

## 1.1 Introduction

Patients with disorders described in this chapter present either with or without hyperphenylalaninemia (HPA). In those presenting with HPA (1.1–1.5 in the table below), the main goal of treatment is to reduce or normalize blood phenylalanine levels. This can be done either by introduction of the low-phenylalanine or low-protein diet or by administration of the synthetic cofactor tetrahydrobiopterin (BH<sub>4</sub>). The mode of treatment depends on the type of disease and may differ with the patient's age, and the policies are different in different countries. In addition, patients with HPA due to a cofactor defect need more strict plasma phenylalanine control and additional supplementations with neurotransmitter precursors L-dopa and 5-hydroxytryptophan in a combination with the peripheral decarboxylase inhibitor carbidopa. Patients with dihydropteridine reductase (DHPR) deficiency (disorder 1.4) need additional folinic acid substitution. In patients revealing levodopa-induced peak-dose dyskinesia, slow-release forms of drugs can be used, and reaching the upper therapeutic limits of L-dopa may be an indication for the use of monoamine oxidase (MAO) and/or catecholamine-*O*-methyl transferase (COMT) inhibitors.

Patients with dopa-responsive dystonia (DRD, dominant GTP cyclohydrolase I (GTPCH I) deficiency; disorder 1.6) and sepiapterin reductase (SR) deficiency (disorder 1.7) respond to low-dosage L-dopa/carbidopa therapy, and patients with SR deficiency need additional supplementation with 5-hydroxytryptophan and probably also BH<sub>4</sub>.

Prognosis and outcome strongly depend on the age when the diagnosis is made and treatment introduced, but also on the type of mutation.

Recommendations for treatment and monitoring are not completely uniform worldwide. Therefore, where possible and necessary, recommendations have been combined and ranges of values indicating lower and upper limits are reported (Fig. 1.1).

