AST/ALT elevation is less in children (3.5%) compared with adults. • Teratogenicity and male infertility are risks.	COR IIa / LOE C COR IIa / LOE B Eisenmenger • Data have been published on efficacy in Eisenmenger PH. • Caution in concomitant use of CYP3A4 inducers and inhibitors.
Macitentan (dual $ET1_A$ and $ET1_B$ receptor antagonist)	Approved by EMA and FDA for adult PH Group 1 (IPAH/HPAH only).	• Increase in CI • Decrease in PVR	• Class specific side effects are similar to bosentan. • Headache, nasopharyngitis, anemia • Not recommended in patients with moderate or severe hepatic impairment. • Dependent edema may limit usefulness. • Teratogenicity and male infertility are risks (decreases in sperm count have been observed).	COR IIb / LOE C • RCTs in adults (SERAPHIN 2013) • Safety and efficacy data in children not available in 2018. • Caution in concomitant use of CYP3A4 inducers and inhibitors.
Ambrisentan		• Increase in CI		COR IIa / LOE C

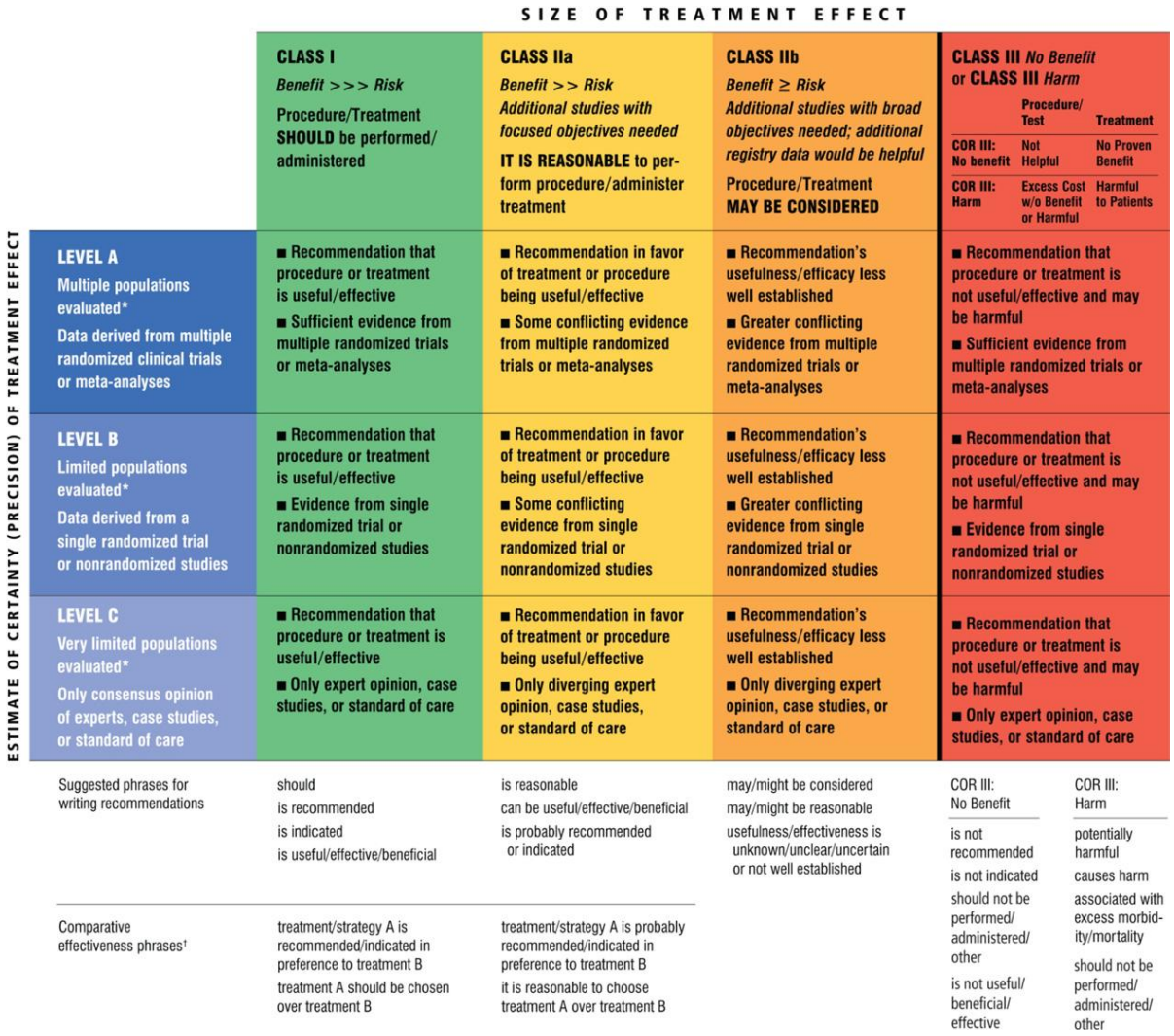
(selective ET1$_A$ receptor antagonist)	• Approved for adult PH Group 1 by FDA and EMA. • Use in pediatrics has not been extensively evaluated. • In children > 12 years old with intolerance to bosentan, there may be a benefit.	• Decrease in PVR	• Class specific side effects are similar to bosentan. • Incidence of serum aminotransferase elevation is low. • May decrease effectiveness of birth control. • Dependent edema may limit usefulness. • Teratogenicity and male infertility are risks. • No drug-drug interactions between ambrisentan and sildenafil or tadalafil observed.	• Safety and efficacy data in children are limited. • Caution in concomitant use of CYP3A4 inducers and inhibitors.
