ESC Guidelines 2015

Pulmonary Arterial Hypertension

By
Wael El Kilany. MD
Associate Professor Of Cardiology
Ain Shams University
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Pulmonary HTN

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Comprehensive clinical classification of pulmonary hypertension

1. Pulmonary arterial hypertension

1.1 Idiopathic
1.2 Heritable
- 1.2.1 BMPR2 mutation
- 1.2.2 Other mutations

1.3 Drugs and toxins induced
1.4 Associated with:
- 1.4.1 Connective tissue disease
- 1.4.2 human immunodeficiency virus (HIV) infection
- 1.4.3 Portal hypertension
- 1.4.4 Congenital heart disease (Table 5)
- 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1'.1 Idiopathic
1'.2 Heritable
- 1'.2.1 EIF2AK4 mutation
- 1'.2.2 Other mutations

1'.3 Drugs, toxins and radiation induced
1'.4 Associated with:
- 1'.4.1 Connective tissue disease
- 1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
- 4.2.1 Angiosarcoma
- 4.2.2 Other intravascular tumors
- 4.2.3 Arteritis
- 4.2.4 Congenital pulmonary arteries stenoses
- 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

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Anatomical-pathophysiological

Classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension

1. Type

1.1 Simple pre-tricuspid shunts
- 1.1.1 Atrial septal defect (ASD)
  - 1.1.1.1 Ostium secundum
  - 1.1.1.2 Sinus venous
  - 1.1.1.3 Ostium primum
- 1.1.2 Total or partial unobstructed anomalous pulmonary venous

1.2 Simple post-tricuspid shunts
- 1.2.1 Ventricular septal defect (VSD)
- 1.2.2 Patent ductus arteriosus

1.3 Combined shunts
- Describe combination and define predominant defect

1.4 Complex congenital heart disease
- 1.4.1 Complete atrioventricular septal defect
- 1.4.2 Truncus arteriosus
- 1.4.3 Single ventricle physiology with unobstructed pulmonary blood flow
- 1.4.4 Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
- 1.4.5 Other

2. Dimension (specify for each defect if more than one congenital heart defect exists)

2.1 Haemodynamic (specify Qp/Qs)[a]
- 2.1.1 Restrictive (pressure gradient accross the defect)
- 2.1.2 Non-restrictive

2.2 Anatomic[b]
- 2.2.1 Small to moderate (ASD ≤2.0 cm and VSD ≤1.0 cm)
- 2.2.2 Large (ASD >2.0 cm and VSD >1.0 cm)

3. Direction of shunt

3.1 Predominantly systemic-to-pulmonary

3.2 Predominantly pulmonary-to-systemic

3.3 Bidirectional

4. Associated cardiac and extracardiac abnormalities

5. Repair status

5.1 Unoperated

5.2 Palliated (specify type of operation/s, age at surgery)

5.3 Repaired (specify type of operation/s, age at surgery)

[a] Ratio of pulmonary (Qp) to systemic (Qs) blood flow.
[b] The size applies to adult patients.