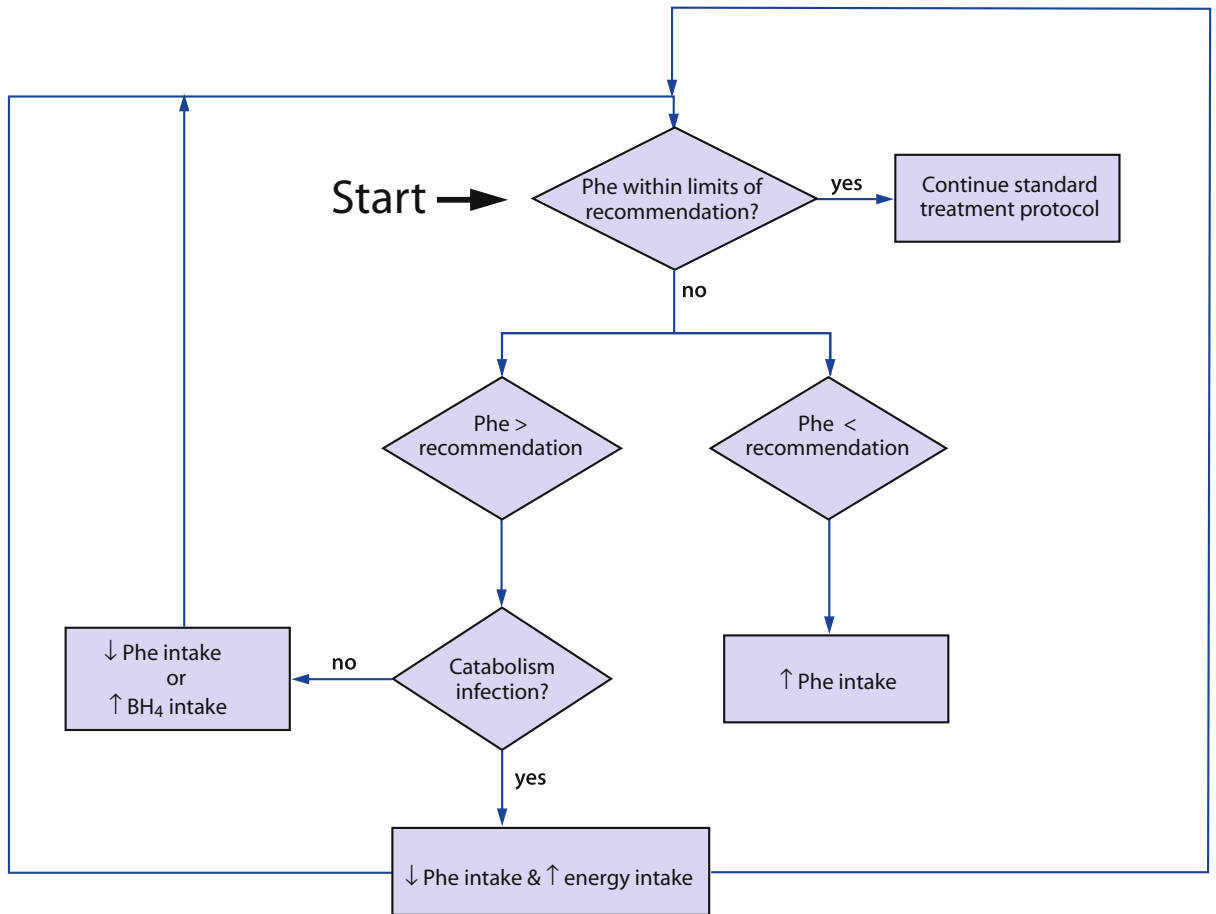


Fig. 1.1. Management of plasma phenylalanine concentrations

## 1.2 Nomenclature

No.	Disorder	Symbol	Definition/comment	Gene Symbol	OMIM No.
1.1	Phenylalanine hydroxylase deficiency	PAH	Autosomal recessive	<i>PAH</i>	261600
1.1.1	Classic phenylketonuria	PKU	Phe > 1200 µmol/l Autosomal recessive	<i>PAH</i>	261600
1.1.2	Mild PKU		360–600 µmol/l ≤ Phe ≤ 1200 µmol/l Autosomal recessive	<i>HPA</i>	261600
1.1.3	Non-PKU hyperphenylalaninemia	MHPA	80 µmol/l ≤ Phe < 360–600 µmol/l Autosomal recessive	<i>HPA</i>	261600
1.1.4	Tetrahydrobiopterin (BH <sub>4</sub> )-responsive PKU/HPA	BH <sub>4</sub> -PKU	Phe > 360 µmol/l Autosomal recessive	<i>HPA</i>	261600
1.1.5	Maternal PKU/HPA	MPKU	Phe > 250–360 µmol/l Autosomal recessive	<i>HPA</i>	261600
1.2	GTP cyclohydrolase I deficiency	GTPCH	Autosomal recessive	<i>GCHI</i>	233910
1.3	6-Pyruvoyl-tetrahydropterin synthase deficiency	PTPS	Autosomal recessive	<i>PTS</i>	261640
1.3.1	Severe PTPS deficiency	PTPS	Autosomal recessive	<i>PTS</i>	261640
1.3.2	Mild/peripheral PTPS deficiency	PTPS	Normal CSF neurotransmitters Autosomal recessive	<i>PTS</i>	261640
1.4	Dihydropteridine reductase deficiency	DHPR	Autosomal recessive	<i>QDPR</i>	261630
1.5	Pterin-4α-carbinolamine dehydratase deficiency	PCD	Transient hyperphenylalaninemia Autosomal recessive	<i>PCD</i>	264070
1.6	Dopa-responsive dystonia/autosomal dominant GTPCH deficiency	DRD	Without hyperphenylalaninemia	<i>GCHI</i>	600225
1.7	Sepiapterin reductase deficiency	SR	Without hyperphenylalaninemia Autosomal recessive	<i>SPR</i>	182185

CSF cerebrospinal fluid

### 1.3 Treatment

#### ■ 1.1 PAH deficiency

##### ● 1.1.1 Classic phenylketonuria (PKU)

##### ● 1.1.2 Mild PKU

Age	Protein requirement (g/kg BW/day) <sup>a</sup>	Phe tolerance (mg/day)	Target blood Phe (μmol/l)			Phe-free AAM	
			Germany	UK	USA	Type	g/day <sup>b</sup>
0–3 months	2.3–2.1	~130–400	40–240	120–360	120–360	1	3–10
4–12 months	2.1–2.0	~130–400	40–240	120–360	120–360	1	3–10
1–2 years	1.7	~130–400	40–240	120–360	120–360	2	20–50
2–3 years	1.7	~200–400	40–240	120–360	120–360	2	20–50
4–6 years	1.6	~200–400	40–240	120–360	120–360	2	20–50
7–9 years	1.4	~200–400	40–240	120–480	120–360	2	20–50
10–12 years	1.1	~350–800	40–900	120–480	120–360	2	50–90
13–15 years	1.0	~350–800	40–900	120–700	120–600	2	50–90
Adolescents/adults	0.9	~450–1000	40–1200	120–700	120–900	3	60–150

