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ESC Guidelines for the management of grown-up congenital heart disease (new version 2010)

The Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC)

Endorsed by the Association for European Paediatric Cardiology (AEPC)

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Abbreviations and acronyms

ACE	angiotensin-converting enzyme
AP	angina pectoris
APC	atriopulmonary connection
AR	aortic regurgitation
AS	aortic stenosis
ASD	atrial septal defect
AV	atrioventricular
AVA	aortic valve area
AVSD	atrioventricular septal defect
BAV	bicuspid aortic valve
BNP	B-type natriuretic peptide
BSA	body surface area
CAD	coronary artery disease
ccTGA	congenitally corrected transposition of the great arteries
CHD	congenital heart disease
CMR	cardiac magnetic resonance
CoA	coarctation of the aorta
CPET	cardiopulmonary exercise testing
CRT	cardiac resynchronization therapy
CT	computed tomography
DCRV	double-chambered right ventricle
ECG	electrocardiogram
EF	ejection fraction
EP	electrophysiology
ERA	endothelin receptor antagonist
FISH	fluorescent *in situ* hybridization
GUCH	grown-up congenital heart disease
ICD	implantable cardioverter defibrillator
IE	infective endocarditis
INR	international normalized ratio
IVC	inferior vena cava
LA	left atrium
LPA	left pulmonary artery
L–R shunt	left-to-right shunt
LV	left ventricle
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic diameter
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract
LVOTO	left ventricular outflow tract obstruction
MAPCAs	major aortic pulmonary collaterals
MCV	mean corpuscular volume
NYHA	New York Heart Association
PA	pulmonary artery
PA+VSD	pulmonary atresia with ventricular septal defect
PAH	pulmonary arterial hypertension

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PAP	pulmonary artery pressure
PDA	patent ductus arteriosus
PFO	patent foramen ovale
PLE	protein-losing enteropathy
PM	pacemaker
PPVI	percutaneous pulmonary valve implantation
PR	pulmonary regurgitation
PS	pulmonary stenosis
PVR	pulmonary vascular resistance
PVRep	pulmonary valve replacement
RA	right atrium
R–L shunt	right-to-left shunt
RPA	right pulmonary artery
RV	right ventricle
RVEF	right ventricular ejection fraction
RVH	right ventricular hypertrophy
RVOT	right ventricular outflow tract
RVOTO	right ventricular outflow tract obstruction
RVP	right ventricular pressure
SCD	sudden cardiac death
SubAS	subaortic stenosis
SupraAS	supravalvular aortic stenosis
SVC	superior vena cava
SVR	systemic vascular resistance
TCPC	total cavopulmonary connection
TEE	transoesophageal echocardiography
TGA	transposition of the great arteries
TGF	transforming growth factor
ToF	tetralogy of Fallot
TR	tricuspid regurgitation
TTE	transthoracic echocardiography
UVH	univentricular heart
VF	ventricular fibrillation
Vmax	maximum Doppler velocity
VSD	ventricular septal defect
VT	ventricular tachycardia
WHO-FC	World Health Organization-functional class
WPW	Wolff–Parkinson–White
WU	Wood units

1. Preamble

Guidelines summarize and evaluate all currently available evidence on a particular issue with the aim of assisting physicians in selecting the best management strategies for an individual patient, suffering from a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes for textbooks, and their legal implications have been discussed previously. Guidelines and recommendations should help physicians to make decisions in their daily practice. However, the ultimate judgement regarding the care of an individual patient must be made by his/her responsible physician(s).

A large number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC Web Site (http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx).

Members of this Task Force were selected by the ESC to represent all physicians involved with the medical care of patients in this pathology. In brief, experts in the field are selected and undertake a comprehensive review of the published evidence for management and/or prevention of a given condition. A critical evaluation of diagnostic and therapeutic procedures is performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger populations are included, where data exist. The level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels have provided disclosure statements of all relationships they may have which might be perceived as real or potential sources of conflicts of interest. These disclosure forms have been compiled into one file and can be found on the ESC Web Site (http://www.escardio.org/guidelines). Any changes in disclosures of interest that arise during the writing period must be notified to the ESC. The Task Force report received its entire financial support from the ESC without any involvement from the pharmaceutical, device, or surgical industry.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines.

Table 1 Classes of recommendations

Classes of recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Table 2 Levels 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.

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The finalized document has been approved by all the experts involved in the Task Force, and was submitted to outside specialists for review. The document was revised, and finally approved by and subsequently published in the *European Heart Journal*.

After publication, dissemination of the message is of paramount importance. Pocket-sized versions and personal digital assistant (PDA) downloadable versions are useful at the point of care. Some surveys have shown that the intended end-users are sometimes unaware of the existence of guidelines, or simply do not translate them into practice, so this is why implementation programmes for new guidelines form an important component of the dissemination of knowledge. Meetings are organized by the ESC, and directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at national levels, once the guidelines have been endorsed by the ESC member societies, and translated into the national language. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Thus, the task of writing guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. The loop between clinical research, writing of guidelines, and implementing them in clinical practice can then only be completed if surveys and registries are performed to verify that real-life daily practice is in keeping with what is recommended in the guidelines. Such surveys and registries also make it possible to evaluate the impact of implementation of the guidelines on patient outcomes. The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, in consultation with that patient, and where appropriate and necessary the patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

2. Specific background

Recognition of the advances in the care of the increasing population of adults with congenital cardiac malformations has prompted publication of this update to the previous European Society of Cardiology Guidelines on the Management of Grown-Up Congenital Heart Disease (GUCH). The large variety of congenital heart disease (CHD) and related specific problems on the one hand and the strict space limit of practice guidelines on the other hand presented a challenging task to the writing groups of both documents. In order to accomplish this task the previous version provided a comprehensive section of general considerations [which remains relevant (http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/grown-up-congenital-heart-disease.aspx)], but it had to reduce the part on specific congenital heart defects to a table format. This may frequently not meet the reader's needs when a guideline document is consulted in clinical practice. The new version tries to provide more detailed information on specific defects and therefore had to reduce the general considerations as well as references to a minimum in order stay within space limits.

The aim of practice guidelines is to be evidence based, but, in a relatively young specialty dealing with a variety of diseases and frequently small patient numbers, there is a lack of robust data. It is therefore difficult to use categories of strength of endorsement as have been used in other guidelines documents. The vast majority of recommendations must unfortunately remain based on expert consensus rather than on solid data (level of evidence C).

3. General considerations

3.1 Prevalence of grown-up congenital heart disease and organization of care

Precise data on the size and composition of the GUCH population are still lacking and can be assumed to change constantly. The remarkable improvement in survival of patients with CHD has led to a continuously growing number of GUCH patients, in particular those with more complex disease. In addition, some defects [e.g. atrial septal defect (ASD), coarctation of the aorta (CoA), Ebstein's anomaly, and congenitally corrected transposition of the great arteries (ccTGA)] may be diagnosed for the first time in adult life. The 32nd Bethesda Conference report in 2000[1] estimated that there were ~2800 adults with CHD per 1 million population, with more than half of them having moderate or high complexity of their defect. It is particularly this growing number of adults with moderate and high complexity of CHD that requires specialist care. Special health care organization and training programmes for those involved in GUCH care are required to meet the needs of this special population. An ESC publication is being prepared to update the recommendations on organization of care and GUCH training. The present document refers to the previous ESC guidelines[2] where recommendations for the transition from paediatric to adult care, the infrastucture and network of specialist GUCH centres with models of delivery, the actual delivery of patient care, and the requirements for training are covered in more detail. The previous guidelines stratified patient care into three levels: (i) patients who require care exclusively in the specialist centre; (ii) patients in whom shared care can be established with the appropriate general adult cardiac services; and (iii) patients who can be managed in 'non-specialist' clinics (with access to specialized care if required). The current document in general did not attempt to assign a certain level of care just by diagnosis. Although the complex defects can easily be assigned to high level care, even simple defects may require specialist care under certain circumstances [e.g. ASD with pulmonary arterial hypertension (PAH)]. Many experts therefore feel that the best care is provided when most GUCH patients are seen once in a specialist centre, and recommendations are then made with regard to follow-up intervals and level of care on an individualized basis. A well working network of specialist centres with general adult care is of critical importance.

3.2 Diagnostic work-up

A thorough clinical evaluation is of critical importance in the diagnostic work-up of GUCH patients. The aim of analysing patient history is to assess present and past symptoms as well as to look for intercurrent events and any changes in medication. The patient should be questioned on his/her lifestyle to detect progressive changes in daily activity in order to limit the subjectivity of symptom analysis. Clinical examination plays a major role and

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includes, during follow-up, careful evaluation with regard to any changes in auscultation findings or blood pressure or development of signs of heart failure. An electrocardiogram (ECG) and pulse oximetry are routinely carried out alongside clinical examination. Chest X-ray is no longer performed routinely at each visit, but rather when indicated. It remains, nevertheless, helpful for long-term follow-up, providing information on changes in heart size and configuration as well as pulmonary vascularization.

Strategies for investigation of anatomy and physiology of CHD are changing rapidly, with a shift from invasive studies to non-invasive protocols involving not only echocardiography but, more recently, cardiovascular magnetic resonance (CMR) and computed tomography (CT). Nuclear techniques may be required in special indications.

Evaluation of arrhythmias, primarily in symptomatic patients, may require Holter monitoring, event recorders, and eventually electrophysiology (EP) testing (see Section 3.3.2). Cardiopulmonary exercise testing (CPET) has gained particular importance in the assessment and follow-up of GUCH patients. It plays an important role in the timing of intervention and re-intervention.

3.2.1 Echocardiography

Echocardiography remains the first-line investigation and continues to evolve, with improved functional assessment using three-dimensional echocardiography, Doppler tissue imaging and its derivatives, contrast echocardiography, and perfusion imaging. Transoesophageal echocardiography (TEE) with superior image quality in adults is advantageous in certain indications, but is required in a minority of examinations. It is excellent for cardiac monitoring during procedures such as ASD closure, but usually requires sedation or general anaesthesia. Intracardiac echocardiography can be used as an alternative, but at greater expense.

Echocardiography provides, in most instances, information on the basic cardiac anatomy including orientation and position of the heart, venous return, connection of the atria and ventricles, and origin of the great arteries. It allows evaluation of the morphology of cardiac chambers, ventricular function, and detection and evaluation of shunt lesions, as well as the morphology and function of heart valves. Assessment of ventricular volume overload (increase in end-diastolic volume and stroke volume) and pressure overload (hypertrophy, increase in ventricular pressure) is of major importance. Doppler echocardiographic information also includes haemodynamic data such as gradients across obstructions and right ventricle (RV) pressure/pulmonary artery pressure (PAP) [obtained from tricuspid regurgitation (TR) velocity], but also flow calculations. Although echocardiography can provide comprehensive information, it is highly user dependent, requiring special expertise in GUCH patients; its limitations must also be taken into consideration. Assessment of ventricular volumes and function may be complicated by geometry and regional incoordination, particularly in systemic and non-systemic RVs or univentricular hearts (UVHs). Doppler gradients may sometimes be misleading, particularly in right ventricular outflow tract obstruction (RVOTO), CoA, and stenoses in series. Venous return and great arteries may be difficult to image.

In any case, echocardiography will be the first-line diagnostic tool. Depending on the quality of the echocardiogram and any information that is missing, further non-invasive imaging or invasive assessment of haemodynamics will be required.

3.2.2 Cardiac magnetic resonance imaging

CMR has become increasingly important in GUCH patients and is an essential facility in the specialist unit. It enables excellent three-dimensional anatomical reconstruction, which is not restricted by body size or acoustic windows and has rapidly improving spatial and temporal resolution. It is particularly useful for volumetric measurements, assessment of vessels, and detection of myocardial fibrosis. ESC recommendations for the use of CMR in GUCH patients have recently been published.[3]

There are several groups of indications for CMR when assessing adult CHD in clinical practice:

- *CMR as an alternative to echocardiography, when both techniques can provide similar information but echocardiography cannot be obtained with sufficient quality*. The vast majority of the information described in Section 3.2.1 can also be provided by CMR, although echocardiography is superior in estimating gradients and PAP, and detecting small, highly mobile structures such as vegetations.
- *CMR as a second method when echocardiography measurements are borderline or ambiguous*: Left ventricle (LV) volumes and left ventricular ejection fraction (LVEF) may be critical in the management of GUCH patients (particularly in the setting of volume overload), and the same applies to quantification of valvular regurgitation. When the values provided by Doppler echocardiography are borderline or ambiguous, CMR should be applied as a second method in order to corroborate or to dismiss the echocardiographic values before making clinical decisions.
- *Indications where CMR is considered superior to echocardiography and should be regularly used when the information is essential for patient management*. These indications include:

☐ quantification of RV volumes and right ventricular ejection fraction (RVEF) [tetralogy of Fallot (ToF), systemic RV]
☐ evaluation of the RVOTO and RV–pulmonary artery (PA) conduits
☐ quantification of pulmonary regurgitation (PR)
☐ evaluation of pulmonary arteries (stenoses, aneurysms) and the aorta (aneurysm, dissection, coarctation)
☐ evaluation of systemic and pulmonary veins (anomalous connection, obstruction, etc.)
☐ collaterals and arteriovenous malformations (CT is superior)
☐ coronary anomalies and coronary artery disease (CAD) (CT is superior)
☐ evaluation of intra- and extracardiac masses (ct is superior)
☐ quantification of myocardial mass (LV and RV)
☐ detection and quantification of myocardial fibrosis/scar (gadolinium late enhancement)
☐ tissue characterization (fibrosis, fat, iron, etc.).

Currently, patients with implanted pacemakers (PMs) or defibrillators should in general not be imaged by CMR, and in this case CT provides an alternative.

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3.2.3 Computed tomography

CT plays an increasing role in imaging of GUCH patients, providing excellent spatial resolution and rapid acquisition time. It is particularly good for imaging epicardial coronary arteries and collateral arteries, and for parenchymal lung disease. Ventricular size and function can be assessed, with inferior temporal resolution compared with CMR. The major drawback of most current CT systems is its high dose of ionizing radiation, making serial use unattractive. CT is currently more widely available than CMR and thus plays a role in acute situations. Moreover, recent developments, such as ECG-triggered acquisition and newer rotational techniques, reduce the amount of radiation substantially, which may possibly make CT a more attractive alternative to CMR in the coming years.

All of these techniques require staff with expertise in complex CHD as well as in imaging, and this has training and resource implications.

3.2.4 Cardiopulmonary exercise testing

Formal exercise testing has an important role in the GUCH population, in which quality of life and functional capacity are key measures of the success of intervention. Traditional exercise testing uses protocols that are largely designed for risk stratification of ischaemic heart disease and are often not appropriate in GUCH patients. CPET, including assessment of objective exercise capacity (time, maximum oxygen uptake), ventilation efficiency (VE/VCO_2 slope), chronotropic and blood pressure response, as well as exercise-induced arrhythmia, gives a broader evaluation of function and fitness, and has endpoints which correlate well with morbidity and mortality in GUCH patients.[4] Serial exercise testing should therefore be a part of long-term follow-up protocols and interventional trials. It plays an important role in the timing of interventions and re-interventions.

3.2.5 Cardiac catheterization

Cardiac catheterization is now reserved for resolution of specific anatomical and physiological questions, or for intervention. Continuing indications include assessment of pulmonary vascular resistance (PVR), LV and RV diastolic function, pressure gradients, and shunt quantification when non-invasive evaluation leaves uncertainty, coronary angiography, and the evaluation of extracardiac vessels such as aortic pulmonary collateral arteries.

In shunt lesions with Doppler echocardiographically documented pulmonary hypertension (PAP >50% of systemic pressure), catheterization remains essential for therapeutic decision making. Estimation of PVR requires accurate calculation of pulmonary flow which may be difficult, particularly in complex CHD. Measurement of oxygen uptake rather than estimation may be required. If PAH is severe, testing of vasoreactivity may be required for the decision to intervene (shunt closure). Oxygen has been traditionally used, but nitric oxide may be preferable.[5]

Before surgery, coronary angiography should be performed in men >40 years of age, postmenopausal women, and patients with signs of or risk factors for CAD.

3.3 Therapeutic considerations

With exceptions, medical management is largely supportive (e.g. for heart failure, arrhythmias, pulmonary and systemic arterial hypertension, prevention of thrombo-embolic events, or endocarditis) and significant structural abnormalities usually require interventional treatment.

3.3.1 Heart failure

Heart failure is a frequent problem in the GUCH population. In general, GUCH practitioners try to follow current treatment recommendations for heart failure.[6] However, as the pathophysiology of cardiorespiratory dysfunction is often very different from the failing 'normal' circulation, extrapolation of results from published studies to GUCH patients may be difficult, particularly in settings such as transposition of the great arteries (TGA) with atrial switch repair (Mustard or Senning operation) or a Fontan circulation. The few available data on heart failure treatment in GUCH patients are not conclusive and are derived from small patient numbers. Thus, GUCH-specific recommendations can in general not be given. Cardiac resynchronization therapy (CRT) has gained increasing interest for use in GUCH patients with congestive heart failure. There is, as yet, little evidence on which to define indications and outcomes.

3.3.2 Arrhythmias and sudden cardiac death

Arrhythmias are the main reason for the hospitalization of GUCH patients and they are an increasingly frequent cause of morbidity and mortality.[7] Risk stratification, investigation, and choice of treatment are often different from those applied to the normally formed heart. Furthermore, the onset of arrhythmias may be a signal of haemodynamic decompensation, and the risk associated with arrhythmias may be amplified in the presence of the often abnormal underlying circulation. Adult cardiologists, even electrophysiologists, are often unaware of this. Results of catheter ablation are generally worse in GUCH patients than in other patients, but are improving with technical developments. Although requiring specific expertise, catheter ablation should be considered when symptomatic tachyarrhythmias require action and interventional treatment is feasible. Antiarrhythmic drug therapy is frequently poorly tolerated due to negative inotropic and other side effects. Few data exist on its safety and efficacy.

Sudden cardiac death (SCD) is of particular concern in GUCH patients. The five defects with the greatest known risk of late SCD are ToF, TGA, ccTGA, aortic stenosis (AS), and UVHs.[8,9] Various risk factors have been defined (see Sections 4.10 and 4.12). Unexplained syncope is an alarming event. Algorithms for risk assessment of SCD and indications for implantation of an implantable cardioverter defibrillator (ICD) have so far not been well established. Current guidelines for the prevention of SCD[9] give the following recommendations for patients with CHD:

- ICD implantation is indicated in survivors of cardiac arrest after exclusion of reversible causes (IB[9]).
- Patients with spontaneous sustained ventricular tachycardia (VT) should undergo invasive haemodynamic and EP evaluation. Recommended therapy includes catheter ablation or surgical resection to eliminate VT. If that is not successful, ICD implantation is recommended (IC[9]).
- Invasive haemodynamic and EP evaluation is reasonable in patients with unexplained syncope and impaired ventricular

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function. In the absence of a defined and reversible cause, ICD implantation is reasonable (IIaB[9]).
- EP testing may be considered for patients with ventricular couplets or non-sustained VT to determine the risk of sustained VT (IIbC[9]).
- Prophylactic antiarrhythmic therapy is not indicated for asymptomatic patients with isolated premature ventricular beats (IIIC[9]).

3.3.3 Surgical treatment

Many GUCH patients will have undergone intervention in childhood, but surgery during adulthood may be required in various situations:

(i) Patients with prior repair and residual or new haemodynamic complications.
(ii) Patients with conditions not diagnosed or not considered severe enough to require surgery in childhood.
(iii) Patients with prior palliation.

Surgery in GUCH patients (including anaesthesia and intensive care) is very different from conventional adult cardiac surgery, and this provides a strong case for concentrating resources into specialist units for both treatment and training.

It should be appreciated that even minor non-cardiac surgery may carry a high risk; consultation with specialists, and careful preoperative planning and intra-operative monitoring, are vital to avoid complications.

One of the most challenging ongoing issues for surgery in GUCH patients is heart and heart–lung transplantation. The increased complexity of GUCH patients (previous thoracotomies, presence of aortic pulmonary collaterals, etc.) may affect outcome, and the worsening donor situation is such that patients will rarely receive a transplant in many countries. Alternatives, such as long-term mechanical support and/or xenotransplantation, are therefore important areas of research.

3.3.4 Catheter intervention

There has been a marked increase in the number and range of interventional catheterization procedures in GUCH, which in some patients obviates the need for surgery. In others, treatment of congenital cardiac malformations is best achieved by a collaborative ('hybrid') approach involving interventional catheterization and surgery. Newer techniques include stenting of systemic or pulmonary vessels and percutaneous valve implantation. The decision to perform an intervention should involve a process of rigorous peer review and multidisciplinary discussion, as currently few data exist to demonstrate non-inferiority over surgery for many of these approaches.

An interventional programme is essential for the specialist GUCH unit, and requires appropriate facilities and allied medical and technical support. In the future, this is likely to include hybrid imaging/catheterization/operating theatres.

3.3.5 Infective endocarditis

The endocarditis risk in GUCH patients is substantially higher than in the general population, with marked variation between lesions. The ESC guidelines on prevention, diagnosis, and treatment of infective endocarditis (IE) have recently been updated and the present document refers to them for more detailed information (http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/infective-endocarditis.aspx). It has to be emphasized that good oral hygiene and regular dental review have an essential role in reducing the risk of IE. Aseptic measures are mandatory during manipulation of venous catheters and during any invasive procedure in order to reduce the rate of healthcare-associated IE. GUCH patients should also be discouraged from getting piercings and tattoos.