Prostacyclin Analogues (Prostanoids)				
Epoprostenol	Approved by EMA and FDA for adult PH Group 1.	• Increase in CI • Decrease in PVR • Increased survival	• Flushing, jaw, foot and bone pain, headaches, nausea and diarrhea • Systemic hypotension is possible. • The half-life is short (2 – 5 min), so PH crisis occur rapidly if the infusion is stopped. • Ice pack cooling and remixing every 24 h needed for epoprostenol GM. • Epoprostenol AM does not need ice packs but cassettes need to be changed every 7 days at the latest. • Central line complications (infection, occlusion, extravasation) occur.	COR I / LOE B / LOE C • Standard therapy for severe PH (WHO FC class IV). • A temperature stable formulation is now available. Epoprostenol sodium with arginine-mannitol excipients (epoprostenol AM) and epoprosentol sodium with glycine-mannitol excipients (epoprostenol GM) are intravenous treatments for pulmonary arterial hypertension (PAH). Epoprostenol AM contains different inactive excipients, resulting in greater stability at room temperature compared with epoprostenol GM.
Treprostinil	Approved by EMA and FDA for adult PH Group 1.	• Increase in CI • Decrease in PVR • Improved or unchanged 1-year functional class • Less severe side effects than epoprostenol	• Flushing, jaw, foot and bone pain, headaches, nausea and diarrhea are common side effects that reoccur after each dose increase.	COR IIa / LOE C (IV) COR IIb / LOE B (SC) Safety and efficacy data in children are limited. COR IIb / LOE C (intermittent inhalation)

