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Clinical approach to treatable inborn metabolic diseases: An introduction

J.-M. Saudubray · F. Sedel · J. H. Walter

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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 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, glycogenosis, 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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J.-M. Saudubray (✉)
Centre de Référence des Maladies Héréditaires du Métabolisme, Hôpital Necker Enfants-Malades, Université René Descartes, 149 rue de Sèvres, 75743 Paris Cedex 15, France
e-mail: elisabeth.saudubray@nck.ap-hop-paris.fr

F. Sedel
Fédération des Maladies du Système Nerveux, Hôpital Pitié-Salpétrière, AP-HP, Paris, France

J. H. Walter
Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Manchester, UK

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	lysinuric 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
		Congenital magnesium malabsorption
	Seizures + microcephaly	3PGD, cerebral glucose carrier: GLUTI
Hepatic	Liver failure	Galactosaemia
		Hereditary fructose intolerance
		Tyrosinaemia type I
		CDG Ib (phosphomannoisomerase)
	Jaundice, cholestasis	Galactosaemia
		LCHADD
		Bile acid synthesis defects
		Cerebrotendinous xanthomatosis
	Hepatosplenomegaly	Congenital erythropoietic porphyria
Cardiac	Cardiac failure	Long-chain FAO defects
	Cardiomyopathy	(CPT II deficiency, VLCADD, LCHADD, TFP deficiency, TL deficiency)
	Heart beat disorders	
Severe hypoglycaemia	Hepatomegaly	Glycogenosis type I/III
		Fructose bisphosphatase deficiency
	High glucose infusion rate	Congenital hyperinsulinism
	Cardiac/liver involvement	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 acidaemias (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 Q_{10} 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	Acidosis	Multiple carboxylase deficiency
		Organic acidurias, MSUD
Acute ataxia with lethargy		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
	Thromboembolic accidents	Homocystinurias (all types)
Hepatic coma	Hyperammonaemia, lactic acidosis	FAO defects
Cytolysis		UCD
Reye syndrome	Haemolytic jaundice	Wilson disease
	Enteropathy, hypoglycaemia	CDG Ib
Psychiatric symptoms, hallucinations, delirium	Hyperammonaemia	UCD
		Lysinuric protein intolerance
	Ketoacidosis	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
	Acute attacks	Nonketotic hyperglycinaemia, PTP deficiency, PDH deficiency, BRBGD
Polyneuropathy	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	LCHADD, TFP deficiency
	Recurrent attacks	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
	Recurrent attacks	Arginase deficiency, Triple H
Ataxia	Isolated	PDH deficiency, coenzyme Q_{10} deficiency
	Spastic paraparesis	CTX, nonketotic hyperglycinaemia, vitamin E deficiency
	Dystonia/parkinsonism	CTX, PDH deficiency, Cbl synthesis defects
	Recurrent attacks	CTX, UCD
Psychiatric signs	Isolated	Cbl synthesis defects, MTHFR deficiency, PKU, Homocystinuria, Wilson disease, CTX
	Leukodystrophy	Cbl synthesis defects, MTHFR deficiency, PKU, CTX
	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	Carnitine uptake (major sign), FAO defects, Fabry disease, thiamin deficiency
	Heart beat disorders	
Dermatology	Alopecia	MCD, porphyria, calciferol defects
	Hyperkeratosis (palmoplantar)	Tyrosinaemia type II (major sign)
	Ichthyosis	Serine deficiency syndrome
	Skin rashes	Porphyrias, Hartnup disease
Gastroenterology	Abdominal pain	OTC deficiency, porphyrias, organic acidurias, tyrosinaemia type I, LPI, Fabry disease
	HELLP syndrome	CPT I deficiency, LCHADD
Haematology	Macrocytic anaemias	Hereditary orotic aciduria
		Cbl metabolism
		Congenital folate malabsorption
		Thiamin-responsive anaemia
	Pancytopenia	Gaucher disease type I, glycogenosis type Ib, Cbl and folate metabolism, LPI, organic acidurias
Hepatic	Liver failure	See Tables 1 and 2
Immune system	Macrophage activating syndrome	Gaucher disease, LPI, propionic acidaemia
Myology	Exercise intolerance	FAO defects (CPT II deficiency, VLCADD, LCHADD, TL deficiency, TFP deficiency), hyperkalaemic paralysis
Nephrology	Haemolytic uraemic syndrome	Cobalamin deficiencies (CblC, CblG)
	Nephrolithiasis	Cystinuria, oxalurias, xanthine oxidase deficiency (major sign)
	Tubulopathy	HFI, galactosaemia, tyrosinaemia type I, cystinosis (major sign)
Ophthalmology	Cataracts	Galactosaemias, LPI, Wilson disease, CTX, Fabry disease, homocystinurias
	Corneal opacities	Cystinosis (major sign), Fabry disease, Wilson disease
	Keratitis	Tyrosinaemia type II (major sign)
	Ectopia lentis	Homocystinurias (major sign)
Pneumology	Pneumopathy (interstitial)	Gaucher disease, LPI
Osteology	Bone crisis	Calciferol metabolism, rickets, porphyrias, tyrosinaemia type I, Gaucher disease, Fabry disease (major sign)
Stomatology	Glossitis	Cobalamin metabolism
	Stomatitis	Folate malabsorption
Vascular symptoms	Raynaud syndrome	Fabry disease (major sign)
	Thromboembolic accidents (see also Table 2)	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 Remethylation defects	100–150 mg/kg per day in 2–3 divided doses, max. dose 6–9 g/day	Oral	
Biotin	Co-factor for carboxylases	Biotinidase deficiency Multiple carboxylase deficiency	5–20 mg/day	Oral or i.v.	
	Treatment of presumed transporter defect (Zeng et al 2005)	Biotin-responsive basal ganglia disease			
Chenodeoxycholic acid	Inhibits cholesterol 7α-hydroxylase (rate-limiting enzyme in bile acid biosynthesis)	3β-dehydrogenase deficiency (3βDD); Δ^{4-}3-oxosteroid 5β-reductase deficiency (3-ORD); cerebrotendinous xanthomatosis (CTX)	3β-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 × 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 5β-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 Cerebral folate transporter	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	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 μ g/kg once daily	s.c.	
Glycine	Forms isovalerylglycine with high renal clearance	Isovaleric acidaemia	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 (vitamin 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 hypocalcemia	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
N-Carbamoylglutamate	Stimulates *N*-acetylglutamate synthase	*N*-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)ine 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 Removes N_2 to ammonia and reduces blood ammonia	Hyperammonaemia	250 mg per day in divided doses or by continuous i.v. infusion Dose may be doubled if severe hyperammonaemia	Oral or i.v.	I.v. loading dose: 250 mg/kg over 90 min
Sodium phenylbutyrate	Converted to phenylacetate, which combines with glutamine to form phenylglutamine which has high renal clearance	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 Glutathione synthase deficiency Abetalipoproteinaemia	200–1000 mg per day	Oral	
Vitamin E (α-tocopherol)	Replenishes vitamin E stores; free radical scavenger	Glutathione synthetase deficiency	10 mg/kg per day 100 mg/kg per day	Oral	
Zinc sulphate	Increases Zn, impairs Cu absorption	Acrodermatitis enteropathica (AE); Wilson disease	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-hydroxytrytophan; 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-Lelmli-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).