The approach to antibiotic endocarditis prophylaxis has changed for several reasons. In short, transient bacteraemia occurs not only after dental procedures but frequently in the context of daily routine activities such as tooth brushing, flossing, or chewing. Due to the lack of scientific evidence for the efficacy of antibiotic prophylaxis, the estimated huge number of patients that may need to be treated to prevent one single case of IE, the small but existing risk of anaphylaxis, and the general problem of emergence of resistant microorganisms resulting from widespread, often inappropriate use of antibiotics, it is currently recommended by expert consensus to limit antibiotic prophylaxis to patients with the highest risk of IE undergoing the highest risk procedures (IIaC). This recommendation includes the following patient groups:

- Patients with a prosthetic valve or a prosthetic material used for cardiac valve repair
- Patients with previous IE
- Patients with CHD:
  - ☐ cyanotic CHD, without surgical repair, or with residual defects, palliative shunts, or conduits
  - ☐ CHD after repair with prosthetic material whether placed by surgery or by percutaneous technique, up to 6 months after the procedure (until endothelialization)
  - ☐ when a residual defect persists at the site of implantation of a prosthetic material or device by cardiac surgery or percutaneous technique.

The recommendation is limited to dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa. Antibiotics are not recommended for respiratory tract, gastrointestinal, genitourinary, dermatological, or musculoskeletal procedures unless there is an established infection.

The updated recommendations dramatically change long-established practice for primary care physicians, cardiologists, dentists, and their patients. For ethical reasons, these practitioners need to discuss the potential benefit and harm of antibiotic prophylaxis with their patients before a final decision is made. Following informed review and discussion, some patients (and also physicians) may wish to continue with routine prophylaxis in the individual case, and these views should be respected.

3.4 Non-cardiac issues

GUCH patients are confronted with numerous non-cardiac challenges, which include non-cardiac surgery, exercise and sport, contraception and pregnancy, and social and psychological issues (these issues cannot be covered in detail in this document). In addition, life and health insurance may be difficult to obtain.

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GUCH practitioners must be aware of these challenges, be prepared to help patients and their families with numerous psychosocial issues, and work on a multidisciplinary basis to provide psychological support. Many of these issues should begin to be discussed during the transition process between paediatric and adult care.

3.4.1 Insurance

Despite recommendations from cardiac societies, availability of insurance varies considerably not only between but also within countries, with surprising discordance between insurance policies and available outcome data. Health insurance, in particular, may exclude treatment for the cardiac condition in some countries. This has important consequences in 'insurance-based' medical systems. Patients currently need to shop around, and patient associations can often help. In the future, consistent national strategies for insurance need to be developed if medical care is not to be compromised by financial considerations. Another problem is where life insurance companies frequently refuse young patients with underlying heart disease.

3.4.2 Exercise and sports

Recommendations for exercise and sports need to be based on the patient's ability, the impact on underlying haemodynamics, and the risk of acute decompensation and arrhythmias. Counselling should be based on the type of sport and the anticipated effort levels. Formal testing is invaluable and, in general, physicians have been over-conservative in their advice. Participation in regular exercise has a well documented benefit for fitness, psychological well-being, and social interaction, as well as having a positive effect on the future risk of acquired heart disease. As a general recommendation, dynamic exercise is more suitable than static exercise. In patients with known cardiac conditions, sudden death during exercise is very rare.[10] Detailed recommendations for the participation in competitive sports are beyond the scope of this document and have previously been published.[11,12] Some lesions are not compatible with competitive sports, due to their morphological severity/complexity and tendency to serious arrhythmias, including Eisenmenger syndrome, PAH, UVH, coronary artery anomalies, Ebstein's anomaly, and ccTGA and TGA repaired by atrial switch or Rastelli procedure.[13]

3.4.3 Pregnancy, contraception, and genetic counselling

The majority of GUCH patients tolerate pregnancy well, but specialist care is best provided in a multidisciplinary team setting. This team should have input from GUCH cardiology, obstetrics, anaesthesia, haematology, neonatology, and genetics. Timely counselling should be an essential component of the service provided. The team should be involved early in pregnancy in order to plan antenatal care, including delivery and post-partum follow-up. Severe PAH (Eisenmenger patients and others) remains a condition with a high maternal mortality rate (30–50%)[14] despite modern-day therapies, and women should be advised against pregnancy. Other conditions associated with a high maternal risk are severe left heart outflow/inflow obstruction, poor systemic ventricular function [ejection fraction (EF) $<$40%], and aortic root dilation in Marfan and similar syndromes (Ehlers–Danlos, Loeys–Dietz). Cyanosis poses a significant risk to the foetus, with a live birth unlikely ($<$12%) if oxygen saturation is $<$85%.[15] For all other GUCH conditions, counselling must be individualized and lesion-specific. Detailed ESC guidelines on pregnancy and heart disease will be published shortly. The significant increase in cardiac output and decrease in peripheral vascular resistance in pregnancy, with its haemodynamic consequences for the different lesions, must be considered. Functional status before pregnancy and history of previous cardiac events are of particular prognostic value. A prospective study identified systemic ventricular EF $<$40%, baseline New York Heart Association (NYHA) functional class $>$II or cyanosis, left heart obstruction [aortic valve area (AVA) $<$1.5 cm and gradient $>$30 mmHg, mitral valve area $<$2.0 cm^2], and prior cardiac event (heart failure, cerebral event, or arrhythmia) as risk factors.[16] Patients without these findings (and no PAH, mechanical heart valve, or dilation of the aorta) can be considered to have a particularly low risk for pregnancy.

Foetal echocardiography should be recommended at 16–18 weeks gestation.

The potential for drugs to affect the foetus should always be considered. In particular, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and amiodarone should not be used.

For contraception, barrier methods are safe, and protect against sexually transmitted diseases. However, they have a high contraceptive efficacy only with compliant couples. Annual failure rates of up to 10% mean that they should be used with an additional, more effective method.

Hormonal contraceptives are highly efficacious, but there are few data on their safety in the GUCH population. The combined oral contraceptive is highly effective (99.9%), but is best avoided in those patients with a pre-existing thrombotic risk (Fontan circulation, cyanotic patients, poor systemic ventricular function), especially as there are few data to suggest that concomitant oral anticoagulation therapy will negate this risk. Progesterone-only contraceptives, on the other hand, do not pose such a high thrombosis risk, and newer preparations available for oral administration or with intrauterine implants have a high efficacy ($>$95%). The risk of endocarditis after insertion of gestagen-coated intrauterine devices is probably low. However, there is a risk of vasovagal reactions (5%) at the time of insertion or removal. Female sterilization or male partner sterilization should only be considered after careful discussion, with particular reference to long-term prognosis.

Appropriate genetic counselling should be provided. The recurrence rate of CHD in offspring ranges from 2 to 50% and is higher when the mother has CHD than when the father has CHD. The highest recurrence risks are found in single gene disorders and/or chromosomal abnormalities such as Marfan, Noonan, and 22q11 deletion syndromes, and Holt–Oram syndrome. For the others the recurrence rate is between 2 and 4% on average, and may reach 13–18% for AS and 6–10% for ventricular septal defect (VSD).[17]

4. Specific problems

Consensus advice on the follow-up and management of the common individual conditions that adult cardiologists are likely to encounter with increasing frequency is summarized in the

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following sections. As far as background and diagnostic work-up are concerned, only key findings are highlighted. For details please refer to textbooks on CHD.

4.1 Atrial septal defect

Introduction and background

ASD may not uncommonly remain undiagnosed until adulthood.

ASD types include:

- Secundum ASD (80% of ASDs; located in the region of the fossa ovalis and its surrounding)
- Primum ASD [15%, synonyms: partial atrioventricular septal defect (AVSD), partial atrioventricular (AV) canal; located near the crux, AV valves are typically malformed resulting in various degrees of regurgitation; see Section 4.3]
- Superior sinus venosus defect [5%, located near the superior vena cava (SVC) entry, associated with partial or complete connection of right pulmonary veins to SVC/right atrium (RA)]
- Inferior sinus venosus defect [<1%, located near the inferior vena cava (IVC) entry]
- Unroofed coronary sinus [<1%, separation from the left atrium (LA) can be partially or completely missing].

Associated lesions include anomalous pulmonary venous connection, persistent left SVC, pulmonary valve stenosis, and mitral valve prolapse. Secundum ASD may be associated with heart–hand syndromes (e.g. Holt–Oram syndrome, upper limb deformity).

The shunt volume depends on RV/LV compliance, defect size, and LA/RA pressure. A simple ASD results in left-to-right shunt (L–R shunt) because of the higher compliance of the RV compared with the LV (relevant shunt in general with defect sizes ≥10 mm), and causes RV volume overload and pulmonary overcirculation. Reduction in LV compliance or any condition with elevation of LA pressure (hypertension, ischaemic heart disease, cardiomyopathy, aortic and mitral valve disease) increases L–R shunt. Reduced RV compliance (pulmonic stenosis, PAH, other RV disease) or tricuspid valve disease may decrease L–R shunt or eventually cause shunt reversal, resulting in cyanosis.

Clinical presentation and natural history

Patients frequently remain asymptomatic until adulthood; however, the majority develop symptoms beyond the fourth decade including reduced functional capacity, exertional shortness of breath, and palpitations (supraventricular tachyarrhythmias), and less frequently pulmonary infections and right heart failure. Life expectancy is reduced overall, but survival is much better than previously assumed. PAP can be normal, but on average increases with age. Severe pulmonary vascular disease is nevertheless rare (<5%) and its development presumably requires additional factors, including genetic predisposition (similarities to idiopathic PAH). With increasing age and with increasing PAP tachyarrhythmias become more common (atrial flutter, atrial fibrillation).[18] Systemic embolism may be caused by paradoxical embolism (rare) or atrial fibrillation.

Diagnostic work-up

See Section 3.2 for general principles.

Key clinical findings include fixed splitting of the second heart sound and a systolic pulmonary flow murmur. ECG typically shows an incomplete right bundle branch block and right axis deviation (superior left axis deviation in partial AVSD). An increased pulmonary vascularity on chest X-ray is frequently overlooked.

Echocardiography is the key diagnostic technique, providing diagnosis and quantification. RV volume overload, which may be the first unexpected finding in a patient with previously undiagnosed ASD, is the key finding and best characterizes the haemodynamic relevance of the defect (preferable to the shunt ratio). Sinus venosus defects require in general TEE for accurate diagnosis, as does the precise evaluation of secundum defects before device closure, which should include sizing, exploration of the residual septum's morphology, the rim size and quality, exclusion of additional defects, and confirmation of a normal pulmonary venous connection. Other key information to be provided includes PAP and TR.

CMR and ***CT*** can serve as an alternative if echocardiography is insufficient, particularly for assessment of RV volume overload and pulmonary venous connection.

Cardiac catheterization is required in cases of high PAP on echocardiography to determine PVR (see Section 3.2.5 for details).

Surgical/catheter interventional treatment (*Table 3*)

Surgical repair has low mortality (<1% in patients without significant co-morbidity) and good long-term outcome (normal life expectancy and low long-term morbidity) when performed early (childhood, adolescence) and in the absence of pulmonary

Table 3 Indications for intervention in atrial septal defect

Indications	Class[a]	Level[b]
Patients with significant shunt (signs of RV volume overload) and PVR <5 WU should undergo ASD closure regardless of symptoms	I	B[26]
Device closure is the method of choice for secundum ASD closure when applicable	I	C
All ASDs regardless of size in patients with suspicion of paradoxical embolism (exclusion of other causes) should be considered for intervention	IIa	C
Patients with PVR ≥5 WU but <2/3 SVR or PAP <2/3 systemic pressure (baseline or when challenged with vasodilators, preferably nitric oxide, or after targeted PAH therapy) and evidence of net L–R shunt (Qp:Qs >1.5) may be considered for intervention	IIb	C
ASD closure must be avoided in patients with Eisenmenger physiology	III	C

[a]Class of recommendation.
[b]Level of evidence.
ASD = atrial septal defect; L–R shunt = left-to-right shunt; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; Qp:Qs = pulmonary to systemic flow ratio; SVR = systemic vascular resistance; WU = Wood units.

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hypertension.[19,20] However, mortality may be higher in the elderly and in patients with co-morbidities.

Device closure has become first choice for secundum defect closure when feasible from morphology (includes stretched diameter <38 mm and sufficient rim of 5 mm except towards the aorta). This is the case in ~80% of patients. Although it cannot be assumed to be zero, several recent studies have reported no mortality. Serious complications were observed in ≤1% of patients.[21,22] Atrial tachyarrhythmias occurring early after intervention are mostly transient. Erosion of the atrial wall or the aorta as well as thrombo-embolic events appear to be very rare.[23,24] Antiplatelet therapy is required for at least 6 months (aspirin 100 mg daily minimum). Potential incidence of late arrhythmias or adverse events still requires investigation. Studies comparing surgery and catheter intervention have reported similar success rates and mortality, but morbidity was lower and hospital stay shorter with catheter intervention.[21,25]

Outcome is best with repair at age <25 years.[19,20] ASD closure after the age of 40 years appears not to affect the frequency of arrhythmia development during follow-up.[26,27] However, patients benefit from closure at any age with regard to morbidity (exercise capacity, shortness of breath, right heart failure), particularly when it can be done by catheter intervention.[26,27]

Poor LV function (systolic and diastolic) may cause pulmonary congestion after ASD closure and may require pre-interventional testing (balloon occlusion with reassessment of haemodynamics) and treatment.

In patients with atrial flutter/fibrillation, cryo- or radiofrequency ablation (modified Maze procedure) should be considered at the time of surgery.

In patients of advanced age with ASDs not feasible for device closure, individual surgical risk due to co-morbidities must be carefully weighed against the potential benefits of ASD closure.

Follow-up recommendations

Follow-up evaluation should include assessment of a residual shunt, RV size and function, TR and PAP by echocardiography, and also assessment of arrhythmias by history, ECG, and, only if indicated (not routinely), Holter monitoring. Patients repaired under the age of 25 years without relevant sequelae or residuae (no residual shunt, normal PAP, normal RV, no arrhythmias) do not require regular follow-up. However, patients and referring physicians should be informed about the possible late occurrence of tachyarrhythmias.

Patients with residual shunt, elevated PAP, or arrhythmias (before or after repair) and those repaired at adult age (particularly >40 years) should be followed on a regular basis including evaluation in specialized GUCH centres (intervals depending on the severity of residual problems). After device closure, regular follow-up during the first 2 years and then, depending on results, every 2–4 years is recommended.

Late post-operative arrhythmias after surgical repair at age <40 years are most frequently intra-atrial re-entrant tachycardia or atrial flutter which can be successfully treated with radiofrequency ablation. Without repair or with repair after 40 years, atrial fibrillation becomes more common and may require antiarrhythmic therapy (little is known about ablative therapy in this setting). Access to the LA may be restricted after device closure. Patients with atrial fibrillation should have oral anticoagulation. Sick sinus syndrome or heart block are less common.

Additional considerations

Exercise/sports: No restrictions in asymptomatic patients before or after intervention without pulmonary hypertension, significant arrhythmias, or RV dysfunction; limitation to low-intensity recreational sports in PAH patients (see Section 3.4.2).

Pregnancy: The risk from pregnancy in patients without pulmonary hypertension is low. Closure before pregnancy may prevent paradoxical embolism and worsening of clinical status. Pregnancy is contraindicated in patients with severe PAH or Eisenmenger syndrome (see Section 3.4.3). The recurrence rate of CHD is 3–10% (excluding familial ASD and heart–hand syndromes with autosomal dominant inheritance).

IE prophylaxis: Recommended for 6 months after device closure (see Section 3.3.5).

4.2 Ventricular septal defect

Introduction and background

As an isolated finding, VSD is the most common congenital heart malformation at birth (30–40%), if bicuspid aortic valve (BAV) is not counted. It is mostly diagnosed and—when indicated—treated before adulthood. Spontaneous closure is frequent. Several locations of the defect within the interventricular septum are possible and can be divided into four groups (nomenclature varies and synonyms are added):[28]

- Perimembranous/paramembranous/conoventricular (most common, ~80% of VSDs; located in the membranous septum with possible extension into inlet, trabecular or outlet septum; adjacent to tricuspid and aortic valve; aneurysms of the membranous septum are frequent and may result in partial or complete closure)
- Muscular/trabecular (up to 15–20%; completely surrounded by muscle; various locations; frequently multiple; spontaneous closure particularly frequent)
- Outlet supracristal/subarterial/subpulmonary/infundibular/supracristal/conal/doubly committed juxta-arterial [~5%; located beneath the semilunar valves in the conal or outlet septum; often associated with progressive aortic regurgitation (AR) due to prolapse of the aortic cusp, usually right]
- Inlet/AV canal/AVSD type (inlet of the ventricular septum immediately inferior to the AV valve apparatus; typically occurring in Down syndrome).

Often there is one single defect, but multiple defects do occur. VSD is also a common component of complex anomalies, such as ToF, ccTGA, etc. Spontaneous closure of a VSD can occur, most often in muscular/trabecular but also perimembranous defects. It is uncommon in outlet defects and occurs mainly during childhood.[29]

The direction and magnitude of the shunt are determined by PVR, the size of the defect, LV/RV systolic and diastolic function, and the presence of RVOTO.

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Clinical presentation and natural history

The usual clinical presentations in adults include:

- VSD operated on in childhood, without residual VSD
- VSD operated on in childhood, with residual VSD. The residual shunt size determines the presence of symptoms and the degree of LV volume overload
- Small VSD with insignificant L–R shunt, without LV volume overload or pulmonary hypertension which was not considered for surgery in childhood
- VSD with L–R shunt, pulmonary hypertension (various degrees), and various degrees of LV volume overload (rare)
- Eisenmenger syndrome: large VSD with originally large L–R shunt and development of severe pulmonary vascular disease eventually resulting in shunt reversal [right-to-left shunt (R–L shunt), cyanosis; see Sections 4.17 and 4.18].

A large majority of patients with a VSD that has been closed entirely in childhood, or patients with a small VSD who were either never operated on or who had a residual defect after surgical repair with no LV volume overload on echocardiography, usually remain asymptomatic and do not require surgery.[30] However, an unknown percentage of patients with a small residual VSD develop problems later in life.[31,32]

Several possible problems may occur with advancing age:

- Endocarditis, which has been reported to occur in up to 2 per 1000 patient-years (six times higher than in the normal population)
- Due to an increase in LV systolic and diastolic pressure the extent of the L–R shunting may increase in time, leading to LV volume overload and eventually heart failure. These patients are candidates for closure
- A double-chambered right ventricle (DCRV) can develop over time and may be a result of the jet lesion of the RV endothelium caused by the high velocity VSD jet
- Discrete subaortic stenosis (SubAS) can develop (rare)
- In the case of an outlet (supracristal) VSD, less common perimembranous, there is a substantial risk for prolapse of the right coronary (or non-coronary) cusp of the aortic valve, resulting in progressive AR
- Arrhythmias can occur, but are less frequent than in other forms of CHD[33]
- Complete heart block—rare nowadays—was not uncommon in the earlier years of cardiac surgery, so can occur especially in older patients. These patients usually require lifelong pacing.

Diagnostic work-up

See Section 3.2 for general principles.

Specific clinical findings include a holosystolic murmur over the third to fourth intercostal space, and a pre-cordial thrill may be felt.

Echocardiography is the key diagnostic technique, providing in general the diagnosis and assessment of disease severity. Key findings to provide are location, number, and size of defects, severity of LV volume overload, and estimated PAP. AR due to prolapse of the right or non-coronary cusp must be checked for, especially in the case of outlet (supracristal) and high perimembranous VSDs. DCRV must be excluded.

CMR can serve as an alternative if echocardiography is insufficient, particularly for assessment of LV volume overload and shunt quantification.

Cardiac catheterization is required in cases of high PAP on echocardiography to determine PVR (see Section 3.2.5 for details).

Surgical/catheter interventional treatment (*Table 4*)

Surgical closure (mostly pericardial patch) can be performed with low operative mortality (1–2%) and good long-term results, and remains the treatment of choice.[34] Transcatheter closure can be considered in patients with increased risk factors for surgery, multiple previous cardiac surgical interventions, or VSDs that are poorly accessible for surgical closure. In muscular VSDs that are located centrally in the interventricular septum, it can be considered as an alternative to surgical closure. In perimembranous VSD it has been shown to be feasible. Whether the risk of complete AV block and entrapment of tricuspid valve tissue leading to TR, or the risk of AR that has been observed in children, are relevant in adults remains to be seen.

Table 4 Indications for intervention in ventricular septal defect

Indications	Class[a]	Level[b]
Patients with symptoms that can be attributed to L–R shunting through the (residual) VSD and who have no severe pulmonary vascular disease (see below) should undergo surgical VSD closure	I	C
Asymptomatic patients with evidence of LV volume overload attributable to the VSD should undergo surgical VSD closure	I	C
Patients with a history of IE should be considered for surgical VSD closure	IIa	C
Patients with VSD-associated prolapse of an aortic valve cusp causing progressive AR should be considered for surgery	IIa	C
Patients with VSD and PAH should be considered for surgery when there is still net L–R shunt (Qp:Qs >1.5) present and PAP or PVR are <2/3 of systemic values (baseline or when challenged with vasodilators, preferably nitric oxide, or after targeted PAH therapy)	IIa	C
Surgery must be avoided in Eisenmenger VSD and when exercise-induced desaturation is present	III	C
If the VSD is small, not subarterial, does not lead to LV volume overload or pulmonary hypertension, and if there is no history of IE, surgery should be avoided	III	C

[a]Class of recommendation.
[b]Level of evidence.
AR = aortic regurgitation; IE = infective endocarditis; L–R shunt = left-to-right shunt; LV = left ventricle; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; Qp:Qs = pulmonary to systemic flow ratio; VSD = ventricular septal defect.

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Follow-up recommendations

Development of AR or TR, degree of (residual) shunt, LV dysfunction, elevation of PAP, development of DCRV, and development of discrete SubAS should be excluded or assessed if present by echocardiography.

Possible development of complete AV block requires attention (patients who develop bifascicular block or transient trifascicular block after VSD closure are at risk in later years for the development of complete AV block).

