

Clinical approach to treatable inborn metabolic diseases: An introduction

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Summary In view of the major improvements in treatment, it has become increasingly important that in order for first-line physicians not to miss a treatable disorder they should be able to initiate a simple method of clinical screening, particularly in the emergency room. We present a simplified classification of treatable inborn errors of metabolism in three groups. *Group 1* includes inborn errors of intermediary metabolism that give rise to an acute or chronic intoxication. It encompasses aminoacidopathies, organic acidurias, urea cycle disorders, sugar intolerances, metal disorders and porphyrias. Clinical expression can be acute or systemic or can involve a specific organ, and can strike in the neonatal period or later and intermittently from infancy to late adulthood. Most of these disorders are treatable and require the emergency removal of the toxin by special diets, extracorporeal procedures, cleansing drugs or vitamins. *Group 2* includes inborn errors of intermediary metabolism that affect the cytoplasmic and mitochondrial energetic processes. Cytoplasmic

defects encompass those affecting glycolysis, glycogenesis, gluconeogenesis, hyperinsulinisms, and creatine and pentose phosphate pathways; the latter are untreatable. Mitochondrial defects include respiratory chain disorders, and Krebs cycle and pyruvate oxidation defects, mostly untreatable, and disorders of fatty acid oxidation and ketone bodies that are treatable. *Group 3* involves cellular organelles and includes lysosomal, peroxisomal, glycosylation, and cholesterol synthesis defects. Among these, some lysosomal disorders can be efficiently treated by enzyme replacement or substrate reduction therapies. Physicians can be faced with the possibility of a treatable inborn error in an emergency, either in the neonatal period or late in infancy to adulthood, or as chronic and progressive symptoms – general (failure to thrive), neurological, or specific for various organs or systems. These symptoms are summarized in four tables. In addition, an extensive list of medications used in the treatment of inborn errors is presented.

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Abbreviations

3PGD	3-phosphoglycerate dehydrogenase
BCAA	branched-chain amino acid
BRBGD	biotin-responsive basal ganglia disease
Cbl	cobalamin
CDG	congenital disorder of glycosylation
CPT I	carnitine palmitoyltransferase type I
CPT II	carnitine palmitoyltransferase type II
CTX	cerebrotendinous xanthomatosis
FAO	fatty acid oxidation
GTP	guanosine triphosphate
HELLP	haemolysis, elevated liver function, low platelets
HFI	hereditary fructose intolerance
IE	inborn error
IEM	inborn error of metabolism

LPI	lysineric protein intolerance
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A
IVA	isovaleric acidaemia
LCHADD	long-chain 3-hydroxy-acyl-CoA dehydrogenase deficiency
MCD	multiple carboxylase deficiency
MMA	methylmalonic acidaemia
MSUD	maple syrup urine disease
MTHFR	methylene tetrahydrofolate reductase
OA	organic aciduria
OTC	ornithine transcarbamylase
PA	propionic acidaemia
PC	pyruvate carboxylase
PDH	pyruvate dehydrogenase
PKU	phenylketonuria
PNPO	pyridox(am)ine-5'-phosphate oxidase
PTP	6-pyruvoyltetrahydropterin synthase
TFP	trifunctional protein
TH	tyrosine hydroxylase
TL	carnitine acyltranslocase
UCD	urea cycle disorders
VLCADD	very long-chain acyl-CoA dehydrogenase deficiency

Introduction

Some 50 years after the first nutritional treatment of phenylketonuria (PKU) and 30 years after the publication of the first book entirely devoted to the treatment of inborn errors of metabolism (IEMs) (Raine 1975), we felt that this was an appropriate time to choose 'Treatment of Inborn Errors of Metabolism' as the main theme for the 42nd Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, held in Paris in September 2005. During the last half century, many new disorders have been discovered and many therapeutic procedures have been tried. Some of these are well established and life-saving; others are still experimental. The long-term outcome of our oldest patients, who have already reached adulthood, must question our methods for diagnosis, management and treatment. The new field of adult metabolic medicine also raises many new therapeutic problems, including the management of pregnancy in affected mothers. Finally, our technical ability to undertake systematic neonatal screening for many metabolic disorders raises a number of ethical issues.

This special issue of the Journal gathers original papers and reviews on the diverse aspects of treatment that were presented at the Paris Symposium. We largely focused on diseases in which treatment is both well tried and successful. This issue contains a great deal of specialist information, but it also shows how the paediatrician and various adult physicians with little experience of these individually uncommon

diseases can cooperate with special centres. Given these very important instances of therapeutic progress, it becomes ever more important to initiate a simple method of clinical screening by the first-line physicians with the goal 'Do not miss a treatable disorder', in particular in the emergency room.

