Review Article on Pediatric Pulmonary Hypertension

Treatment of adults with Eisenmenger syndrome—state of the art in the 21st century: a short overview

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Abstract: Eisenmenger syndrome (ES) develops in association with unrepaired, non-restrictive cardiac shunt lesions at the atrial, ventricular or arterial level over time. In developed countries, cardiac defects are being operated on in a timely manner, before pulmonary vascular disease develops. However, with rising immigration from underserved countries, we increasingly see patients with shunt lesions, that are not amenable for repair as pulmonary vascular disease has already established. ES describes a symptom complex and patients present with heterogeneous problems involving many organ systems (multisystem disorder). Care in tertiary specialist cardiac centers with access to multidisciplinary subspecialities is required. Central cyanosis with secondary erythrocytosis is one of the key features of patients with ES. Clinical consequences of longstanding hypoxia can lead to other organ complications, that involve other organs than the heart alone. Although ES patients have a better prognosis compared to other patients with pulmonary arterial hypertension, ES grossly affects quality of life and morbidity is frequent. Follow-up and care at specialist congenital heart disease centers is highly recommended to prevent, to early diagnose and to timely manage complications of ES. This is necessary to maintain functional capacity, decrease morbidity and increase life expectancy for these vulnerable patients. The leading reasons for mortality are sudden cardiac death, progressive heart failure, and infectious diseases. Various factors have been shown to be associated with mortality like decreased arterial oxygen saturation, functional class, impaired exercise tolerance, syncopal events, iron deficiency, presence of pre-tricuspid shunts, arrhythmias, increased (NT-pro) brain natriuretic peptide, echocardiographic variables of right ventricular dysfunction and hospitalization for heart failure. Although to date there is no causal therapy to reverse pulmonary vascular disease, a greater armamentarium of targeted therapies is available, which have been shown to be beneficial in patients with ES.

Keywords: Eisenmenger syndrome (ES); adult congenital heart disease (ACHD); diagnosis; risk stratification; pulmonary arterial hypertension targeted therapy

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Despite the increased availability of early reparative surgery and interventions—avoiding long-term complications such as severe pulmonary arterial hypertension—Eisenmenger syndrome remains a challenging diagnosis in a subset of adult congenital heart disease (ACHD) patients (1). It represents a cyanotic shunt condition with a pulmonary arterial pressure at the systemic (post-tricuspid shunts) or even at the suprasystemic level (pre-tricuspid shunt) which results in a bidirectional or reversed shunt and a plethora of multiple end-organ complications (2,3). Patients are almost always symptomatic with reduced exercise capacity and life expectancy is limited in this condition (2-6). The first description of the syndrome dates to the 19th century, with a case report by the Viennese physician Victor Eisenmenger (7). The initial description was labeled as Eisenmenger complex in a 32-year-old man with a non-restrictive VSD, but it was Paul Wood in his landmark paper who described the anatomical and pathophysiological phenotypes in a very large population and introduced the term Eisenmenger syndrome as it doesn't matter where the large shunt happens to be (8). Since then, our understanding of the condition has evolved but only within the last one and a half decades medical therapeutic options became available improving symptoms and potentially survival in this vulnerable cohort.

The prevalence of Eisenmenger syndrome is not well defined but traditional estimates suggest that around 5% of ACHD patients under follow-up at large supra-regional centers have Eisenmenger syndrome (2,3). The prevalence of the condition is most likely much higher in low and middle income countries while in high resource countries it is likely to decrease further due to better diagnostic and surgical/interventional therapeutic options early in life; in fact, we shouldn't see any Eisenmenger syndrome patients born in these countries anymore (9). In patients presenting late with established Eisenmenger syndrome, shunt closure is contraindicated as this will worsen prognosis in this setting (1). This short article aims to give an overview over the pathophysiology and especially the relevant medical aspects of care for Eisenmenger patients. It therefore represents a focused overview over selected aspects of the condition. It should be noted that recent reviews have also addressed this condition potentially covering some additional relevant aspects.

