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Review

Eisenmenger Syndrome: A Multisystem Disorder—Do Not Destabilize the Balanced but Fragile Physiology

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ABSTRACT

Eisenmenger syndrome is the most severe and extreme phenotype of pulmonary arterial hypertension associated with congenital heart disease. A large nonrestrictive systemic left-to-right shunt triggers the development of pulmonary vascular disease, progressive pulmonary arterial hypertension, and increasing pulmonary vascular resistance at the systemic level, which ultimately results in shunt reversal. Herein, we review the changing epidemiological patterns and pathophysiology of Eisenmenger syndrome. Multiorgan disease is an integral manifestation of Eisenmenger syndrome and includes involvement of the cardiac, hematological, neurological, respiratory, gastrointestinal, urinary, immunological, musculoskeletal, and endocrinological systems. Standardized practical guidelines for the assessment, management, risk stratification, and follow-up of this very fragile and vulnerable population are discussed. Multidisciplinary care is the best clinical practice. An approach to the prevention and management of a broad spectrum of complications is provided. Relevant therapeutic questions

RÉSUMÉ

Le syndrome d'Eisenmenger est le phénotype le plus sévère et extrême de l'hypertension artérielle pulmonaire associée aux cardiopathies congénitales. Un important shunt gauche-droit systémique non restrictif engendre une maladie vasculaire pulmonaire, l'apparition d'une hypertension artérielle pulmonaire et la majoration des résistances vasculaires pulmonaires; les pressions pulmonaires atteignent un seuil systémique à l'origine du renversement du shunt. Cet article discute des bases physiopathologiques et du changement épidémiologique du syndrome d'Eisenmenger. L'atteinte multiviscérale est caractéristique du syndrome d'Eisenmenger impliquant le système cardio-vasculaire, hématologique, neurologique, respiratoire, gastro-intestinal, urinaire, immunologique, musculo-squelettique et endocrinien. Nous proposons des lignes directrices pratiques pour l'évaluation, la prise en charge, la stratification des risques et le suivi de cette population fragile et vulnérable. Les pratiques cliniques exemplaires recommandent des soins multidisciplinaires. Nous

Eisenmenger syndrome (ES) is the most severe and extreme phenotype of pulmonary arterial hypertension associated with congenital heart disease (CHD). It requires a large nonrestrictive systemic left-to-right shunt that is either intracardiac (ie, atrial or ventricular) or extracardiac (ie, arterial). The systemic left-to-right shunt triggers the development of pulmonary vascular disease, progressive pulmonary arterial hypertension, and increasing pulmonary vascular resistance by transmission of systemic pressures to pulmonary arteries. Over time, this results in a bidirectional shunt or shunt reversal (ie, right-to-left).[1,2] The ensuing central cyanosis is the major clinical manifestation that leads to secondary erythrocytosis as a physiologic response to chronic hypoxemia and cyanotic multisystemic organ involvement. ES is an acquired phenotype that develops in the setting of a constellation of congenital and hemodynamic conditions that include atrial and/or ventricular septal, and/or arterial shunts or complex forms of CHD (eg, discordant ventriculoarterial connection, univentricular heart, common arterial trunk) without pulmonary outflow tract obstruction, and large aortopulmonary connections. The type of CHD, size of the defects, concomitant congenital syndromes, genetic factors, and environmental exposures influence the risk of developing ES.

European guidelines have classified pulmonary hypertension into 5 categories. ES falls within the group 1 lesions known as pulmonary arterial hypertension (PAH). This

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are discussed, including anticoagulation, noncardiac surgery, physical activity, transplantation, and advanced-care planning (palliative care). Advanced pulmonary arterial hypertension therapies are indicated in patients with Eisenmenger syndrome and World Health Organization functional class II or higher symptoms to improve functional capacity, quality of life, and—less well documented—survival. Specific recommendations regarding monotherapy or combination therapy are provided according to functional class and clinical response. The ultimate challenge for all care providers remains early detection and management of intracardiac and extracardiac shunts, considering that Eisenmenger syndrome is a preventable condition.

présentons aussi une approche pour la prévention et la prise en charge d'un grand éventail de complications et nous abordons des questions thérapeutiques pertinentes, notamment l'anticoagulothérapie, la chirurgie non cardiaque, l'activité physique, la greffe et la planification préalable des soins (soins palliatifs). Les traitements spécifiques de l'hypertension artérielle pulmonaire sont indiqués chez les patients atteints de syndrome d'Eisenmenger avec une classe fonctionnelle de II ou plus de l'Organisation mondiale de la Santé afin d'améliorer la capacité fonctionnelle, la qualité de vie, et bien que moins documentée la survie. Enfin, nous formulons des recommandations spécifiques concernant le recours à la monothérapie ou à l'association thérapeutique selon la classe fonctionnelle et la réponse clinique. Le diagnostic précoce et la prise en charge optimale des shunts intracardiaques et extracardiaques sont les défis ultimes des équipes traitantes médicales pour prévenir le syndrome d'Eisenmenger.

category is defined by a precapillary mean pulmonary arterial pressure (mPAP) $\geq$ 25 mm Hg at rest, along with a left atrial pressure (LAP) $<$ 15 mm Hg.[3] A more recent proposed definition is an mPAP >20 mm Hg associated with a pulmonary vascular resistance (PVR) $\geq$ 3 Wood Units.[4]

Changing Epidemiological Landscape

The Austrian physician Victor Eisenmenger first described the classical phenotype of severe pulmonary vascular disease in a 32-year-old man with a very large ventricular septal defect.[5] It was Paul Wood who defined the term *Eisenmenger syndrome* as pulmonary hypertension with bidirectional or reversed shunt at any level to include all conditions that present like the patient described by Victor Eisenmenger 60 years earlier: "It matters very little where the shunt happens to be. The distinguishing feature is not anatomy but the physiologic behavior of the pulmonary circulation".[1,2] In the mid-19th century, Paul Wood described an 18% prevalence of ES in his cohort of 727 patients with CHD in his landmark publication. The primary diagnoses were atrioventricular septal defects or primum atrial septal defects (43%), systemic-to-pulmonary communications (17%), ventricular septal defects (16%), patent ductus arteriosus (16%), and atrial septal defects (6%).[1,2] With improved recognition and management of shunts, ES has become less prevalent over time, particularly in western countries. In 2005, the Euro Heart Survey reported a 5.7% prevalence of ES in a cohort of 4110 patients with CHD.[6] In 2007, the CONCOR (**Con**genital **Cor** Vitia) registry in the Netherlands described a 1% prevalence of ES in a cohort of 5970 patients with CHD.[7]

