



Improving medical care and prevention in adults with congenital heart disease—reflections on a global problem—part II: infective endocarditis, pulmonary hypertension, pulmonary arterial hypertension and aortopathy

Rhoia Neidenbach¹, Koichiro Niwa², Oeztekin Oto³, Erwin Oechslin⁴, Jamil Aboulhosn⁵, David Celermajer⁶, Joerg Schelling⁷, Lars Pieper⁸, Linda Sanftenberg⁷, Renate Oberhoffer^{1,9}, Fokko de Haan¹⁰, Michael Weyand¹¹, Stephan Achenbach¹², Christian Schlensak¹³, Dirk Lossnitzer¹⁴, Nicole Nagdyman¹, Yskert von Kodolitsch¹⁵, Hans-Carlo Kallfelz¹⁶, David Pittrow¹⁷, Ulrike M. M. Bauer¹⁸, Peter Ewert¹, Thomas Meinertz¹⁵, Harald Kaemmerer¹

¹Department of Pediatric Cardiology and Congenital Heart Disease, German Heart Center Munich, Technical University Munich, Munich, Germany; ²Department of Cardiology, Cardiovascular Center, St. Luke's International Hospital, Tokyo, Japan; ³Dokuz Eylul University Hospital air Esref Cad, İzmir, Turkey; ⁴Toronto Congenital Cardiac Centre for Adults, Peter Munk Cardiac Centre, University Health Network, Toronto General Hospital, University of Toronto, Toronto, CA, Canada; ⁵Ahmanson/UCLA Adult Congenital Heart Disease Center, Los Angeles, USA; ⁶Central Clinical School Heart Research Institute C39 - Royal Prince Alfred Hospital, The University of Sydney, NSW, Australia; ⁷Institute of General Practice and Family Medicine, University Hospital of Ludwig-Maximilians-University Munich, Munich, Germany; ⁸Behavioral Epidemiology, Institute for Clinical Psychology und Psychotherapy, Technical University Dresden, Dresden, Germany; ⁹Preventive Pediatrics, Technical University Munich, Munich, Germany; ¹⁰Cardiological Clinic Solingen, Solingen, Germany; ¹¹Department of Cardiac Surgery, ¹²Department of Cardiology, University of Erlangen, Erlangen, Germany; ¹³Clinic for Thorax-, Heart- and Vessel Surgery, German Heart Competence Center, Tübingen, Germany; ¹⁴Medical Clinic I, University Mannheim, Mannheim, Germany; ¹⁵University Heart Center Hamburg, University Clinic Hamburg-Eppendorf, Hamburg, Germany; ¹⁶Clinic for Pediatric Cardiology und Intensive medicine, Medical School Hannover, Hannover, Germany; ¹⁷Institute for Clinical Pharmacology, Medical Faculty, Technical University Carl Gustav Carus, Dresden, Germany; ¹⁸Competence Network Congenital Heart Defects, Berlin, Germany

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Correspondence to: Linda Sanftenberg, Institute of General Practice and Family Medicine, University Hospital of Ludwig-Maximilians-University Munich, Pettenkoferstr. 10, 80336 München, Germany. Email: linda.sanftenberg@med.uni-muenchen.de.

Abstract: Despite relevant residua and sequels, follow-up care of adults with congenital heart disease (ACHD) is too often not performed by/in specialized and/or certified physicians or centers although major problems in the long-term course may develop. The most relevant encompass heart failure, cardiac arrhythmias, heart valve disorders, pulmonary vascular disease, infective endocarditis (IE), aortopathy and non-cardiac comorbidities. The present publication emphasizes current data on IE, pulmonary and pulmonary arterial hypertension and aortopathy in ACHD and underlines the deep need of an experienced follow-up care by specialized and/or certified physicians or centers, as treatment regimens from acquired heart disease can not be necessarily transmitted to CHD. Moreover, the need of primary and secondary medical prevention becomes increasingly important in order to reduce the burden of disease as well as the socioeconomic burden and costs in this particular patient group.