			• The frequency and severity of side effects are less than with epoprostenol. • Elimination half-life is 4.5 h with distribution half-life of 40 minutes. • The drug is stable at room temperature, so it does not require cooling. • Central line complications (infection, occlusion, extravasation) can occur. • Subcutaneously implanted pumps connected to a central intravenous catheter are available for long-term i.v. use. • Inhaled drug can worsen reactive airway symptoms.	The nebulizer requires patient activation and controlled inhalation limited by age and development.
Iloprost	Approved for adult PH Group 1.	• Improved CI • Improved PVR	• Intravenous infusion (rarely used): similar to epoprostenol and trepostinil. • For inhalation: jaw pain, wheezing, especially at the initiation of therapy. • A new chip for the adaptive aerosol delivery (AAD) systems allows now to reduce the duration of inhalations from 10 – 15 down to 4 – 5 minutes.	COR IIb / LOE C (intravenous infusion) In pediatrics, the dosing frequency is not established. COR IIa / LOE C (for intermittend inhalation) • In pediatrics, the dosing frequency and lack of compliance may limit its use. • Many experts recommend q3h inhalations during the day time for better compliance that can be recorded and monitored with a chip within the inhaler.
Selexipag (oral use)	Prostacyclin IP receptor agonist, pending approval for adult PH group 1 (PAH), limited pediatric data.	• Reduction of morbidity/mortality event • Improved CI • Improved PVR	To be determined (RCT and post marketing surveillance pending)	COR IIb / LOE C GRIPHON trial (1,156 PAH patients): Significant risk reduction of morbidity/mortality events.
Mineralcorticoid receptor (MR) antagonists				
Spironolactone	• Improves hepatic congestion and edema. • Inhibits mineralcorticoid receptors and may improve RV and LV diastolic dysfunction.	Decreased signs of right heart failure	Hyperkalemia	COR IIb / LOE C • Better outcome of adult PAH patients in post hoc analysis with add-on spironolactone to ambrisentan (ARIES-1/-2). • Better outcome in adult patients with LV diastolic dysfunction/HFpEF, a similar

				benefit was noted for the oral MR antagonist eplerenone in HFpEF.
Diuretics				
Furosemide (loop diuretic)	May improve hepatic congestion and edema.	• Decreased signs of right heart failure • May be overused in PAH	Caution: Moderate to excessive diuresis can reduce the preload of the failing RV, and worsen clinical status.	COR IIb / LOE C
Hydrochlorothiazide (thiazide)	Improves hepatic congestion and edema.	Decreased signs of right heart failure	Care is needed, as over diuresis can reduce the preload of the failing RV.	COR IIb / LOE C
Inhalative therapies other than prostanoids				
Oxygen	Helpful for cyanotic patients with an element of CLD or intrapulmonary shunt.	Improved sense of well-being	Too high a flow rate can dry the nares and cause epistaxis or rhinitis.	COR I / COR IIa / LOE C • Oxygen is not usually prescribed for children with PH unless day time saturations are low (< 92%). • Polysomnography helpful in delineating need for O_2 therapy at night. • Oxygen with exertion for patients with clinically significant desaturation with exertion.
Nitric Oxide (continuous inhalation)	• PPHN • Acute exacerbation of PAH, including PH crisis • Acute PH in respiratory distress syndrome	Selective fall in PVR	• Methemoglobin and NO_2 at higher doses • Rebound PH on weaning off iNO (risk can be reduced by concomitant use of sildenafil).	COR I / LOE B Not approved by EMA or FDA for post-operative CHD.
Anticoagulative and Antiplatelet Agents				
Warfarin (Coumadin®) Phenprocoumon (Marcumar®, Falithrom®) (Vitamin K antagonists)	• No definitive studies in children. • Oral anticoagulation in patients with a history of thrombosis, hypercoagulation or central lines. • Some PH centers use coumadin or warfarin in pediatric IPAH or HPAH.	Prevention of thrombosis and thromboembolic events	• The risk of anticoagulation in pediatrics must be balanced with the hypothetical benefits. • Teratogenic effects	COR IIb / LOE C COR III (harm) in children prone to hemorrhagic complications. Use of Coudamin® in children prior to walking well may add risk.
Acetylsalicylic acid (ASA, Aspirin)	Alternative to oral anticoagulation (warfarin, coudamin) in pediatric IPAH/HPAH, especially in small/active children.	Inhibition of platelet aggregation, thrombosis, and thromboembolic events	• Usual risks for ASA: bleeding, Reye syndrome, asthma • Combination with clopidogrel or Vitamin K antagonist carries moderate to high bleeding risk	COR IIb / LOE C COR III (harm) in children prone to hemorrhagic complications.
Contraceptives				COR I / LOE B