The classical form of ES caused by unrepaired shunts is largely being replaced by residual PAH or the development of PAH, despite complete or partial shunt closure. In the CONCOR registry, among the 1824 patients with septal defects, 112 (6.1%) had PAH, 58% of whom later presented with ES.[7] In patients with established PAH, fenestrated shunt closure carries the potential to reduce the likelihood of developing ES in selected patients. In western countries, patients with simple shunt defects developing ES are becoming increasingly rare; therefore, ES will predominantly develop as a consequence of complex forms of CHD or genetic syndromes with multiorgan involvement. Current estimates indicate that one third of patients with ES have Down syndrome, with the poorer prognosis linked to difficulties with follow-up, nonadherence to treatment, and poorer tolerance to secondary effects.[8] More proactive surgical treatment of patients with CHD and Down syndrome is associated with a decrease in the development of ES and a better survival.[9] The number of patients with ES is decreasing, and—theoretically—we should not see any patients with ES because of advanced medical imaging and early diagnosis of shunts in high-income countries. ES resulting from shunt lesions persists in low- and middle-income countries so that immigrants from such countries present with previously undiagnosed ES and late manifestations.

Pathophysiology

Shunt reversal is the consequence of elevated PVR, with irreversible changes to the pulmonary vasculature. In 1958, Edwards and Heath of the Mayo Clinic proposed the first histological classification scheme for pulmonary vascular changes consisting of the following 6 grades: (1) medial hypertrophy of small muscular arteries and arterioles; (2) intimal cellular proliferation; (3) progressive intimal proliferation and concentric fibrosis, leading to obstruction of arterioles; (4) aneurysms; (5) plexiform—glomerular proliferations; and (6) fibrinoid necrosis of the arterioles and arteries.[10] The early stage, which is characterized by muscularization of distal precapillary arterioles with medial hypertrophy, is thought to be reversible even if PVR is increased.[11] Irreversible pulmonary vascular changes generally occur early in post-tricuspid shunts. For example, irreversible changes were observed before 24 months in a series of patients with Down syndrome and complete atrioventricular septal defects.[12] Upon meeting stage-6 criteria, patients face a greater risk of pulmonary artery rupture with clinical hemoptysis and death. Genetic predisposing factors to developing irreversible pulmonary vascular changes have been described, including a bone morphogenetic protein receptor type 2 mutation that is associated with rapid progression of disease.[13]

Eisenmenger Syndrome Is a Systemic Condition

ES is a heterogeneous syndrome with variable underlying primary types of CHD and variable levels of oxygen desaturation; compensatory, secondary erythrocytosis; and multiorgan involvement. It is usually diagnosed in infancy in patients with ventricular and interarterial shunts (so-called

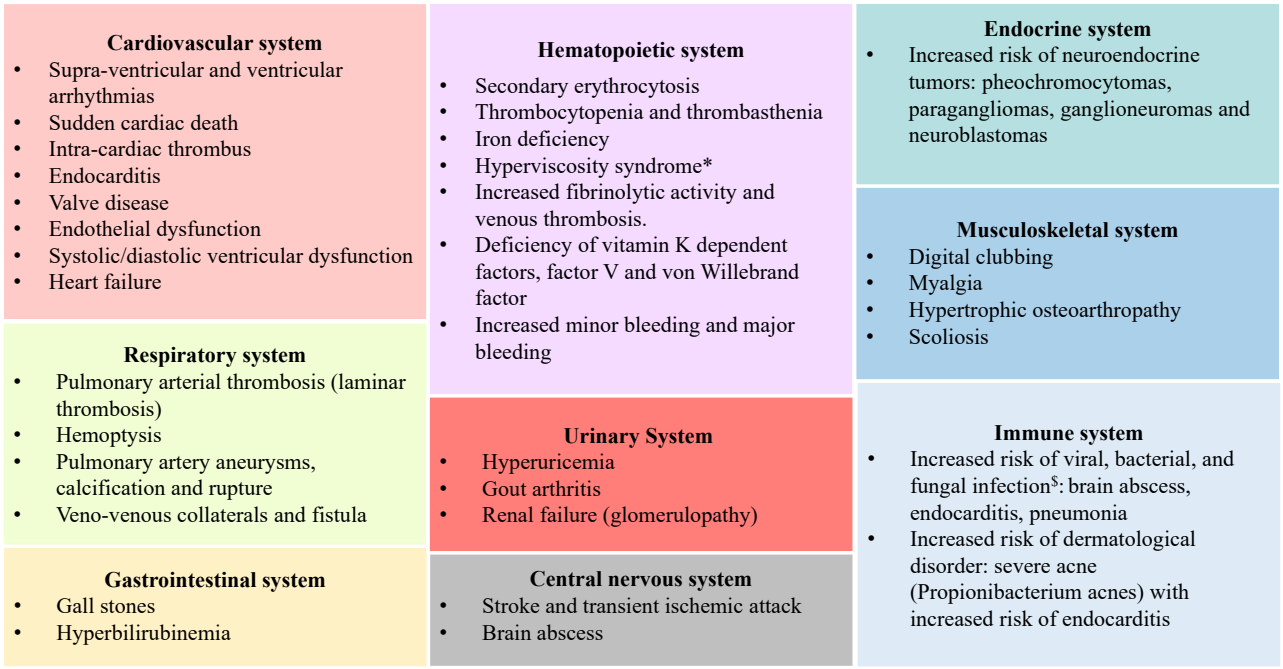

Figure 1. This is a summary of multisystemic involvement in Eisenmenger syndrome. *Hyperviscosity syndrome: headaches, dizziness, syncope, tinnitus, diplopia, blurred vision, amaurosis, paresthesias, mental fatigue, restless leg.†Pneumococcus, staphylococcus, haemophilus, pseudomonas, atypical mycobacteria, and candida.