Pathophysiology

Eisenmenger syndrome represents a clinical diagnosis based on physiologic factors. The underlying anatomic diagnosis can therefore be variable. Most commonly, isolated large, unrestrictive, unrepaired shunt lesions at the ventricular or arterial level as well as complex univentricular conditions represent the underlying morphological lesions. Occasionally also large atrial septal defects (ASD) may be associated with this condition. Due to the prevailing distribution of vascular resistance between pulmonary and systemic circulation, patients initially develop left-to-right shunting with volume overload of the pulmonary circulation, often accompanied by increased pressure due to post-tricuspid shunt lesions. In this situation, over time, pulmonary vascular disease develops and progresses to the point where shunt reversal occurs. This is labelled as Eisenmenger reaction which manifests itself first during exercise and later also at rest. Patients therefore develop cyanosis, often accompanied by the typical stigmata of cyanotic disease such as clubbing and visible cyanosis. It should be noted, however, that not all patients are desaturated at rest and arterial desaturation may become apparent only during exercise in some patients (10). Important additional features of the condition are typical laboratory findings mainly secondary erythrocytosis, low platelet count, iron deficiency, and hyperuricemia. In addition, overt Eisenmenger syndrome is a multisystem disorder characterized by hepatic, renal, immunologic, neurological and orthopedic complications (2,3,11).

Clinical presentation and outcome

The clinical presentation of Eisenmenger patients is variable. Depending on the underlying heart defect and associated end-organ complications, patients may be oligosymptomatic, while the majority has dyspnea (NYHA class II or III). Occasionally, patients also present in NYHA class IV (6,12). Main symptoms include shortness of breath, fatigue, exercise intolerance and palpitations. Patients with Eisenmenger syndrome, by and large, represent the most symptomatic subgroup of ACHD patients and the group with the lowest average exercise capacity (13). Hemoptysis, an external manifestation of an intrapulmonary hemorrhage and previously reported as a common complication, is, however, nowadays rarely encountered (3,14). Due to their predisposition for bacterial infections, patients may present with pneumonia or bacterial endocarditis. Cerebral abscess should be suspected in patients presenting with neurological symptoms, pronounced cephalgia and signs of

infection. Arrhythmias are not uncommon in this setting and may be associated with malignant arrhythmias and sudden cardiac death in selected patients. Furthermore, hyperbilirubinemia may lead to gallstones and associated symptoms. Hematological abnormalities include secondary erythrocytosis with hyperviscosity syndromes in selected patients (relatively rare) and bleeding complications due to thrombocytopenia and abnormal coagulation parameters. Due to the possibility of paradoxical embolism and air embolism, ischemic neurological complications may occur, and neurological symptoms should be taken seriously in Eisenmenger patients.

Survival prospects of Eisenmenger patients are variable and predicting individual prognosis remains challenging (15). Given the degree of pulmonary arterial hypertension, survival prospects of Eisenmenger patients are relatively preserved compared to patients with idiopathic pulmonary hypertension. On the other hand, there is a misconception and misperception of highly benign outcome of the Eisenmenger population. Recent data suggests, however, that untreated Eisenmenger patients have significantly confined life expectancy especially in the presence of complex underlying heart defects (5). The reason for the superior survival of Eisenmenger patients compared to idiopathic pulmonary arterial hypertension patients is likely due to a better adaptation of the right ventricle to increased afterload given the slower disease progression and potentially the higher plasticity of cardiac myocytes earlier in life (3,16,17). This has led to the postulate that 'the integrity of right ventricular function, rather than the degree of vascular injury, … is the major determinant of symptoms and survival in pulmonary arterial hypertension' (18). As such, progressive dilatation or worsening of right ventricular function in Eisenmenger syndrome should be considered an ominous sign as they may herald failure of the balanced but fragile physiology. Risk factors of mortality in Eisenmenger patients include age, lower oxygen saturation, complexity of the underlying heart defect, signs and symptoms of heart failure, levels of brain natriuretic peptides, low six minute walk test distance, NYHA functional class, presence of Down syndrome, absence of sinus rhythm or arrhythmias, the presence of a pre-tricuspid shunt, worse right ventricular function [especially lower tricuspid annular plane systolic excursion (TAPSE)], low albumin and increased C-reactive protein (2,12,15,19). Assessing prognosis is paramount as it may help to guide specific pulmonary arterial hypertension therapy in this setting. There has been a shift in the cause of death during the last decades: the leading causes of death include heart failure, infections, sudden cardiac death, thromboembolism, hemorrhage and peri-procedural complications in the current era (14).