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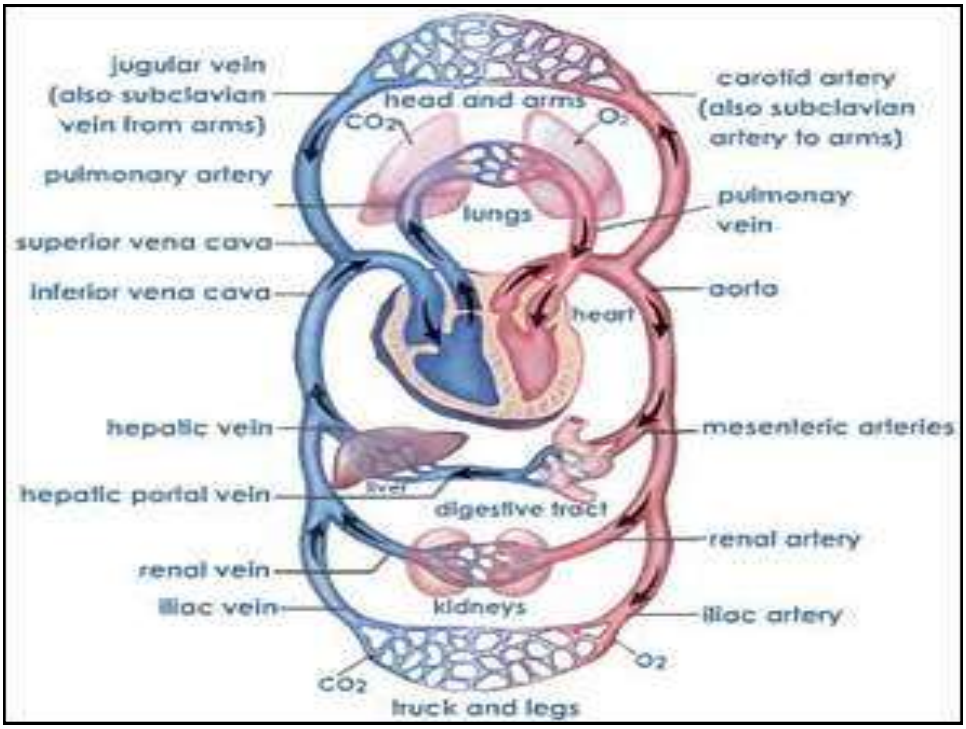
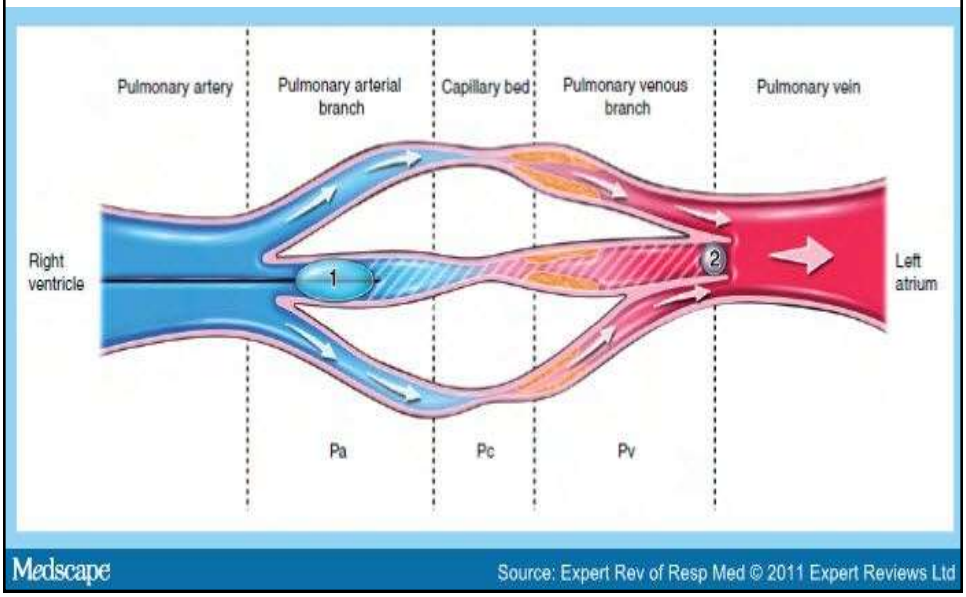


Pre &Post Capillary P++



Haemodynamic definitions of pulmonary hypertension

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP - mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.

[a]All values measured at rest; see also section 7.
[b]According to Table 4.
[c]Wood Units are preferred to dynes.s.cm^{-5}.

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Right heart catheterization in pulmonary hypertension

Recommendations	Class	Level
RHC is recommended to confirm the diagnosis of pulmonary arterial hypertension (Group 1) and to support treatment decisions.	I	C
In patients with PH, it is recommended to perform RHC in expert centres (Table 34) as it is technically demanding and may be associated with serious complications.	I	B
RHC should be considered in pulmonary arterial hypertension (Group 1) to assess the treatment effect of drugs (Table 12).	IIa	C
RHC is recommended in patients with congenital cardiac shunts to support decisions on correction (Table 23).	I	C
RHC is recommended in patients with PH due to left heart disease (Group 2) or lung disease (Group 3) if organ transplantation is considered .	I	C
When measurement of PAWP is unreliable, left heart catheterization should be considered to measure LVEDP.	IIa	C
RHC may be considered in patients with suspected PH and left heart disease or lung disease to assist in the differential diagnosis and support treatment decisions.	IIb	C
RHC is indicated in patients with Chronic Thromboembolic Pulmonary Hypertension (Group 4) to confirm the diagnosis and support treatment decisions.	I	C

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Vasoreactivity testing

Recommendations	Class	Level
Vasoreactivity testing is indicated only in expert centres.	I	C
Vasoreactivity testing is recommended in patients with IPAH, HPAH and PAH associated with drugs use to detect patients who can be treated with high doses of a calcium channel blocker.	I	C
A positive response to vasoreactivity testing is defined as a reduction of mean PAP ≥10 mmHg to reach an absolute value of mean PAP ≤40 mmHg with an increased or unchanged cardiac output.	I	C
Nitric oxide is recommended for performing vasoreactivity testing.	I	C
Intravenous epoprostenol is considered for performing vasoreactivity testing as an alternative.	I	C
Adenosine should be considered for performing vasoreactivity testing as an alternative.	IIa	C
Inhaled iloprost may be considered for performing vasoreactivity testing as an alternative.	IIb	C
The use of oral or intravenous calcium channel blockers in acute vasoreactivity testing is not recommended.	III	C
Vasoreactivity testing to detect patients who can be safely treated with high doses of a calcium channel blocker is not recommended in patients with PAH other than IPAH, HPAH and PAH associated with drugs use, and is not recommended in pulmonary hypertension Groups 2, 3, 4 and 5.	III	C