Patients with LV dysfunction, residual shunt, PAH, AR, RVOTO, or left ventricular outflow tract obstruction (LVOTO) should be seen every year, including evaluation in specialized GUCH centres. In patients with a small VSD (native or residual, normal LV, normal PAP, asymptomatic) and no other lesion, 3–5 year intervals may be reasonable. After device closure, regular follow-up during the first 2 years and then, depending on the result, every 2–4 years is recommended. After surgical closure without residual abnormality 5 year intervals may be reasonable.

Additional considerations

Exercise/sports: No restrictions are required in patients after VSD closure, or with small VSD without pulmonary hypertension, significant arrhythmias, or LV dysfunction. Patients with PAH must limit themselves to low-intensity recreational activity/sports (see Section 3.4.2).

Pregnancy: Pregnancy is contraindicated in Eisenmenger syndrome. The risk is low in asymptomatic patients with normal LV and no PAH (see Section 3.4.3). The recurrence rate of CHD has been reported at 6–10%.[17]

IE prophylaxis: Recommended only for high-risk patients (see Section 3.3.5).

4.3 Atrioventricular septal defect

Introduction and background

An AVSD (AV canal or endocardial cushion defect) is characterized by the presence of a common AV annulus, guarded by five leaflets. In the partial form, the anterior and posterior bridging leaflets are fused centrally, creating separate left- and right-sided orifices. In the complete AVSD the central fusion is not present and there is only one orifice. The partial AVSD (primum ASD, partial AV canal) has a defect only at the atrial level. A complete AVSD (complete AV canal) has a septal defect in the crux of the heart, extending into both the interatrial and interventricular septum. The AV node is positioned posterior and inferior to the coronary sinus. The bundle of His and the left bundle branch are displaced posteriorly. This accounts for an abnormal activation sequence of the ventricles.

AVSD accounts for ~3% of all congenital cardiac defects.

Thirty-five per cent of patients with AVSD have Down syndrome. Most complete AVSDs occur in Down patients (>75%), and most partial AVSDs occur in non-Down patients (>90%). AVSD may occur in association with ToF and other forms of complex CHD. It is very common in heterotaxy syndromes.

Since surgical treatment was in the past frequently withheld in patients with Down syndrome, these patients may present unoperated with complete AVSD and Eisenmenger syndrome.

Clinical presentation and natural history

Clinical presentation will mainly depend on the presence and size of the ASD and VSD and competence of the left-sided AV valve. Symptoms are not specific for an AVSD and are caused by intracardiac shunting (L–R, R–L, or bidirectional), pulmonary hypertension, AV valve regurgitation, ventricular dysfunction, or LVOTO. Exercise intolerance, dyspnoea, arrhythmia, and cyanosis may be present. SubAS may be present or develop in time.

The history of unoperated complete AVSD is that of Eisenmenger syndrome unless the VSD is only small (see Sections 4.17 and 4.18).

Unrepaired partial AVSD is not uncommon in adults. The presenting clinical symptoms are that of an L–R shunt at the atrial level (see Section 4.1) and/or that of left-sided AV valve regurgitation ('cleft'). Patients may still be asymptomatic, but symptoms tend to increase with age. Most adults are symptomatic by 40 years of age.

Diagnostic work-up

See Section 3.2 for general principles.

Clinical findings depend on the individual variant (see above). Fifty per cent of the patients have a prolonged AV conduction time and virtually all have a left axis or extreme left axis deviation on ECG.

Echocardiography is the key diagnostic technique. It provides assessment of each anatomic component of the AVSD, of the AV valves and their connections (straddling, overriding), the severity and exact substrate of AV valve regurgitation, the magnitude and direction of intracardiac shunting, LV and RV function, PAP, and assessment of the presence/absence of SubAS.

CMR is indicated when additional quantification of ventricular volumes and function or intracardiac shunting is required for decision making.

Cardiac catheterization is indicated in the case of high PAP on echocardiography for assessment of PVR (see Section 3.2.5 for details).

Surgical/catheter interventional treatment (*Table 5*)

Catheter closure of AVSDs is not feasible, and intervention is therefore surgical (defect closure, valve repair). In cases of residual interatrial or interventricular communications, endocardial pacing causes an elevated risk of paradoxical emboli. This should be taken into account when pacing is indicated. Epicardial pacing may be required.

Follow-up recommendations

Lifelong regular follow-up of all patients, operated and unoperated, with an AVSD is recommended, including evaluation in specialized GUCH centres. Particular attention should be paid to residual shunt, AV valve malfunction, LV and RV enlargement and dysfunction, PAP elevation, SubAS, and arrhythmias.[36] The frequency of outpatient visits depends on the presence and severity of residual abnormalities. A surgically repaired AVSD without significant residual abnormalities should be seen at least every 2–3 years. In the case of residual abnormalities, the intervals should be shorter.

Indications for reoperation for residual abnormalities are comparable with the indications for primary surgery. In operated

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Table 5 Indications for intervention in atrioventricular septal defect

Indications	Class[a]	Level[b]
Complete AVSD:		
• Cardiac surgery must be avoided in patients with Eisenmenger physiology. In case of doubt, PVR testing is recommended • For indication of intervention see also VSD (Section 4.2)	III	C
Partial AVSD:		
• Surgical closure should be performed in case of significant volume overload of the RV For further details see ASD (Section 4.1)	I	C
AV valve regurgitation:		
• Symptomatic patients with moderate to severe AV valve regurgitation should undergo valve surgery, preferably AV valve repair	I	C
• Asymptomatic patients with moderate or severe left-sided valve regurgitation and LVESD >45 mm and/or impaired LV function (LVEF <60%) should undergo valve surgery when other causes of LV dysfunction are excluded	I	B[35]
• Surgical repair should be considered in asymptomatic patients with moderate or severe left-sided AV valve regurgitation who have signs of volume overload of the LV and a substrate of regurgitation that is very likely to be amenable for surgical repair	IIa	C
SubAS:		
• See Section 4.5.3	–	–

[a]Class of recommendation.
[b]Level of evidence.
ASD = atrial septal defect; AV = atrioventricular; AVSD = atrioventricular septal defect; LV = left ventricle; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; PVR = pulmonary vascular resistance; RV = right ventricle; SubAS = subaortic stenosis; VSD = ventricular septal defect.

patients, the most frequently occurring problem is left-sided AV valve regurgitation.[37,38] Left-sided AV valve stenosis (most often a result of previous repair) that causes symptoms should be operated upon (IC).

Additional considerations

Exercise/sports: For most patients with uncomplicated, repaired AVSD, physical activity does not need restriction. Many will, however, have subnormal exercise performance measured objectively. Patients with important residual problems require individual recommendations (see Section 3.4.2).

Pregnancy: Pregnancy is well tolerated in patients with complete repair and no significant residual lesions. An unoperated partial AVSD presents with increased risk of paradoxical embolization. Closure of any significant ASD before pregnancy should be considered. In patients with severe PAH, pregnancy is contraindicated. As a rule, patients with residual left-sided AV valve regurgitation who have no indication for surgery tolerate pregnancy relatively well, although arrhythmias and worsening of AV valve regurgitation may occur[39] (see Section 3.4.3). The recurrence risk of CHD is relatively high, up to 11%, and genetic counselling is necessary.[40]

IE prophylaxis: Recommended only for high-risk patients (see Section 3.3.5)

4.4 Patent ductus arteriosus

Introduction and background

Patent ductus arteriosus (PDA) is the persistent communication between the proximal left PA (LPA) and the descending aorta just distal to the left subclavian artery. It can be associated with a variety of CHD lesions. However, in the adult it is usually an isolated finding.

PDA originally results in L–R shunt and LV volume overload. In moderate and large PDA, pulmonary pressure is elevated. In patients who reach adulthood with a moderate PDA, either LV volume overload or PAH may be predominant (genetic predisposition). Adult patients with a large PDA have in general developed Eisenmenger physiology.

Clinical presentation and natural history

Presentations of adult patients with PDA include:

- Small duct with no LV volume overload (normal LV) and normal PAP (generally asymptomatic)
- Moderate PDA with predominant LV volume overload: large LV with normal or reduced function (may present with left heart failure)
- Moderate PDA with predominant PAH: pressure-overloaded RV (may present with right heart failure)
- Large PDA: Eisenmenger physiology with differential hypoxaemia and differential cyanosis (lower extremities cyanotic, sometimes left arm, too); see Sections 4.17 and 4.18.

There is a potential risk of endarteritis but it seems to be low. Aneurysm formation of the duct is a rare complication and may even compress the left main coronary artery.

Diagnostic work-up

See Section 3.2 for general principles.

Specific clinical findings include a continuous murmur which disappears with development of Eisenmenger syndrome (for differential cyanosis, see above).

Echocardiography is the key diagnostic technique and provides the diagnosis (may be difficult in patients with Eisenmenger physiology), the degree of LV volume overload, PAP, PA size, and right heart changes.

CMR/CT are indicated when additional quantification of LV volumes or evaluation of PA anatomy are required.

Cardiac catheterization is indicated when PAP is high on echocardiography for estimation of PVR (see Section 3.2.5 for details).

Surgical/catheter interventional treatment (*Table 6*)

In adults, calcification of the PDA may cause a problem for surgical closure. Device closure is the method of choice, even if cardiac

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Table 6 Indications for intervention in patent ductus arteriosus

Indications	Class[a]	Level[b]
PDA should be closed in patients with signs of LV volume overload	I	C
PDA should be closed in patients with PAH but PAP <2/3 of systemic pressure or PVR <2/3 of SVR	I	C
Device closure is the method of choice where technically suitable	I	C
PDA closure should be considered in patients with PAH and PAP >2/3 of systemic pressure or PVR >2/3 of SVR but still net L–R shunt (Qp:Qs >1.5) or when testing (preferably with nitric oxide) or treatment demonstrates pulmonary vascular reactivity	IIa	C
Device closure should be considered in small PDAs with continuous murmur (normal LV and PAP)	IIa	C
PDA closure should be avoided in silent duct (very small, no murmur)	III	C
PDA closure must be avoided in PDA Eisenmenger and patients with exercise-induced lower limb desaturation	III	C

[a]Class of recommendation.
[b]Level of evidence.
L–R shunt = left-to-right shunt; LV = left ventricle; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PDA = patent ductus arteriosus; PVR = pulmonary vascular resistance; Qp:Qs = pulmonary to systemic flow ratio; SVR = systemic vascular resistance.

operations are indicated due to other concomitant cardiac lesions, and can be successfully performed in the vast majority of adults with a very low complication rate.[41–43] Surgery is reserved for the rare patient with a duct too large for device closure or with unsuitable anatomy such as aneurysm formation.

Follow-up recommendations

Echocardiographic evaluation should include LV size and function, PAP, residual shunt, and associated lesions.

Patients with no residual shunt, normal LV and normal PAP do not require regular follow-up after 6 months.

Patients with LV dysfunction and patients with residual PAH should be followed at intervals of 1–3 years depending on severity, including evaluation in specialized GUCH centres.

Additional considerations

Exercise/sports: No restrictions in asymptomatic patients before or after intervention without pulmonary hypertension; limitation to low-intensity sports in PAH patients.

Pregnancy: No significantly increased risk for pregnancy in patients without pulmonary hypertension. Pregnancy is contraindicated in patients with severe PAH and Eisenmenger syndrome (see Section 3.4.3).

IE prophylaxis: Limited to high-risk patients (see Section 3.3.5).

4.5 Left ventricular outflow tract obstruction

LVOTO can occur at the valvular, subvalvular, or supravalvular levels, isolated or at multiple levels. The most common site of obstruction is valvular (75%).

4.5.1 Valvular aortic stenosis

Introduction and background

The most common cause for congenital valvular AS is BAV, with an estimated prevalence of 1–2% in the general population. Mutations in the *NOTCH 1* gene have been related to BAV. Abnormalities of the aortic wall which are associated with BAV can lead to progressive dilation, aortic aneurysm, rupture, or dissection. For the management of AR associated with BAV see the Guidelines on the management of valvular heart disease.[35]

Clinical presentation and natural history

Patients frequently remain asymptomatic for many years. Progression of stenosis varies and depends on initial severity, degree of calcification, age, and atherosclerotic risk factors. In BAV, progression is faster in those patients with greater closure line eccentricity and an anteroposterior-oriented line of closure.

Prognosis is good and sudden death is rare in asymptomatic patients with good exercise tolerance, even when stenosis is severe.[44] Once symptoms [angina pectoris (AP), dyspnoea, or syncope] occur the prognosis deteriorates rapidly. In patients with BAV, cardiac mortality has been reported to be 0.3% per patient-year of follow-up, the frequency of aortic dissection 0.1%, and endocarditis 0.3%. Dilated aortic sinuses and/or ascending aorta have been found in 45% of patients after 9 years of follow-up.[45]

Diagnostic work-up (*Table 7*)

See Section 3.2 for general principles.

Specific clinical findings include the typical systolic ejection murmur over the aortic valve, radiating into the carotid arteries.

Table 7 Diagnostic criteria for degree of aortic stenosis severity[35]

	Mild AS	Moderate AS	Severe AS
Vmax (m/s)[a]	2.0–2.9	3.0–3.9	≥4.0
Mean gradient (mmHg)[a]	<30	30–49	≥50
AVA (cm²)	>1.5	1.0–1.5	<1.0
AVAi (cm²/m² BSA)	≥1.0	0.6–0.9	<0.6

[a]At normal transvalvular flow.
AS = aortic stenosis; AVA = aortic valve area; AVAi = indexed AVA; BSA = body surface area; Vmax = maximum Doppler velocity.

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A thrill may be palpable. The ECG may show left ventricular hypertrophy (LVH) with or without strain.

Echocardiography is the gold standard for the diagnosis of AS and for assessing the degree of calcification, LV function, LVH, and associated lesions. With Doppler echocardiography the degree of severity of AS is determined from transvalvular peak velocity (Vmax), mean gradient, and continuity equation-calculated effective orifice area (AVA). For more details, see recent recommendations for valve stenosis assessment.[46]

TEE may occasionally be helpful to planimeter AVA in non-calcified valves.

Exercise testing is recommended in asymptomatic patients, particularly in severe AS, to confirm asymptomatic status and evaluate exercise tolerance, blood pressure response, and arrhythmias for risk stratification and timing of surgery.

Low-dose dobutamine echocardiography is helpful in AS with impaired LV function (low flow, low gradient AS).[35]

CMR/CT, despite having potential for assessing AS, are mainly required to assess dilation of the aorta, which may be undectable with echocardiography when occurring distal to the sinotubular junction.

Cardiac catheterization is only required if non-invasive evaluation yields uncertain results and for evaluation of coronary arteries (see Section 3.2.5).

Medical therapy

Symptomatic patients require urgent surgery. Medical treatment for heart failure is reserved only for non-operable patients. Neither statin treatment nor any other medical treatment has so far been shown to retard progression of AS.[47]

Surgical/catheter interventional treatment (*Table 8*)

In selected adolescents and young adults with non-calcified valves, balloon valvuloplasty may be considered. In patients with calcified valves the treatment of choice is valve replacement. Mechanical valves are more durable than biological valves or homografts, but require lifelong anticoagulation. The Ross procedure has been suggested for patients of childbearing age and for those wanting to avoid anticoagulation. This is a more extensive procedure (two-valve operation) with a significant reoperation rate after the first post-operative decade.[48] Percutaneous valve implantation has become an alternative technique for treating stenosis of the pulmonary valve substitute (homograft). Transcatheter aortic valve implantation currently has no place in the treatment of congenital AS.

Follow-up recommendations

Lifelong and regular follow-up is required, and the intervals depend upon the degree of stenosis severity. It is also necessary after valve intervention at yearly intervals.

Echocardiographic imaging of the aortic valve and aortic root to determine progression of valve stenosis and aortic dilation is mandatory. CMR of the aorta is recommended in patients with BAV, and also after valve surgery.

Additional considerations

Exercise/sports: Patients with severe symptomatic and asymptomatic AS and those with moderate stenosis due to BAV and dilated aorta should avoid strenuous or isometric exercise and competitive sports. In mild and moderate AS sport is allowed. A prior exercise test for counselling is recommended.

Pregnancy: Pregnancy is contraindicated in severe symptomatic AS. Treatment by either balloon valvotomy or surgery should be performed before conception. In asymptomatic patients with severe AS and a normal exercise test, pregnancy may be possible

Table 8 Indications for intervention in aortic stenosis[35]

Indications	Class[a]	Level[b]
Patients with severe AS and any valve-related symptoms (AP, dyspnoea, syncope) should undergo valve replacement	I	B
Asymptomatic patients with severe AS should undergo surgery when they develop symptoms during exercise testing	I	C
Regardless of symptoms, surgery should be performed when systolic LV dysfunction is present in severe AS (LVEF <50%), unless it is due to other causes	I	C
Regardless of symptoms, surgery should be performed when patients with severe AS undergo surgery of the ascending aorta or of another valve, or coronary artery bypass grafting	I	C
Regardless of symptoms, aortic surgery should be considered if the ascending aorta is >50 mm (27.5 mm/m² BSA) and no other indications for cardiac surgery are present	IIa	C
Asymptomatic patients with severe AS should be considered for surgery when they present with a fall in blood pressure below baseline during exercise testing	IIa	C
Asymptomatic patients with severe AS and moderate-to-severe calcification and a rate of peak velocity progression of ≥0.3 m/s/year should be considered for surgery	IIa	C
Patients with moderate AS undergoing coronary artery bypass surgery or surgery of the ascending aorta or another valve should be considered for additional valve replacement	IIa	C
Severe AS with low gradient (<40 mmHg) and LV dysfunction with contractile reserve should be considered for surgery	IIa	C
Severe AS with low gradient (<40 mmHg) and LV dysfunction without contractile reserve may be considered for surgery	IIb	C
Asymptomatic patients with severe AS and excessive LV hypertrophy (≥15 mm), unless this is due to hypertension, may be considered for surgery	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
AP = angina pectoris; AS = aortic stenosis; BSA = body surface area; LV = left ventricle; LVEF = left ventricular ejection fraction.

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in selected patients, but this is controversial. The aorta requires particular attention as BAV-related aortic dilation may be induced and progress during pregnancy. There is a risk of dissection (see Section 3.43). The rate of recurrence of CHD is at least 5%, but has also been reported higher.

IE prophylaxis: Recommended only for high-risk patients (see Section 3.3.5).

4.5.2 Supravalvular aortic stenosis

Introduction and background

Supravalvular aortic stenosis (SupraAS) accounts for <7% of all fixed forms of LVOTO. Its occurrence has been associated with a loss-of-function mutation of the elastin gene on chromosome 7q11.23, leading to an obstructive arteriopathy of varying severity, which is most pronounced at the sinotubular junction.[49] It can occur either as a localized fibrous diaphragm just distal to the coronary artery ostia or, most commonly, as an external hourglass deformity with a corresponding luminal narrowing of the aorta, or as diffuse stenosis of the ascending aorta. It frequently occurs as part of the Williams–Beuren syndrome, and may be associated with hypoplasia of the entire aorta, involvement of coronary ostia, or stenosis of major branches of the aorta or pulmonary arteries.

Clinical presentation and natural history

Patients present with symptoms of either outflow obstruction or myocardial ischaemia. Sudden death occurs rarely, but it is more common in SupraAS with Williams–Beuren syndrome, with diffuse peripheral PA stenosis, or with CAD.

Diagnostic work-up

See Section 3.2 for general principles.

Due to a preferential jet of blood flow from a SupraAS into the right brachiocephalic artery (Coanda effect), clinical examination may reveal a marked increase in the right upper extremity systolic pressure relative to the left and a thrill in the suprasternal notch.

Echocardiography enables the anatomic diagnosis of SupraAS to be made. Doppler echocardiography provides pressure gradients but these may overestimate the actual pressure drop across the obstruction.

For exercise testing see valvular AS (Section 4.5.1).

CMR/CT provide a precise anatomic definition of the lesion itself and identify additional lesions in the aorta and its branches (carotid and renal artery stenosis) and pulmonary arteries.

Cardiac catheterization may be risky,[50] particularly in Williams–Beuren syndrome, yet haemodynamic assessment is recommended when non-invasive quantification remains uncertain. Coronary angiography should be performed in all patients in whom surgical resection is planned. CT may avoid invasive angiography.

Genetic evaluation, using fluorescent *in situ* hybridization (FISH), is suggested to define the diagnosis of Williams–Beuren syndrome.

Surgical/catheter interventional treatment (*Table 9*)

Surgery is the primary treatment. The operative mortality rate for fibrous diaphragm and hourglass deformity is <5%. Since the coronary arteries are under high pressure, surgery might be considered earlier than in patients with valvular AS, particularly when no valve substitute is required. Following operative repair the survival rate has been reported to be 85% at 15 years.[51] AR may be present in ~25% of patients, but usually it is not progressive after surgical relief of SupraAS.

Table 9 Indications for intervention in supravalvular aortic stenosis

Indications	Class[a]	Level[b]
Patients with symptoms (spontaneous or on exercise test) and mean Doppler gradient ≥50 mmHg should undergo surgery	I	C
Patients with mean Doppler gradient <50 mmHg should undergo surgery when they have:		
• symptoms attributable to obstruction (exertional dyspnoea, angina, syncope) and/or	I	C
• LV systolic dysfunction (without other explanation)	I	C
• severe LVH, attributable to obstruction (not related to hypertension)	I	C
• when surgery for significant CAD is required	I	C
Patients with mean Doppler gradient ≥50 mmHg[c] but without symptoms, LV systolic dysfunction, LVH, or abnormal exercise test may be considered for repair when the surgical risk is low	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
[c]Doppler-derived gradients may overestimate the obstruction and may need confirmation by left heart catheterization.
CAD = coronary artery disease; LV = left ventricle; LVH = left ventricular hypertrophy.

Follow-up recommendations

Lifelong and regular follow-up, including echocardiography, is required to determine progression of obstruction (rare), LV size/function, and development of symptoms, as well as after surgery to detect late restenosis, development of aneurysm (CMR/CT), and the occurrence or progression of CAD. Follow-up should include evaluation in specialized GUCH centres.