Management strategies

The key principle in the clinical management of Eisenmenger syndrome patients remains to cause no harm to the fragile balanced pathophysiological state (2). As a consequence, Eisenmenger patients require life-long expert assessment and therapy at specialized centers. Preventing complications and avoiding management errors should be the primary goal of regular outpatient assessment (1). *Table 1* and *Figure 1* summarize the key elements of diagnostic, preventive and therapeutic approaches (2).

Secondary erythrocytosis—a physiologic response: do not phlebotomize

Given the obvious central cyanosis, often accompanied by pronounced secondary erythrocytosis, non-congenital heart specialists may be tempted to offer regular, routine phlebotomies to the patients in a well-meant intention to 'normalize' blood rheology. However, this idea is based on a flawed physiologic concept, derived from patients with polycythemia vera (a completely different population), and has been shown to be associated with worse outcome, iron deficiency and increased risk of stroke in Eisenmenger patients (20,21). In fact, the elevated hemoglobin levels represent a physiologic adaptation to reduced oxygenation, intending to maintain tissue oxygen delivery by increasing the oxygen carrying capacity of blood. As such iatrogenic interventions disabling this adaptive mechanism have delirious consequences and should be avoided. Hyperviscosity symptoms are driving the indication for phlebotomy; i.e., selected patients with true hyperviscosity syndrome may benefit from occasional phlebotomies with isovolumic substitution in expert hands. As perceived hyperviscosity symptoms may indeed represent signs of iron deficiency or dehydration, meticulous clinical assessment is required prior to intervention and iron deficient anemia or dehydration should be excluded. When iron deficiency is identified, iron replacement should be initiated. Usually, a low dose of ferrous sulfate is administered orally to this end to avoid hyperreactive erythrocytosis responses. Parenteral iron therapy is also possible in selected patients, intolerant to oral iron substitution (22,23).

Table 1 A standardized approach to multidisciplinary management of patients with Eisenmenger syndrome (ES)

Cardiac management	Hematology management	Infection management	Hemoptysis
• Defect closure is contraindicated	• Exclude relative anemia (normal hemoglobin reflects anemia in ES!), consider iron supplementation and blood transfusion	• Prevention of endocarditis:	• 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
• Maintain adequate hydration	• 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	• Antibiotic prophylaxis before dental visits	• Codeine should be administered to avoid coughing spasms
• Oxygen: no evidence of increased survival or improved symptoms compared to placebo; supplemental oxygen may be beneficial if additional underlying lung disease	• 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%	• Periodical dental visits	• Broad spectrum antibiotics to avoid pulmonary superinfection. Consider tuberculosis and atypical mycobacterium causing hemoptysis
• Management of cardiovascular risks factors: smoking and drug cessation, treatment of dyslipidemia, diabetes, systemic arterial hypertension	• Anticoagulation	• Soft-bristle tooth brushes to avoid gum trauma	• 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
• Heart failure therapy: caution with medications that decrease SVR and increase right-to-left shunting	• Balance benefit/risks	• Advise against tattoos or piercings	
• Percutaneous intervention: to discuss in a multidisciplinary setting	• No proven benefit of routine anticoagulation/aspirin	• Good nail hygiene	
• 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	• Warfarin if anticoagulation indicated	• Immunization: Influenzae immunization every year, Pneumococcus immunization every 5–10 years	