Classification of inborn errors

Pathophysiology

From a therapeutic perspective, metabolic disorders can be divided into the following three useful groups.

Group 1: Disorders that give rise to intoxication

This group includes inborn errors of intermediary metabolism that lead to an acute or progressive intoxication from the accumulation of toxic compounds proximal to the metabolic block. In this group are the inborn errors of amino acid catabolism (phenylketonuria, maple syrup urine disease, homocystinuria, tyrosinaemia, etc.), most organic acidurias (methylmalonic, propionic, isovaleric, etc.), congenital urea cycle defects, sugar intolerances (galactosaemia, hereditary fructose intolerance), metal intoxication (Wilson disease, Menkes disease, haemochromatosis), and porphyrias. All the conditions in this group share clinical similarities: they do not interfere with the embryofetal development and they present with a symptom-free interval and clinical signs of 'intoxication', which may be acute (vomiting, coma, liver failure, thromboembolic complications) or chronic (failure to thrive, developmental delay, ectopia lentis, cardiomyopathy). Circumstances that can provoke acute metabolic attacks include catabolism, fever, intercurrent illness and food intake. Clinical expression is often both late in onset and intermittent. Most of these disorders are treatable and require the emergency removal of the toxin by special diets, extracorporeal procedures or 'cleansing' drugs (carnitine, sodium benzoate, penicillamine, vitamins, etc.). Nutritional therapy is the backbone of the treatment in this group. It includes approaches to deplete the toxic substrate that accumulates or to replace the crucial metabolic product that is deficient. Breast milk can still play an important role in these special diets. The long-term consequences of artificial diets on the offspring will have to be evaluated particularly as regards possible mechanisms of metabolic imprinting (Junien 2006, this issue). Strategies to decrease the concentration of toxic substrates or their precursors also involve the administration of a variety of cleansing drugs that bind the accumulated metabolites and allow their excretion. Pharmacological doses of vitamins have also shown remarkable efficiency in vitamin-responsive disorders.

Table 1 Treatable IEMs presenting in neonates and infants <3 months

Main clinical presentation	Presenting sign	Treatable metabolic disease
Neurological	Metabolic encephalopathy (coma, abnormal movements)	BCAA disorders (MSUD, MMA, PA, IVA, MCD) Glutaric aciduria type II, UCD, Triple H
	Seizures	B ₆ -responsive seizures PNPO MCD Folinic acid-responsive seizures
Hepatic	Seizures + microcephaly	Congenital magnesium malabsorption 3PGD, cerebral glucose carrier: GLUTI
	Liver failure	Galactosaemia Hereditary fructose intolerance Tyrosinaemia type I CDG Ib (phosphomannoisomerase)
Cardiac	Jaundice, cholestasis	Galactosaemia LCHADD Bile acid synthesis defects Cerebrotendinous xanthomatosis
	Hepatosplenomegaly	Congenital erythropoietic porphyria Long-chain FAO defects
Severe hypoglycaemia	Cardiac failure	(CPT II deficiency, VLCADD, LCHADD, TFP deficiency, TL deficiency)
	Cardiomyopathy	Glycogenosis type I/III Fructose biphosphatase deficiency
Severe hypoglycaemia	Heart beat disorders	Congenital hyperinsulinism
	Hepatomegaly	FAO defects Carnitine uptake defect

Although the pathophysiology is somewhat different, the inborn errors of neurotransmitter synthesis and catabolism (monoamines, GABA and glycine) and the inborn errors of amino acid synthesis (serine, glutamine, and proline/ornithine) can also be included in this group since they share many characteristics: they are inborn errors of intermediary metabolism, their diagnosis relies on plasma, urine and CSF investigations (amino acids, organic acid analyses, etc.), and some are amenable to treatment even when the disorder starts *in utero*, for example 3-phosphoglycerate dehydrogenase deficiency (de Koning 2006, this issue). These various aspects of the nutritional treatment are presented in the first part of this issue.