post-tricuspid shunts). However, it is more often diagnosed in adult life in those with atrial level shunts.[2] Patients with large patent ductus arteriosus are less symptomatic as a result of carotid chemoreceptors being exposed to the high level of oxygen that reaches the upper body (differential cyanosis with lower oxygen saturation in the lower limbs). Low oxygen saturation sensed by carotid chemoreceptors contributes to an increased ventilatory drive, arousal response to hypoxia during sleep, upper airway muscle activity, and sympathetic tone.[14]

Cyanosis is the key consequence of right-to-left shunting that leads to the hypoxemic syndrome, which affects various organs. Secondary erythrocytosis is a maladaptive, physiologic response to chronic hypoxemia to increase the supply of oxygen to organs. In patients with erythrocytosis, particularly those with concomitant iron deficiency, the erythrocytes are less deformable, thereby increasing blood viscosity.[15-21] A hyperviscosity syndrome usually manifests when the hemoglobin level exceeds 20 mg/dL and hematocrit exceeds 65%. Symptoms are aggravated in the context of iron deficiency. Systemic endothelial dysfunction is evident in patients with ES and may contribute to the risk of ischemic events.[22] Secondary erythrocytosis *per se* is not a risk factor for stroke, but microcytotic anemia frequently caused by inappropriate phlebotomy is a strong risk factor for cerebrovascular events.[23,24] Figure 1 summarizes the multisystemic features of ES. Quality of life is greatly reduced with multisystemic ES.

Risk Assessment and Prognosis

Because ES is a rare and complex syndrome with multisystemic manifestations, it is essential that patients be assessed by specialized teams in tertiary hospitals with dedicated expertise. The multiorgan involvement requires a multidisciplinary approach to care. Adults diagnosed with ES must be followed in an adult congenital cardiology clinic with access to dedicated specialists (in hepatology, nephrology, microbiology, and gynecology).

General recommendations for the assessment and follow-up of patients with ES are summarized in Figure 2. The diagnosis and follow-up of pulmonary hypertension by transthoracic echocardiography can be challenging because the usual signs of pulmonary hypertension are not applicable to patients with ES. Criteria vary depending on the underlying type of CHD.[25] Transesophageal echocardiography should be performed by qualified experts, including the support of anesthesiologists with experience in CHD and PAH. Cardiac catheterization is the reference method in establishing the diagnosis, assessing the severity of PAH and pulmonary vascular resistance, and determining prognosis. Acute vasoreactivity studies with inhaled nitric oxide could be performed at baseline for additional prognostic information.[26] Initial cardiac catheterization is indicated in selected patients and should be repeated in the event of unclear symptoms, unclear clinical deterioration, or increased cyanosis. Importantly, diagnostic heart catheterization in patients with ES should be performed by physicians with expertise in CHD because measurement and calculation errors are not uncommon.

The degree of cyanosis correlates with poorer quality of life and functional impairment. However, the prognosis of patients with ES has often been described as superior to those with idiopathic pulmonary hypertension. Patients with ES appear to be more resistant to right ventricular (RV) failure than those with idiopathic pulmonary hypertension for 2 main reasons. First, regression of RV hypertrophy that is present in fetal life does not occur if the RV is never exposed to low pulmonary pressures.[27,28] Second, the shunt confers a relief for a RV subjected to high pressures. However, there is a