Table 1 *(continued)*

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Cardiac management	Hematology management	Infection management	Hemoptysis
• Increased cyanosis: imaging for exclusion of pulmonary emboli/ infarction or lung disease; cardiac catheterization for hemodynamic assessment and embolization of fistula or collaterals	• Follow-up with hematologist for INR titration (typical target 2–2.5)	• In case of infection: refer to a microbiologist, treat chest infections promptly to avoid decompensation	
	• Thrombosis	• Brain abscess: consider brain abscess if new headache! Brain MRI/CT if new headache. Refer to a neurosurgeon, (abscesses are heavily encapsulated)	
	• Anticoagulation	Hyperuricemia/gout arthritis	Cholecystic attacks
	• Consider vena caval filter	• Allopurinol if symptomatic gout	• Refer to gastroenterologist
		• Pain reliever in case of arthritis	• Pain medication
			• Antibiotics +/– surgery

CT, computed tomography; MRI, magnetic resonance imaging; SVR, systemic vascular resistance. Reproduced with permission from (2).

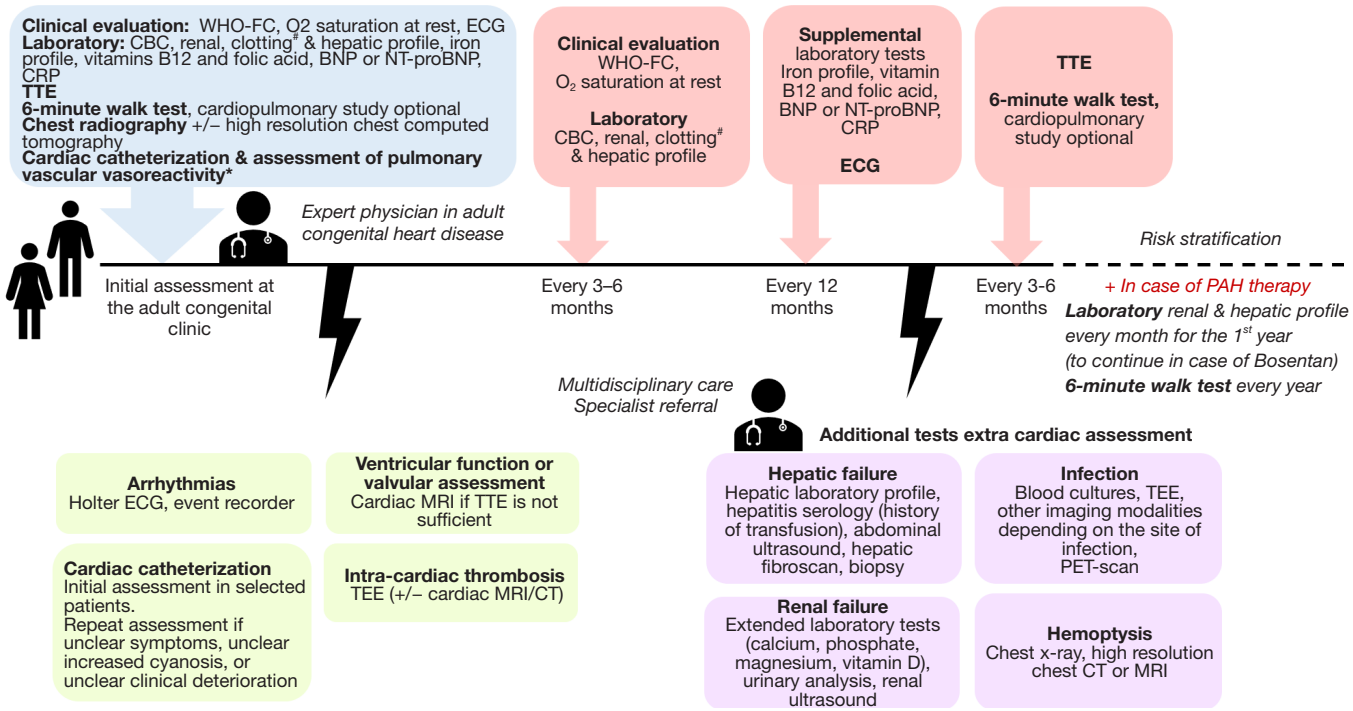

Figure 1 Initial assessment and follow-up of patients with Eisenmenger syndrome. The frequency of laboratory analysis should be adapted to clinical parameters and to the results. The different laboratory profiles are (I) renal profile: creatinine, eGFR (estimated Glomerular Filtration Rate), blood urea nitrogen, electrolytes; (II) clotting profile: INR, aPTT, thrombin time, fibrinogen, bleeding time, #frequency of clotting profile should be adapted if anticoagulation therapy; (III) hepatic profile: ALT (alanine aminotransferase), AST (aspartate aminotransferase), total bilirubin, albumin, total protein, GGT (Gamma-Glutamyl Transferase), ALP (alkaline phosphatase); (IV) 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 (e.g., subpulmonary stenosis). Acute vasoreactivity studies with inhaled nitric oxide carry prognostic information in patients with ES. 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. Reproduced with permission from (2).

Relative anemia

Relative iron-deficient anemia is frequently missed or even ignored in patients with Eisenmenger syndrome because the hemoglobin level may be perceived as normal like in an acyanotic patient, but in fact, it is far too low for a patient with cyanotic congenital heart disease. The hemoglobin level must always be interpreted in relation to the oxygen saturation in each individual patient. Eisenmenger patients may need early iron replacement therapy or even red blood cell transfusion to achieve an appropriate hemoglobin level to improve the amount of oxygen carriers and to facilitate oxygen delivery to the tissue.

Oxygen therapy