Group 2: Disorders involving energy metabolism

These consists of inborn errors of intermediary metabolism with symptoms due at least partly to a deficiency in energy production or utilization within liver, myocardium, muscle, brain or other tissues. This group can be divided into mitochondrial and cytoplasmic energy defects. Mitochondrial defects are the most severe. They encompass the congenital lactic acidemias (defects of pyruvate transporter, pyruvate carboxylase (PC), pyruvate dehydrogenase (PDH), and the

Krebs cycle), and mitochondrial respiratory chain disorders, which are in general not amenable to treatment with the exception of coenzyme Q₁₀ synthesis defect (Quinzii et al 2006), PDH and PC deficiency (Roe and Mochel 2006, this issue), and the fatty acid oxidation and ketone body defects, which are partly treatable. Cytoplasmic energy defects are generally less severe. They include disorders of glycolysis, glycogen metabolism and gluconeogenesis, hyperinsulinism (all treatable disorders), the more recently described disorders of creatine metabolism (partly treatable), and the new inborn errors of the pentose phosphate pathways (untreatable). Some of the mitochondrial disorders and pentose phosphate pathway defects can interfere with the embryofetal development and give rise to dysmorphism, dysplasia and malformations (Valayannopoulos et al 2006; Van Spronsen et al 2005).

Group 3: Disorders involving complex molecules

This group involves cellular organelles and includes diseases that disturb the synthesis or the catabolism of complex molecules. Symptoms are permanent, progressive, independent of intercurrent events and unrelated to food intake. All lysosomal storage disorders, peroxisomal disorders, disorders of intracellular trafficking and process-

Table 2 Late-onset (late infancy to adulthood) recurrent comas, ataxia, psychiatric signs

Main clinical presentation	Other important signs	Treatable metabolic disease
Metabolic coma without focal neurological signs Acute ataxia with lethargy	Acidosis	Multiple carboxylase deficiency Organic acidurias, MSUD Ketolysis, ketogenesis defects FAO disorders Fructose bisphosphatase deficiency PDH deficiency
	Hyperammonaemia	Urea cycle disorders, Triple H Lysinuric protein intolerance FAO defects HMGCoA lyase deficiency
	Hypoglycaemia	Gluconeogenesis defects Glycogen synthetase deficiency HMGCoA lyase/synthetase deficiency FAO defects
	Hyperlactacidaemia	Multiple carboxylase deficiency PDH deficiency Gluconeogenesis defects FAO defects
Neurological coma with focal signs, seizures, or intracranial hypertension	Cerebral oedema	MSUD OTC deficiency Organic acidurias
	Extrapyramidal signs (dystonia, Parkinson)	Glutaric aciduria type I MMA Wilson disease Homocystinuria BRBGD
	Stroke-like	UCD Organic acidurias Homocystinurias B ₁ -responsive macrocytic megaloblastic anemias Fabry disease
Hepatic coma Cytolysis Reye syndrome	Thromboembolic accidents Hyperammonaemia, lactic acidosis	Homocystinurias (all types) FAO defects UCD
	Haemolytic jaundice Enteropathy, hypoglycaemia Hyperammonaemia	Wilson disease CDG Ib UCD
Psychiatric symptoms, hallucinations, delirium	Ketoacidosis	Lysinuric protein intolerance Organic acid disorders
	Hyperhomocysteinaemia	MTHFR deficiency, CblC deficiency
	Portwine urine	Acute intermittent porphyria Hereditary coproporphyria

ing such as α_1 -antitrypsin, carbohydrate deficient glycoprotein (CDG) syndrome, and inborn errors of cholesterol synthesis belong to this group. For many years, none was treatable. In the last decade however, efficient enzyme replacement therapy has become available for several lysosomal disorders such as Gaucher and Fabry diseases.

Various cell and organ transplantation strategies have been also developed for certain disorders, some of them successful, but many others are still experimental or under evaluation. Finally, besides gene therapy, new therapeutic

approaches such as chaperon therapy appear promising but currently remain mostly inaccessible in clinical practice. All these aspects of treatment are presented in the second part of this issue.

Clinical presentation

Besides newborn screening in the general population (as for phenylketonuria) or in at-risk families, there are four groups