	• Pregnancy in women with moderate to severe PH bares a high risk of maternal and fetal death. • Endothelin receptor antagonists are teratogenic. • Bosentan use requires two separate methods of contraception.	Prevention of pregnancy and associated morbidity/mortality		
COR and LOE grading (higher than COR IIb and LOE C) is based on pediatric study data, adult RCTs that included > 10% children, and studies on adults on congenital heart disease (ACHD).				

Abbildung 3: Applying Classification of Recommendations and Level of Evidence (Abman SH et al., 2015 [1].)



SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be performed/ administered/ other is not useful/ beneficial/ effective COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

Abbildung 4: AHA/ATS Consensus Pediatric PAH Treatment Algorithm (Abman SH et al., 2015 [1].)

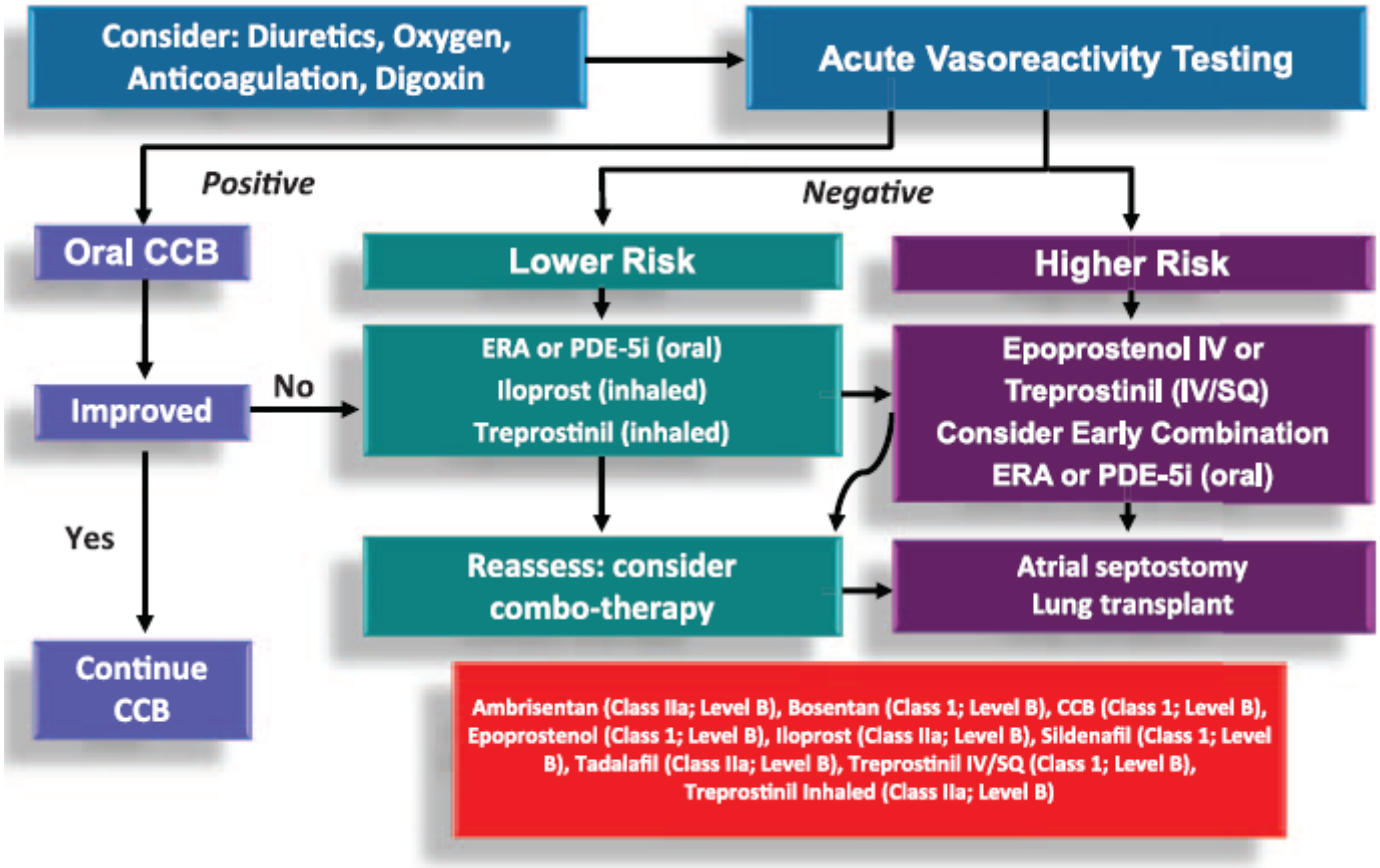
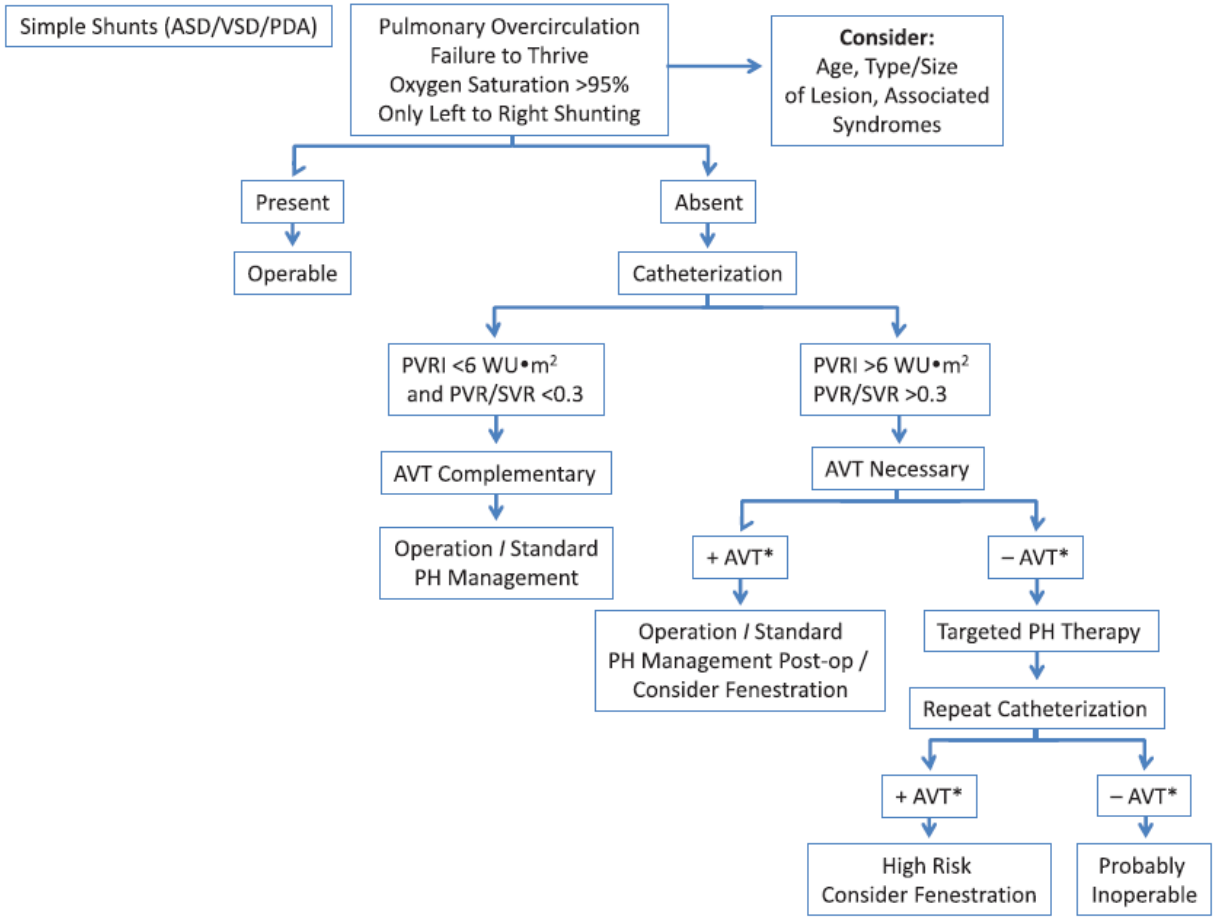