Chronic oxygen therapy is not indicated as it does not substantially increase oxygenation of tissue, does not improve outcome and may lead to drying of the mucous pharyngeal tissue, potentially predisposing patients to epistaxis (2). Additionally, the need to carry oxygen tanks represents a burden for patients, further reducing mobility in this group of patients with severely curtailed exercise capacity.

Pregnancy

Pregnancy is contraindicated in women with Eisenmenger

syndrome as it carries a maternal mortality risk of 30–50% associated with generally low prospects of successful pregnancy especially if maternal arterial oxygen saturation is below 85% (24).

Neurological complications

Neurologic complications are common in Eisenmenger patients and require immediate attention. These include both ischemic events (paradoxical embolism or air embolism) and infections complications (cerebral abscess). Given the risk of paradoxical/air embolism, Eisenmenger patients require the use of air-eliminating filters whenever intravenous lines are established.

Thrombotic and embolic complications

Pulmonary thrombosis has been reported in a substantial number of Eisenmenger patients and may represent in-situ thrombosis as well as the consequence of thromboembolism. As a consequence, routine anticoagulation of Eisenmenger patients has been suggested but has to be balanced against the generally increased risk of bleeding due to co-existing hematological abnormalities with in intrinsic, increased risk of bleeding. No study has shown any survival patients of Eisenmenger patients on oral anticoagulants (6,25). Oral anticoagulation is generally required in patients with supraventricular arrhythmias (especially atrial fibrillation/flutter) and in those with a history of thromboembolic events. Mechanical heart valves are another indication, but this clinical scenario is very rare in Eisenmenger patients.

Given the scarce data on safety and efficacy of new oral anticoagulants as well as suggestions of a potential harmful effect (26), these drugs should be used very restrictively (if at all) in this population (26,27).

Prevention of infectious complications

It is recommended to meticulously encourage patients to obtain yearly influenza immunization as well as immunization against pneumococcal disease every 5 years. Furthermore, respiratory infections should be pro-actively diagnosed and treated accordingly to avoid pulmonary or cardiac complications. As per current guidelines, Eisenmenger patients should be offered appropriate antibiotic endocarditis prophylaxis before dental procedures (1). This of course, does not obviate the need for good dental hygiene and regular visits to the dentist.