Table 3 Neurological symptoms

Presenting or predominant symptom	Other accompanying signs	Treatable metabolic disease
Dystonia Parkinsonism	Isolated	Homocystinuria, PKU GTP cyclohydrolase deficiency PTP synthase deficiency Sepiapterin reductase deficiency TH deficiency
	Basal ganglia involvement	BRBGD, PDH deficiency, Wilson disease, CTX, glutaric aciduria type I
	Bitemporal atrophy	Glutaric aciduria type I
	Spastic (or pseudo-spastic) paraparesia	GTP cyclohydrolase deficiency TH deficiency, homocystinuria CTX, cerebral folate deficiency
	Polyneuropathy	PDH deficiency, CTX, homocystinurias
	Psychiatric signs	Homocystinurias, Wilson disease, CTX, PKU, PDH deficiency
Polyneuropathy	Acute attacks	Nonketotic hyperglycinaemia, PTP deficiency, PDH deficiency, BRBGD
	Isolated	PDH deficiency, Refsum disease, CTX, TFP deficiency, MTHFR deficiency, serine deficiency
	Ataxia	PDH deficiency, cerebral folate deficiency, Refsum, disease, CTX, vitamin E deficiency, abetalipoproteinaemia
	Exercise intolerance Recurrent attacks	LCHADD, TFP deficiency Porphyria, tyrosinaemia type I, Refsum disease, PDH deficiency
Spastic paraplegia (and pseudo-spastic)	Isolated	PKU, cerebral folate deficiency, TH deficiency, arginase deficiency, GTP cyclohydrolase deficiency
	Extrapyramidal signs	Cerebral folate deficiency, GTP cyclohydrolase deficiency, TH deficiency, CTX, homocystinurias
	Polyneuropathy	CTX, MTHFR deficiency, Cbl synthesis defects, cerebral folate deficiency
Ataxia	Recurrent attacks	Arginase deficiency, Triple H
	Isolated	PDH deficiency, coenzyme Q ₁₀ deficiency
	Spastic paraparesis	CTX, nonketotic hyperglycinaemia, vitamin E deficiency
Psychiatric signs	Dystonia/parkinsonism Recurrent attacks	CTX, PDH deficiency, Cbl synthesis defects CTX, UCD
	Isolated	Cbl synthesis defects, MTHFR deficiency, PKU, Homocystinuria, Wilson disease, CTX
	Leukodystrophy	Cbl synthesis defects, MTHFR deficiency, PKU, CTX
Psychiatric signs	Recurrent attacks	UCD, PDH deficiency, Cbl synthesis defects, porphyrias
	Progressive	Wilson disease, CTX

of clinical circumstances in which physicians are faced with the possibility of a metabolic disorder:

- Early symptoms in the antenatal and neonatal period
- Later-onset acute and recurrent attacks of symptoms such as coma, ataxia, vomiting and acidosis
- Chronic and progressive symptoms which can be general (failure to thrive), muscular or neurological (developmental delay, neurological deterioration, psychiatric signs)
- Specific and permanent adverse effects on various organ or systems

Table 4 Acute or progressive general symptoms

Symptom groups	Presenting sign	Treatable metabolic disease
Cardiac	Cardiomyopathy Heart beat disorders	Carnitine uptake (major sign), FAO defects, Fabry disease, thiamin deficiency
Dermatology	Alopecia Hyperkeratosis (palmoplantar) Ichthyosis Skin rashes	MCD, porphyria, calciferol defects Tyrosinaemia type II (major sign) Serine deficiency syndrome Porphyrias, Hartnup disease
Gastroenterology	Abdominal pain HELLP syndrome	OTC deficiency, porphyrias, organic acidurias, tyrosinaemia type I, LPI, Fabry disease CPT I deficiency, LCHADD
Haematology	Macrocytic anaemias	Hereditary orotic aciduria Cbl metabolism Congenital folate malabsorption Thiamin-responsive anaemia
Hepatic	Pancytopenia Liver failure	Gaucher disease type I, glycoconosis type Ib, Cbl and folate metabolism, LPI, organic acidurias See Tables 1 and 2
Immune system	Macrophage activating syndrome	Gaucher disease, LPI, propionic acidemia
Myology	Exercise intolerance	FAO defects (CPT II deficiency, VLCADD, LCHADD, TL deficiency, TFP deficiency), hyperkalaemic paralysis
Nephrology	Haemolytic uraemic syndrome Nephrolithiasis	Cobalamin deficiencies (CblC, CblG) Cystinuria, oxalurias, xanthine oxidase deficiency (major sign)
Ophthalmology	Tubulopathy Cataracts Corneal opacities Keratitis	HFI, galactosaemia, tyrosinaemia type I, cystinosis (major sign) Galactosaemias, LPI, Wilson disease, CTX, Fabry disease, homocystinurias Cystinosis (major sign), Fabry disease, Wilson disease
Pneumology	Ectopia lentis	Tyrosinaemia type II (major sign)
Osteology	Pneumopathy (interstitial) Bone crisis	Homocystinurias (major sign) Gaucher disease, LPI
Stomatology	Glossitis Stomatitis	Calciferol metabolism, rickets, porphyrias, tyrosinaemia type I, Gaucher disease, Fabry disease (major sign) Cobalamin metabolism
Vascular symptoms	Raynaud syndrome Thromboembolic accidents (see also Table 2)	Folate malabsorption Fabry disease (major sign) Homocystinurias, Fabry disease (major sign)