AAM amino acid mixture

<sup>a</sup> DGE 1985; RDA; WHO protein requirement for PKU diet is assigned higher than recommendations for healthy people, because bioavailability of amino acids mixtures is equivalent to natural protein

<sup>b</sup> Spread as evenly as possible through the 24 h

##### ● 1.1.3 Non-PKU hyperphenylalaninemia (MHPA)

Treatment is only necessary for pregnant women with blood Phe levels > 250–360 mol/l (see disorder 1.1.4). Clinical monitoring of all patients with Phe > 360 mol/l is desirable.

##### ● 1.1.4 Tetrahydrobiopterin BH<sub>4</sub>-responsive PKU/HPA

There are no recommendations for the treatment of this group of HPA patients. The following table summarizes the current knowledge based on several experimental trials.

Age	Protein requirement (g/kg BW/day)	Phe tolerance (mg/day)	Target blood Phe (μmol/l)	mg BH <sub>4</sub> /kg BW <sup>a</sup>
All ages	See disorder 1.1.1	Near normal	See disorder 1.1.1	5–20

AAM amino acid mixture

<sup>a</sup> To be distributed over at least two doses; no long-term clinical experience; BH<sub>4</sub> tablets contain 100 mg ascorbic acid/100 mg BH<sub>4</sub>

● 1.1.5 Maternal PKU/HPA

Trimenon	Protein requirement (μmol/l)	Phe tolerance (mg/kg BW/day)	Target blood Phe (mg/day)	Phe-free AAM Type	g/day <sup>a</sup>
1	1.1	~180–1600	120–360	3	60–150
2–3	1.3–1.5	~180–1600	120–360	3	60–150

<sup>a</sup> Spread as evenly as possible over the 24 h

■ 1.2 GTP cyclohydrolase I deficiency

● 1.3.1 6-Pyruvoyl-tetrahydropterin synthase deficiency (severe form)

No.	Symbol	Age	Medication/diet	Dosage (mg/kg per day)	Dose/day (n)
1.2	GTPCH	Newborn	L-Dopa	1–3	3–6
1.3.1	PTPS (severe)		Carbidopa	10–20% <sup>a</sup>	3–6
			5-Hydroxytryptophan	1–2	3–6
			Tetrahydrobiopterin (BH <sub>4</sub> ) <sup>b</sup>	5–10	2
		< 1–2 years	L-Dopa	4–7	3–6
			Carbidopa	10–20% <sup>a</sup>	3–6
			5-Hydroxytryptophan	3–5	3–6
			Tetrahydrobiopterin (BH <sub>4</sub> ) <sup>b</sup>	5–10	2
		> 1–2 years	L-Dopa	8–15	3–6
			Carbidopa	10–20% <sup>a</sup>	3–6
			5-Hydroxytryptophan	6–9	3–6
			Tetrahydrobiopterin (BH <sub>4</sub> ) <sup>b</sup>	5–10	2

<sup>a</sup> Percentage of L-dopa

<sup>b</sup> BH<sub>4</sub> tablets contain 100 mg ascorbic acid/100 mg BH<sub>4</sub>

### Dangers/Pitfalls

1. Patients are on a unrestricted (i. e. protein-rich) diet.
2. BH<sub>4</sub> may significantly reduce plasma and CSF tyrosine levels. Consider nutrition and tyrosine supplementation.
3. L-Dopa/carbidopa/5-hydroxytryptophan therapy should be introduced slowly and increased in steps of not more than 1 mg/kg over days or weeks. 5-hydroxytryptophan may not be tolerated due to gastrointestinal side-effects; in these cases monotherapy with L-dopa/carbidopa may be sufficient.
4. L-Dopa/carbidopa/5-hydroxytryptophan therapy may reduce CSF folates (CH<sub>3</sub>-group trapping by L-dopa to 3-O-methyl-dopa). Determine 5-methyltetrahydrofolate in CSF. Consider folinic acid (5-formyltetrahydrofolate, Leucovorine) substitution (10–20 mg/day).
5. Drugs such as trimethoprim sulfamethoxazoles or methotrexate may induce hyperphenylalaninemia by inhibiting DHPR.