Additional considerations

Exercise/sports: See valvular AS (Section 4.5.1).

Pregnancy: See valvular AS (Section 4.5.1). Offspring are at higher risk for recurrence of CHD (family screening recommended).

IE prophylaxis: Recommended only for high-risk patients (see Section 3.3.5).

4.5.3 Subaortic stenosis

Introduction and background

SubAS can occur as an isolated lesion, but is frequently associated with a VSD, an AVSD, or Shone complex, or may develop after correction of these lesions. The prevalence has been reported to be 6.5% in the GUCH population.[52] It is caused by a fibrous ridge in the left ventricular outflow tract (LVOT) proximal to the aortic valve or as fibromuscular narrowing, and has to be differentiated from hypertrophic cardiomyopathy.

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Clinical presentation and natural history

The clinical course is highly variable. In one study in adults, progression in severity of obstruction occurred only in patients older than 50 years.[52] AR is frequent but rarely haemodynamically significant or progressive.

Diagnostic work-up

See section 3.2 for general principles.

Clinical findings include a systolic ejection murmur at the left sternal border and the apex without radiation into the carotids and without systolic ejection click. A diastolic murmur indicates AR.

Echocardiography visualizes LVOT anatomy, associated aortic valve abnormality, amount of AR, LV function, LVH, and associated lesions. With Doppler echocardiography the severity of the subvalvular obstruction is determined, but Doppler-derived gradients may overestimate the obstruction and may require confirmation by cardiac catheterization. Occasionally TEE is necessary to demonstrate the membrane. Three-dimensional TEE can be helpful to characterize the complex LVOT anatomy.

Surgical/catheter interventional treatment (*Table 10*)

Surgical treatment involves a circumferential resection of the fibrous ring and parts of the muscular base along the left septal surface. Fibromuscular or tunnel-type SubAS require more extensive resection or a Konno procedure. Surgical results are good, but restenosis may occur. In patients with low surgical risk and a morphology well suited to repair, the threshold for intervention is lower than in aortic valve stenosis, in particular since no implant is required. In the case of moderate or severe AR, the aortic valve must be replaced at the time of surgery.

Follow-up recommendations

Lifelong regular follow-up, including echocardiography, is required in the non-operated state to determine progression of obstruction, AR, and LV function and size. Also regular post-operative follow-up is necessary to detect late restenosis (frequent, especially in isolated forms and surgical treatment in childhood), progressive AR, complications such as arrhythmias, heart block, and iatrogenic VSD. Follow-up should include evaluation in specialized GUCH centres.

Additional considerations

Exercise/sports: See valvular AS (Section 4.5.1)

Pregnancy: Only contraindicated in severe, symptomatic SubAS where surgery should be performed before pregnancy (even in asymptomatic severe SubAS it should be considered). See Section 3.4.3.

IE prophylaxis: Recommended only for high-risk patients (see Section 3.3.5).

Table 10 Indications for intervention in subaortic stenosis

Indications	Class[a]	Level[b]
Symptomatic patients (spontaneous or on exercise test) with a mean Doppler gradient ≥50 mmHg[c] or severe AR should undergo surgery	I	C
Asymptomatic patients should be considered for surgery when:		
• LVEF is <50% (gradient may be <50mmHg due to low flow)	IIa	C
• AR is severe and LVESD >50mm (or 25 mm/m² BSA) and/or EF <50%[d]	IIa	C
• mean Doppler gradient is ≥50 mmHg[c] and LVH marked	IIa	C
• mean Doppler gradient is ≥50 mmHg[c] and blood pressure response is abnormal on exercise testing	IIa	C
Asymptomatic patients may be considered for surgery when:		
• mean Doppler gradient is ≥50 mmHg[c], LV normal, exercise testing normal, and surgical risk low	IIb	C
• progression of AR is documented and AR becomes more than mild (to prevent further progression)	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
[c]Doppler-derived gradients may overestimate the obstruction and may need confirmation by cardiac catheterization.
[d]See ESC guidelines on the management of valvular heart disease.[35]
AR = aortic regurgitation; BSA = body surface area; EF = ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction; LVESD = left ventricular end systolic diameter; LVH = left ventricular hypertrophy.

4.6 Coarctation of the aorta

Introduction and background

CoA is considered as part of a generalized arteriopathy, and not only as a circumscript narrowing of the aorta. Its occurs as a discrete stenosis or as a long, hypoplastic aortic segment. Typically CoA is located in the area where the ductus arteriosus inserts, and only in rare cases occurs ectopically (ascending, descending, or abdominal aorta).

CoA accounts for 5–8% of all congenital heart defects. The prevalence of isolated forms is ~3 per 10 000 live births.

Associated lesions include BAV (up to 85%), subvalvular, valvular, or supravalvular AS, mitral valve stenosis (parachute mitral valve, a complex known as Shone syndrome), or complex congenital heart defects. CoA can be associated with Turner, Williams–Beuren, or congenital rubella syndromes, neurofibromatosis, Takayasu aortitis, or trauma.

CoA imposes significant afterload on the LV, resulting in increased wall stress, compensatory LVH, LV dysfunction, and the development of arterial collaterals.

'Cystic medial necrosis' with early elastic fibre fragmentation and fibrosis was found in the ascending and descending aorta, resulting in an increased stiffness of the aorta and carotid arteries.[53]

Clinical presentation and natural history

Signs and symptoms depend on the severity of CoA. Patients with serious CoA exhibit signs and symptoms early in life, while particularly mild cases may not become evident until adulthood.

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Key symptoms may include headache, nosebleeds, dizziness, tinnitus, shortness of breath, abdominal angina, claudication, leg cramps, exertional leg fatigue, and cold feet.

The natural course may be complicated by left heart failure, intracranial haemorrhage (from berry aneurysm), IE, aortic rupture/dissection, premature coronary and cerebral artery disease, and associated heart defects.[54,55]

Diagnostic work-up

See Section 3.2 for general principles.

Clinical features include upper body systolic hypertension, lower body hypotension, a blood pressure gradient between upper and lower extremities (>20 mmHg indicates significant CoA), radio-femoral pulse delay, and palpable collaterals.

Other findings include a suprasternal thrill, a vascular murmur in the back, or continuous murmurs (due to collateral vessels). Chest X-ray findings may include rib notching of the third and fourth (to the eighth) ribs from collaterals, an ectatic ascending aorta, kinking or double contouring in the descending aorta ('figure 3' sign), and widening of the left subclavian artery.

Echocardiography provides information regarding site, structure, and extent of CoA, LV function and hypertrophy, associated cardiac abnormalities, and aortic and supra-aortic vessel diameters. Doppler gradients are not useful for quantification, neither in native nor in post-operative coarctation. A diastolic 'run-off' phenomenon is presumably the most reliable sign of significant coarctation or recoarctation.

In the presence of extensive collaterals the gradients are not reliable. After surgical repair, increased systolic flow rates may develop, even in the absence of significant narrowing, due to a lack of aortic compliance.

CMR and CT are the preferred non-invasive techniques to evaluate the entire aorta in adults. Both depict site, extent, and degree of the aortic narrowing, the aortic arch, the pre- and post-stenotic aorta, and collaterals. Both methods detect complications such as aneurysms, restenosis, or residual stenosis (see Sections 3.2.2 and 3.2.3).

Cardiac catheterization with manometry (a peak-to-peak gradient >20 mmHg indicates a haemodynamically significant CoA in the absence of well-developed collaterals), and angiocardiography is still the gold standard for CoA evaluation at many centres before and after operative or interventional treatment (see Section 3.2.5).

Surgical/catheter interventional treatment (*Table 11*)

In native CoA with appropriate anatomy, stenting has become the treatment of first choice in adults in many centres. Whether to use covered or non-covered stents is unresolved. Biodegradable stents are in development.

For adults with recurring or residual CoA, angioplasty with or without stent implantation has been shown to be effective in experienced hands,[56] and preferably stenting has also become first choice if anatomy is appropriate.

Operative techniques include resection and end-to-end anastomosis, resection and extended end-to-end anastomosis, prosthetic patch aortoplasty, subclavian flap aortoplasty, interposition of a (tube) graft, and bypass tube (jump) grafts.

Table 11 Indications for intervention in coarctation of the aorta

Indications	Class[a]	Level[b]
All patients with a non-invasive pressure difference >20 mmHg between upper and lower limbs, regardless of symptoms but with upper limb hypertension (>140/90 mmHg in adults), pathological blood pressure response during exercise, or significant LVH should have intervention	I	C
Independent of the pressure gradient, hypertensive patients with ≥50% aortic narrowing relative to the aortic diameter at the diaphragm level (on CMR, CT, or invasive angiography) should be considered for intervention	IIa	C
Independent of the pressure gradient and presence of hypertension, patients with ≥50% aortic narrowing relative to the aortic diameter at the diaphragm level (on CMR, CT, or invasive angiography) may be considered for intervention	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
CMR = cardiac magnetic resonance; CoA = coarctation of the aorta; CT = computed tomography; LVH = left ventricular hypertrophy.

Re-CoA repair in adults can be complicated, and ascending-to-descending aorta conduits may be preferable in cases of difficult anatomy. Although the surgical risk in simple CoA may currently be <1%, it increases significantly beyond the age of 30–40 years. It also carries the risk of spinal cord injury.

As coarctation is not a localized disease of the aorta, associated problems that may require intervention have to be considered:

- Associated significant aortic valve stenosis or regurgitation
- Aneurysm of the ascending aorta with a diameter >50 mm [>27.5 mm/m^2 body surface area (BSA)] or rapid progression
- Aneurysm at the previous CoA site
- Symptomatic or large aneurysms of the circle of Willis.

Treatment should be performed in centres with extensive experience in the treatment of CHD.

Follow-up recommendations

Residua, sequelae, and complications are listed below:

- Arterial hypertension at rest or during exercise is common, even after successful treatment, and is an important risk factor for premature CAD, ventricular dysfunction, and rupture of aortic or cerebral aneurysms.[57] The geometry of the arch (gothic, crenel, normal) may play a role in the development of hypertension. The significance of isolated, exercise-induced hypertension is a matter of debate.
- Recurring or residual CoA may induce or aggravate systemic arterial hypertension and its consequences.
- Aneurysms of the ascending aorta or at the intervention site present a risk of rupture and death.[58] Patch repairs (e.g. with

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Dacron) are at particular risk of repair site aneurysm and should be imaged on a regular basis.
- Attention is required for BAV, mitral valve disease, premature CAD, and berry aneurysms of the circle of Willis (currently, most clinicians see no indication for their routine screening in asymptomatic patients).

All coarctation patients require regular follow-up at least every second year including evaluation in specialized GUCH centres. Imaging of the aorta (preferably with CMR) is required to document the post-repair or post-interventional anatomy and complications (restenosis or aneurysm formation). Imaging intervals depend on baseline pathology.

Additional considerations

Exercise/sports: Patients without residual obstruction who are normotensive at rest and with exercise can usually lead normally active lives without restriction, except for extensive static sports at a competition level. Patients with arterial hypertension, residual obstruction, or other complications should avoid heavy isometric exercises, in proportion to the severity of their problems.

Pregnancy: After successful treatment of CoA, many women tolerate pregnancy without major problems.[59] In particular, women with unrepaired CoA, but also those after repair with arterial hypertension, residual CoA, or aortic aneurysms have an increased risk of aortic rupture and rupture of a cerebral aneurysm during pregnancy and delivery. An excess of miscarriages and hypertensive disorders is reported (see Section 3.4.3).

IE prophylaxis: Recommended only for high-risk patients (see Section 3.3.5).

4.7 Marfan syndrome

Introduction and background

Marfan syndrome is an autosomal dominant disorder of connective tissue, in which cardiovascular, skin and skeletal, ocular, pulmonary, and dura mater abnormalities may be present to a highly variable degree. Prevalence is ~2–3 per 10 000, and ~25–30% are new mutations. Marfan syndrome is caused by mutations in the *FBN1* gene on chromosome 15q21 encoding fibrillin-1, a glycoprotein in the extracellular matrix. A deficiency of fibrillin may lead to weakening of the supportive tissues and dysregulation of transforming growth factor-β (TGF-β). More than 1000 mutations have been identified, almost all unique to an affected family. In 10% of patients with a definite diagnosis of Marfan syndrome it is still not possible to find an *FBN1* mutation.

Clinical presentation and natural history

Prognosis is mainly determined by progressive dilation of the aorta, leading to aortic dissection or rupture, which are the major causes of death. Mean survival of untreated patients is 40 years. Dilation of the aortic root is found in 60–80% of patients. The rate of dilation is heterogeneous and unpredictable. The risk of type A dissection clearly increases with increasing aortic root diameter, but dissection may occasionally occur even in patients with only mild aortic dilation. Other parts of the aorta may also be dilated. Patients with a dilated aorta are usually asymptomatic. The presence of significant aortic, tricuspid, or mitral regurgitation may lead to symptoms of ventricular volume overload, but LV disease may also occur independently. Marfan syndrome can be confused with other heritable connective tissue disorders that closely mimic Marfan symptoms, such as Loeys–Dietz syndrome, familial aortic aneurysm, BAV with aortic dilation, familial ectopia lentis, MASS phenotype, and Ehlers–Danlos syndrome, because of the considerable clinical overlap between the various syndromes.

Diagnostic work-up

Early identification and establishment of the diagnosis is critical, since prophylactic surgery can prevent aortic dissection and rupture. Elucidation of the molecular mechanisms behind Marfan syndrome will allow improvement in diagnostic testing. The correct diagnosis definitely requires a multidisciplinary team. Currently, the diagnosis of Marfan syndrome is primarily based on clinical manifestations; a definite diagnosis requires occurrence of a major manifestation in two different organ systems and involvement of a third organ system (Ghent nosology).[60] These criteria have just been revised, and the new nosology[61] will probably replace the old one in future practice. More weight will be given to the two cardinal features of Marfan syndrome: aortic root aneurysm/dissection and ectopia lentis. In addition, a more prominent role is assigned to molecular genetic testing.[61]

Echocardiographic assessment of the aortic root should include—in addition to determining the maximum diameter—measurements at the ring, sinus, sinotubular junction, and distal ascending aortic levels. Echocardiography provides evaluation of LV function, aortic valve and AR, or mitral valve and/or tricuspid valve prolapse and regurgitation. TEE may be useful if aortic dissection is suspected, and pre-operatively.

CMR or CT should be performed in every patient, providing imaging of the entire aorta including aortic dimensions beyond the root. Aortic elasticity of the thoracic descending aorta, which can be measured by CMR, appeared to be an independent predictor for progressive descending aortic dilation.[62]

Since catheter manipulation may carry a certain risk of dissection of the weakened aortic wall, CT coronary angiography should preferably be used for exclusion of CAD before surgery.

Holter monitoring should be performed in symptomatic patients, as ventricular arrhythmias, conduction disturbances, and SCD occur.

Medical therapy

Both medical and surgical therapies have improved life expectancy substantially up to 60–70 years. β-Blockers might reduce the rate of aortic dilation and might improve survival, at least in adults.[63,64] Rigorous antihypertensive medical treatment, aiming at a systolic blood pressure <120 mmHg, and 110 mmHg in patients with aortic dissection, is important. The angiotensin II receptor 1 blocker losartan is potentially useful because it leads to TGF-β antagonism. Clinical trials are presently ongoing to evaluate its beneficial effect. Presently, the standard of care for prevention of aortic complications remains, in most centres, β-blockade. Medical treatment should be continued after surgery.

Surgical/catheter interventional treatment (*Table 12*)

Composite replacement of the aortic valve and ascending aorta has become a low-risk and a very durable operation in experienced

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Table 12 Indications for aortic surgery in Marfan syndrome[67]

Indications	Class[a]	Level[b]
Patients should undergo surgery when aortic root maximal diameter is:		
• >50 mm	I	C[c]
• 46–50 mm with		
- family history of dissection or	I	C
- progressive dilation >2 mm/year as confirmed by repeated measurement or	I	C
- severe AR or MR or	I	C
- desire of pregnancy	I	C
• Patients should be considered for surgery when other parts of the aorta >50 mm or dilation is progressive	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
[c]ESC guidelines for valvular heart disease are slightly more strict, recommending only one diameter (45 mm) regardless of other findings.
AR = aortic regurgitation; MR = mitral regurgitation.

hands (reported operative mortality 1.5% for elective and 11.7% for emergency operations). Five- and 10-year survival rates of 84 and 75%, respectively, have been reported.[65] Marfan syndrome has, however, been associated with a considerably higher risk of re-dissection and recurrent aneurysm than other aetiologies of aortic disease.

In patients with anatomically normal valves, in whom the insufficiency is due to the dilated annulus or dissection, valve-sparing operations with root replacement by a Dacron prosthesis and with reimplantation of the coronary arteries into the prosthesis (David's procedure) or remodelling of the aortic root (Yacoub's procedure) have now become the preferred surgical procedures. AR is, however, a common complication, requiring reoperation in 20% of patients after 10 years.[66] Long-term results of valve-sparing aortic root replacement in Marfan syndrome are still unknown.

Women have, on average, a 5 mm smaller aorta, only partly explained by a smaller BSA.[68] In small individuals, the use of an indexed diameter adjusted for BSA of 2.75 cm/m^2 should probably be used for operative decision making.[69]

If necessary, all parts of the aorta can be replaced with prosthesis.

Although there are few reports of short-term success after endovascular stent grafting of the descending thoracic aorta, stent grafting in patients with Marfan syndrome is not recommended unless the risk of conventional open surgical repair is deemed prohibitive.[70]

Follow-up recommendations

Lifelong and regular follow-up requires involvement of specialists with ample expertise in a specialist centre. Echocardiographic imaging of the aortic root and CMR imaging (or CT if CMR is contraindicated) of the entire aorta is of critical importance, especially if a dissection remains. Valvular regurgitation and ventricular function can be followed by means of echocardiography.

Stable patients need a yearly visit with echocardiography. CMR should be performed at baseline and repeated at least once in 5 years if the aortic size beyond the root is normal. In the case of aneurysm formation beyond the root, CMR should be repeated at least yearly.

Additional considerations

Exercise/sports: Patients should be advised to avoid exertion at maximal capacity, competitive, contact, and isometric sports.

Pregnancy: There is a 50% chance that a child born to a mother with Marfan syndrome would be affected with the condition (genetic counselling). Women with an aortic diameter >45 mm are strongly discouraged from becoming pregnant without prior repair because of the high risk of dissection. An aortic diameter <40 mm rarely presents a problem, although a completely safe diameter does not exist. With an aorta between 40 and 45 mm, previous aortic growth and family history are important for advising pregnancy with or without aortic repair.[71] Even after repair of the ascending aorta, Marfan patients remain at risk for dissection of the residual aorta. See Section 3.4.3.

IE prophylaxis: Recommended only for high-risk patients (see Section 3.3.5).

4.8 Right ventricular outflow tract obstruction

Introduction and background

RVOTO can occur at the subinfundibular, infundibular, valvular, or supravalvular levels.

Subinfundibular stenosis or DCRV is commonly associated with a VSD. It is caused by narrowing between prominent and hypertrophied muscle bands or ridges that separate the hypertrophied, high-pressure inlet and apical portions from a low-pressure, non-hypertrophied and non-obstructive infundibular portion of the RV.[72]

Infundibular stenosis usually occurs in combination with other lesions, particularly VSD, ToF, and secondary to valvular pulmonary stenosis (PS) (reactive myocardial hypertrophy). At the infundibular level, and to some extent the subinfundibular level, the obstruction tends to be dynamic, meaning that the orifice narrows during systole.

Valvular PS is usually an isolated lesion, occurs in ~7–12% of all congenital heart defects, and accounts for 80–90% of all RVOTOs. Its inheritance rate ranges from 1.7 to 3.6%. Mainly due to intrinsic wall abnormalities and independent of haemodynamics, dilation of the pulmonary trunk and the LPA may occur, the right PA (RPA) generally being less affected. Most often, there is a typical dome-shaped pulmonary valve with a narrow central opening but a preserved mobile valve base. A dysplastic pulmonary valve, with poorly mobile cusps and myxomatous thickening, is less common (15–20%; even less in untreated adults) and frequently part of the Noonan syndrome. An hourglass deformity of the pulmonary valve, with 'bottle-shaped' sinuses and stenosis at the commissural ridge of the valve, has also been described. In adults, a stenotic pulmonary valve may calcify late in life.

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Supravalvular PS or pulmonary arterial stenosis is caused by narrowing of the main pulmonary trunk, pulmonary arterial bifurcation, or pulmonary branches. It seldom occurs in isolation, and may occur in ToF, Williams–Beuren syndrome, Noonan syndrome, Keutel syndrome, congenital rubella syndrome, or Alagille syndrome. The stenosis may be located in the main branches or more peripherally; it may be discrete or diffuse (hypoplastic) or there may be frank occlusion, and may occur as single or multiple stenoses. Stenosis may be secondary to previous placement of a PA band or at a previous shunt site. A diameter stenosis ≥50% is usually considered to be significant, and would be expected to have a pressure gradient and result in hypertension in the proximal PA.

Clinical presentation and natural history

Subinfundibular/infundibular: Adult patients with unoperated DCRV may be asymptomatic or they may present with angina, dyspnoea, dizziness, or syncope. The degree of obstruction is progressive over time.[73]

Valvular: Patients with mild to moderate valvular PS are usually asymptomatic. Mild valvular PS in unoperated adults is usually not progressive.[74] Moderate PS can progress at the valvular level (calcification) or at the subvalvular level, due to reactive myocardial hypertrophy. Patients with severe stenosis may present with dyspnoea and reduced exercise capacity, and have a worse prognosis.

Supravalvular: Patients may be asymptomatic or have symptoms of dyspnoea and reduced exercise capacity. They are usually recognized in the context of certain syndromes or referred for suspicion of pulmonary hypertension. Peripheral PA stenosis may progress in severity.

Diagnostic work-up

See Section 3.2 for general principles.