Keywords: Congenital heart defect (CHD); endocarditis; heart failure; primary health care; pulmonary hypertension; aortopathy; prevention

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Infective endocarditis (IE) in congenital heart disease

The exact percentage of IE in the general population is unknown. A scientific statement for healthcare professionals from the American Heart Association quotes an annual incidence ranging from 3–7 per 100,000 person-years in the most contemporary population surveys (1-4). The wide range of incidence rates, reported from 1–15 cases per 100,000 per year, vary due to different inclusion data. They result from inclusion of different populations at risk, diverse diagnostic criteria and inclusion of cases with “possible” IE and referral bias (5-8). Epidemiological studies on IE from hospital case series suffer from selection bias, while well conducted prospective studies from population-based investigations are scarce (6). Amongst adults with CHD the incidence of IE remains according to contemporary reports between 0.91 and 1.32 cases/1,000 patient-years (9,10).

The risk is particularly high in adults, in patients with complex congenital heart anomalies, ventricular septal defects, prosthetic valves, and with left sided heart disease (10,11).

Male gender appears to be an independent predictor for developing endocarditis. Right-sided IE is more frequently seen in CHD compared to acquired heart disease. The impact of cyanosis, of types of valves and valved conduits, or whether a valve has been surgically or percutaneously implanted, on the risk of endocarditis is not clearly defined (11-13).

If IE is suspected, all diagnostic measures should be initiated at an early stage, especially in patients with CHD and corresponding symptoms, e.g., fever, night sweats, unclear loss of body weight, and/or newly occurring heart failure. These tests include the modified Duke criteria, laboratory tests, blood cultures, transthoracic and transesophageal echocardiography, and sometimes computed tomography (CT) and positron emission computed tomography (PET-CT) (14).

Before the introduction of antibiotics, IE was almost always lethal. Despite the modern antibiotics and aggressive surgical procedures, this still applies to up to 20% of cases (7).

In any case, particularly in adult CHD a multidisciplinary approach to IE is strongly recommended, including congenital cardiologists, microbiologists, CHD surgeons, and specialists in infectious disease and other disciplines (9). Given the high mortality, IE-prophylaxis should be given to patients at risk. This hypothesis, based on the assumption

Dental procedures that involve: (I) manipulation of gingival tissue; (II) manipulation of the periapical region of teeth; (III) perforation of the oral mucosa

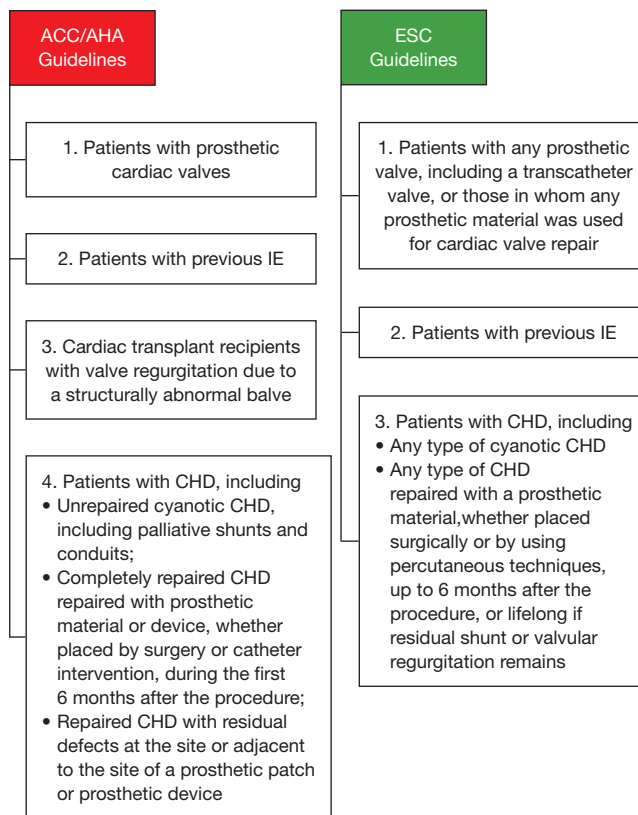


Figure 1 Use of antibiotic prophylaxis for the prevention of IE due to dental procedures, according to the ACC/AHA and ESC guidelines (20,21). IE, infective endocarditis; ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology.

that bacteremia during medical procedures can lead to IE in patients at risk, is not confirmed by randomized, placebo controlled studies. Since about 1955, national and international societies have published guidelines for IE-prophylaxis, with subsequent adjustments in accordance with the latest findings. Since about 2007, a substantial liberalization of IE-prophylaxis recommendations has taken place (15-18). At present, IE-prophylaxis is only recommended for high-risk patients and an expected severe course and fewer medical procedures have been classified as requiring IE-prophylaxis (1,16,19,20) (Figure 1).