### ● 1.3.2 6-Pyruvoyl-tetrahydropterin synthase deficiency (mild form)

No.	Symbol	Age	Medication/diet	Dosage (mg/kg per day)	Dose/day (n)
1.3.2	PTPS (mild)	All ages	Tetrahydrobiopterin (BH <sub>4</sub> ) <sup>a</sup>	5–10	2

<sup>a</sup> BH<sub>4</sub> tablets contain 100 mg ascorbic acid/100 mg BH<sub>4</sub>

#### Dangers/Pitfalls

1. Patients are on an unrestricted (i. e. protein-rich) diet.
2. BH<sub>4</sub> may significantly reduce plasma and CSF tyrosine levels. Monitor and consider tyrosine supplementation.
3. Drugs such as trimethoprim sulfamethoxazoles or methotrexate may induce hyperphenylalaninemia by inhibiting DHPR.

### ■ 1.4 Dihydropteridine reductase deficiency

No.	Symbol	Age	Medication/diet	Dosage (mg/kg per day)	Dose/day (n)	
1.4	DHPR	Newborn	L-Dopa	1–3	3–6	
			Carbidopa	10–20% <sup>a</sup>	3–6	
			5-Hydroxytryptophan	1–2	3–6	
			Folinic acid	15–20 mg/day	1–2	
		< 1–2 years	Diet (see disorder 1.1, PKU)			
			L-Dopa	4–7	3–6	
			Carbidopa	10–20% <sup>a</sup>	3–6	
			5-Hydroxytryptophan	3–5	3–6	
		> 1–2 years	Folinic acid	15–20 mg/day	1–2	
			Diet (see disorder 1.1 PKU)			
			L-Dopa	8–15	3–6	
			Carbidopa	10–20% <sup>a</sup>	3–6	
	5-Hydroxytryptophan	6–9	3–6			
	Folinic acid	15–20 mg/day	1–2			
		Diet (see disorder 1.1 PKU)				

<sup>a</sup> Percentage of L-dopa

#### Dangers/Pitfalls

1. Patients are on a low-Phe diet (see disorder 1.1); however, blood Phe levels should be close to normal. These patients are more sensitive to high Phe levels than PKU.
2. L-Dopa/carbidopa/5-hydroxytryptophan therapy should be introduced slowly and increased in steps of not more than 1 mg/kg over days or weeks.
3. Drugs such as trimethoprim sulfamethoxazoles or methotrexate may induce hyperphenylalaninemia by inhibiting DHPR.

### ■ 1.5 Pterin-4 $\alpha$ -carbinolamine dehydratase deficiency

No.	Symbol	Age	Medication/diet	Dosage (mg/kg per day)	Dose/day ( <i>n</i> )
1.5	PCD	Newborn > 1 year	Tetrahydrobiopterin (BH <sub>4</sub> ) <sup>a</sup> No treatment	5–10	2

<sup>a</sup> BH<sub>4</sub> tablets contain 100 mg ascorbic acid/100 mg BH<sub>4</sub>

#### Dangers/Pitfalls

1. Patients are on an unrestricted (i. e., protein-rich) diet.
2. BH<sub>4</sub> may significantly reduce plasma and CSF tyrosine levels. Consider tyrosine supplementation.
3. Drugs such as trimethoprim sulfamethoxazoles or methotrexate may induce hyperphenylalaninemia by inhibiting DHPR.

### ■ 1.6 Dopa-responsive dystonia/autosomal dominant GTPCH deficiency

No.	Symbol	Age	Medication	Dosage (mg/kg per day)	Dose/day ( <i>n</i> )
1.6	DRD	Newborn	L-Dopa	1–3	3–4
			Carbidopa	10–20% <sup>a</sup>	3–4
		> 1 year	L-Dopa	4–12	3–4
			Carbidopa	10–20% <sup>a</sup>	3–4

<sup>a</sup> Percentage of L-dopa

#### Dangers/Pitfalls

1. L-Dopa/carbidopa therapy should be introduced slowly and increased in steps of not more than 1 mg/kg over days or weeks.