Clinical findings include the harsh systolic murmur across the obstruction and wide splitting of the second heart sound. In peripheral PS the systolic murmur is typically heard over the lung fields. Findings on chest X-ray may include calcification of the pulmonary valve, dilatation of the pulmonary trunk and left PA, and right heart enlargement.

Echocardiography is the first-line diagnostic technique providing visualization of the level of RVOTO, pulmonary valve anatomy, right ventricular hypertrophy (RVH), and co-existing lesions. Doppler echocardiography provides the gradient across the obstruction, the presence and severity of PR and TR, and RV systolic pressure. Particular care is needed to distinguish the jet of a DCRV from that of a VSD or of infundibular or valvular stenosis. The peak RV systolic pressure may be the result of more than one obstruction at multiple levels that can exist simultaneously. Doppler gradients may be unreliable (overestimation) in patients with tubular stenosis and in patients with stenoses in series (subvalvular and valvular). In patients with DCRV the peak gradient may lead to underestimation of stenosis, because sampling of flow may not be axial. Echocardiography is of less value for identification of peripheral PS.

RVOTO is considered mild when the peak gradient across the obstruction is <36 mmHg (peak velocity <3 m/s), moderate from 36 to 64 mmHg (peak velocity 3–4 m/s), and severe when the gradient is >64 mmHg (peak velocity >4 m/s). Since Doppler measurements may be unreliable (see above), TR velocity with estimation of RV pressure should always be used in addition when assessing severity.[46]

CMR and CT frequently provide additional important information identifying the level(s) of obstruction, particularly at the subinfundibular, conduit, or branch PA levels, and assessment of the RV. They are the methods of choice for visualization of pulmonary dilation and peripheral PS.

Nuclear techniques may reveal the perfusion abnormalities in different lung segments in cases of peripheral PS (can also be measured by CMR).

Cardiac catheterization may be required to confirm the extent, severity, and level of obstruction (e.g. DCRV). For coronary angiography, see Section 3.2.5.

Surgical/catheter interventional treatment (*Table 13*)

Catheter intervention is recommended for patients with valvular PS with valves which are not dysplastic (balloon valvotomy) and with peripheral PS (stent).[75]

Surgery is recommended for patients with subinfundibular or infundibular PS and hypoplastic pulmonary annulus, with dysplastic

Table 13 Indications for intervention in right ventricular outflow tract obstruction

Indications	Class[a]	Level[b]
RVOTO at any level should be repaired regardless of symptoms when Doppler peak gradient is >64 mmHg (peak velocity >4m/s), provided that RV function is normal and no valve substitute is required	I	C
In valvular PS, balloon valvotomy should be the intervention of choice	I	C
In asymptomatic patients in whom balloon valvotomy is ineffective and surgical valve replacement is the only option, surgery should be performed in the presence of a systolic RVP >80 mmHg (TR velocity >4.3 m/s)	I	C
Intervention in patients with gradient <64 mmHg should be considered in the presence of: • symptoms related to PS or, • decreased RV function or, • double-chambered RV (which is usually progressive) or, • important arrhythmias or, • right-to-left shunting via an ASD or VSD.	IIa	C
Peripheral PS, regardless of symptoms, should be considered for repair if >50% diameter narrowing and RV systolic pressure >50 mmHg and/or lung perfusion abnormalities are present	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
ASD = atrial septal defect; PS = pulmonary stenosis; RV = right ventricle; RVOTO = right ventricular outflow tract obstruction; RVP = right ventricular pressure; TR = tricuspid regurgitation; VSD = ventricular septal defect.

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pulmonary valves, and for patients with associated lesions which need a surgical approach, such as severe PR or severe TR. Surgery may be necessary in patients with peripheral PS, anatomically not amenable for percutaneous therapy. The surgical approach to subinfundibular stenosis and an associated VSD can be via the RA, conserving the unobstructed infundibulum and pulmonary valve.

Both surgical and catheter interventions should only be performed in centres specialized in CHD.

In patients with subvalvular, valvular, and supravalvular PS a markedly dilated pulmonary trunk may be present. Rupture is extremely rare in these low-pressure, highly elastic vessels and these pulmonary aneurysms generally do not require intervention.[76]

For RV–PA conduit see Section 4.16.

Follow-up recommendations

Patients with RVOTO need lifelong follow-up with regular echocardiographic imaging. The frequency of follow-up depends on the severity of the lesion, but most patients will need a yearly visit including evaluation in specialized GUCH centres. Patients with mild valvular or mild residual PS need to be seen only once in 5 years.[77]

Additional considerations

Exercise/sports: No restrictions for patients with mild (residual) PS. Patients with moderate PS should avoid competitive and static sports. Patients with severe PS should be restricted to low-intensity sports.

Pregnancy: Pregnancy is well tolerated unless the RVOTO is extremely severe or unless RV failure is a major issue. Percutaneous balloon valvotomy can be performed during pregnancy, but is rarely necessary (see Section 3.4.3)

IE prophylaxis: Recommended only for high-risk patients (see Section 3.3.5).

4.9 Ebstein's anomaly

Introduction and background

Ebstein's anomaly—a relatively rare disease—is characterized by abnormally formed and apically displaced leaflets of the tricuspid valve. Tricuspid valve opening is dislocated away from the tricuspid valve annulus towards the apex or the right ventricular outflow tract (RVOT). The anterior leaflet usually originates appropriately at the annular level but is enlarged and sail-like, while the septal and posterior leaflets are displaced towards the right ventricular apex and often tethered to the endocardium.

The apical displacement of the tricuspid valve means that the right heart consists of an RA, an atrialized portion of the RV, and the remaining functional RV. The tricuspid valve is often regurgitant.

The most frequently associated anomalies include a shunt at the atrial level [secundum ASD or patent foramen ovale (PFO)] and accessory pathways [Wolff–Parkinson–White (WPW) syndrome]. VSD, PS, pulmonary atresia, ToF, CoA, or mitral valve abnormalities can also occur. Ebstein-like anomaly of the systemic tricuspid valve is present in one-third of ccTGA.

Ebstein's anomaly occurs more commonly if the mother has received lithium or benzodiazepines during pregnancy.

The morphological and haemodynamic spectrum is wide. Haemodynamic changes depend on the severity of the tricuspid valve dysfunction, the degree of atrialization of the RV, contractility of the remaining functional and the systemic ventricle, type and severity of concomitant anomalies, and arrhythmias.

The pathophysiology is characterized by systolic regurgitation of blood from the functional RV, across the tricuspid valve, into the atrialized ventricle or RA, which tend to dilate. An interatrial connection permits an L–R shunt or, especially during exercise, an R–L shunt. Ebstein's anomaly may result in a chronically low systemic cardiac output.

Clinical presentation and natural history

The clinical presentation ranges from trivial symptoms to the presentation of a profound cyanotic heart defect.

Patients with mild forms can be asymptomatic over decades until they are diagnosed. Older studies, often including more severe cases, show that in the natural course 50% of the patients die before the age of 20 years, and 80% before the age of 30. Some survive even into their ninth decade.

Typical complications include high-grade TR, RV dysfunction, RV failure, cerebral abscesses, paradoxical embolism, pulmonary embolism, tachyarrhythmias, SCD, and IE (rare).

Key symptoms are arrhythmias, dyspnoea, fatigue, poor exercise tolerance, chest pain, and peripheral and/or central cyanosis.

Diagnostic work-up

See Section 3.2 for general principles.

Clinical findings may include cyanosis and hepatomegaly. Auscultation findings include a widely split first sound and second sound, serial clicks, third and fourth sound, triple or quadruple rhythm, and a systolic murmur from TR. ECG may show right atrial hypertrophy, a prolonged PR interval, right bundle branch block (often with a splintered QRS complex), deep Q in II, III, F, and V1–V4, a pre-excitation syndrome, low voltage, and supraventricular and ventricular arrhythmias. Chest X-ray is helpful to follow changes in the heart's size.

Echocardiography is the key diagnostic technique, providing information on anatomy and function of the tricuspid valve, apical distal displacement of the septal or posterior leaflet (in adults $\geq$0.8 cm/m^2 BSA), size of the anterior leaflet, 'tethering' of the septal or posterior tricuspid valve leaflet on the septum or ventricular wall, size and function of the different cardiac sections (RA, atrialized ventricle, remaining functional RV, and LV), RVOTO, and associated lesions.

CMR has value with regard to evaluation for surgery as it offers unrestricted views for assessment of the dilated right heart, RV function, and the tricuspid valve.

Surgical/catheter interventional treatment (*Table 14*)

Clinical symptoms determine the treatment. A conservative therapy can alleviate symptoms temporarily and create a beneficial basis for the following operation.[78] Oral anticoagulation is recommended for patients with a history of paradoxical embolism or atrial fibrillation. Symptomatic rhythm disorders can be treated conservatively or, preferably, with EP intervention.[79] In the presence of an increased thrombo-embolic risk or an R–L shunt, oral anticoagulation may be considered. Occasionally there may be an indication to close the atrial communication in isolation. However, this needs to be discussed

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Table 14 Indications for intervention in Ebstein's anomaly

Indications	Class[a]	Level[b]
Indications for surgery		
• Surgical repair should be performed in patients with more than moderate TR and symptoms (NYHA class >II or arrhythmias) or deteriorating exercise capacity measured by CPET	I	C
• If there is also an indication for tricuspid valve surgery, then ASD/PFO closure should be performed surgically at the time of valve repair	I	C
• Surgical repair should be considered regardless of symptoms in patients with progressive right heart dilation or reduction of RV systolic function and/or progressive cardiomegaly on chest X-ray	IIa	C
Indications for catheter intervention		
• Patients with relevant arrhythmias should undergo electrophysiologic testing, followed by ablation therapy, if feasible, or surgical treatment of the arrhythmias in the case of planned heart surgery	I	C
• In the case of documented systemic embolism probably caused by paradoxical embolism, isolated device closure of ASD/PFO should be considered	IIa	C
• If cyanosis (oxygen saturation at rest <90%) is the leading problem, isolated device closure of ASD/PFO may be considered but requires careful evaluation before intervention (see text)	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
ASD = atrial septal defect; CPET = cardiopulmonary exercise testing; NYHA = New York Heart Association; PFO = patent foramen ovale; RV = right ventricle; TR = tricuspid regurgitation; VSD = ventricular septal defect.

carefully as it may lead to a further increase in right heart pressures and a decrease in systemic cardiac output.

Surgical repair remains challenging and should only be performed by surgeons with specific experience in this lesion. Tricuspid valve repair, if feasible, is preferred over tricuspid valve replacement (with closure of an associated interatrial communication). Tricuspid valve repair by creating a 'monocusp valve' may be possible in the case of a mobile anterior tricuspid valve leaflet and if the functional RV is more than one-third of the total RV.[80] An additional bidirectional cavopulmonary anastomosis may be required if the RV is too small for correction or RV dysfunction has developed. In patients with failed repair or in severe biventricular dysfunction, heart transplantation may be the only option.

The previously high operative mortality (>25%) has fallen to <6% in specialized centres. Over 90% of patients operated on by an experienced surgeon survive >10 years, many in functional class I or II. Late fatalities are proabably due to arrhythmias. In a large series, survival free of late reoperation was 86, 74, 62, and 46% at 5, 10, 15, and 20 years, respectively.[81]

Follow-up recommendations

Regular follow-up (at least yearly) is required in all patients in specialized GUCH centres. Typical post-operative residual anomalies to look for are persisting or new TR, the usual complications after valve replacement, failure of RV or LV, residual atrial shunts, arrhythmias, and higher grade heart blocks.

Re-intervention may become necessary for recurrent TR and failure of prosthetic valves.

Additional considerations

Exercise/sports: Patients without residual anomalies can usually lead normally active lives without restriction, except for extensive static sports to competition level. Patients with more than mild TR, ventricular dysfunction, shunting, arrhythmias, or other complications should avoid heavy isometric exercises, in proportion to the severity of their problems.

Pregnancy: Asymptomatic females with good ventricular function may tolerate pregnancy well. There is a certain risk of RV failure, arrhythmia, and paradoxical embolism. Pregnancy will be of higher risk in the presence of significant cyanosis, serious arrhythmia, and right heart failure (see Section 3.4.3). The risk of CHD in offspring is ~6%.

IE prophylaxis: Recommended only for high-risk patients (see Section 3.3.5).

4.10 Tetralogy of Fallot

Introduction and background

ToF is the most common form of cyanotic CHD after 1 year of age, with an incidence approaching 10% of all forms of CHD. The defect is due to antero-cephalad deviation of the outlet septum resulting in the following four features: a non-restrictive VSD, overriding aorta (but <50%), RVOTO which may be infundibular, valvular, or (usually) a combination of both, with or without supravalvular or branch PA stenosis, and consequent RVH. Associated lesions include ASD, additional muscular VSD, right aortic arch, anomalous (can be dual) left anterior descending coronary artery (3%) which may necessitate a conduit type of repair, and complete AVSD (rare, usually in association with Down syndrome). Approximately 15% of patients with ToF have a deletion of chromosome 22q11 (previously called Di George syndrome) with subsequent autosomal dominant type of inheritance and frequent early onset of depression or psychiatric disease.[82]

Clinical presentation and natural history

Early clinical presentation: Early clinical presentation is dominated by a heart murmur in infancy and progressive cyanosis (from right to left shunting at the ventricular level secondary to RVOTO). Unoperated tetralogy carries a poor prognosis (>95% of patients used to die before 40 years of age). Early management may include palliative procedures to increase pulmonary blood flow (Blalock–Taussig shunt: classic or modified—subclavian artery to PA end-to-side or with interposition graft, respectively; Waterston shunt: ascending aorta to right PA shunt; Potts shunt: descending

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aorta to left PA shunt) followed by repair. Repair involves VSD closure and relief of RVOTO (with resection of the infundibulum and pulmonary valvotomy; many patients require additional RVOT or transannular patches). Primary repair between 6 and 18 months of age is common practice nowadays, with a perioperative mortality <1%.[83]

Late clinical presentation: Late survival after tetralogy repair is excellent, with a 35-year survival of ~85%.[84,85] Common complications in adulthood are:

- **PR:** Significant PR is almost always encountered following a transannular patch repair. PR is usually well tolerated for years. Severe chronic PR, however, eventually leads to symptomatic RV dilation and dysfunction.[86] The severity of PR and its deleterious long-term effects are augmented by co-existing distal PA stenoses or PAH (the latter is uncommon).
- **Residual RVOTO:** This can occur at the infundibulum, at the level of the pulmonary valve and main pulmonary trunk, distally, beyond the bifurcation, and occasionally into the branches of the left and right PAs (the latter frequently because of sequelae from previous palliative surgery).
- **RV dilation and dysfunction:** RV dilation is usually due to residual longstanding free PR ± RVOTO. Significant TR may occur as a consequence of RV dilation, which begets more RV dilation.
- **Residual VSD:** This can be due to partial patch dehiscence or failure of complete closure at the time of surgery; it may lead to LV volume overload.
- **Aortic root dilation with AR:** Aortic root dilation (progressive) is seen in ~15% of adults late after repair and relates to both intrinsic abnormalities of the aorta (cystic medial necrosis) and increased flow (i.e. patients with pulmonary atresia).[87] It commonly leads to AR and rarely to aortic dissection.
- **LV dysfunction:** Due to longstanding cyanosis before repair and/or inadequate myocardial protection during repair (old era), LV volume overload from longstanding palliative arterial shunts, residual VSDs, and/or AR. It can also be the result of an adverse ventricular–ventricular interaction (PR).[88]
- **Atrial/ventricular tachycardia and SCD:** This is related to progressive haemodynamic problems and/or surgical scarring, and thus is seen with increasing frequency with longer follow-up. SCD is reported in 1–6% of cases [in most instances due to VT/ventricular fibrillation (VF)], accounting for approximately a third to a half of late deaths.[89]
- **Endocarditis:** Endocarditis is rare.

Diagnostic work-up of repaired patients

See Section 3.2 for general principles.

Clinical findings include a mostly widely split second heart sound. A low-pitched early ending diastolic murmur suggests severe PR. A long, loud ejection systolic murmur indicates RVOTO, a high-pitched diastolic murmur indicates AR, and a pansystolic murmur indicates a residual VSD.

ECG shows in general complete right bundle branch block, with the QRS width reflecting the degree of RV dilation. A QRS >180 ms, particularly if progressive, is a risk factor for VT and SCD.[86,89]

Echocardiography is the first-line diagnostic technique, providing the assessment of residual RVOTO and PR, residual VSD, RV and LV size and function,[90] TR, right ventricular pressure (RVP), aortic root size, and AR.

CMR is the method of choice for assessment of RV volume and function, PR, size, shape, and expansion of the PAs, the ascending aorta and the position of great vessels or conduits in relation to the sternum (resternotomy). For details see recommendations for the use of CMR in GUCH.[3] Gadolinium enhancement demonstrates fibrosis, the extent of which relates to other risk factors for VT and SCD.[91]

CT may be an alternative to CMR for patients with PMs/ICDs. It also provides information on coronary arteries, lung parenchyma, and the extent of conduit calcification (percutaneous valve anchoring).

CPET assists timing of re-intervention and provides prognostic information.[4]

Arrhythmias and risk assessment for SCD require particular attention. ***Holter monitoring, event recorder***, and ***EP*** testing are required for selected patients (high risk, investigated for suspected or clinical arrhythmia, and/or patients evaluated for RVOT reoperation).[89,92,93] Inducible sustained VT carries prognostic value for clinical VT and SCD.[93]

Cardiac catheterization should be restricted to patients undergoing catheter-based interventions (i.e. relief of distal PA stenosis, percutaneous valve implantation) and when non-invasive evaluation is inconclusive.

Late surgical/catheter interventional treatment (*Table 15*)

Pulmonary valve replacement (PVRep) and/or relief of RVOTO can be performed with low mortality (<1%) in patients without heart failure and/or advanced ventricular dysfunction. PR is the most frequent reason for consideration of surgery. Optimal timing remains challenging. Longitudinal data are more important than single measurements to assist timing for re-intervention. Normalization of RV size after re-intervention becomes unlikely as soon as the end-diastolic volume index exceeds 160 mL/m^2.[90] Distal PA stenosis must be addressed, either at the time of surgery (including intra-operative stenting) or with a percutaneous approach. Tissue PVRep seems to have a mean life span of 10–15 years. There is little experience with mechanical valves in this setting and there is concern about adequate anticoagulation. Residual VSDs and/or aortic root dilation/AR should also be addressed at the time of surgery.

For percutaneous valve implantation see Section 4.16.

Indications for EP testing and ICD

EP testing and/or ablation must be considered for symptomatic patients with suspected or documented clinical arrhythmia, atrial or ventricular.[93]

An ICD should be implanted for secondary prevention of SCD (patients with cardiac arrest or sustained VT) (IC). ICD implantation for primary prevention remains controversial, and no ideal risk stratification scheme has so far been developed. The following risk markers—although not consistently—have been reported: right and/or left ventricular dysfunction, extensive ventricular fibrosis (on CMR), QRS ≥180 ms, significant PR, non-sustained VT on Holter monitoring, inducible VT at EP testing, long-lasting palliative shunts,

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Table 15 Indications for intervention after repair of tetralogy of Fallot

Indications	Class[a]	Level[b]
Aortic valve replacement should be performed in patients with severe AR with symptoms or signs of LV dysfunction	I	C
PVRep should be performed in symptomatic patients with severe PR and/or stenosis (RV systolic pressure >60 mmHg, TR velocity >3.5 m/s)	I	C
PVRep should be considered in asymptomatic patients with severe PR and/or PS when at least one of the following criteria is present: • Decrease in objective exercise capacity • Progressive RV dilation • Progressive RV systolic dysfunction • Progressive TR (at least moderate) • RVOTO with RV systolic pressure >80 mmHg (TR velocity >4.3 m/s) • Sustained atrial/ventricular arrhythmias	IIa	C
VSD closure should be considered in patients with residual VSD and significant LV volume overload or if the patient is undergoing pulmonary valve surgery	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
AR = aortic regurgitation; LV = left ventricle; PR = pulmonary regurgitation; PVRep = pulmonary valve replacement; RV = right ventricle; RVOTO = right ventricular outflow tract obstruction; TR = tricuspid regurgitation; VSD = ventricular septal defect.

and older age at time of repair.[88,89,91–94] Patients with unexplained syncope and impaired ventricular function should undergo haemodynamic and EP evaluation. In the absence of a defined and reversible cause, ICD implantation should be considered (see Section 3.3.2).

Follow-up recommendations

All patients with ToF should have periodic cardiac follow-up in a specialized GUCH centre, which in most patients should be done annually, but can be less frequent in those patients at the best end of the spectrum with minimal/stable haemodynamic disturbance. Follow-up evaluation needs to look for the complications listed above (see late clinical presentation). Echocardiography is performed as part of each visit. All patients should have CMR. The intervals for repeat studies depend on the pathology found.

Additional considerations

Exercise/sports: There are no restrictions in asymptomatic patients with good haemodynamics. High-risk patients for clinical arrhythmia/SCD, patients with advanced biventricular dysfunction, and patients with marked ascending aortopathy should limit themselves to low-intensity activity/sports and avoid isometric exercise.

Pregnancy: Pregnancy in unrepaired patients constitutes a considerable risk of maternal and foetal complications and death. The risk of pregnancy in repaired patients depends on the haemodynamic status (low in patients with good haemodynamics). In patients with significant residual lesions there is a risk of arrhythmia and right heart failure, and pregnancy may have an adverse long-term effect on cardiovascular function (see Section 3.4.3). The risk of recurrence of CHD is ~3% unless the patient has microdeletion 22q11 (when the risk rises to 50%).

IE prophylaxis: Recommended only for high-risk patients (see Section 3.3.5).