In international comparison, however, the new recommendations and strategy changes are not uniform (22).

It must be emphasized that the new recommendations are viewed controversial in the area of CHD and that at least some experienced clinicians see a wider spectrum of indications.

Before performing IE-prophylaxis, it has to be clarified, whether there is an increased risk of IE, which procedures are planned for diagnostic or therapeutic interventions, how IE-prophylaxis is optimally performed and the risks associated with antibiotic application.

In addition to antibiotic prophylaxis, good body and oral hygiene is of great importance. Tattoos and body piercing are generally not recommended. It is indispensable that not only physicians and dentists, but also all patients at risk, are given these information.

Unfortunately, the knowledge of the patients about the importance and the performance of IE-prophylaxis are often insufficient, despite intensive information from their treating physicians (23). In our experience, it is very successful to hand leaflets with precise recommendations on the IE-prophylaxis to the patients.

Pulmonary hypertension and pulmonary arterial hypertension in congenital heart disease [P(A)H-CHD]

Pulmonary hypertension and pulmonary arterial hypertension in children and adults with CHD [P(A)H-CHD] is a continuum from treatable CHD to severe pulmonary vascular disease (24).

Current estimates suggest that up to 10% of patients with CHD develop a P(A)H, which has a decisive impact on the ability and prognosis of those affected (25-27).

Primary left-right-shunt lesions, congenital obstructions of the left heart, cyanotic heart defects with increased pulmonary flow, and anomalies of the pulmonary artery are the most frequent lesions which can be complicated by a P(A)H, and in which P(A)H may considerably impair the quality and duration of life. Another group includes patients with univentricular hearts after Fontan operation that can develop pulmonary vascular disease (28-30).

Of clinical and prognostic importance is the assignment of the P(A)H-CHD to different classes of PH, including Eisenmenger syndrome, left-right shunt lesions with increased lung flow without cyanosis, PAH randomly associated with a small left-right shunt, or PAH persistent or developing after repair (*Table 1, Figure 2*) (25).

Early and correct diagnosis of P(A)H is of outstanding importance for the care of these patients, as quite often a timely surgical or interventional treatment can improve the

clinical course and the prognosis considerably.

The complexity of the underlying diseases makes it advisable to guide all ACHD jointly in cooperation between congenital cardiologists and P(A)H-experts (32). This is particularly important when decisions are made on the initiation of a PAH-targeted therapy, the options for an operative or interventional treatment (e.g., interventional Pott-shunt, atrioseptostomy) or decisions on intensive care measures and/or lung- or heart-lung transplantation (25,33).

Adults with P(A)H-CHD differ fundamentally from other P(A)H forms regarding diagnostics, risk stratification, and therapy decisions. This is especially true for cyanotic patients with and without Eisenmenger syndrome (34). Referring to this, certain special features, such as life style, IE prophylaxis, vaccination (influenza and pneumococcae), psychological support, physical activity and physical training, behavior on flights and recommendations for pregnancy, contraception or elective operations have to be taken into consideration (25,34).

It is important to recognize that some treatment forms may have negative systemic site-effects in these vulnerable patients. Therefore, the respective individual disorder has to be taken into account meticulously, particularly concerning of supportive therapy with vasodilators (AT-blockers, ACE-inhibitors), diuretics, oxygen, oral anticoagulation, phlebotomy as well as replacement for anemia and/or iron deficiency (35,36).

For specific pharmacotherapy in PAH-CHD several drug classes are available, including endothelin antagonists, PDE 5 inhibitors, prostanoids or IP prostacyclin receptor agonists, as well as stimulants of the soluble guanylyl cyclase (sGC). Their application can lead to a significant improvement in quality of life and prognosis (25,32).

Current trial data on P(A)H-CHD leave many questions unanswered, particularly which drugs are primarily used and whether mono- or combination therapy is preferable. Currently, treatment decisions for ACHD are based largely on clinical expertise and only to a limited extent on clinical trials; they must hence remain limited to experienced specialists (*Figure 3*) (25,32,36).

Aortopathy in ACHD

The association of aortic pathophysiological degeneration, aortic dilation and aortic-ventricular interaction can be recognized as a new clinical entity: "Aortopathy" (37,38).