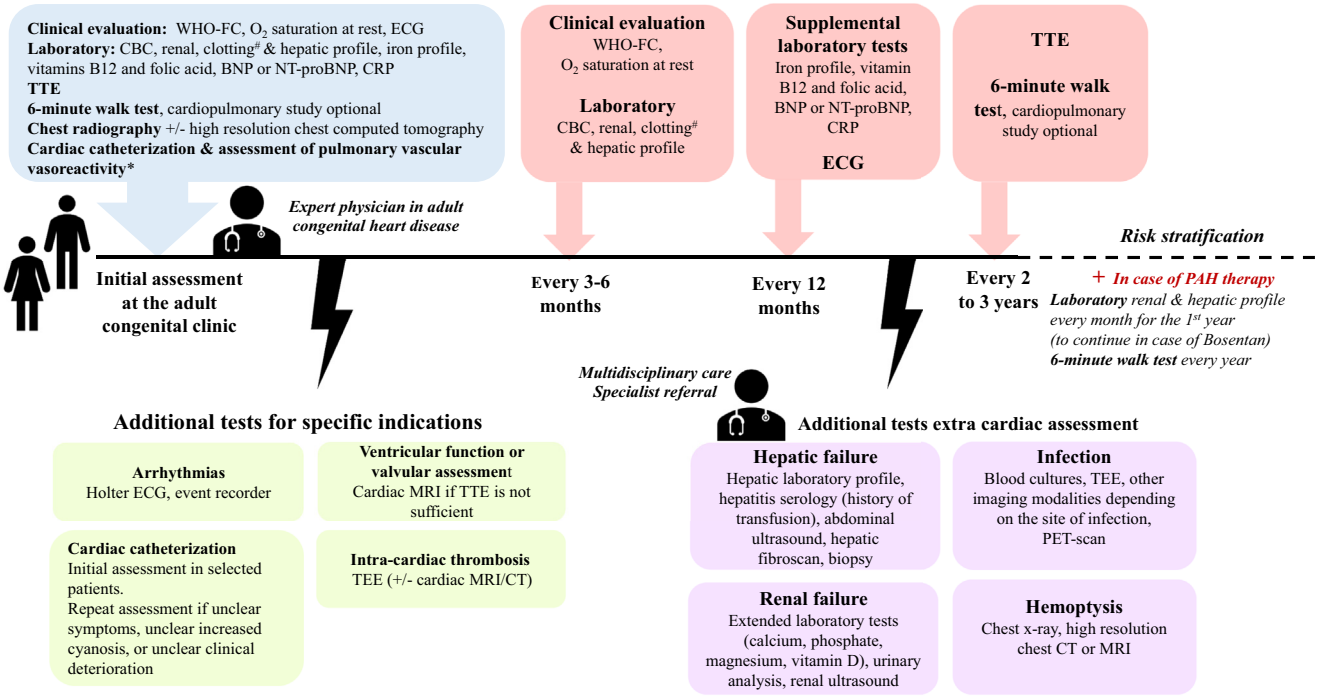

Figure 2. Initial assessment and follow-up of patients with Eisenmenger syndrome. The frequency of laboratory analysis should be adapted to clinical parameters and to the results. The different laboratory profiles are (1) renal profile: creatinine, eGFR (estimated Glomerular Filtration Rate), blood urea nitrogen, electrolytes; (2) clotting profile: INR, aPTT, thrombin time, fibrinogen, bleeding time, #frequency of clotting profile should be adapted if anticoagulation therapy; (3) hepatic profile: ALT (alanine aminotransferase), AST (aspartate aminotransferase), total bilirubin, albumin, total protein, GGT (Gamma-Glutamyl Transferase), ALP (alkaline phosphatase); (4) iron profile: serum ferritin, transferrin, transferrin saturation, and iron saturation. *Cardiac catheterization could be performed to establish or confirm a diagnosis, to document increasing pulmonary vascular resistance and pulmonary arterial hypertension or to exclude other potential contributors to right-to-left shunting (eg, subpulmonary stenosis). Acute vasoreactivity studies with inhaled nitric oxide carry prognostic information in patients with ES.[26] BNP, brain natriuretic peptide; CBC, complete blood count; CRP, C-reactive protein; CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro B-type natriuretic peptide; PAH, pulmonary arterial hypertension; TEE, transoesophageal echocardiogram; TTE, transthoracic echocardiogram; WHO-FC, World Health Organization functional class.

misperception of optimistic survival prospect in patients with ES. Recent studies have suggested that the discrepancy in prognosis between patients with ES and other forms of PAH may be due, in part, to a statistical bias, referred to as an immortal time bias; that is, most retrospective studies considered time "zero" as the time of entry into the study instead of the patient's age, which then overestimates survival. For inclusion in adult follow-up studies, patients with ES

Table 1. Determinants of prognosis in Eisenmenger syndrome

Determinants of prognosis	Better prognosis	Worse prognosis
Level of shunt	Post-tricuspid shunt	Pretricuspid shunt
Complexity of CHD	Simple defect	Complex defect
Cyanosis	Mild resting oxygen desaturation (85-90%)	Moderate/severe resting oxygen desaturation (< 85%)
Iron-deficiency anemia	Transferrin saturation > 20%	Transferrin saturation < 20%
NHYA functional class	I, II	III, IV
Rate of symptom progression	Slow	Rapid
Right ventricular failure	No	Yes (guarded prognosis)
6-minute-walk distance	> 400 m	< 300 m
Biomarkers (BNP, CRP)	BNP < 13.9 pmol/L, CRP normal	BNP > 30 pmol/L, CRP >10 mg/L
Echocardiographic markers	TAPSE ≥ 1.5 cm, RA area < 25 cm^2, RA/LA < 1.5, No pericardial effusion	TAPSE < 1.5 cm, RA area ≥ 25 cm^2, RA/LA ≥ 1.5, Pericardial effusion
Baseline hemodynamics	RAP < 8mmHg and CI ≥ 2.5L/min/m^2	RAP > 15mmHg and CI ≤ 2.0L/min/m^2
Acute vasoreactivity testing*	Decrease in PVRi ≥ 25%	No change or decrease in PVRi ≤ 25%

Adapted from Brida et al.[8] with permission from BMJ Publishing Group Ltd.

BNP, brain natriuretic peptide; CHD, congenital heart disease; CRP, C reactive protein; CI, cardiac index; LA, left atrium; NYHA, New York Heart Association; PDA, patent ductus arteriosus; PVRi, pulmonary vascular resistance index; RA, right atrium; RAP, right atrium pressure; TAPSE, tricuspid annular plane systolic excursion; VSD, ventricular septal defect.

*Hemodyanamic assessment and especially acute vasoreactivity testing are not recommended merely for prognostication in ES owing to their invasive nature.

Cardiac management	Hematology management	Infection management	Hemoptysis

• **Defect closure is contraindicated**
• **Maintain adequate hydration**
• **Oxygen**: no evidence of increased survival or improved symptoms compared to placebo; supplemental oxygen may be beneficial if additional underlying lung disease
• **Management of cardiovascular risks factors:** smoking and drug cessation, treatment of dyslipidemia, diabetes, systemic arterial hypertension
• **Heart failure therapy:** caution with medications that decrease SVR and increase right-to-left shunting
• **Percutaneous intervention:** to discuss in a multidisciplinary setting
• **Arrhythmia management**: prompt rhythm control, rate control if cardioversion contra-indicated, ablation of supra-ventricular arrhythmia; epicardial pacemaker and leadless defibrillator to minimize thromboembolic events
• **Increased cyanosis:** imaging for exclusion of pulmonary emboli/infarction or lung disease; cardiac catheterization for hemodynamic assessment and embolization of fistula or collaterals
	• **Exclude relative anemia** (normal hemoglobin reflects anemia in ES!), consider iron supplementation and blood transfusion
	• If ferritin <20 mg/L, or ferritin <50 mg/L and transferrin saturation <20%: oral or intravenous iron supplementation to achieve optimal secondary erythrocytosis/adequate hemoglobin to oxygen saturation
	• **No routine phlebotomy!** Critically consider phlebotomy in selected patients if moderate to severe hyperviscosity symptoms (hematocrit >65%) in the absence of dehydration and iron deficiency. Consider preoperative phlebotomy to improve hemostasis if hematocrit >65%
	• **Anticoagulation**
	  • Balance benefit/risks
	  • No proven benefit of routine anticoagulation/aspirin
	  • Warfarin if anticoagulation indicated
	  • Follow-up with hematologist for INR titration (typical target 2-2.5)
	• **Thrombosis**
	  • Anticoagulation
	  • Consider vena caval filter
		• **Prevention of endocarditis:**
		  • Antibiotic prophylaxis before dental visits
		  • Periodical dental visits
		  • Soft-bristle tooth brushes to avoid gum trauma
		  • Advise against tattoos or piercings
		  • Good nail hygiene
		• **Immunization:** Influenzae immunization every year, Pneumococcus immunization every 5-10 years
		• **In case of infection**: refer to a microbiologist, treat chest infections promptly to avoid decompensation
		• **Brain abscess**: consider brain abscess if new headache! Brain MRI/CT if new headache. Refer to a neurosurgeon, (abscesses are heavily encapsulated)
			• **Stop anticoagulation, aspirin and non-steroidal anti-inflammatory drugs; reverse anticoagulation medication** depending on the severity of bleeding and drugs; prescribe platelets and/or fresh plasma; correct hypovolemia and transfuse red blood cells to correct anemia
			• Codeine should be administered to avoid coughing spasms
			• **Broad spectrum antibiotics** to avoid pulmonary superinfection. Consider tuberculosis and atypical mycobacterium causing hemoptysis.
			• If hemoptysis is refractory, a chest CT with contrast should be performed to localize the bleeding; selective arteriography to embolize the bleeding vessel. Avoid bronchoscopy (risk of provocation of bleeding and hypoxia); bronchoscopy rarely provides useful information