4.11 Pulmonary atresia with ventricular septal defect

Introduction and background

Pulmonary atresia with VSD (PA + VSD), sometimes also called ToF with pulmonary atresia, shares the intracardiac anatomy of tetralogy but lacks a direct communication between the RV and PAs. Patients with discordant cardiac connections and/or a 'single ventricle physiology' and their management will be discussed in the appropriate sections. While patients with PA + VSD have a good size RV, and from this perspective are suitable for biventricular repair, major problems with the PAs are common and determine both clinical presentation and management (the complexity of the pulmonary vascular bed may make repair unattractive or impossible). There are three patterns of PAs:

- Unifocal with confluent good size PAs supplied by a PDA
- Multifocal, with confluent but hypoplastic PAs ('seagull' appearance) supplied by multiple major aortic pulmonary collaterals (MAPCAs)
- Multifocal with non-confluent PAs supplied by MAPCAs.

PA + VSD comprises ~1–2% of congenital heart defects. Microdeletion 22q11.2 is common (facial anomalies, nasal speech, and developmental delay).[82]

Clinical presentation and natural history

Early clinical presentation[95,96] varies between cyanosis (for patients with reduced or threatened pulmonary blood flow), failure to thrive, and/or exertional dyspnoea, to heart failure (for patients with excessive pulmonary blood flow through large MAPCAs, who may develop segmental PAH with time).

When pulmonary blood flow is duct dependent, profound cyanosis and cardiovascular collapse ensue as the duct closes. Patients with confluent, good-sized PAs and a pulmonary trunk (usually with valvar atresia) are suitable for a Fallot-like repair using a transannular patch. Patients with good-sized PAs but without a pulmonary trunk should undergo repair with an RV–PA conduit. Patients with confluent but hypoplastic PAs often require an arterial shunt or reconstruction of the RVOT (without VSD closure), which may enhance PA growth, and then be reviewed at a later stage for repair using a valved conduit. Patients with non-confluent PAs with adequate, but not excessive, pulmonary blood flow in infancy can survive into adulthood without surgery. There are proponents of a staged unifocalization approach for this latter challenging group of infants, ultimately aiming for a conduit repair.[97,98]

Late clinical presentation for repaired patients is similar to those with tetralogy (see Sections 4.10 and 4.16), whereas unrepaired patients present with exertional dyspnoea, fatigue, and progressive chronic cyanosis,[95] the latter leading to multiorgan involvement (see Section 4.18) and, with time, to a number of complications:

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- Haemoptysis may be due to rupture of usually small collateral vessels and/or to small PA thrombosis
- Chronic heart failure is usually multifactorial and may be due to chronic cyanosis, early excessive pulmonary blood flow, increased PVR, RV dysfunction, AR, and other causes
- Progressive dilation of the ascending aorta with increasing AR and aortic dissection (very rare complication) may occur
- Endocarditis can be particularly compromising in patients with limited cardiovascular reserve and those with significant cyanosis
- Increasing cyanosis may be due to decreased pulmonary blood flow from collateral stenosis, PA stenosis, increased PVR, or increasing ventricular end-diastolic pressures
- Arrhythmia and SCD are not uncommon.

Diagnostic work-up

See Section 3.2 for general principles.

Clinical findings may include RV lift with thoracotomy ± medial sternotomy scars for patients with previous surgical intervention(s). Cyanosis in unrepaired patients may be profound, even with minimal physical effort. Continuous murmurs at the back suggest MAPCAs. ECG findings include right axis deviation and RVH. Chest X-ray may show a boot-shaped cardiac contour ('empty PA bay') with abnormal, decreased pulmonary vascularity (alternating with some areas of increased vascularity through large MAPCAs).

Echocardiography is the first-line diagnostic technique. Findings depend on the type of repair (see Sections 4.10 and 4.16). For unrepaired patients, absence of direct flow from the RV to the PA, with continuous flow on multiple sites on colour Doppler from the MAPCAs, may be seen.

CMR, CT, and ***cardiac catheterization*** are required to determine sources of pulmonary blood supply and size of PAs, and to assess PAH and MAPCAs (for PAH and MAPCAs, catheterization is required).

Surgical/catheter interventional treatment

For follow-up and intervention in patients with Fallot-like repair with transannular patch, see Section 4.10; for patients with repair using a valved RV–PA conduit see Section 4.16.

Patients with PA + VSD surviving unrepaired to adulthood or with previous palliative procedures[99–102] may have been considered unoperable years ago, but may actually benefit from modern surgical or interventional procedures. This may particularly be the case in patients with good-sized confluent PAs, but occasionally also in those with large MAPCAs anatomically suitable for unifocalization who have not developed severe pulmonary vascular disease due to protecting stenoses. In the absence of advanced RV or LV dysfunction such patients may be considered for repair.[99] All unrepaired patients should therefore be critically re-evaluated in specialized centres. However, many unrepaired patients may not be suitable for further surgery, mainly because of the complexity of their pulmonary vasculature.

It is important to appreciate that while cardiac surgery may improve clinical status or prognosis (the latter is purely speculative), it is also a major cause of mortality. Despite the additional challenge of an abnormal pulmonary vascular bed, the survival of repaired individuals may be approaching that of ToF in selected individuals where haemodynamics are good (VSD is closed, RVOTO is relieved, and pulmonary vascular bed and resistance are at or near normal). Survival falls to much lower levels the more complex the pulmonary malformations and the less satisfactory the repair (survival in palliated patients is reported as 61% at 20 years follow-up). Heart–lung transplantation may be a remote option, again for highly selected individuals, but it is associated with major technical challenges, higher operative risk, and worse outcome; there is also the current shortage of organs.

Catheter intervention may include balloon dilation/stenting of collateral vessels to enhance pulmonary blood flow.[103]

Follow-up recommendations

Patients with PA + VSD should have periodic follow-up in a specialized GUCH centre (at least once a year). For the management of cyanosis-related multiorgan involvement, see Section 4.18

Patients with segmental PAH have been considered for targeted PAH therapy, although there is a lack of data (see Section 4.17).

Symptoms such as dyspnoea, increasing cyanosis, change in the shunt murmur, heart failure, or arrhythmias warrant special attention and should necessitate an earlier review and assessment for intervention.

Additional considerations

Exercise/sports: Those with excellent haemodynamics should be encouraged to exercise regularly, perhaps avoiding only extreme isometric exercise. Those with less optimal haemodynamics will be more functionally limited. Extremes of exertion or competitive contact sports should be avoided, but regular low-intensity physical activity (walking, swimming, even cycling) should be encouraged.

Pregnancy: The risk of pregnancy in repaired patients with good haemodynamics and no history of arrhythmias is low. The risk increases with hypoxaemia, PAH, ventricular dysfunction, heart failure symptoms, and arrhythmias (see Section 3.4.3). As microdeletion 22q11 is fairly common with this defect, patients should be checked before pregnancy.

IE prophylaxis: Recommended only for high-risk patients (including all unrepaired patients; see Section 3.3.5).

4.12 Transposition of the great arteries

Introduction and background

TGA—which accounts for ~5% of CHD—is characterized by ventriculo-arterial discordance: the LV gives rise to the PA, and the RV to the aorta. There is AV concordance. If no significant additional cardiac lesions are present, it is referred to as simple TGA. A complex TGA has associated intracardiac anomalies including VSD (in up to 45% of cases), LVOTO (~25%), and CoA (~5%).

In general, it is not familial. There is no known association with syndromes or chromosomal abnormalities. There is a 2:1 male preponderance.

Adult patients are in general seen after surgical procedures. Because of the fundamental differences in presentation and clinical course, depending on the initial pathology and the type of operation these patients will have had, the post-operative course will be described separately.

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Clinical presentation and natural history

Most adult patients with a simple TGA will still have had a Mustard or a Senning atrial switch procedure. Most patients have a diminished exercise capacity when compared with the normal population.[104] Dysfunction of the RV, which serves as a systemic ventricle, is the most severe clinical problem.[105] The prevalence increases substantially with longer duration of follow-up.[106,107] TR often develops as a sign of RV dilation and progresses if cardiac failure becomes more prominent.[108] Tachyarrhythmias occur frequently. Atrial flutter is the most typical presentation, but atrial fibrillation and all other types of supraventricular arrhythmias can occur.[109] VT and VF have been reported, and are associated with SCD.[110] With longer follow-up, there is ongoing loss of sinus node function. Bradycardia due to sinus node dysfunction necessitating PM therapy is common.[111] The intra-atrial tunnels are often referred to as baffles. They can leak with either L–R or R–L shunt, or can obstruct systemic venous and/or pulmonary venous drainage. The latter may lead to pulmonary hypertension. Systemic venous baffle stenosis, most often the superior baffle, is reported to be present in up to 25% of the patients after Mustard repair. SVC obstruction may lead to venous congestion of the upper body half and necessitate re-intervention. Obstruction of the systemic venous inferior baffle can cause venous congestion of the lower body half, hepatic congestion, and hepatic cirrhosis. However, in either a superior or inferior baffle stenosis, clinical symptoms may be entirely absent, because of an effective collateral circulation provided by the azygos or hemiazygos vein. Narrowing of the subpulmonary outflow tract can occur due to leftward bulging of the interventricular septum. This can lead to a substantial gradient, which is often well tolerated by the subpulmonary LV. It may even be protective for systemic ventricular function due to ventricular septal shift to the right. Other reported problems are residual VSD or PAH.

Young adult patients will most probably have had an arterial switch operation. A large majority of these patients are asymptomatic and are in NYHA functional class I. Long-term complications include: LV dysfunction and arrhythmias (both may be related to problems with the coronary arteries, which were re-implanted in the new aorta during the arterial switch operation); dilation of the proximal part of the ascending aorta resulting in AR;[112,113] supravalvular PS; and pulmonary branch stenosis (unilaterally or bilaterally), resulting from the positioning of the pulmonary bifurcation anterior to the ascending aorta in the Lecompte technique.

Adult patients with complex transposition who had a Rastelli-type repair, in which the anatomical LV is connected through a VSD patch to the aorta and the RV with a valved conduit to the PA, can be entirely asymptomatic with a normal exercise capacity; however, residual abnormalities—or problems that develop years after the operation—are common. The most common problems are related to the valved conduit between the RV and the PA and residual VSDs. Arrhythmias—ventricular and supraventricular—can occur as well.

4.12.1 Atrial switch operation

Diagnostic work-up

See Section 3.2 for general principles.

Clinical evaluation should include looking for signs of venous congestion in the upper and/or lower body half. An ejection-type systolic murmur suggests subpulmonary outflow tract obstruction, and a systolic regurgitant-type murmur suggests systemic tricuspid valve regurgitation. ECG findings include RVH and, not uncommonly, narrow-QRS escape rhythm. Atrial flutter is frequently seen (but also other types of supraventricular arrhythmias).

Echocardiography is the first-line diagnostic technique, providing information on systemic and subpulmonary ventricular size and function, subpulmonary outflow tract obstruction, TR, leakage or obstruction of the atrial baffles, and assessment of pulmonary venous return. SVC stenosis is, however, mostly difficult to assess by transthoracic echocardiography (TTE).

Contrast echo is indicated if there is suspicion of baffle leakage and is very helpful in the detection of baffle stenosis. If contrast is injected in an arm and enters the heart from below, this is a reliable sign of a superior baffle stenosis (if it enters the heart from above when injected in a leg, this indicates inferior baffle stenosis). TEE is useful for evaluation of baffles.

CMR is indicated for assessment of systemic RV function and patency of the atrial baffles. CT is an alternative, particularly in patients with PMs or claustrophobia.

CPET can 'unmask' baffle leakage that is asymptomatic at rest. It is also useful for evaluation of arrhythmia and is recommended on a regular basis.

Arrhythmias and risk assessment for SCD require particular attention. ***Holter monitoring, event recorder***, and ***EP testing*** are required for selected patients (high risk, investigated for suspected or clinical arrhythmia).

Cardiac catheterization is indicated when non-invasive assessment is inconclusive or when PAH requires evaluation (see Section 3.2.5).

Medical treatment

Systemic RV failure: Diuretics and digoxin are the cornerstone of medical treatment. The role of ACE inhibitors[114] and β-blockers is controversial. The use of CRT is experimental.

Surgical/catheter interventional treatment

See *Table 16*.

EP testing, ablation, and ICD

These procedures are complicated by the fact that the atria are not normally accessible for catheters and 'normal' EP procedures because of the course of the baffles,[115] and should only be done in specialized centres with specific expertise.

Patients are at increased risk of SCD. Atrial tachyarrhythmias,[116] impaired systemic RV function, and QRS duration $\geq$140 ms[117] have been reported to be risk factors. Specific criteria for ICD implantation for primary prevention have not been well defined yet (see Section 3.3.2 for general recommendations).

4.12.2 Arterial switch operation

Diagnostic work-up

See Section 3.2 for general principles.

Clinical findings of AR or PS may be present.

Echocardiography is the key diagnostic technique, providing information on LV function (global and regional), stenosis at the

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Table 16 Indications for intervention in transposition of the great arteries after atrial switch

Indications	Class[a]	Level[b]
Indications for surgical intervention		
Valve repair or replacement should be performed in patients with severe symptomatic systemic (tricuspid) AV valve regurgitation without significant ventricular dysfunction (RVEF ≥45%)	I	C
Significant systemic ventricular dysfunction, with or without TR, should be treated conservatively or eventually with cardiac transplantation	I	C
LVOTO if symptomatic or if LV function deteriorates should be treated surgically	I	C
In *symptomatic* pulmonary venous obstruction surgical repair (catheter intervention rarely possible) should be performed	I	C
Symptomatic patients with baffle stenosis not amenable for catheter intervention should be treated surgically	I	C
Symptomatic patients with baffle leaks not amenable for stenting should be treated surgically	I	C
Valve repair or replacement should be considered for severe asymptomatic systemic (tricuspid) AV valve regurgitation without significant ventricular dysfunction (RVEF ≥45%)	IIa	C
Pulmonary artery banding in adult patients, to create septal shift, or as left ventricular training with subsequent arterial switch, is currently experimental and should be avoided	III	C
Indications for catheter intervention		
Stenting should be performed in *symptomatic* patients with baffle stenosis	I	C
Stenting (covered) or device closure should be performed in *symptomatic* patients with baffle leaks and substantial cyanosis at rest or during exercise	I	C
Stenting (covered) or device closure should be performed in patients with baffle leaks and symptoms due to L–R shunt	I	C
Stenting (covered) or device closure should be considered in *asymptomatic* patients with baffle leaks with substantial ventricular volume overload due to L–R shunt	IIa	C
Stenting should be considered in asymptomatic patients with baffle stenosis who require a PM	IIa	C
Stenting may be considered in other *asymptomatic* patients with baffle stenosis	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
AV = atrioventricular; L–R shunt = left-to-right shunt; LV = left ventricle; LVOTO = left ventricular outflow tract obstruction; PM = pacemaker; RVEF = right ventricular ejection fraction; TR = tricuspid regurgitation.

arterial anastomotic sites, most commonly PS, neoaortic valve regurgitation, dimension of the ascending aorta,[118] and the acute angulation of the aortic arch.[112] The pulmonary trunk, the bifurcation, and both branches should be evaluated for the presence, localization, and severity of stenoses. RV function should be judged and systolic pressures should be estimated (TR velocity). Ostia of coronary arteries and proximal course can be evaluated with TEE.

Stress echocardiography can unmask LV dysfunction and detect provocable myocardial ischaemia.

CMR may be required when echocardiography information is insufficient, in particular for evaluation of the aorta, pulmonary branch stenosis, and flow distribution between left and right lung.

CT might be used for non-invasive imaging of coronary arteries, including the ostia, in the case of suspicion of stenosis and as an alternative to CMR.

Nuclear techniques can be used for evaluation of coronary perfusion when myocardial ischaemia is suspected, and a lung perfusion test is recommended in the case of pulmonary branch stenosis to measure the flow distribution between the left and right lung (CMR is an alternative).

Cardiac catheterization including coronary angiography is indicated in the case of LV dysfunction and suspicion of myocardial ischaemia. In asymptomatic patients, a one-time invasive evaluation of the patency of the coronary circulation can be considered. In the case of severe pulmonary branch stenosis and inconclusive non-invasive assessment, cardiac catheterization is also indicated.

Surgical/catheter interventional treatment

See *Table 17*.

4.12.3 Rastelli type operation

Diagnostic work-up

See Section 3.2 for general principles.

Clinical findings may suggest conduit stenosis, residual VSD, TR, mitral regurgitation, or AR.

Echocardiography is the first-line diagnostic technique providing LV and RV function. The connection between the posteriorly positioned LV and the anteriorly positioned (due to the TGA) aortic valve, and the function of the conduit between the RV and the pulmonary trunk should be visualized and assessed with Doppler interrogation. Residual VSDs are often difficult to assess, due to the unusual course of the conduit or patch used to connect the LV to the aortic valve. Doppler gradients across the conduit may be difficult to measure and may in addition be unreliable. Therefore, RVP estimation from TR velocity is of particular importance for assessment of conduit stenosis (see Section 4.16).

CMR can be used for non-invasive assessment of LV and RV function. Conduits and semilunar valves can be assessed, as well the presence of a residual VSD, including Qp:Qs.

Cardiac catheterization may be required for haemodynamic assessment of conduit stenoses. Angiography can be helpful for assessing the level of stenosis and peripheral PA stenosis (see Section 3.2.5).

Surgical/catheter interventional treatment

For indications for treatment of conduit stenosis, see Section 4.16.

Stenosis in the connection between the LV and aortic valve with a mean gradient >50 mmHg (less when LV function and cardiac

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Table 17 Indications for intervention in transposition of the great arteries after arterial switch operation

Indications	Class[a]	Level[b]
Stenting or surgery (depending on substrate) should be performed for coronary artery stenosis causing ischaemia	I	C
Surgical repair of RVOTO should be performed in symptomatic patients with RV systolic pressure >60 mmHg (TR velocity >3.5 m/s)	I	C
Surgical repair of RVOTO should be performed regardless of symptoms when RV dysfunction develops (RVP may then be lower)	I	C
Surgical repair should be considered in asymptomatic patients with RVOTO and systolic RVP >80 mmHg (TR velocity >4.3 m/s)	IIa	C
Aortic root surgery should be considered when the (neo-)aortic root is >55 mm, providing average adult stature (for aortic valve replacement for severe AR see guidelines for AR[35])	IIa	C
Stenting or surgery (depending on substrate) should be considered for peripheral PS, regardless of symptoms, if >50% diameter narrowing and RV systolic pressure >50 mmHg and/or lung perfusion abnormalities are present	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
AR = aortic regurgitation; AV = atrioventricular; RV = right ventricle; RVOTO = right ventricular outflow tract obstruction; RVP = right ventricular pressure; TR = tricuspid regurgitation.

output are reduced) should be considered for surgical repair (IIaC).

If L–R shunting through a residual VSD causes symptoms or substantial left-sided volume overload, surgical treatment should be performed (IC).

Follow-up recommendations (irrespective of type of repair)

All patients with TGA, regardless of their type of operation, should be seen at least annually in a specialized GUCH centre, with attention given to specific issues described above.

Additional considerations (irrespective of type of repair)

Exercise/sports: Patients with symptoms or a history of arrhythmias should be counselled carefully on an individual basis because of a possibly elevated risk of arrhythmias provoked by exercise (exercise testing recommended). Those with excellent haemodynamics should be encouraged to exercise regularly, and avoid only extreme exercise. Those with less optimal haemodynamics will be more functionally limited. Extremes of exertion or competitive contact sports should be avoided, but regular medium- or low-intensity physical activity should be encouraged.

Pregnancy: Patients with haemodynamic compromise have elevated risks during pregnancy. Patients with TGA and atrial switch carry an increased risk of developing life-threatening arrhythmias, or RV dysfunction that may be irreversible.[119] Patients with a TGA, irrespective of the type of surgical repair, who are in good clinical condition have a high likelihood of going through a normal pregnancy, although the risks of miscarriage, foetal growth retardation, and early delivery are higher than in the normal population[120] (see Section 3.4.3). The recurrence risk of TGA is low.

IE prophylaxis: Recommended only for high-risk patients (see Section 3.3.5).

4.13 Congenitally corrected transposition of the great arteries

Introduction and background

ccTGA, or atrio-ventricular and ventriculo-arterial discordance, is uncommon, accounting for <1% of all CHD. The ventricles are inverted when compared with the normal situation, with the aorta arising anteriorly from the RV (on the left side) and the PA arising posteriorly from the LV (on the right side). The abnormal connections in 'double' discordance may be present in hearts with usual or mirror-image atrial arrangement. Cardiac orientation or base–apex axis may include levocardia, dextrocardia, or mesocardia. Associated lesions are common (80–90%), including VSD (70%) and PS (40%). Abnormalities of the systemic tricuspid valve are frequent, and features of Ebstein's malformation may be present.

The AV node and bundle of His may be positioned abnormally and lead to conduction abnormalities.

Clinical presentation and natural history

The natural history and clinical presentation are usually determined by the associated cardiac malformations.[108,121–123] In patients with a large VSD, congestive cardiac failure may develop in infancy. When there is a VSD and PS, increasing cyanosis may develop.

Isolated ccTGA may have no haemodynamic consequences in childhood and early adulthood. Patients are often asymptomatic and the diagnosis may be made at adult age because of an abnormal chest radiograph or ECG (often at routine medical examination). Systemic right (subaortic) ventricular failure and/or severe systemic AV valve regurgitation (especially with an Ebstein-like tricuspid valve) may cause dyspnoea and exercise intolerance in the fourth or fifth decade. At this stage, patients may be misdiagnosed as having dilated cardiomyopathy. A mismatch between myocardial blood supply and workload of the systemic (subaortic) ventricle may contribute to heart failure.

There is a progressive tendency to develop AV conduction problems (2% per year incidence of complete heart block), and AV block is even more common after repair of a VSD or after tricuspid valve replacement. Palpitations from supraventricular arrhythmias may arise in the fifth or sixth decade. Ventricular arrhythmias may be associated with haemodynamic abnormalities and/or ventricular dysfunction.

Diagnostic work-up

See Section 3.2 for general principles.