Aortic ectasia is well recognized in Marfan syndrome, Turner syndrome, bicuspid aortic valve or aortic

Table 1 Clinical classification of pulmonary arterial hypertension in congenital shunt lesions; modified from (28,31)

Group	Class	Definition
A	Eisenmenger syndrome	<ul style="list-style-type: none"> All major intra- and extra-cardiac cardiovascular defects with initial systemic to pulmonary blood flow (shunt), in which 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-multiple organ involvement
B	Left-to-right shunts correctable (by intervention or surgery)	<ul style="list-style-type: none"> Medium- to large-size defects with mild to moderate systemic-pulmonary blood flow but no cyanosis at rest
C	PAH, coincidentally associated with a CHD	<ul style="list-style-type: none"> 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 precise 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
D	PAH after previous repair	<ul style="list-style-type: none"> Persistent PAH that reoccurs within months or years after repair of the CHD, without haemodynamically relevant re- or residual shunts
E	Others	<ul style="list-style-type: none"> Segmental PAH Pulmonary vascular disease after previous Fontan-Operation

PVR, pulmonary vascular resistance; PAH, pulmonary arterial hypertension; CHD, congenital heart defect.

coarctation, and consistently associated with ascending aortic and/or para-coarctation medial degeneration (39-41). CHD, such as univentricular hearts, truncus arteriosus communis, transposition of the great arteries, hypoplastic left heart syndrome and tetralogy of Fallot, may also be associated with aortic medial degeneration and aortic dilatation (39,42,43).

Aortic medial degeneration, inaccurately called “cystic medial necrosis”, reach their severest form in Marfan syndrome and annuloaortic ectasia. In other CHD they are qualitatively similar but seldom quantitatively so pronounced. Aortic medial degeneration possibly reflect also in CHD a common developmental fault that weakens the aortic wall, causing aortic dilatation with decreased aorta elasticity and increased stiffness (44,45). A subset of adults with CHD exhibit ongoing ectasia of the aortic root and reduced aortic elasticity that may relate to intrinsic properties of the aortic root. This new concept of aortic dilatation is shifting in CHD-patients the paradigm of aortic dilatation from so called “poststenotic dilatation” to

primary intrinsic aortopathy.

Aortic dilatation and increased aortic stiffness can induce aortic aneurysm, rupture and aortic valve regurgitation, but also left ventricular hypertrophy, reduced coronary artery flow and left ventricular failure (45).

For prevention of aortic dilatation beta-blockers and angiotensin-converting enzyme (ACE) inhibitor are frequently prescribed in Marfan syndrome. Since the histopathological changes are similar in CHD, it might be logical to administer beta-blockers and/or angiotensin receptor blocker also to the CHD patients with aortopathy, but scientific data are not robust and definite medication is not yet established.

Monogenetic aortic syndromes

Monogenetic aortic syndromes are a subgroup of CHD, frequently complicated by aortic root aneurysms. These syndromes are rare, and are usually inherited as an autosomal dominant trait. Marfan-, Loeys-Dietz- (46),