General anesthesia carries a high risk

If general anaesthesia is required for any non-cardiac or cardiac diagnostic or therapeutic procedure, this should be supervised by an experienced Anaesthesist, ideally at a tertiary center with experience in ACHD. The anesthetist needs to be familiar with fragile pathophysiology, response to narcotics and to fluid shift/volume loss.

Early referral to transplant center

In case of progressive deterioration discussion of heart lung transplantation should be initiated early and patients be offered referral to a transplantation service experienced in congenital heart disease. Due to surgical/technical difficulties as well as the multiorgan nature of end-stage Eisenmenger syndrome the prospects of obtaining a transplantation are often limited (albeit depending on local practice and geography).

Specific disease-targeting therapies

Since the advent of targeted therapies for pulmonary arterial hypertension approximately 20 years ago and subsequent positive results in Eisenmenger patients, these patients can be offered a therapeutic option that improves symptoms, exercise capacity and potentially outcome (6,28-30). Therapy is based on various pathophysiologic pathways. These include the nitric oxide, the endothelin and the prostacyclin pathway. The majority (as well as the most robust) data exist on the effect of endothelin receptor antagonists in patients with Eisenmenger syndrome. The landmark BREATHE-5 trial was the first to convincingly demonstrate that (I) Eisenmenger patients do not suffer from 'fixed' pulmonary hypertension and reduction in pulmonary vascular resistance can be achieved with appropriate therapy, (II) symptoms and exercise capacity can be improved by endothelin receptor antagonists (Bosentan in this case) and (III) this therapy is safe in this population (29). This has sparked interest in various treatment approaches using also phosphodiesterase-5 inhibitors (mainly Sildenafil) in this setting.

While the data is less robust for this substance, positive effects have also been observed with Sildenafil therapy (2,31). At most centers, endothelin receptor antagonist therapy remains the first choice for symptomatic Eisenmenger patients (especially those in NYHA class III and those deteriorating over time). If unsatisfactory results

are achieved with monotherapy, Sildenafil is generally added. Therapy initiation or escalation is also useful in patients with low oxygen saturation and symptoms interfering with daily activities (32). We and others have had positive experience with Selexipag (an oral prostacyclin receptor agonist) especially in patients with persistent symptoms and those deemed at high risk of complications or mortality despite dual oral therapy. In addition, patients in NYHA class IV and those with ominous clinical signs should be considered for parenteral prostacyclin therapy (33). Where available, especially subcutaneous preparation appear a reasonable choice in this setting.

Macicentan a novel oral endothelin receptor antagonist with favorable pharmacodynamic characteristics appears to be a reasonable alternative to other endothelin receptor antagonists, especially in patients not tolerating Bosentan or women on oral contraceptives (30). While a recent study was neutral on the primary endpoint (improvement of 6-minute walk distance), a significant reduction in NT-pro BNP levels in the main study cohort and pulmonary vascular resistance in the hemodynamic substudy cohort was observed with this drug (30). While not confirmed yet by prospective randomized trials, available data consistently suggest that specific disease targeted drug therapy may improve prognosis in Eisenmenger patients. This observation is based on various large observational studies and patients should be informed about these data (6,28). All Eisenmenger syndrome patients need to be referred to an ACHD expert center with access to pulmonary hypertension specialists so that this fragile population is early evaluated for specific disease targeted therapy (1).

Summary

Eisenmenger syndrome represents a relatively rare population with a balanced, but very fragile pathophysiology and severe multiorgan disorder associated with significant symptoms, morbidity and high mortality. This population is best served in a tertiary care center with expertise in adult congenital heart disease. A pro-active approach, avoiding disturbing the fragile physiological balance, complications and early initiation of specific disease target therapies is warranted in this setting. Limited data exists on risk stratification and the approach to combination therapy in this setting.

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