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Evaluation of severity of pulmonary arterial hypertension and clinical response to therapy

Recommendations	Class	Level
It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers and echocardiographic and haemodynamic evaluations (Tables 12 and 13).	I	C
It is recommended to perform regular follow-up assessments every 3–6 months in stable patients (Table 12).	I	C
Achievement/maintenance of a low-risk profile (Table 13) is recommended as an adequate treatment response for patients with PAH.	I	C
Achievement/maintenance of an intermediate-risk profile (Table 13) should be considered an inadequate treatment response for most patients with PAH.	IIa	C

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PAH general treatment measures

Recommendations	Class	Level
It is recommended to avoid pregnancy in patients with PAH.	I	C
Immunization of PAH patients against influenza and pneumococcal infection is recommended.	I	C
Psychosocial support is recommended in patients with PAH.	I	C
Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy.	IIa	B
In-flight O_2 administration should be considered for patients in WHO-FC III and IV and those with arterial blood O_2 pressure consistently less than 8 kPa (60 mmHg).	IIa	C
In elective surgery, epidural rather than general anaesthesia should be preferred whenever possible.	IIa	C
Excessive physical activity that leads to distressing symptoms is not recommended in patients with PAH.	III	C

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Table 13 Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

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Calcium channel blocker therapy in patients who respond to the acute vasoreactivity test

Recommendations	Class	Level
High doses of CCBs are recommended in patients with IPAH, HPAH and DPAH responder to acute vasoreactivity testing.	I	C
Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) is recommended in patients with IPAH, HPAH and DPAH treated by high doses of CCB.	I	C
Continuation of high doses CCB treatment is recommended in patients with IPAH, HPAH and DPAH in WHO-FC I or II with marked haemodynamic improvement (near normalization).	I	C
Initiation of specific PAH therapy is recommended in patients in WHO-FC III or IV or those without marked haemodynamic improvement (near normalization) after high doses CCB treatment.	I	C
High doses of CCBs are not indicated in patients without vasoreactivity study or non-responders, unless standard doses are prescribed for other indications (e.g.,Raynaud phenomenon).	III	C

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Efficacy of drug monotherapy, for PAH (Group 1)

Recommendations			Class - Level					
Measure/treatment			WHO-FC II		WHO-FC III		WHO-FC IV	
Calcium channel blockers			I	C	I	C	-	-
Endothelin receptor antagonists	Ambrisentan		I	A	I	A	IIb	C
	Bosentan		I	A	I	A	IIb	C
	Macitentan[d]		I	B	I	B	IIb	C
Phosphodiesterase type-5 inhibitors	Sildenafil		I	A	I	A	IIb	C
	Tadalafil		I	B	I	B	IIb	C
	Vardenafil*		IIb	B	IIb	B	IIb	C
Guanylate cyclase stimulators	Riociguat		I	B	I	B	IIb	C
Prostanoids	Epoprostenol	intravenous[d]	-	-	I	A	I	A
	Iloprost	Inhaled	-	-	I	B	IIb	C
		Intravenous*	-	-	IIa	C	IIb	C
	Treprostinil	subcutaneous	-	-	I	B	IIb	C
		Inhaled*	-	-	I	B	IIb	C
		Intravenous*	-	-	IIa	C	IIb	C
		Oral*	-	-	IIb	B	-	-
	Beraprost*		-	-	IIb	B	-	-
IP-receptor agonists	Selexipag (oral)*		I	B	I	B	-	-

*Only in responders to acute vasoreactivity tests: Class I for idiopathic PAH, heritable PAH and PAH due to drugs; Class IIa for APAH conditions. - *Time to clinical worsening as primary end-point in RCTs or drugs with demonstrated reduction in all-cause mortality. - [d]In patients not tolerating the subcutaneous form.
*This drug is not approved by the EMA at the time of publication of these guidelines.