Table 5 Medications used in the treatment of inherited metabolic disease^a

Medication	Mode of action	Disorders	Recommended dose	Route	Remarks
Agalsidase alfa	Recombinant analogue of human α -galactosidase A manufactured by gene activation in human fibroblast cell line	Fabry disease	0.2 mg/kg per 2 weeks	I. v.	
Agalsidase beta	Recombinant analogue of human α -galactosidase A manufactured in Chinese hamster ovary (CHO) cell line	Fabry disease	1.0 mg/kg per 2 weeks	I. v.	
Allopurinol	Xanthine-oxidase inhibitor	Disorders leading to hyperuricaemia (PRPP synthetase superactivity; deficiency) and APRT deficiency	Initial dosage 10–20 mg/kg per day in children and 2–10 mg/kg per day in adults	Oral	Reduce dose in hepatic and renal impairment
Ammonium tetrathiomolybdate	Chelating agent	Wilson disease	160 mg/day in 6 divided doses	Oral	
Betaine	Remethylates Hct to Meth	Classical homocystinuria	100–150 mg/kg per day in 2–3 divided doses, max. dose 6–9 g/day	Oral	
Biotin	Co-factor for carboxylases	Remethylation defects	5–20 mg/day	Oral or i. v.	
	Treatment of presumed transporter defect (Zeng et al 2005)	Biotinidase deficiency Multiple carboxylase deficiency Biotin-responsive basal ganglia disease			
Chenodeoxycholic acid	Inhibits cholesterol 7 α -hydroxylase (rate-limiting enzyme in bile acid biosynthesis)	3 β -dehydrogenase deficiency (3 β DD); Δ^4 -3-oxosteroid 5 β -reductase deficiency (3-ORD); cerebrotendinous xanthomatosis (CTX)	3 β -DD: 12–18 mg/kg per day for 1st 2 months then 9–12 mg/kg per day; 3-ORD: 8 mg/kg per day; CTX: 750 mg/day (adults)	Oral	
Cholesterol	Replenishes cholesterol	Smith–Lemli–Opitz syndrome (SLO)	20–40 mg/kg per day in 3–4 divided doses	Oral	
Cholestyramine	Bile acid sequestrant	Familial hypercholesterolaemia	Adults: 12–24 g/day Children: (weight in kg/70 \times adult dose) in 4 divided doses	Oral	Possible vitamin A, D, and K deficiency with prolonged treatment. Other bile acid resins include colestipol and colesevalam
Cholic acid		Δ^4 -3-Oxosteroid 5 β -reductase deficiency (3-ORD)	8 mg/kg per day	Oral	

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Table 5 (Continued)

Medication	Mode of action	Disorders	Recommended dose	Route	Remarks
Copper histidine	Increases intracellular copper	Menkes disease	100–200 µg Cu/day (newborn) 1 mg Cu/day in older children	i.m. s.c.	
Creatine monohydrate	Replenishes creatine	Guanidinoacetate methyltransferase (GAMT) deficiency arginine:glycine amidinotransferase (AGAT) deficiency	300–400 mg/kg per day in 3–6 divided doses	Oral	
Cysteamine/ phosphocysteamine	Depletes lysosomal cystine	Cystinosis	1.3 g/m ² per day of free-base), given every 6 h	Oral and eye drops	Phosphocysteamine more palatable
Dextromethorphan	NMDA channel antagonist	NKH	5–7 mg/kg per day in 4 divided doses	Oral	Doses up to 35 mg/day have been used
Diazoxide	Inhibits insulin secretion	Persistent hyperinsulinism	15 mg/kg per day (newborn), 10 mg/kg per day (infants), in 3 divided doses	Oral	
Dichloroacetate	Stimulates PDH activity by inhibiting PDH kinase	Primary lactic acidosis	50 mg/kg per day in 3–4 divided doses	Oral	May cause polyneuropathy with prolonged use
Entacapone	Prevents the peripheral breakdown of L-dopa	Disorders of BH ₄ synthesis	15 mg/kg per day in 2–3 divided doses	Oral	
Ezetimibe	Inhibits cholesterol absorption	Familial hypercholesterolaemia	10 mg per day	Oral	
Folinic acid	Provides accessible source of folate for CNS	DHPR deficiency UMP synthase deficiency (hereditary orotic aciduria) Methylene synthase deficiency Methionine synthase deficiency Hereditary folate malabsorption Some disorders of cobalamin metabolism	5–15 mg per day	Oral, i.v.	
Galsulfase	Recombinant analogue of human N-acetylgalactosamine 4-sulphatase manufactured in Chinese hamster ovary (CHO) cell line	Cerebral folate transporter Mucopolysaccharidosis type VI	1.0 mg/kg per week	I.v.	FDA approval 1 June 2005