Clinical findings may include murmurs of TR, VSD, and/or PS. ECG may reveal a prolonged PR interval or a complete heart

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block. Since the bundle branches are inverted, there is an early septal activation from right to left which may cause deep Q waves in II, III, aVF, and V1–V3. This can be misdiagnosed as a myocardial infarction. Reversal of the normal pre-cordial progression may be seen as a QR pattern in V1 and rS in V6. WPW syndrome is present in 2–4% of patients.

Chest X-ray may show an abnormally straight left heart border due to the leftward and anterior position of the ascending aorta, dextrocardia (20%), or mesocardia (relatively common).

Echocardiography is the key diagnostic technique, demonstrating double discordance. (The inverted position of the ventricles in the usual atrial arrangement can be recognized by the fundamental morphological differences between the two ventricles. The anatomic RV has increased trabeculation, a moderator band, and a more apically inserted tricuspid valve. There is a discontinuity between the AV valve and the arterial valve. In the LV the mitral valve has a higher insertion, the muscular wall is smoother, and continuity exists between the mitral valve and the arterial valve.) It is important to identify associated anomalies, particularly AV abnormalities (Ebstein-like malformation) and regurgitation, VSD, LVOTO, and PS. Systolic function of the systemic (subaortic) ventricle and severity of AV valve regurgitation can be qualitatively assessed.

CMR provides intracardiac and great vessel anatomy and is indicated for quantification of ventricular volumes, mass, and EF.[124]

Arrhythmias, progressive AV block, and risk assessment for SCD require particular attention. ***Holter monitoring, event recorder***, and ***EP testing*** are required for selected patients (high risk, investigated for suspected or clinical arrhythmia).

Cardiac catheterization is indicated when non-invasive assessment is inconclusive or PAH requires evaluation (see Section 3.2.5).

Surgical/catheter interventional treatment (*Table 18*)

Catheter intervention may be recommended for patients with PA stenosis or conduit stenosis, which can be dilated or stented. However, a residual LVOTO may have a beneficial effect on the dilated systemic RV (subaortic ventricle) and systemic AV (tricuspid) valve regurgitation because of the septal shift.

Table 18 Indications for intervention in congenitally corrected transposition of the great arteries

Indications	Class[a]	Level[b]
Systemic AV valve (tricuspid valve) surgery for severe regurgitation should be considered before systemic (subaortic) ventricular function deteriorates (before RVEF <45%)	IIa	C
Anatomic repair (atrial switch + arterial switch or Rastelli when feasible in case of non-restrictive VSD) may be considered when LV is functioning at systemic pressure	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
AV = atrioventricular; LV = left ventricle; RVEF = right ventricular ejection fraction; VSD = ventricular septal defect.

Corrective surgery by double switch (atrial and arterial switch) or atrial switch and Rastelli operation (intraventricular rerouting + conduit) has been shown to be feasible in children.[125–127] The aim has been to permit the LV to become the systemic (subaortic) ventricle. The results remain uncertain and the procedure is considered controversial in infancy and childhood. In adults, mortality is high, and therefore this operation is not recommended. Systemic AV valve (tricuspid) regurgitation is most often the focus for surgical treatment. Repair is mostly not feasible, because the valve is frequently morphologically abnormal. Surgery for severe valve regurgitation should be performed before systemic ventricular EF is <45%.[128] Systemic AV valve (tricuspid) regurgitation may be improved by a residual LV (subpulmonary) outflow obstruction by inducing a shift in the interventricular septum towards the dilated systemic (subaortic) RV. It has been suggested that PA banding has a beneficial effect on the dilated systemic (subaortic) RV and systemic AV valve (tricuspid) regurgitation, but this remains controversial.

Pacing may be required because of progressive AV block. Fixation of the ventricular wire in the smooth-walled subpulmonary LV can be difficult and requires specific experience.

In some patients with impaired systemic ventricular function, biventricular pacing might be helpful, but sufficient data to support such therapy are lacking.

Follow-up recommendations

Patients with ccTGA need lifelong follow-up in a specialized GUCH centre[129] with annual intervals, particularly because of conduction disturbances, and systemic ventricular and systemic AV valve dysfunction. ACE inhibitors to treat or prevent RV dysfunction have been used with increasing frequency. However, data from small studies on their efficacy are contradictory. For arrhythmias, see above and Section 3.3.2.

Additional considerations

Exercise/sports: Patients with ccTGA should avoid competitive and static sports. Patients with significant associated lesions and/or decreased systemic RV function should be restricted to low-intensity sports (see Section 3.4.2).

Pregnancy: Risk depends on functional status, ventricular function, presence of arrhythmias, and associated lesions (see Section 3.4.3). The risk of CHD recurrence appears to be low.

IE prophylaxis: Recommended only for high-risk patients (see Section 3.3.5).

4.14 Univentricular heart

This section deals with unoperated and palliated UVH. For patients after Fontan operation see Section 4.15.

Introduction and background

The term ‘univentricular heart’ summarizes a variety of malformations where either the RV or LV is missing or, if present, is hypoplastic, and thus not amenable for biventricular repair, such as:

- Tricuspid atresia
- Hypoplastic right heart syndrome variants, e.g. pulmonary atresia with intact ventricular septum variants

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- Hypoplastic left heart syndrome variants, including mitral atresia
- Double-inlet LV
- Double-inlet RV
- Extreme forms of unbalanced complete AV septal defects
- Single ventricle with undefined morphology.

These malformations are always associated with additional intra- and/or extracardiac lesions such as:

- ASD, VSD, AVSD, PDA
- AS (valvular, subvalvular)
- Aortic arch anomalies: hypoplasia, interruption, coarctation
- PS (valvular, subvalvular), pulmonary atresia
- PA anomalies: peripheral stenosis, hypoplasia, one-sided absence
- Discordant connections, malposition of the great arteries
- AV valve stenosis, regurgitation, overriding, straddling
- Left or right atrial isomerism, abnormal systemic or pulmonary venous connections
- Left SVC, absent innominate vein, absent right SVC, absent infrahepatic IVC with azygos or hemiazygos continuity
- Aortic-to-pulmonary collateral arteries
- Polysplenia or asplenia.

Detailed anatomic description is beyond the scope of these guidelines and can be found in textbooks.[130] Owing to the lack of data, recommendations are mainly based on expert consensus.[130–135]

Basically, two different haemodynamic situations can be identified:

(1) *No anatomic restriction to pulmonary blood flow:* if pulmonary circulation remains unmodified (i.e. no surgery), many patients will die in childhood due to intractable heart failure. Those who survive this period will have developed severe pulmonary vascular disease. This will be a main determinant of long-term outcome. Many will have had pulmonary banding to restrict pulmonary blood flow in early childhood. An effective banding will protect against pulmonary vascular disease, while allowing enough pulmonary blood flow to limit the degree of cyanosis. A banding that is too loose will result in pulmonary overflow and pulmonary vascular disease despite the banding. If the banding is too tight, pulmonary blood flow will be extremely limited, resulting in severe cyanosis.

(2) *Obstruction to pulmonary blood flow (frequently valvular and/or subvalvular PS or atresia):* sometimes the obstruction is such that the pulmonary circulation is adequate (not excessive, thus avoiding development of pulmonary hypertension, and not too restricted, thus without extreme cyanosis). These balanced situations are the exception but allow survival into adulthood without having surgery. Most patients have a very restricted pulmonary blood flow, necessitating a systemic-to-PA shunt operation in childhood—most commonly Blalock–Taussig (subclavian to PA), rarely Waterston or Potts (ascending or descending aorta to PA, respectively). If a systemic-to-PA shunt is too large, pulmonary overflow will result in pulmonary vascular disease at adult age. If the shunt is too small, patients will be extremely cyanotic. Beyond infancy, an anastomosis between the SVC and PA is a possibility: the classical Glenn anastomosis to the right PA (historical) or an end-to-side anastomosis with the PA, creating a bidirectional cavopulmonary anastomosis. An adequate shunt will lead to a balanced situation (see above).

When presenting as adults, the vast majority of patients with these conditions will have undergone previous palliation with some type of systemic-to-PA shunt, cavopulmonary connection (Glenn), or now preferably a Fontan operation or one of its modifications. The latter is covered in Section 4.15.

Clinical presentation and natural history

Depending on the extent of pulmonary blood flow, presence or absence of pulmonary vascular disease, and ventricular function, patients may present with various degrees of cyanosis and congestive heart failure. Exercise ability is in general substantially reduced (with exceptions); complete AV block, arrhythmias (supraventricular, but also ventricular, SCD not unusual), stroke, brain abscess, and thrombo-embolism can occur. Endocarditis is relatively common in this population. For more details, see sections on Eisenmenger syndrome and cyanotic patients (4.17 and 4.18, respectively).

Cyanosis is typically present in patients with UVH without a Fontan operation. Arterial oxygen saturation commonly ranges between 75 and 85% but may, in exceptional cases with ideally balanced circulations, reach values beyond 90%.

Patients may present with progressive obstruction towards the aorta. This will lead to ventricular hypertrophy and eventually to reduced cardiac output. Progressive obstruction towards the PA will cause progressive cyanosis. In Glenn patients, worsening cyanosis may also be due to development of pulmonary AV malformations or IVC-to-SVC collaterals.

The UVH has to accommodate both systemic and pulmonary venous return. This chronic volume overload will lead to a high likelihood of ventricular failure relatively early in life. AV valve regurgitation may develop or progress, if present previously. The already diminished exercise capacity will deteriorate further. Eventually, overt heart failure may develop, in addition to the cyanosis.

In rare cases, with a well-balanced haemodynamic situation, ventricular dysfunction does not develop, and survival until the fifth, sixth, and even seventh decade has been reported.

Diagnostic work-up

See Section 3.2 for general principles.

Clinical findings include central cyanosis, clubbing of fingers and toes, and an often asymmetric chest with a pre-cordial heave at the side where the heart lies in the chest. Scoliosis is a common problem. The second heart sound is typically single, but the rest of the auscultation depends on the associated abnormalities. ECG may reveal rhythm or conduction disturbances. Atrial re-entrant tachycardia with 2:1 block and only modest tachycardia may be easily overlooked.

Echocardiography is the key diagnostic technique, providing information on anatomy and monitoring cardiac function during follow-up. The segmental approach is required in the echocardiographic examination, since UVHs are always complex and can present with a wide range of abnormalities in situs, orientation, and connections.

Fundamental in the diagnosis of the UVHs are:

- Abdominal and atrial situs
- Position of the heart in the chest and position of the apex

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- Viscero-atrial, atrio-ventricular, ventriculo-arterial connections
- Morphological and haemodynamic information has to be obtained on the entire heart.
  - ☐ Exact anatomy of the ventriculo-arterial connection and its functional status have to be assessed, with special focus on obstruction towards the aorta or pulmonary vascular bed
  - ☐ AV valve function should be evaluated with special focus on regurgitation
  - ☐ Ventricular function/hypertrophy
  - ☐ ASD/VSD type, size, number, location
  - ☐ Ascending aorta, aortic arch, and descending aorta; detect/exclude coarctation
  - ☐ Pulmonary arteries—common trunk, branches, and sources of pulmonary blood supply
  - ☐ Visualization of shunts (Blalock–Taussig, Waterston, etc.).

TEE may be indicated in cases of inadequate TTE images.

CMR is the imaging modality of choice for extracardiac anatomy, including veno-atrial and ventriculo-arterial connections (CT is an alternative). Detailed morphological information of intracardiac anatomy can also be obtained. CMR is also the method of choice for quantification of the ventricular volumes, EF, and relative distribution of blood flow in the left and right lungs.

Cardiac catheterization is required when intervention is considered for haemodynamic assessment, in particular of PAP and transpulmonary gradient (PVR is often difficult to assess in this setting). It is mandatory when patients are evaluated for a Fontan operation. Evaluation of systemic-to-PA or Glenn shunts—and their sequelae (stenosis of the pulmonary branches) and other vascular anomalies (arteriovenous collateral vessels, fistulas, etc.)—may also require catheterization.

Surgical/interventional treatment (*Table 19*)

Interventional treatment such as pulmonary valvotomy to increase pulmonary blood flow in cases of severe PS is debatable.

If the clinical situation is stable, the (frequently high) risk of any type of surgical intervention should be weighed very carefully against the possible benefit.

A Fontan operation can only be considered in very well selected patients (see Section 4.15). For patients with severe cyanosis, with decreased pulmonary blood flow without elevated PVR, a bidirectional Glenn shunt (SVC-to-PA) can be an option. If a systemic-to-pulmonary shunt (e.g. arteriovenous axillary fistula or systemic artery pulmonary shunt) is the only option (bidirectional Glenn shunt not sufficient or PAP not low enough for this shunt), the benefit of increased pulmonary blood flow should be weighed against increased volume load to the systemic ventricle.

For transplantation, previous sternotomies/thoracotomies, aorto-pulmonary collaterals and the multisystem nature of cyanotic CHD are technical and medical challenges, and limit the outcome.

Conservative management

See sections on Eisenmenger syndrome and cyanotic patients (4.17 and 4.18, respectively) for haematological management and the role of targeted therapy in pulmonary vascular disease.

Follow-up recommendations

Regular evaluation is required in a specialized GUCH centre.

Table 19 Special considerations and indications for intervention in univentricular hearts

Special considerations and indications	Class[a]	Level[b]
Only well-selected patients after careful evaluation [low pulmonary vascular resistances, adequate function of the AV valve(s), preserved ventricular function] should be considered candidates for a Fontan operation	IIa	C
Patients with increased pulmonary blood flow—unlikely at adult age—should be considered for PA banding or tightening of a previously placed band	IIa	C
Patients with severe cyanosis, with decreased pulmonary blood flow without elevated PVR, should be considered for a bidirectional Glenn shunt	IIa	C
Heart transplantation and heart–lung transplantation should be considered when there is no conventional surgical option in patients with poor clinical status	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
AV = atrioventricular; PA = pulmonary artery; PVR = pulmonary vascular resistance.

Frequency is individualized, but at least yearly, with physical examination, measurement of oxygen saturation, laboratory controls (haematological indices, iron status, kidney function, etc.), ECG, X-ray, and echocardiography (see also Section 4.18).

CMR is required at least once at adult age and further on indication.

Additional considerations

Exercise/sports: As a rule, patients do not have an elevated risk of death during exercise, but they do have a substantially reduced exercise capacity. Recreational sports can be considered on a symptom-limited level.

Pregnancy: Pregnancy is contraindicated in patients with severely reduced pulmonary blood flow or with severe pulmonary vascular disease (Eisenmenger syndrome) or if ventricular function is poor. Cyanosis poses a significant risk to the foetus, with a live birth unlikely (<12%) if oxygen saturation is <85%[15] (see Section 3.4.3).

For contraception, a combined oral contraceptive pill must be avoided because of the risk of thrombogenicity and thromboembolism. Progestogen-only pills, and progestogen-eluting intrauterine devices or implantation systems provide safe contraception with a smaller cardiovascular risk.

IE prophylaxis: Indicated in all patients (see Section 3.3.5).

4.15 Patients after Fontan operation

Introduction and background

The Fontan operation was introduced in 1968 and has become the definitive treatment for suitable patients with a range of cardiac malformations characterized by a single functional ventricle (see

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Section 4.14). Surgery consists of the separation of the systemic and pulmonary venous returns without a subpulmonary ventricle and restores them to being 'in series'. Since its introduction, a number of modifications have been made to the original procedure, designed to streamline the systemic venous return to the pulmonary arteries. Currently the total cavopulmonary connection (TCPC) has replaced the atriopulmonary connection (APC, right atrial appendage to PA), with either an intracardiac or an extracardiac conduit between the IVC and the PA, together with an SVC-to-PA anastomosis (bidirectional Glenn).[136] This circulation is frequently established in two stages.

The natural history and outcome of other palliations for hearts with a 'single ventricle' are poor, so that the Fontan is usually undertaken in all patients in whom the haemodynamics are suitable. It is now appreciated that the operative mortality and subsequent outcome depend on the suitability of the circulation and adherence to defined criteria. Strict selection gives the best early and late results, with operative mortality of $<5\%$ in modern series, and includes low PVR and PAP (mean <15 mmHg), preserved ventricular function, adequate PA size, no relevant AV valve regurgitation, and normal rhythm. A 'fenestration' has been performed in selected or all cases by some centres.[137] Because of the limited long-term outcome, Fontan is not always the palliation of choice.

Clinical presentation and natural history

The lack of a subpulmonary ventricle results in chronic systemic venous hypertension, markedly altered pulmonary haemodynamics, and a chronically 'preload-deprived' ventricle. A number of important problems have emerged during long-term follow-up. Although 10-year survival may approach 90%, it should be appreciated that a premature decline in cardiovascular performance, with reduced survival, is inevitable even in the best Fontan patients.[138] Important haemodynamic issues contributing to late Fontan failure include a progressive decline in systemic ventricular function, AV valve regurgitation, a rise in PVR, atrial enlargement, pulmonary venous obstruction, and the consequences of chronic systemic venous hypertension including hepatic congestion and dysfunction.[139] Further complications include atrial and PA thrombus formation, development of pulmonary arteriovenous malformations, systemic arterial-to-pulmonary venous or systemic arterial-to-pulmonary arterial connection, and systemic-to-pulmonary venous collaterals.

After the Fontan operation, the majority of patients do well during childhood and adolescence, although exercise capacity is reduced when measured objectively. However, clinical complications may develop subsequently, with a progressive decline in exercise performance and heart failure, cyanosis (especially with a fenestration), chronic venous insufficiency, and development of important arrhythmias.[140] By 10 years after a Fontan operation, $\sim$20% of patients have supraventricular tachyarrhythmias (including typically intra-atrial re-entry tachycardia and atrial flutter but also atrial fibrillation and focal atrial tachycardia).[141] The incidence may be lower after TCPC, compared with APC Fontan, but this is not yet proven.[142]

Protein-losing enteropathy (PLE) is a rare but important complication and results in peripheral oedema, pleural effusions, and ascites. It can be diagnosed by documentation of low serum albumin and elevated α1-antitrypsin levels in the stool.[143] It is associated with a very poor prognosis (5-year survival $<50\%$) and available treatments are of limited effectiveness.[143]

Diagnostic work-up

See Section 3.2 for general principles.

Clinical findings include commonly mild, non-pulsatile jugular venous distension. Significant jugular venous distension and hepatomegaly, however, raise suspicion of Fontan obstruction or ventricular failure. ECG frequently shows junctional rhythm or atrial arrhythmias. Pleural effusion on chest X-ray raises suspicion of PLE.

Echocardiography is the first-line diagnostic tool, providing information on ventricular and valve function. To image the Fontan pathway, TEE or other imaging modalities are generally required.

Annual blood tests should include haematology, serum albumin, and liver and renal function. When PLE is suspected, α1-antitrypsin clearance must be calculated.

CMR and ***CT*** are particularly helpful for evaluation of the Fontan pathway, collaterals and pulmonary veins (e.g. right pulmonary vein obstruction by enlarged RA), and differential pulmonary flow.

Hepatic evaluation by ultrasound (and CT) is important (for fibrosis, cirrhosis, and cancer).

Cardiac catheterization should be performed at a low threshold in cases of unexplained oedema, exercise deterioration, new-onset arrhythmia, cyanosis, and haemoptysis. It provides information on ventricular and valvular function, haemodynamics including PVR, and Fontan obstruction and anomalous vascular connections (see above).

Medical treatment

Anticoagulation: Right atrial blood stasis and disturbed coagulation may predispose to thrombosis. The potential for subclinical, recurrent pulmonary embolism leading to a rise in PVR has led to a recommendation by some for lifelong anticoagulation.[144] There is, however, no evidence of benefit, and practice varies among centres. Anticoagulation is definitely indicated in the presence of atrial thrombus, atrial arrhythmias, or thromboembolic events.

Antiarrhythmic therapy: Loss of sinus rhythm may precipitate rapid haemodynamic decline, and sustained arrhythmia should be considered a medical emergency. Electrical cardioversion is the mainstay of treatment as drug therapy is often ineffective. Amiodarone may be effective in preventing recurrence, but it has many long-term side effects. Sotalol can be an alternative. There should be a low threshold for radiofrequency ablation, although these are difficult arrhythmias to treat in the catheterization laboratory.[145] Antitachycardia atrial PMs may assist. If AV pacing is required, this will need an epicardial approach. Occurrence of arrhythmias should prompt haemodynamic evaluation. See Section 3.3.2.

Medical therapy of PLE: Medical therapy remains challenging, and various treatments have been proposed (after exclusion of haemodynamic problems) including salt restriction, high protein diet, diuretics, ACE inhibitors (may be poorly tolerated), steroids, albumin infusion, chronic subcutaneous heparin, creation of a fenestration (by interventional catheter), and eventually consideration of transplantation.

See also Section 3.3.1.

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Surgical/interventional treatment

Patients with a 'failing Fontan' (with a combination of intractable arrhythmia, right atrial dilation, worsening AV valve regurgitation, deterioration of ventricular function, and/or atrial thrombus) should be considered for surgery.[146] Conversion of an atrial–pulmonary connection to a more 'energy-efficient' TCPC, together with arrhythmia surgery, has provided good early results in a very experienced setting, but is associated with surgical mortality and ongoing morbidity, with the need for both continued drug therapy and PM implantation in the majority of cases.[147] If performed late, conversion may be less likely to result in a good outcome, and cardiac transplantation may be required. However, the best timing for a conversion remains a matter of uncertainty. In selected adult patients it may be appropriate to consider device closure of a fenestration if there is significant cyanosis, but this may also worsen the patient's condition. Catheter intervention may also be required in the case of flow obstruction or anomalous vascular connections (see above).

Follow-up recommendations

As a result of these many complex issues, the care of Fontan patients is one of the major challenges for GUCH practitioners, and they should all be followed in specialized GUCH centres, usually at least annually, and include echocardiography, ECG, blood, and exercise testing. Intervals for CMR and hepatic ultrasound (CT) must be decided on an individual basis. Comprehensive assessment is mandatory for patients with manifestations of the 'failing Fontan' complex, with particular care to exclude even minor obstructions to cavopulmonary flow and pulmonary venous return which may have a major haemodynamic impact.