		Hyperuricemia/ gout arthritis	**Cholecystic attacks**
		• Allopurinol if symptomatic gout • Pain reliever in case of arthritis	• Refer to gastroenterologist • Pain medication • Antibiotics +/- surgery

Figure 3. A standardized approach to multidisciplinary management of patients with Eisenmenger syndrome (ES). CT, computed tomography; MRI, magnetic resonance imaging; SVR, systemic vascular resistance.

necessarily survived to an age at which they could enter clinical follow-up at research institutions.[29] Limiting analyses to adult survivors results in an underestimation of overall mortality. By adjusting for immortal time bias, the 10-year mortality rate approaches 40%, with no change in survival over the past decade.[29] In fact, among patients with CHD, ES is associated with the worst prognosis, with poorer exercise performance, even when compared with patients who have other forms of cyanotic heart disease.[30]

There has been a shift in the cause of death over the past decades. In a retrospective study of 1546 patients with ES from 13 countries, the most common cause of death was heart failure (34%), followed by infection (26%), sudden cardiac death (10%), thromboembolism (8%), hemorrhage (7%), and periprocedural death (7%).[31] Rates of death due to heart failure have increased over the past decades, in contrast to a reduction in periprocedural and hemoptysis-related deaths.[31]

The prognostic assessment of patients with ES is based on a combination of clinical factors and ancillary tests, as summarized in Table 1.[8] Worsening of exercise capacity and oxygen saturation at rest are associated with worse prognosis.[32,33] In a study of 1098 patients with ES over the past 15 years, 278 (25%) of whom died during a median follow-up of 3.1 years, independent predictors of mortality were older age, pretricuspid shunt, lower oxygen saturation at rest, absence of sinus rhythm, and presence of a pericardial effusion.[34] Patients with pretricuspid shunts develop RV pressure overload later in life, so RV adaption mechanisms may be more susceptible to failing.[35]

Laboratory Precautions

Patient with ES have a reduced amount of plasma for a given amount of whole blood. Hence, caution must be exercised in interpretation of coagulation factors, clotting factor dosages and efficiency of anticoagulants by adjusting the quantity of sodium citrate to the hematocrit level, as advocated by the Clinical and Laboratory Standards Institute guidelines (https://clsi.org). Furthermore, it is not uncommon for blood glucose levels to be underestimated as a result of increased *in vitro* glycolysis (because of the increased amount of red blood cells); addition of sodium fluoride to the tube can prevent this artificial hypoglycemia.

Management of a Multiorgan Disease

Management of patients with ES involves lifelong monitoring in a tertiary care congenital cardiac clinic with a multidisciplinary medical team. An approach to prevention and management is proposed in Figures 3 and 4. Cardiac issues predominantly involve heart failure and arrhythmias. Heart failure, which is often triggered or exacerbated by arrhythmias or pulmonary infections, is a common complication that has implications with regard to major organs including the kidneys, liver, gut, and brain. Interventional treatment options should be discussed in a multidisciplinary setting to balance risks and benefits in the context of the very fragile physiology. Endocarditis should be suspected in patients with sepsis, whereas a cerebral abscess should be excluded in those with neurological symptoms or new headache. Key issues detailed in the following paragraphs include