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Efficacy of initial drug combination therapy, for PAH (Group 1)

Recommendations	Class - Level					
Measure/treatment	WHO-FC II		WHO-FC III		WHO-FC IV	
Ambrisentan + tadalafil[c]	I	B	I	B	IIb	C
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C
Bosentan + sildenafil +i.v. epoprostenol	-	-	IIa	C	IIa	C
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C
Other ERA or PDE-5i + s.c. trepostinil	-	-	IIb	C	IIb	C
Other ERA or PDE-5i + other i.v. prostacyclin analogues	-	-	IIb	C	IIb	C

*Time to clinical failure as primary end-point in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined).

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Efficacy of sequential drug combination therapy, for PAH (Group 1)

Recommendations	Class - Level					
Measure/treatment	WHO-FC II		WHO-FC III		WHO-FC IV	
Macitentan added to sildenafil	I	B	I	B	IIa	C
Riociguat added to bosentan	I	B	I	B	IIa	C
Selexipag added to ERA and/or PDE-5i	I	B	I	B	IIa	C
Sildenafil added to epoprostenol	-	-	I	B	IIa	B
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C
Iloprost inhaled added to bosentan	IIb	B	IIb	B	IIb	C
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C
Ambrisentan added to sildenafil	IIb	C	IIb	C	IIb	C
Bosentan added to epoprostenol	-	-	IIb	C	IIb	C
Bosentan added to sildenafil	IIb	C	IIb	C	IIb	C
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C
Other double combinations	IIb	C	IIb	C	IIb	C
Other triple combinations	IIb	C	IIb	C	IIb	C
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B

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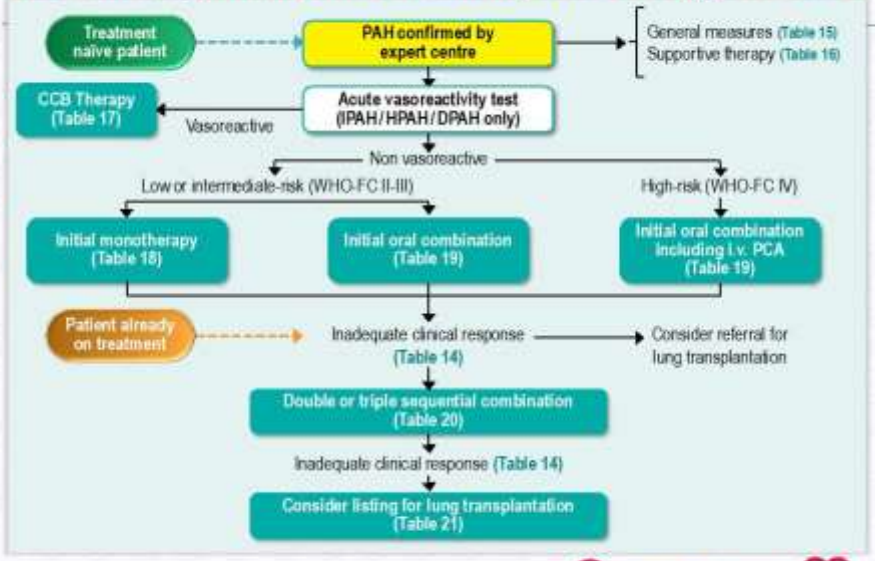
Treatment Algorithm for Pulmonary Arterial Hypertension



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The Ten Commandments

1. Right heart catheterization is recommended to confirm the diagnosis of pulmonary arterial hypertension (PAH - Group 1) and to support treatment decisions.
2. Vasoreactivity testing performed during right heart catheterization is recommended in patients with idiopathic PAH, heritable PAH and PAH induced by drugs or toxins use to detect patients who can be treated with high doses of a calcium channel blocker.
3. It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers, and echocardiographic and haemodynamic evaluation and to perform regular follow-up assessments every 3-6 months in stable patients.
4. It is recommended to avoid pregnancy in patients with PAH.
5. It is recommended for referral centres to provide care by a multi-professional team (cardiology and respiratory medicine physicians, clinical nurse specialist, radiologists, psychological and social work support, appropriate on-call expertise).

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The Ten Commandments

6. Initial drugs monotherapy or initial oral drugs combination therapy is recommended in treatment naïve, low or intermediate risk patients with PAH.
7. Sequential drugs combination therapy is recommended in PAH patients with inadequate treatment response to initial monotherapy or to initial oral drugs combination therapy.
8. Initial combination therapy including an intravenous prostacyclin analogue is recommended in high risk PAH patients.
9. The use of PAH approved therapies is not recommended in patients with pulmonary hypertension due to left heart disease or lung diseases.
10. Surgical pulmonary endarterectomy in deep hypothermia circulatory arrest is recommended for patients with CTEPH and it is recommended that the assessment of operability and decisions regarding other treatment strategies (drugs therapy or balloon pulmonary angioplasty) be made by a multidisciplinary team of experts.

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