Additional considerations

Exercise/sports: Patients after Fontan have significant limitation in exercise capacity as part of their 'circulation' and they should be advised to limit their ambitions to recreational sports.

Pregnancy: Successful pregnancy is possible in selected patients with intensive monitoring, including after delivery. There is a higher maternal risk if the Fontan circuit is not optimal and a higher miscarriage rate, especially in the setting of cyanosis. ACE inhibitors must be withdrawn and anticoagulant management is an issue.

IE prophylaxis: Only recommended in patients with a recent redo Fontan (<6 months), cyanosis, a prosthetic valve, residual patch leak, or prior endocarditis.

4.16 Right ventricular to pulmonary artery conduit

Introduction and background

Conduits establish the continuity between the RV and the PA in complex defects when the native outflow tract is not amenable to reconstruction, including pulmonary atresia, common arterial trunk, ToF, absent pulmonary valve syndrome, Rastelli procedure, and Ross operation.

Types of conduits include valved [pulmonary or aortic homograft, bioprosthetic valves, bovine jugular vein conduits (Contegra)] and non-valved conduits.

There is no ideal conduit. Limited durability implicates early reoperation. Predictors for conduit failure are sterilization/preservation process, smaller conduit, conduit type, younger age at implantation, PA stenosis, and diagnosis of transposition.[101,148,149] Freedom from reoperation for conduit failure at 20 years was reported at 32 and 40%.[101,148]

Complications include outgrowth, progressive obstruction with and without regurgitation, endocarditis, and aneurysms or pseudoaneurysms.

Clinical presentation may include exertional dyspnoea, palpitations, syncope, and SCD.

Diagnostic work-up

See Section 3.2 for general principles.

Clinical findings may include a pre-cordial thrill, prominent A-wave of the jugular veins, and systolic murmur. Conduit calcification may be seen on chest X-ray.

Echocardiography is the first-line diagnostic tool providing size and function of both ventricles, PR, TR, and associated lesions. Gradients across the conduit may be difficult to measure and not reliable. RV pressure derived from TR velocity should be used to assess conduit stenoses.

CMR and ***CT*** may be required to image the conduit (level of stenosis), PA, and coronary artery anatomy, for the assessment of the RV and severity of PR. Before re-sternotomy, the relationship between the conduit/RV and the inner layer of the sternum must be evaluated.

Catheterization with haemodynamic assessment is always required if intervention is considered. Angiography provides information on the level of stenosis, peripheral PA stenoses, and coronary anatomy (anomalies/abnormal course).

Surgical/catheter interventional treatment (*Table 20*)

Balloon dilation/stent implantation is safe and may prolong the life span of failing devices.[150,151] Percutaneous pulmonary valve implantation (PPVI) is the latest innovation for dysfunctional conduits.[152–155] Mid-/long-term outcome data are not available yet. Current exclusions for PPVI include occluded central veins, active infection, outflow tract of native tissue and of unfavourable morphology (>22 mm diameter), or conduit <16 mm and unfavourable coronary anatomy (compression by the expanded implant). Surgery is preferred when additional interventions are considered (tricuspid annuloplasty). Longitudinal data are more important for timing of re-intervention than single measurements.

Follow-up recommendations

Regular follow-up in a specialized GUCH centre is recommended at least every 12 months. Special attention should be given to exercise capacity (CPET), RV systolic pressure (conduit gradient), RV function, TR, and arrhythmias.

Additional considerations

Exercise/sports: No restrictions are required in asymptomatic patients with mild obstruction. High-risk patients with high RV pressure must limit themselves to low-intensity activity/sports and avoid isometric exercise. The others should limit themselves according to symptoms.

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Table 20 Indications for intervention in patients with right ventricular to pulmonary artery conduits

Indications	Class[a]	Level[b]
Symptomatic patients with RV systolic pressure >60 mmHg (TR velocity >3.5 m/s; may be lower in case of reduced flow) and/or moderate/severe PR should undergo surgery	I	C
Asymptomatic patients with severe RVOTO and/or severe PR should be considered for surgery when at least one of the following criteria is present: • Decrease in exercise capacity (CPET) • Progressive RV dilation • Progressive RV systolic dysfunction • Progressive TR (at least moderate) • RV systolic pressure >80 mmHg (TR velocity >4.3 m/s) • Sustained atrial/ventricular arrhythmias	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
CPET = cardiopulmonary exercise testing; PR = pulmonary regurgitation; RV = right ventricle; RVOTO = right ventricular outflow tract obstruction; TR = tricuspid regurgitation.

Pregnancy: Maternal and foetal risks are driven by the underlying congenital heart defect and severity of RVOTO, arrhythmia, and heart failure (see Section 3.4.3)

IE prophylaxis: Recommended in all patients (see Section 3.3.5).

4.17 Eisenmenger syndrome and severe pulmonary arterial hypertension

Introduction and background

A large proportion of patients with CHD, in particular those with relevant systemic-to-pulmonary shunts, if left untreated, develop PAH. Eisenmenger syndrome is defined as a CHD with initially large systemic-to-pulmonary shunt, which in turn induces severe pulmonary vascular disease and PAH, resulting in reversal of the shunt direction and central cyanosis.[156] In the Euro Heart Survey registry on adult patients with CHD, among 1877 patients with ASD, VSD, or cyanotic defects with other underlying pathology, 28% had pulmonary hypertension and 12% had Eisenmenger syndrome. In a more recent survey,[157] the prevalence of PAH (defined by echo RVP) among 1824 adult CHD patients with septal defects was 6.1%, and 3.5% had Eisenmenger syndrome.

The pathological lesions and the pathobiological changes of the pulmonary vasculature observed in patients with PAH associated with congenital systemic-to-pulmonary shunts are considered to be very similar to those observed in the other PAH forms.[158] The monoclonal endothelial cell proliferation found in idiopathic PAH has, however, not been confirmed in the other PAH types, suggesting possible differences in the altered cellular growth mechanisms. Endothelial dysfunction in Eisenmenger patients may also affect the systemic circulation.[159] The initiating processes leading to endothelial dysfunction may include the shear stress and the circumferential stress exerted on the pulmonary endothelium by the increased pulmonary flow and pressure. The initial morphological alterations (medial hypertrophy and intimal proliferation) are potentially reversible. However, as the disease progresses, the more advanced pathological changes (plexiform lesions and arteritis) appear to be irreversible (commonly reached at adult age).

The classification of CHD causing PAH has been recently updated and now considers clinical as well as anatomical–pathophysiological aspects.[160] Clinically, it distinguishes: (i) Eisenmenger syndrome; (ii) moderate to large shunt lesions with severe PAH but not yet shunt reversal (no cyanosis); (iii) small defects with PAH (clinical picture similar to idiopathic PAH); and (iv) PAH after repair of CHD (persisting or recurring). The anatomical–pathophysiological classification has been maintained to take into consideration the haemodynamic and pathophysiological heterogeneity of these conditions. It includes the major factors which carry relevant diagnostic, prognostic, and therapeutic information: the type of defect, the dimensions, the direction of the shunt, the associated extracardiac anomalies, and the repair status.[160]

Clinical presentation and natural history

Eisenmenger syndrome is a multiorgan disorder with progressive deterioration over time (see Section 4.18). Clinical presentation includes central cyanosis, dyspnoea, fatigue, haemoptysis, syncope, and right heart failure in advanced stages. Since patients with reduced arterial oxygen saturation have abnormal haemostasis, including thrombocytopenia, they are at risk for both bleeding and thrombosis. In particular, parietal thrombosis of enlarged proximal pulmonary arteries can be found in up to 20% of patients, it may cause peripheral embolization and pulmonary infarctions, and is associated with biventricular dysfunction and reduced pulmonary flow velocity.[161]

Survival of subjects with Eisenmenger syndrome is reduced as compared with the general population,[162] although many survive into their third or fourth decade, with some even surviving into their seventh decade.[163] Survival appears to be markedly better than that of subjects with idiopathic PAH with comparable functional class. Right heart failure and progressive deterioration of exercise capacity, among others, are considered negative prognostic factors.

Therapy (*Table 21*)

For general measures see Section 4.18.

Oral anticoagulation and the use of antiplatelet agents are controversial and should be guided by case history and risk of bleeding. For example, oral anticoagulation should be considered in patients with atrial fibrillation and may be considered in those with PA thrombosis and low bleeding risk.

There are no consistent data supporting the use of calcium channel-blocking drugs.

Three classes of drugs, targeted to the modification of endothelial dysfunction, have been recently approved for the treatment of PAH: prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase type-5 inhibitors. Their efficacy and safety have been demonstrated in PAH associated with CHD and in Eisenmenger syndrome, mostly by uncontrolled studies.

Only one randomized, controlled trial including 54 patients has reported a favourable effect on exercise capacity and haemodynamics of the treatment with the orally active dual ERA bosentan

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Table 21 Recommendations for targeted pulmonary arterial hypertension therapy in congenital heart disease

Recommendations	Class[a]	Level[b]
Targeted PAH therapy in CHD should only be performed in specialized centres	I	C
The ERA bosentan should be initiated in WHO-FC III[c] patients with Eisenmenger syndrome	I	B
Other ERAs, phosphodiesterase type-5 inhibitors, and prostanoids should be considered in WHO-FC III[c] patients with Eisenmenger syndrome	IIa	C
Combination therapy may be considered in WHO-FC III[c] patients with Eisenmenger syndrome	IIb	C
The use of calcium channel blockers should be avoided in patients with Eisenmenger syndrome	III	C

[a]Class of recommendation.
[b]Level of evidence.
[c]Although recent data support the use of ERAs such as bosentan also in WHO-FC II in patients with idiopathic PAH and PAH associated with connective tissue diseases, such data are currently not available for Eisenmenger patients. Because of marked differences in the natural history between these groups, the results cannot simply be applied to congenital patients, and further studies are required before recommendations.
CHD = congenital heart disease; ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; WHO-FC = World Health Organization-functional class.

in Eisenmenger patients,[164] confirming uncontrolled studies. A recent retrospective analysis of advanced therapy (mainly bosentan) in Eisenmenger patients suggested even a survival benefit.[165]

One small trial[166] with the phosphodiesterase type-5 inhibitor sildenafil documented functional and haemodynamic favourable effects in 10 patients with Eisenmenger syndrome, and similar results were observed in uncontrolled series. Comparable favourable results have also been reported in 16 Eisenmenger patients treated with the phosphodiesterase type-5 inhibitor tadalafil.[167]

In open-label studies, continuous intravenous administration of epoprostenol has shown favourable effects on haemodynamics and exercise capacity, which were comparable with those observed in idiopathic PAH.[168,169] The presence of a central intravenous catheter, however, increases the risk of paradoxical embolism and infection.

In a multicentre randomized study with subcutaneous treprostinil,[170] a subgroup of 109 patients with PAH associated with CHD were enrolled, and the favourable effects on exercise capacity appeared not to differ from that observed in idiopathic PAH.

Lung transplantation with repair of the cardiac defect or combined heart–lung transplantation is a final option for patients with Eisenmenger syndrome who have markers of a poor prognosis such as decline in functional status, episodes of right heart failure, and advanced deteriorating haemodynamic changes, in particular poor ventricular function or high levels of B-type natriuretic peptide (BNP). Timing of listing patients remains challenging.

4.18 Management of cyanotic patients

Introduction and background

Cyanosis is caused by a bidirectional or reversed shunt due to an anatomical communication between the systemic and pulmonary circulation at the atrial, ventricular, or arterial level. Cyanotic patients comprise a heterogeneous group of lesions with different underlying anatomy and pathophysiology: normal or restricted pulmonary blood flow in the presence of an obstruction across the pulmonary outflow tract or increased pulmonary blood flow in the absence of such an obstruction which then results in development of PAH and eventually Eisenmenger syndrome (see Sections 4.14 and 4.17). They may present without or with prior palliative intervention. Cyanotic patients are complex and should be followed by a GUCH specialist.

Adaptive mechanisms

Cyanosis induces adaptive mechanisms to improve oxygen transport and delivery to the tissue: secondary erythrocytosis, rightward shift of the oxyhaemoglobin dissociation curve, and increase in cardiac output.[171,172] Erythrocytosis secondary to erythropoietin stimulus is the physiological response to chronic hypoxaemia. *Compensated* erythrocytosis reflects an equilibrium (stable haemoglobin in an iron replete state) and *decompensated* erythrocytosis indicates failure of an equilibrium (rising haematocrit).

Multisystem disorder

Cyanosis and secondary erythrocytosis imply profound consequences on the entire organ system:

- Blood viscosity is increased and is directly related to red blood cell mass[173]
- Haemostatic abnormalities are common and complex, and are attributed to abnormalities in platelets (thrombocytopenia and thrombasthenia), coagulation pathways, and other abnormal coagulation mechanisms. Vitamin K-dependent clotting factors (factors II, VII, IX, and X) and factor V are reduced, fibrinolytic activity is increased, and the largest von Willebrand multimers are depleted
- Increased turnover of red blood cells/haemoglobin and impaired urate filtration lead to hyperuricaemia.[174] The increased concentration of unconjugated bilirubin puts cyanotic patients at risk for calcium bilirubinate gallstones
- Severe endothelial dysfunction is evident by the striking impairment of endothelium-dependent vasodilation[159]
- Chronic hypoxaemia, increased blood viscosity, and endothelial dysfunction affect microcirculation, myocardial function, and the function of other organ systems.

Clinical presentation and natural history

Clinical presentation includes central cyanosis, a result of an increased quantity of reduced haemoglobin (>5 g/100 mL blood), clubbing, and frequently scoliosis. Cardiac findings vary and are characterized by the underlying anatomy/pathophysiology.

Mortality is significantly higher in cyanotic patients than in acyanotic patients.[175] Outcome is determined by the underlying anatomy, pathophysiology, palliative procedures, complications of

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cyanosis, and preventive measures. Low platelet count, severe hypoxia, cardiomegaly, and elevated haematocrit during childhood are useful parameters to predict premature death and adverse events in both patients with and without pulmonary vascular disease.[176]

Late complications

- Hyperviscosity symptoms include headache, faintness, dizziness, fatigue, tinnitus, blurred vision, paraesthesia of fingers, toes, and lips, muscle pain, and weakness (classified moderate when they interfere with some activities, and severe when they interfere with most activities).[171,172] Hyperviscosity symptoms are unlikely in an iron-replete patient with haematocrit <65%.
- Bleeding and thrombotic diathesis occur and both cause a therapeutic dilemma as patients are at risk from thrombosis and bleeding. Spontaneous bleeding is usually minor and self-limiting (dental bleeding, epistaxis, easy bruising, and menorrhagia). Haemoptysis is the most common major bleeding event and is an external manifestation of an intrapulmonary haemorrhage not reflecting the extent of parenchymal bleeding (reported in up to 100% of Eisenmenger patients).[163,177] Thrombosis is caused by coagulation abnormalities, stasis of blood in dilated chambers and vessels, atherosclerosis and/or endothelial dysfunction, the presence of thrombogenic material (e.g. conduits), and arrhythmias. The haemostatic abnormalities do not protect against thrombotic complications. Laminated thrombi in large, partially calcified and aneurysmal pulmonary arteries are common (up to 30%).[178–180] Female gender, low oxygen saturation, older age, biventricular dysfunction, and dilated PAs were identified as risk factors.[161,180]
- Cerebrovascular accidents may be caused by thrombo-embolic events (paradoxical emboli), rheological factors (microcytosis), endothelial dysfunction and 'traditional' atherosclerotic risk factors. The severity of secondary erythrocytosis *per se* is not a risk factor;[181] microcytosis caused by iron deficiency, due to inappropriate phlebotomies, was the strongest independent predictor for cerebrovascular events.[182]
- Paradoxical emboli may be caused by supraventricular arrhythmias or transvenous leads or catheters.
- Iron deficiency is frequently caused by inappropriate phlebotomies.
- Arrhythmias—supraventricular and ventricular.
- Infectious complications include endocarditis, cerebral abscess, and pneumonia. Fever, associated with new or different headache, raises suspicion of a brain abscess.
- Renal dysfunction is common and is due to functional and structural abnormalities of the kidneys.
- Cholelithiasis is common. Calcium bilirubinate gallstones can be complicated by cholecystitis/choledocholithiasis.
- Rheumatological complications include gouty arthritis, hypertrophic osteoarthropathy, and kyphoscoliosis.

Diagnostic work-up

See Section 3.2 for general principles.

For underlying heart defects see Section 4.14 and sections on specific lesions.

Particular attention must be paid to hyperviscosity symptoms and bleeding/ischaemic complications. Oxygen saturation must be obtained with pulse oximetry at rest for at least 5 min, and exercise capacity should be assessed on a regular basis, preferably with a 6 minute walk test.

Blood work should include cellular blood count, mean corpuscular volume (MCV), serum ferritin (serum iron, transferrin, and transferrin saturation may be required for earlier detection of iron deficiency), creatinine, serum uric acid, clotting profile, BNP or pro-BNP, folic acid, and vitamin B12 in the presence of elevated MCV or normal MCV and low serum ferritin.

Laboratory precautions

- Coagulation parameters: plasma volume is reduced due to secondary erythrocytosis; the amount of sodium citrate must be adjusted to haematocrit if haematocrit is >55%.
- Haematocrit determined with automated electronic particle counts (microhaematocrit centrifugation results in falsely high haematocrit due to plasma trapping).
- Glucose level can be reduced (increased *in vitro* glycolysis which results from the increased number of red blood cells).

Indications for intervention

Risk and benefit must be carefully considered and require expertise. A cyanotic patient without PAH/Eisenmenger syndrome must be periodically evaluated for any procedure that may improve quality of life and reduce morbidity, or for eligibility for physiological repair (see Section 4.14).

Medical therapy

For specific PAH treatment see Section 4.17.

- Arrhythmias: sinus rhythm should be maintained whenever possible. Antiarrhythmic therapy must be individualized (medications, ablation, epicardial PM/ICD). Antiarrhythmic therapy is extremely difficult in this patient group. Drug therapy should be initiated with particular care and generally in a hospital. Transvenous leads must be avoided.
- Therapeutic phlebotomy should only be performed in the presence of moderate/severe hyperviscosity symptoms due to secondary erythrocytosis (haematocrit >65%) and in the absence of dehydration and iron deficiency. Isovolumic fluid replacement (750–1000 mL of isotonic saline while removing 400–500 mL of blood) should be undertaken.
- Blood transfusion may be required in the presence of iron-replete anaemia (haemoglobin inadequate to oxygen saturation).
- Iron supplementation should be performed in the presence of iron deficiency (MCV <80 fL) and carefully followed (rebound effect).
- Routine anticoagulation/aspirin: currently available data do not support any benefit in cyanotic patients to prevent thrombo-embolic complications. There is, however, an increased risk of bleeding.

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Table 22 Risk reduction strategies in patients with cyanotic congenital heart disease

Prophylactic measures are the mainstay of care to avoid complications. The following exposures/activities should be avoided:
• Pregnancy
• Iron deficiency and anaemia (no routine, inappropriate phlebotomies to maintain a pre-determined haemoglobin)
• Dehydration
• Infectious disease: annual influenza vaccination, pneumovax (every 5 years)
• Cigarette smoking, recreational drug abuse including alcohol
• Transvenous PM/ICD leads
• Strenuous exercise
• Acute exposure to heat (sauna, hot tub/shower)
Other risk reduction strategies include:
• Use of an air filter in an intravenous line to prevent air embolism
• Consultation of a GUCH cardiologist before administration of any agent and performance of any surgical/interventional procedure
• Prompt therapy of upper respiratory tract infections
• Cautious use or avoidance of agents that impair renal function
• Contraceptive advice

GUCH = grown-up congenital heart disease; ICD = implantable cardioverter defibrillator; PM = pacemaker.

- Indication for anticoagulation: atrial flutter/fibrillation [target international normalized ratio (INR) 2–2.5; higher target INR in the presence of a mechanical valve].
- Haemoptysis: requires chest X-ray followed by chest CT scan if there is an infiltrate. Bronchoscopy puts the patient at risk and seldom provides useful information. Therapy includes discontinuation of aspirin, non-steroidal anti-inflammatory agents, and oral anticoagulants; treatment of hypovolaemia and anaemia; reduction of physical activity; and suppression of non-productive cough. Selective embolization of bronchial arteries may be required for refractory intrapulmonary haemorrhage/haemoptysis.
- Hyperuricaemia: no indication to treat asymptomatic hyperuricaemia.
- Acute gouty arthritis is treated with oral or intravenous colchicine, probenecid, and anti-inflammatory drugs, with attention paid to the risk of renal failure and bleeding. Uricosuric (e.g. probenecid) or uricostatic agents (e.g. allopurinol) avoid recurrence.

Follow-up recommendations

All cyanotic patients require lifelong evaluation with follow-up visits every 6–12 months in a specialized GUCH centre in close collaboration with the family physician. Evaluation includes:

- Comprehensive evaluation and systematic review of potential complications
- Blood work (see above)
- Education about risk reduction strategies (*Table 22*).

Additional considerations

Exercise/sports: Avoidance of moderate to severe strenuous exercise.

Air flight: Commercial air travel is well tolerated.[183,184] Risk reduction strategies include avoidance of travel- and non-travel-related stress, dehydration, and alcoholic drinks, and measures to prevent deep vein thrombosis.

Exposure to high altitude: Acute exposure to high altitude (>2500 m) should be avoided. Gradual ascent (e.g. cable car) up to 2500 m may be tolerated.

Pregnancy: Pregnancy in cyanotic patients, without pulmonary hypertension, results in significant maternal and foetal complications. Oxygen saturation (>85%) and haemoglobin (<200 g/L) before pregnancy were the strongest predictors for live birth.[15] Pregnancy is contraindicated in Eisenmenger syndrome.

IE prophylaxis: Recommended in all patients (see Section 3.3.5).

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