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Table 5 (Continued)

Medication	Mode of action	Disorders	Recommended dose	Route	Remarks
Gemfibrozil	Fibrates decrease TG levels; other fibrates include bezafibrate and fenofibrate	Mixed or combined hyperlipidaemia	Adult dose: 1.2 g daily, usually in 2 divided doses; range 0.9–1.5 g daily	Oral	Can cause a myositis-like syndrome, especially with impaired renal function; combination with a statin increases risk of rhabdomyolysis
G-CSF	Stimulates granulocyte production	Neutropenia in GSD Ib, Ic	5 µg/kg once daily	s.c.	
Glycine	Forms isovalerylglycine with high renal clearance	Isovaleric acidemia	150 mg/kg per day in 3 divided doses	Oral	Up to 600 mg/kg per day during decompensation
Haem arginate	Inhibits 5-aminolevulinic acid synthase	Acute porphyrias	3–4 mg/kg once daily for 4 days	I.v.	
Hydroxycobalamin (B ₁₂)	Co-factor for methylmalonyl mutase	Disorders of cobalamin metabolism	1 mg i.m. daily; oral dose 10 mg once or twice daily	i.m. or oral	Dose may be reduced to once or twice weekly according to response
5-Hydroxytryptophan	Neurotransmitter replacement	Disorders of neurotransmitter synthesis	1–2 mg/kg increasing gradually to 8–10 mg/kg in 4 divided doses	Oral	Monitor CSF 5HIAA levels
Imiglucerase	Recombinant analogue of human β-glucocerebrosidase manufactured in Chinese hamster ovary (CHO) line	Gaucher disease	Various regimens: 2.5 U/kg 3 × per week to 60 U/kg per 2 weeks for type III Gaucher disease some clinicians recommend higher dosages: 120 U/kg per 2 weeks	I.v.	
Ketamine	NDMA channel antagonist	NKH	1–30 mg/kg per day in 4 divided doses	Oral or i.v.	
L-Arginine	Replenishes arginine; substrate of nitrous oxide	Urea cycle disorders; MELAS (Koga et al 2005)	50–170 mg/kg (OCT and CPS deficiency) up to 700 mg/kg in AL and AS deficiency	Oral or i.v.	I.v. loading dose: (200 mg/kg) over 90 min
Laronidase	Recombinant analogue of human α-L-iduronidase manufactured in CHO cell line	Mucopolysaccharidosis type I	100 U/kg per week	I.v.	

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Table 5 (Continued)

Medication	Mode of action	Disorders	Recommended dose	Route	Remarks
L-Carnitine	Replenishes body stores; removes toxic acyl-CoA intermediates from within the mitochondria	Primary and secondary carnitine deficiencies	100–200 mg/kg per day	Oral or i.v.	Do not use racemic mixture
L-Citrulline	Replenishes citrulline and arginine	Used as an alternative to arginine in CPS deficiency and OTC deficiency; LPI	CPS and OTC deficiency: 170 mg/kg per day or 3.8 gm/m ² /day in divided doses, LPI: 100 mg/kg per day in 3–5 doses	Oral	
L-Dopa	Replacement of neurotransmitters	Disorders of L-dopa synthesis	1–2 mg/kg increasing slowly to 10–12 mg/kg in 4 divided doses	Oral	Give as L-dopa/carbidopa (1:10 or 1:5) monitor CSF HVA levels
L-lysine-HCl	Allows lysine absorption	Lysinuric Protein Intolerance	20–30 mg/kg per day in 3 divided doses	Oral	
L-Serine	Replenishes serine	3-Phosphoglycerate dehydrogenase deficiency	Up to 600 mg per day in 6 divided doses	Oral	
L-Tryptophan	Increases kynurenic acid which is an endogenous antagonist of the NMDA receptor	NKH	100 mg/kg per day in 3 divided doses	Oral	
Magnesium (Mg)	Replenishes Mg	Primary hypomagnesaemia with secondary hypocalcaemia	0.5–1.5 ml/kg per day MgSO ₄ 10% solution i.v.; oral maintenance 0.7–3.5 mmol/kg per day elemental Mg in 3–5 divided doses	I.v./oral	
Mannose	Improves glycosylation	CDG Ib (PMI deficiency)	1 g/kg per day in 5 divided doses	Oral	Not of proven benefit in CDG Ia (Kjaergaard et al 1998; Mayatepek et al 1997)
Mercaptopropionylglycine	Chelating agent	Cystinuria	15–20 mg/kg per day, up to max. of 1000 mg per day in 3 divided doses	Oral	
Metronidazole	Reduces propionate production by gut bacteria	Propionic and methylmalonic acidaemia	7.5 mg three times a day	Oral	
Miglustat	Inhibitor of glucosylceramide synthase, the first enzyme responsible for glycosphingolipid (GSL) synthesis	Gaucher disease	100 mgs t.d.s.	Oral	Only recommended for patients with mild to moderate Gaucher disease who are unsuitable for enzyme replacement therapy