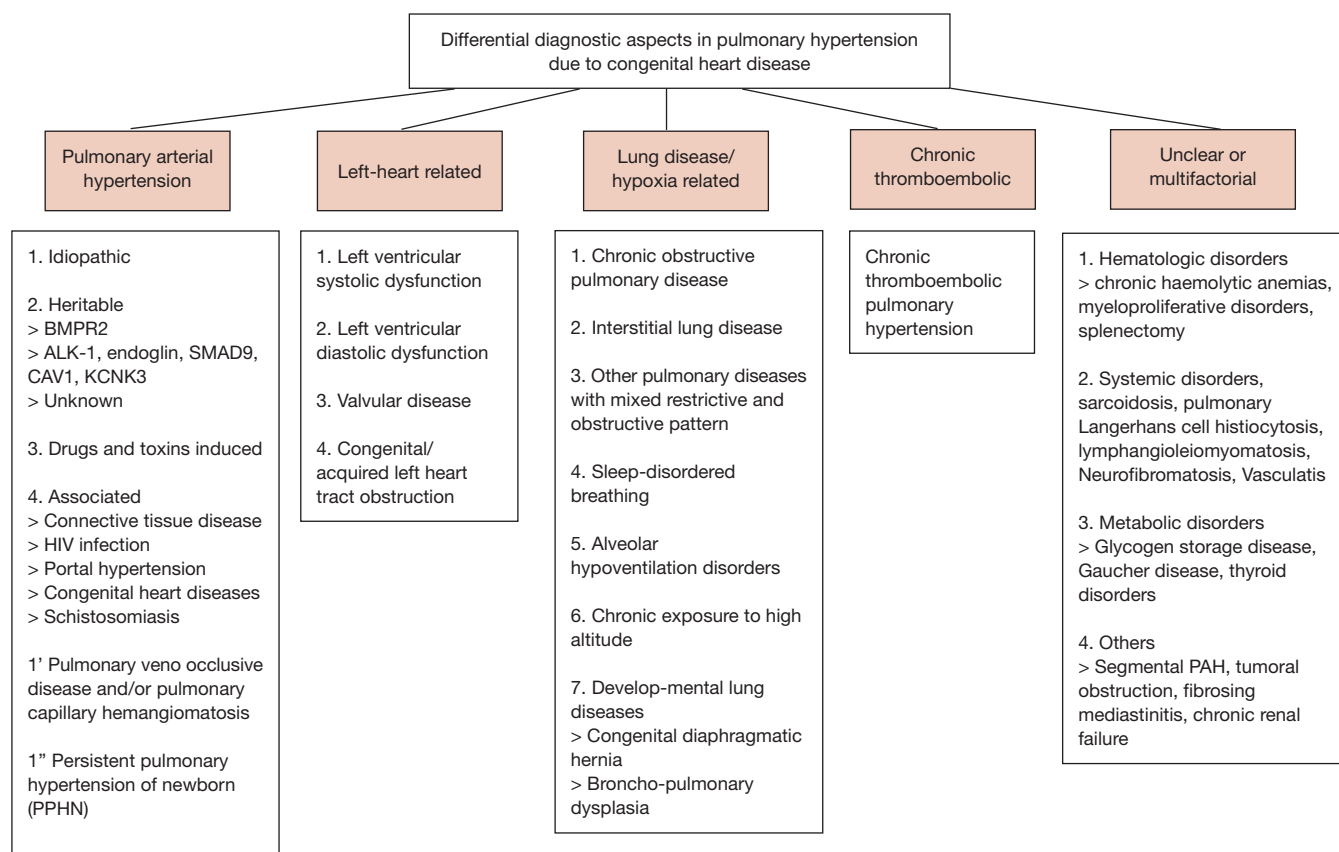


Figure 2 Differential diagnostic aspects in pulmonary hypertension due to congenital heart disease (32). PAH, pulmonary arterial hypertension.

vascular Ehlers-Danlos syndrome (47), or familial non-syndromic thoracic aortic aneurysm or dissection (TAAD) are the most frequent entities (48). In untreated Marfan patients, life expectancy is reduced by 30–40% of the normal population (49), while the other mentioned syndromes have a similar or even worse prognosis (48–50). If left untreated, most patients die from aortic dissection or rupture, but heart failure, ventricular arrhythmia, and IE may also cause mortality and morbidity.

Especially in Marfan syndrome a primary cardiomyopathy may exist, but it is rarely the exclusive cause of severe heart failure. Heart failure results typically from severe aortic valve regurgitation due to aortic root dilatation, from mitral valve prolapse, or after heart surgery. Myocardial dysfunction is probably the major cause of ventricular arrhythmias and sudden death in Marfan syndrome.

Optimal treatment of monogenetic aortic syndromes is possible only in multidisciplinary expert centres (50). Mainstay of treatment is medication with beta blockers,

ACEI, or ARBs, and prophylactic surgery with replacement of the aortic root with aortic valve-sparing root replacement or composite graft-valve replacement. Such treatment has been shown to significantly improve life expectancy at least in Marfan patients. Unfortunately, under-diagnosis of Marfan syndrome remains a substantial problem, where misdiagnosis and diagnostic delay were shown to result in delay of treatment with fatal consequences in many patients (48).

In conclusion, although today most patients with CHD survive into adulthood, many of them have relevant residua and sequels, and deeply need an experienced follow-up care by specialized and/or certified physicians or centres. Thereby, it is important that treatment regimens from acquired heart disease are not necessarily transmitted to CHD. Even simple, postoperative heart defects that were until recently considered to be harmless can lead to problems with age, a fact that had not been expected so far. Moreover, the awareness of ACHD problems must be increased to close actual supply gaps.