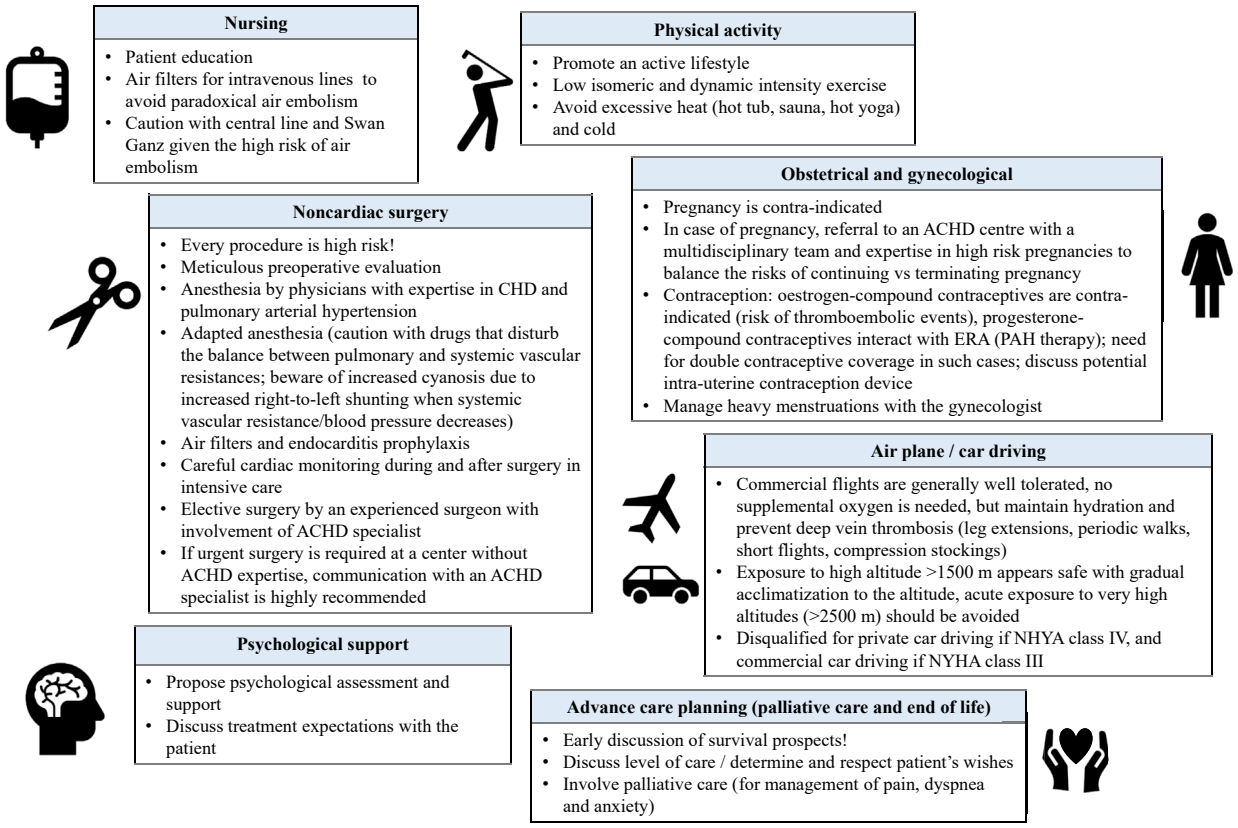

Figure 4. An overview of the various aspects of care in the management of patients with Eisenmenger syndrome. ACHD, adult congenital heart disease; CHD, congenital heart disease; ERA, endothelin receptor antagonists; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension.

anticoagulation, advanced therapies for PAH, noncardiac surgery, physical activity, transplantation, and advanced-care planning including palliative care.

To anticoagulate or not to anticoagulate

From a hematological perspective, ES represents a complex paradox owing to associated hemostatic abnormalities (thrombocythemia, deficiency of vitamin K-dependent factors [II, VII, IX, X], factor V, Von Willebrand factors, and increased fibrinolysis) that enhance both the risk of bleeding and thrombosis.[15,17,18] Whereas bleeding is usually self-limited and minor, major bleeding occurs in one third of cases, predominantly in the form of hemoptysis with intra-parenchymal bleeding.[36,37] Hemoptysis is the external presentation of an intrapulmonary hemorrhage and hence does not reflect the severity of intrapulmonary bleeding. Pulmonary artery thrombosis, mostly laminar, has been identified in more than one third of patients with ES.[38-41] There are conflicting data about risk factors for pulmonary artery thrombosis, which generally occurs in a multifactorial context, in association with predisposing conditions such as heart failure, larger pulmonary arteries, slow pulmonary blood flow velocity, lower oxygen saturation, arrhythmias, and intra- or extracardiac devices.[39,41] Varicose veins, poor peripheral venous circulation, and sedentary lifestyle are known risk factors for thrombosis. The decreased activity of clotting factors does not protect against thrombosis.[41]

In patients with ES, oral anticoagulants and antiplatelet agents can aggravate underlying hemostatic abnormalities and increase the incidence and severity of bleeds. Routine anticoagulation has not been proved to increase survival.[42,43] Hence, there is no legitimate argument for routine anticoagulation in ES because all data are empiric and derived from retrospective studies. Nevertheless, anticoagulation is recommended in the presence of sustained arrhythmias such as atrial flutter or fibrillation, recurrent thromboembolic events, pulmonary artery thrombosis with absent or only mild hemoptysis, and mechanical prosthetic valves (which are extremely rare in patients with ES).[15,17] When indicated, warfarin is the long-term oral anticoagulant of choice, whereas unfractionated heparin and low molecular weight heparin could be used in a hospital setting. Strict control of anticoagulation levels is paramount, with the targeted international normalized ratio (INR) range between 2 and 2.5 (except for mechanical valves, in which 2.5 to 3 may be targeted). We recommend a slightly lower target INR in patients with ES because of the intrinsic risk of bleeding (coagulation abnormalities, thrombocytopenia, and thrombasthenia). There is currently insufficient data on the safety and efficacy of non-vitamin K antagonist oral anticoagulants (NOAC) to recommend their use in patients with ES.

Anesthesia and noncardiac surgery

Noncardiac surgery is associated with a high risk of complications in patients with ES (eg, arrhythmias, bleeding, thrombosis). Hemodynamic instability is further caused by inappropriate adaptive mechanism to any hemodynamic changes related to anesthesia, fluid shift, or surgery itself. Surgeries should be limited to those deemed essential and performed in specialized centres with anesthesiologists experienced in CHD. In case of emergencies, contact between CHD providers and the anesthesia management team can help avert complications. Hypotension and desaturation commonly occur upon induction of anaesthesia by virtue of increased right-to-left shunting as a result of a decrease in systemic vascular resistance. Concomitant administration of vasopressor agents at anesthesia induction could limit the hypotensive response that leads to desaturation.[44] Furthermore, if the surgery permits, regional anesthesia is usually preferable to general anesthesia in patients with PAH, although general anesthesia is preferred over epidural anesthesia. Clear written consent should be obtained for all procedures regardless of whether they involve general or regional anesthesia or sedation. The risk-to-benefit ratio of undergoing surgery should be thoughtfully considered and discussed in a multidisciplinary setting. Moreover, risks of anesthesia should be explicitly explained to the patient and caregivers and conservative management options considered if appropriate. Cholelithiasis, a common condition in patients with ES, caused by an increased red cell count and bilirubin level, often poses a management dilemma. On the one hand, cholecystectomy carries risks connected to anesthesia and the postoperative period, whereas conservative management is associated with an increased risk of severe infections.

Advanced pulmonary arterial hypertension therapy

Advanced specific PAH therapies have been associated with improvements in functional class, 6-minute-walk distance, quality of life, and survival, but the benefit on survival is less well documented. In a retrospective multicentre study of 276 patients with ES followed for a median of 5.5 years, PAH-specific therapy—whether single or dual—was associated with a significant reduction in death or transplantation (heart or heart-lung) when compared with no PAH therapy.[45] Similarly, a retrospective study of 253 patients found that the rate of transplantation or death was lower in patients who received PAH therapy (66% bosentan; 35% sildenafil) compared with no therapy (4.8% per year vs 8.4% per year), despite higher risk features in treated patients.[46] Despite such studies, PAH therapy remains underprescribed in patients with ES, in the order of 37%.[34] The proportion of patients on PAH therapy is lower in those with Down syndrome (18.6% vs 45.5% in the remainder). Most patients (88.4%) receive monotherapy with an endothelin receptor antagonist (41.7% of all treated patients), whereas dual therapy is used in 10.9% of patients.