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Table 5 (Continued)

Medication	Mode of action	Disorders	Recommended dose	Route	Remarks
<i>N</i> -Carbamoylglutamate	Stimulates <i>N</i> -acetylglutamate synthase	<i>N</i> -Acetylglutamate synthase deficiency Carbamoylphosphate synthase deficiency	100–300 mg/kg per day in 4 divided doses	Oral	
Nicotinamide	Replenishes deficiency state	Hartnup disease	50–300 mg/day	Oral	
Nicotinic acid	Inhibits the release of free fatty acids from adipose tissue; increases HDL-cholesterol	Hyperlipidaemia	Adult dose: 100–200 mg 3 times daily, gradually increased over 2–4 weeks to 1–2 g 3 times daily	Oral	
NTBC	Inhibits 4-hydroxyphenylpyruvate dioxygenase	Tyrosinaemia type I	1 mg/kg in 1–2 divided doses	Oral	Combine with low-tyrosine, low-phenylalanine diet to maintain plasma Tyr <600 µmol/L
Octreotide	Somatostatin analogue	Persistent hyperinsulinism	10 µg/day to 60 µg/day, given in 3 or 4 divided doses or by continuous pump	S.c.	
Pantothenic acid	Source of coenzyme A	Type II 3-methylglutaconic aciduria	15–150 mg per day in 3 divided doses		See Ostman-Smith et al (1994)
Penicillamine	Chelating agent	Wilson disease; cystinuria	Wilson disease: up to 20 mg/kg per day in divided doses (min. 500 mg/day) Cystinuria: 2 g/L per 73m ²	Oral	
Pyridoxine	Co-factor	Pyridoxine-responsive γ-cystathionase deficiency; pyridoxine responsive cystathionine β-synthase (CBS) deficiency; pyridoxine dependency with seizures; pyridoxine responsive OAT deficiency; X-linked sideroblastic anaemia; primary hyperoxaluria type I	50–500 mg per day Pyridoxine dependency with seizures: 100 mg i.v. with EEG monitoring or 30 mg/kg per day for 7 days (maintenance 5–10 mg per day)	Oral	Peripheral neuropathy can occur with doses >1000 mg daily
Pyridoxal phosphate	Active co-factor	Pyridox(am)line 5'-phosphate oxidase deficiency	40 mg/kg per day in 4 divided doses	Oral	
Riboflavin	Co-enzyme	Glutaric aciduria I, mild variants of ETF/ETF-DH and SCAD; congenital lactic acidosis (complex I deficiency)	100 mg per day in 2–3 divided doses	Oral	
Selegiline	Monoamine-oxidase B inhibitor	As adjunct to therapy with 5HT and L-dopa in BH ₄ defects	0.1–0.25 mg per day in 3–4 divided doses	Oral	

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Table 5 (Continued)