Abbildung 5: Assessment of operability for shunt lesions in patients with congenital heart disease and pulmonary hypertension (PH) (Abman SH et al., 2015 [1].)



Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2020-B-388

Deutsche Gesellschaft für Pädiatrische Kardiologie und Angeborene Herzfehler (DGPK)

Indikation gemäß Beratungsantrag

… ist indiziert für die Behandlung der pulmonalen arteriellen Hypertonie (PAH) bei Kindern und Jugendlichen im Alter von 6 bis unter 18 Jahren.

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz "für die Behandlung der pulmonalen arteriellen Hypertonie (PAH) bei Kindern und Jugendlichen im Alter von 6 bis unter 18 Jahren"? Wie sieht die Versorgungspraxis in Deutschland aus?

Die einzig mögliche Behandlung ist eine medikamentöse Therapie, die sich am Schweregrad der PAH und damit der resultierenden kardialen Beeinträchtigung richtet. Es gibt nur wenige zugelassene Medikamente für das Kindes- und Jugendalter, aber erfreulicherweise effektive, neuere Medikamente aus neuen Medikationsklassen, die aber für das Kindes- und Jugendalter keine Zulassungsstudien durchlaufen haben.

Da die pulmonale Hypertonie im Einzelfall eine voranschreitende und lebenslimitierende Erkrankung ist, konzentriert sich die federführende Behandlung dieser schwerkranken Kinder mit schlechter Prognose dann auf wenige kinderkardiologische Zentren, in denen dann aus der ärztlichen Erfahrung heraus medizinisch-fachlich begründet individuelle Therapieversuche mit nicht zugelassenen Medikamenten – häufig als Kombinationstherapie aus 2 oder 3 Medikamenten - unternommen werden müssen. Diese Medikamente müssen dann natürlich auch im ambulanten Rahmen weiter verabreicht werden, da die Patienten durch eine Beendigung der Therapie aufgrund von Nichtverfügbarkeit oder Nichtverschreiben vital bedroht sind.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung „der pulmonalen arteriellen Hypertonie (PAH) bei Kindern und Jugendlichen im Alter von 6 bis unter 18 Jahren" die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Die Kriterien für die Behandlungsentscheidungen orientieren sich am Schweregrad der kardialen Belastung und dem Effekt einer medikamentösen Behandlung. Häufig ist dieser Effekt passager, d.h im Verlauf ist eine Intensivierung der medikamentösen Therapie notwendig. Diese besteht

anhand der Empfehlungen in der Fachliteratur und in der gängigen Praxis der Expertenzentren überwiegend aus einer Kombination von Medikamenten aus verschieden Wirkstoffklassen.(2,3,4)

Bei fortschreitender therapierefraktärer Erkrankung ist die Lungentransplantation für einige wenige Patienten die einzig ursächliche Behandlungsoption mit einer allerdings sehr begrenzter Verfügbarkeit, die das Leben der Patienten zumindest für einige Jahre sichern kann.

Literaturverweise (s. Anlagen)

1. Stellungnahme des Präsidenten der DGPK (federführende Fachgesellschaft) 2020
2. Leitlinie der DGPK (2020)
3. Expertenkonsens DACH 2020
4. Europäischer Expertenkonsens 2019