PAH-specific therapies are divided into 3 major classes that target different pathways: endothelin pathway, phosphodiesterase inhibitors, and the prostacyclin pathway (Supplemental Table S1). Endothelin receptor antagonists include bosentan and ambrisentan, which are selective antagonists for the endothelin A receptor, and macitentan, which is a dual antagonist for endothelin A and B receptors. In patients with ES randomized in the **B**osentan **R**andomized Trial of **E**ndothelin **A**ntagonist **The**rapy-5 (BREATHE-5 trial),[47] Bosentan improved functional capacity and hemodynamic parameters. The open-label extension study showed that increase in functional capacity persisted with 24 additional weeks of follow-up,[48] independent of the location of the shunt.[49] Additional long-term studies have reported similar results with regard to improvements in functional class or 6-minute-walk test distance at up to 4 years of follow-up.[50-52] However, other studies have suggested that bosentan affords short-term benefits with a subsequent progressive and slow return to baseline parameters within 2 years, potentially attributable to the development of tolerance to bosentan.[53,54]

Macitentan emerged as an attractive alternative to bosentan for patients with CHD, with the promise of greater efficacy, when the **S**tudy With an **E**ndothelin **R**eceptor **A**ntagonist in **P**ulmonary **H**ypertension to **I**mprove Cli**n**ical Outcome (SERAPHIN) trial—which included 62 (8%) patients with PAH associated with CHD—reported a reduction in morbidity and mortality.[55] Appealing features of macitentan included the once-daily dosing regimen, with its associated potential for greater adherence and the reduction in hepatic toxicity. However, enthusiasm for macitentan was tempered by the recent randomized multicentre **Ma**citentan in **E**isenmenger **S**yndrome **t**o **R**est**o**re Exercise Capacity (MAESTRO) trial that showed no statistical superiority of macitentan over placebo in patients with ES with regard to the 6-minute-walk distance or World Health Organization functional class (WHO-FC).[56] A total of 226 patients were randomized to macitentan (n = 114) vs placebo (n = 112), including 20 with Down syndrome (10 per treatment group). Overall, 221 participants completed 16 weeks of treatment (macitentan n = 111; placebo n = 110). During a median follow-up of 12.6 months, 27.4% of patients also received phosphodiesterase enzyme (PDE) inhibitors at baseline. Positive signals included an 88.7% reduction in NT-pro-BNP levels at 16 weeks of treatment compared with baseline with macitentan, in contrast to a 109.2% increase associated with placebo over the same follow-up. In the hemodynamic study performed in a subgroup of patients (n = 39), the mean PVRi decreased by 85.3% with macitentan compared with a 101.1% increase with placebo. Changes in other hemodynamic parameters were similar between groups. A strong placebo effect was observed in the MAESTRO trial. No concern was raised over safety, with the most common side effects being headache (11.4 vs 4.5%) and upper respiratory tract infection (9.6 vs 6.3%). A reduction in hemoglobin level $\geq$ 2 g/dL from baseline occurred in 36.0% vs 8.9% of patients.

The study designs and patient populations in MAESTRO and BREATHE-5 were different. The study population was more heterogeneous in MAESTRO, which included patients with more complex forms of ES, WHO-FC II to IV symptoms, a subset with Down syndrome, and patients already treated with PAH therapy at baseline.[57] It remains unknown whether the use of macitentan in a more homogenous population similar to BREATHE-5 would have yielded different results. Proponents of macitentan cite demonstrated benefits with regards to NT-proBNP and pulmonary vascular resistance index (PVRi) despite negative primary results. Although there are no head-to-head trials that have directly compared macitentan with bosentan, 1 study suggested a benefit to switching from bosentan to macitentan in 40 patients with

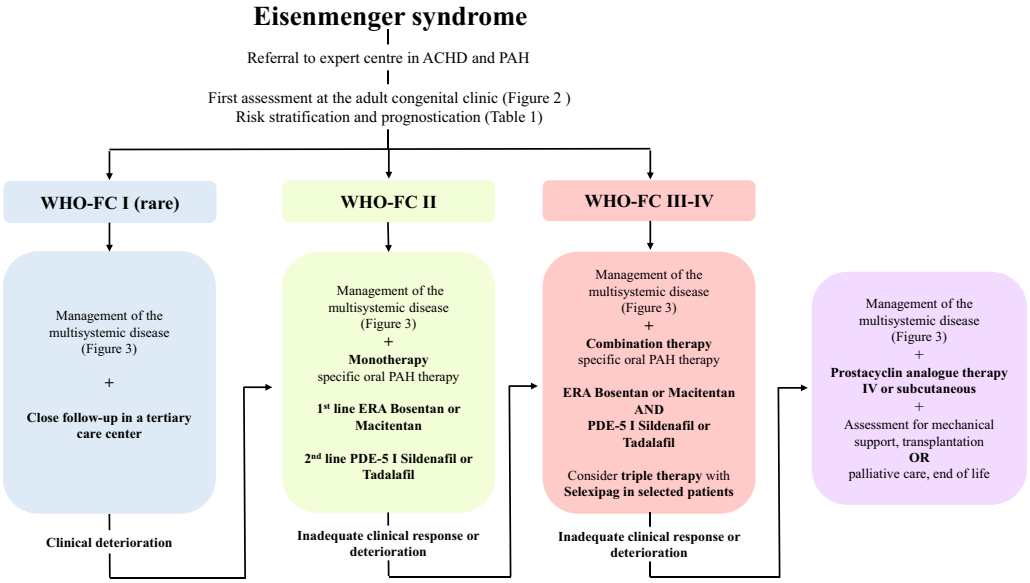

Figure 5. An algorithm for advanced PAH therapy is proposed for patients with Eisenmenger syndrome, including the selection of single vs dual agents and the class of therapy. Dosages: bosentan 62.5 mg twice daily for 4 weeks, with a target dose of 125 mg twice daily; sildenafil 20 mg 3 times daily; macitentan 10 mg once daily; tadalafil 40 mg once daily. ACHD, adult congenital heart disease; ERA, endothelin receptor antagonists; PDE-5 I, phosphodiesterase-5 inhibitors; WHO-FC,World Health Organization functional class.