Medication	Mode of action	Disorders	Recommended dose	Route	Remarks
Statins	HMG-CoA reductase inhibitors	Hyperlipidaemias Simvastatin has been used experimentally in SLO		Oral	
Sodium benzoate	Combines with glycine to form hippuric acid which has high renal clearance	Hyperammonaemia	250 mg per day in divided doses or by continuous i.v. infusion	Oral or i.v.	I.v. loading dose: 250 mg/kg over 90 min
Sodium phenylbutyrate	Removes N ₂ to ammonia and reduces blood ammonia Converted to phenylacetate, which combines with glutamine to form phenylglutamine which has high renal clearance	Hyperammonaemia	Dose may be doubled if severe hyperammonaemia 250–650 mg/kg per day; maxi. oral dose 20 g/day	Oral or i.v.	
Tetrahydrobiopterin (BH ₄)	Replacement of BH ₄	Disorders of BH ₄ synthesis or recycling; BH ₄ -responsive forms of PAH deficiency	1–3 mg/kg per day in BH ₄ defects; 7–20 mg/kg per day in PAH deficiency	Oral	May be contraindicated in DHPR deficiency
Thiamin	Co-factor	Thiamin responsive variants of MSUD, PDH deficiency and complex I deficiency	10–15 mg per day	Oral	Doses of up to 300 mg have been used in CLA; 500–2000 mg per day in thiamin-responsive PDH?
Triethylenetetramine	Chelating agent	Wilson disease	600 mg per day in divided doses increasing to a maximum of 2.4 g/day if necessary	Oral	May reduce serum iron Iron supplements may be necessary
Triheptanoin	Anaplerotic substrate	VLCADD; PC deficiency	To provide 30% of total energy	Oral	

(Continued on next page)

Table 5 *Continued*

Medication	Mode of action	Disorders	Recommended dose	Route	Remarks
Ubiquinone (co-enzyme Q ₁₀)		Inborn errors of CoQ ₁₀ synthesis	100–300 mg per day	Oral	Has been used in other mitochondrial cytopathies but of unproven benefit
Uridine	Replenishes UMP	UMP synthase deficiency (hereditary orotic aciduria)	100–150 mg/kg per day in divided doses	Oral	
Vigabatrin	Irreversible inhibitor of GABA transaminase	Succinic semialdehyde dehydrogenase deficiency	50–100 mg/kg per day in 2 divided doses	Oral	Monitor carefully: increases CSF GABA levels and irreversible visual field deficits possible
Vitamin A	Free radical scavenger	Glutathione synthetase deficiency	100 mg/kg per day	Oral	
Vitamin C	Co-factor; antioxidant	Hawkinsinuria Tyrosinaemia III (4 hydroxyphenylpyruvate dioxygenase deficiency) Transient tyrosinaemia of the newborn	200–1000 mg per day	Oral	
Vitamin E (α-tocopherol)	Replenishes vitamin E stores; free radical scavenger	Glutathione synthase deficiency Abetalipoproteinaemia	10 mg/kg per day	Oral	
Zinc sulphate	Increases Zn, impairs Cu absorption	Glutathione synthetase deficiency Acrodermatitis enteropathica (AE); Wilson disease	100 mg/kg per day AE: 30–100 mg Zn/day; Wilson disease: 600 mg per day (initial adult dose), 300 mg per day (maintenance adult dose). Give in 3–4 divided doses	Oral	

^a Adapted from Walter and Wraith (2006).

Abbreviations: See list of abbreviations. Also: 5HT, 5-hydroxytryptophan; AL, agininosuccinate lyase; APRT, adenine phosphoribosyl-transferase; AS, argininosuccinate synthase; CLA, congenital lactic acidosis; CPS, carbamoyl phosphate synthase, DHPR, dihydropteridine reductase; ETF, electron transfer flavoprotein; ETF-DH, electron transfer flavoprotein dehydrogenase; GABA, gamma aminobutyric acid; Hct, homocysteine; HDL, high density lipoprotein; HVA, homovanillic acid; MELAS, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; Meth, methionine; NKH, non-ketotic hyperglycinaemia; NMDA, *N*-methyl-D-aspartate; NTBC, (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione); OAT, ornithine aminotransferase; PAH, phenylalanine hydroxylase; PMI, phosphomannose isomerase; PRPP, phosphoribosylpyrophosphate; SCAD, short chain acyl CoA dehydrogenase; SLO, Smith-Lemli-Opitz; TG, triglyceride; UMP, uridine monophosphate

The first two categories often present as treatable emergencies, either in the neonatal period (Table 1) or late in infancy to adulthood (Table 2). The main chronic or progressive symptoms and signs that raise suspicion of a treatable IEM are listed in Table 3 (neurological symptoms) and Table 4 (other organ/system symptoms). Of course these tables are not exhaustive and are mostly based on the personal experience of the authors (Saudubray et al 2006). They should be supplemented by readers.

Medications used in the treatment of IEMS (Table 5)

Readers should consult relevant pharmacopoeias for additional details, particularly as regards side-effects and contraindications (for example, BNF for children www.bnfc.org).

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