### ■ 1.7 Sepiapterin reductase deficiency

No.	Symbol	Age	Medication	Dosage (mg/kg per day)	Dose/day (n)
1.7	SR	Newborn	L-Dopa	1–3	3–4
			Carbidopa	10–20% <sup>a</sup>	3–4
			5-Hydroxytryptophan	1–2	3–4
		> 1 year	L-Dopa	4–10	3–4
			Carbidopa	10–20% <sup>a</sup>	3–4
			5-Hydroxytryptophan	3–9	3–4

<sup>a</sup> Percentage of L-dopa

#### Dangers/Pitfalls

1. L-Dopa/carbidopa/5-hydroxytryptophan therapy should be introduced slowly and increased in steps of not more than 1 mg/kg over days or weeks.
2. BH<sub>4</sub> supplementation may be considered.

### 1.4 Alternative Therapies/Experimental Trials

No.	Deficiency symbol	Age	Medication	Dosage (mg/kg/day)	Dose/day (n)
1.1.4	BH <sub>4</sub> -PKU	All ages	BH <sub>4</sub> <sup>a</sup>	5–20	2
1.2	GTPCH	All ages			
1.3.1	PTPS		Deprenyl <sup>b</sup>	0.1–0.3	3–4
1.4	DHPR		Entacapone <sup>c</sup>	~ 30	1–2
1.7	SR				

<sup>a</sup> Tetrahydrobiopterin (BH<sub>4</sub>) treatment has been recently introduced for children with phenylalanine hydroxylase deficiency who show a decrease in Phe levels after BH<sub>4</sub> loading (see disorder 1.1.4 in the Treatment section)

<sup>b</sup> MAO-B inhibitor (Selegiline)

<sup>c</sup> COMT inhibitor

#### Dangers/Pitfalls

1. Administration of MAO-B or COMT inhibitors allows a 30% reduction of the daily dosage of neurotransmitter precursors.

## 1.5 Follow-up/Monitoring

### ■ 1.1 PAH deficiency

Age	Biochemical monitoring (Phe and Tyr)	Clinical monitoring <sup>a</sup>	Intellectual and personality development
0–3 months	Weekly – Fortnightly	1–3 monthly	
4–12 months	Weekly – Fortnightly	1–3 monthly	Check
1–2 years	Weekly – Fortnightly	2–6 monthly	
2–3 years	Weekly – Fortnightly	2–6 monthly	Check
4–6 years	Fortnightly	3–6 monthly	Check
7–9 years	Fortnightly	6 monthly	
10–12 years	Monthly	6 monthly	Check
13–15 years	Monthly	6 monthly	Check
Adolescents/adults	Monthly – Bimonthly	6–12 monthly	Check
Maternal PKU	Weekly <sup>b</sup>	Bimonthly <sup>c</sup>	

<sup>a</sup> Nutrient intake, body growth, and general health. In general special Laboratory tests are not necessary. In patients with poor dietary and aminoacid mixture compliance B12 monitoring is necessary. After long term poor compliance or failure to thrive further tests may be necessary.

<sup>b</sup> Plasma amino acids (AA), albumin, cholesterol, ferritin, folate, vitamin B12

<sup>c</sup> Nutrient intake, including micronutrients, body growth, general health

### ■ 1.2–1.7 BH<sub>4</sub> deficiencies

Plasma Phe and Tyr are monitored in all forms of HPA; CSF investigations are only carried out in disorders affecting BH<sub>4</sub> metabolism with and without HPA (see disorders 1.2–1.7).

Test	Age	Frequency	Target values/levels
Phe and Tyr (blood)	1–3 years	Weekly to fortnightly	Phe levels: 40–360 µmol/l <sup>a</sup> (target value 360 µmol/l) Phe levels: 40–900 µmol/l <sup>a</sup> Phe levels: 40–1200 µmol/l <sup>a</sup>
	4–10 years	Fortnightly to monthly	
	11–16 years	Monthly	
	> 16 years	Every 2–3 months	
Neopterin	< 1 month	Fortnightly	Close to normal range
Biopterin	1 month to 1 year	Every 4–8 weeks	Close to normal range
5-HIAA	> 1 year	Monthly to yearly	Close to normal range
HVA			
Folates (CSF) <sup>b</sup>			

5-HIAA 5-hydroxyindoleacetic acid, HVA homovanillic acid

<sup>a</sup> In BH<sub>4</sub>-deficient patients, Phe levels should be close to 240–360 µmol/l at all ages

<sup>b</sup> Lumbar puncture in the morning before medication. Discard the first 0.5 ml and collect the next 1–2 ml (Storage: –80 °C)

## 1.6 Standard Protocol for Intercurrent Illness

- The best possible intake of fluid, carbohydrates, and Phe-free AAM.
- High-energy intake, low-phenylalanine regimen.

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