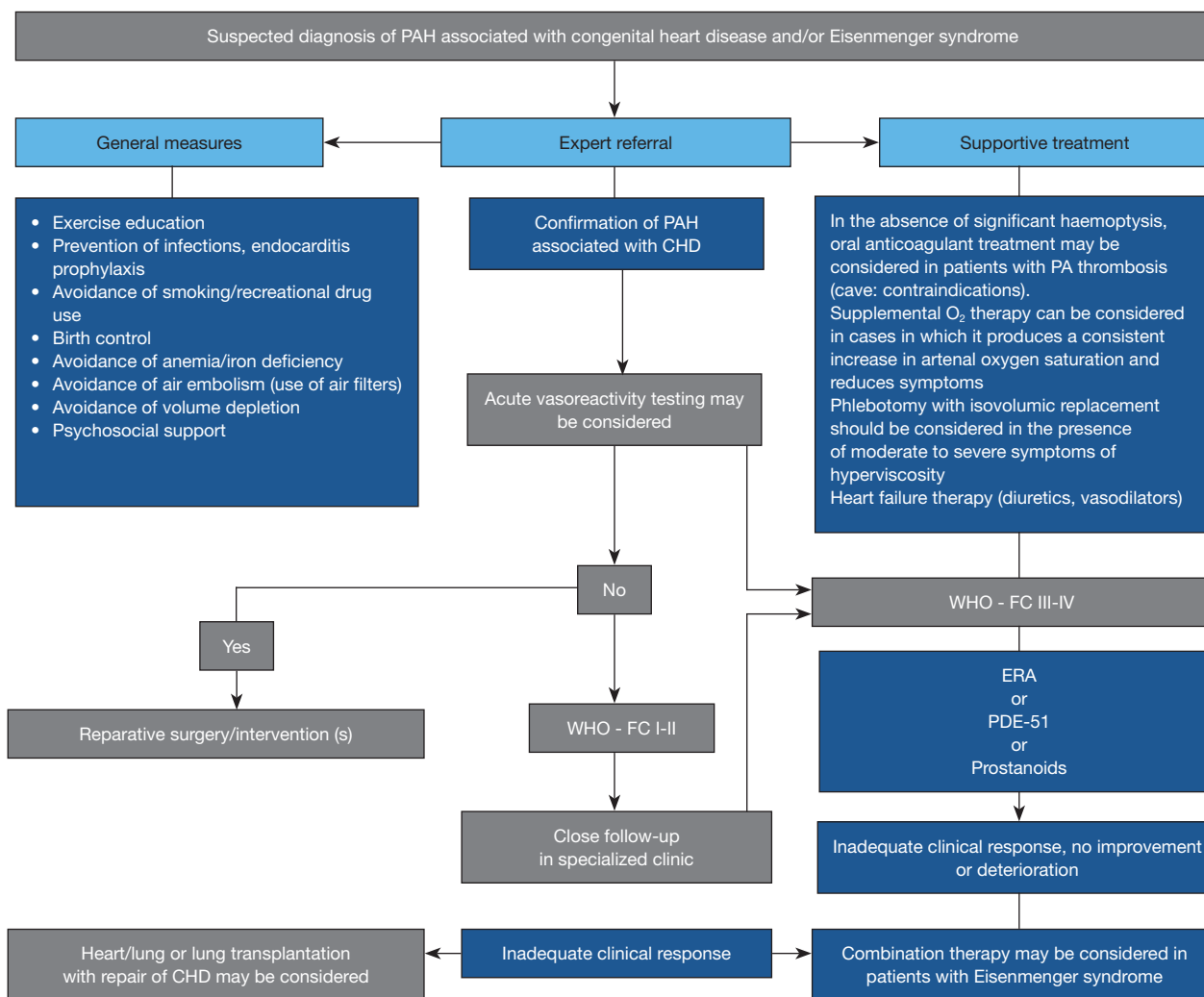


Figure 3 Suspected diagnosis of PAH associated with congenital heart disease/Eisenmenger syndrome. Modified from (31). PAH, pulmonary arterial hypertension.

The field of CHD, primary and secondary medical prevention will henceforth become increasingly important in order to reduce the burden of disease as well as the socioeconomic burden and costs.

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Footnote

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