References

de Koning T (2006) Treatment with amino acids in serine deficiency disorders. *J Inherit Metab Dis* **29**: 347–351.

Junien C (2006) Impact of diets and nutrients/drugs on early epigenetic programming. *J Inherit Metab Dis* **29**: 359–365.

Kjaergaard S, Kristiansson B, Stibler H, et al (1998) Failure of short-term mannose therapy of patients with carbohydrate- deficient glycoprotein syndrome type 1A. *Acta Paediatr* **87**: 884–888.

Koga Y, Akita Y, Nishioka J, et al (2005) L-Arginine improves the symptoms of strokelike episodes in MELAS. *Neurology* **64**: 710–712.

Mayatepek E, Schroder M, Kohlmuller D, et al (1997) Continuous mannose infusion in carbohydrate-deficient glycoprotein syndrome type I. *Acta Paediatr* **86**: 1138–1140.

Ostman-Smith I, Brown G, Johnson A, et al (1994) Dilated cardiomyopathy due to type II X-linked 3-methylglutaconic aciduria: successful treatment with pantothenic acid. *Br Heart J* **72**: 349–353.

Quinzii C, Naini A, Salviati L, et al (2006) A mutation in para-hydroxybenzoate-polyprenyl transferase (COQ2) causes primary Coenzyme Q10 deficiency. *Am J Hum Genet* **78**: 345–349.

Raine DN (ed.) (1975) *The Treatment of Inherited Metabolic Disease*. Lancaster: Medical and Technical Publishing.

Roe CR, Mochel F (2006) Anaplerotic diet therapy in inherited metabolic disease: therapeutic potential. *J Inherit Metab Dis* **29**: 332–340.

Saudubray JM, Desguerre I, Sedel F, Charpentier C (2006) A clinical approach to inherited metabolic disorders. In: Fernandes J, Saudubray JM, van den Berghe G, Walter J, eds. *Inborn Metabolic Diseases: Diagnosis and Treatment*, 4th edn. Berlin: Springer-Verlag, 2006 in press.

Valayannopoulos V, Verhoeven NV, Mention K, et al (2006) Transaldolase deficiency: a new cause of hydrops foetalis and neonatal multiorgan disease. *J Pediatr*, in press.

Van Spronsen FJ, Smit GPA, Erwich JJHM (2005) Inherited metabolic diseases and pregnancy. *BJOG Int J Obstet Gynaecol* **112**: 2–11.

Walter JH, Wraith J (2006) Treatment: present status and new trends. In: Fernandes J, Saudubray JM, van den Berghe G, Walter J, eds. *Inborn Metabolic Diseases: Diagnosis and Treatment*. Berlin: Springer-Verlag, 4th edition, in press.

Zeng WQ, Al Yamani E, Acierno JS Jr, et al (2005) Biotin-responsive basal ganglia disease maps to 2q36.3 and is due to mutations in SLC19A3. *Am J Hum Genet* **77**: 16–26.