PAH and CHD, 30 of whom were diagnosed with ES.[58] Improvements in WHO-FC ($P = 0.004$), NT-proBNP ($P = 0.02$) and tricuspid annular plane systolic excursion ($P = 0.002$) were observed after transitioning to macitentan. In contrast, rate of hospitalization for heart failure, 6-minute-walk distance, and oxygen saturation at rest did not change with macitentan after 6 months.[58] It could be argued that the high proportion of patients with Down syndrome in the study (40%) rendered the 6-minute-walk test an insensitive metric and that the study was underpowered to detect a reduction hospitalization rate. In light of the neutral MAESTRO results, the selection of a first-line endothelin receptor antagonist remains debated. Concerns over hepatic failure or nonadherence in specific patients may tip the balance toward macitentan.

Phosphodiesterase inhibitors—acting on the nitric oxide pathway—include sildenafil and tadalafil. In addition, riociguat also increases tissue nitric oxide availability by stimulating soluble guanylate cyclase. There is some evidence from small uncontrolled studies that support the use of sildenafil in patients with ES.[59-61] One placebo-controlled randomized trial of 10 patients with ES reported an improvement in the 6-minute-walk test, pulmonary pressures, New York Heart Association (NYHA) functional class, and exercise capacity after 6 weeks of sildenafil treatment.[62] In a randomized trial of 28 patients with ES, tadalafil was associated with a significant improvement in exercise capacity, functional class, oxygen saturation, and PVR after 6 weeks of treatment.[63] An uncontrolled preliminary study reported benefits with tadalafil at 12 weeks.[64] No trial has yet been specifically reported on riociguat in ES.

Targeting the prostacyclin pathway has not traditionally been considered the treatment of choice in patients with ES by virtue of the intravenous or subcutaneous administration. Oral medications are preferred in patients with ES for various reasons including risks of infection and paradoxical emboli emanating from thrombosed venous lines. Nevertheless, intravenous epoprostenol showed some benefit as a second-line agent in 8 patients with ES.[65] Other studies in CHD and PAH reported favourable results, although patients with ES were excluded.[66,67] In a prospective study of 13 patients with ES, inhaled iloprost resulted in functional improvements but no change in hemodynamics parameters at 24 weeks.[68] Selexipag is a promising oral prostacyclin analogue that has yet to be studied specifically in patients with ES.[69,70] The Prostacyclin (PGI_2) **R**eceptor Agonist **i**n **P**ulmonary Arterial **H**ypertens**ion** (GRIPHON) trial included 110 patients with PAH associated with CHD, but none had ES.[70]

Calcium channel blockers are not indicated in patients with ES, as they may cause peripheral vasodilation, increased right-to-left shunting with hypoxia, syncope, and sudden cardiac death.

The rationale of combination therapy is to simultaneously target different pathways associated with PAH to improve efficacy and decrease the tolerance effect related to single agents. Whereas combination therapy was initially limited to patients who deteriorated or experienced a suboptimal response to monotherapy, the current trend is to initiate dual therapy in treatment-naïve patients. Two trials have assessed the addition of sildenafil to bosentan therapy in patients with ES, with controversial results. In 1 trial, sildenafil or placebo was added to bosentan after 3 months of therapy. No improvements in 6-minute-walk distance, NYHA functional class, or hemodynamic parameters occurred after 6 months of combined therapy, despite an increase in oxygen saturation.[71] The second trial enrolled 26 patients with ES and showed that functional and

hemodynamics parameters improved after addition of sildenafil to bosentan in 26 patients with ES.[72]

The selection of specific PAH therapies depends, in part, on the functional class and should be adapted according to hemodynamic and clinical responses. Figure 5 proposes a management algorithm for PAH therapy, including the selection of single or dual therapy and the class of agents.

Physical activity

Physical activity is associated with worsening cyanosis as a result of an increase in right-to-left shunting and a limited rise in pulmonary blood flow. Patients are at risk for sudden cardiac death during strenuous physical activity; therefore, moderate to intense intensity physical activity is prohibited, as is participation in competitive sports. Patients should become aware of their limitations, monitor their heart rates during physical activity (maintain heart rate $<$ 50% of maximum predicted heart rate), and limit their activities to low-intensity isomeric and dynamic sports (eg, billiards, bowling, cricket, curling, golf, riflery).[73]

Mechanical support and transplantation

The only definitive treatment for ES is lung transplantation (in combination with shunt closure) or combined heart-lung transplantation. Mechanical circulatory and pulmonary support and lung or heart-lung transplantation have been reported in patients who deteriorated despite maximal medical therapy.[74-76] Indications are not standardized, and data are limited. In the context of a paucity of donor organs and low survival rates after transplantation, consideration of such therapies is generally limited to highly symptomatic patients or those at high risk for death despite maximum pharmacological therapy and after multidisciplinary assessment in an expert centre.

Advanced-Care Planning: Palliative Care and End of Life

Survival prospects of ES patients are very limited. Hence, discussion of advanced-care planning, including palliative care and end-of-life discussions, should not be deferred until a life-threating complication occurs. A holistic approach to advanced care, a comprehensive discussion, and a rational decision can be very difficult or even impossible in the setting of an acute complication in a stressful environment. Timely consultation of palliative care allows the team to understand the patient's perspective and fears, establish a management plan that respects the patient's wishes and values, and introduce end-of-life and comfort-care discussions.[77] Furthermore, the palliative team can help to manage dyspnea, pain, and anxiety.

Conclusions

ES is an acquired rare and severe multiorgan syndrome that requires close follow-up and management in a tertiary centre by a multidisciplinary team of adult congenital heart disease experts. The prevalence of ES is on the decline in western countries such that afflicted patients are aging and, hence, at greater risk of multiorgan complications and acquired disease. Over the past 15 years, major strides have been achieved in the pharmacological management of ES, particularly with regard to PAH-specific therapies. These advanced therapies are indicated in symptomatic patients (ie, WHO-FC II or higher), with the objective of improving functional class and reducing mortality. Additional trials are required to assess the comparative efficacy of the various agents and the added benefits of combination therapy. Despite modern PAH-specific therapies, the mainstay of care remains not to destabilize the fragile and very vulnerable pathophysiology. Importantly, ES is preventable by the early recognition and management of shunt lesions. The hope is that improved access to specialized CHD medical and surgical care worldwide will result in the eventual eradication of ES.

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Supplementary Material

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