3rd Edition

Johannes Zschocke
Georg F. Hoffmann

Vademecum Metabolicum

Diagnosis and Treatment of Inborn Errors of Metabolism

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Patterns of acute presentation

Important laboratory findings

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Diagnosis and Treatment of Inborn Errors of Metabolism

3rd, revised Edition

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With 29 figures and 40 tables

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Foreword

It is my pleasure to write the Foreword for the third edition of the *Vademecum Metabolicum*. This very useful book has now been translated into many languages including German, English, French, Italian, Hungarian, Portugese and Japanese. It has continued to grow in scope, as has the field of inborn errors of metabolism. At the same time, it has remained true to its original objective of providing a systematic approach to the diagnosis of metabolic disease. The book is still small enough to fit in a pocket, and has become a favourite of physicians in training in Paediatrics and Genetics. Revisions have brought the book up to date, impressively so in the disorders of glycosylation, neurotransmission, and vitamin metabolism. Extensive tabular presentation leads the reader logically to the diagnostic possibilities. Optimal therapy, including dosages, makes for a well rounded approach to the various diagnosis and management of genetic diseases of metabolism.

University of California, San Diego, USA **William L. Nyhan, MD, PhD**

Preface

Inborn errors of metabolism, which cumulatively affect approximately one in every 500 newborns, represent a special challenge in general and paediatric practice. They frequently present with acute, life-threatening crises that require immediate specific intervention. The development and prognosis of the affected child may depend on rapid and effective treatment, but the large number of genetic defects in various biochemical pathways makes it difficult to be familiar with all diagnostic strategies and specific therapies. With this in mind, the *Vademecum Metabolicum* aims to provide practical guidance to the clinician.

This 3rd English edition has been completely revised and expanded. As in previous editions, the first section on the diagnosis and management of metabolic disorders includes clinical situations that may be caused by a metabolic disorder. Practical guidelines are discussed in detail and should reflect standard practice in many countries. The second section on individual metabolic pathways and their disorders has been completely revised and includes a considerable number of recently identified disorders. As in the previous editions, special emphasis has been placed on clinical features that are relevant to a whole group of diseases, useful diagnostic procedures (basic and special diagnostic tests) as well as details on emergency intervention and long-term treatment. The pathobiochemistry is described in more detail when it is relevant to the understanding of clinical symptoms and diagnostic tests. The sequence of the entries is either according to metabolic pathways or nomenclature.

The genetic basis of most disorders in the Vademecum Metabolicum has now been clarified, and the causative genes have been included when known. Throughout the text we have removed references to molecular studies as part of the diagnostic strategy since mutation analyses are now a standard option for confirmation of most metabolic disorders. Inheritance of the disorders is autosomal recessive unless specified otherwise.

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Innsbruck and Heidelberg, August 2011

Johannes Zschocke
Georg F. Hoffmann

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Abbreviations

AA	amino acids
AFP	α-fetoprotein
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BH_4	tetrahydrobiopterin
Bioch.	biochemistry
BW	body weight
Cbl	cobalamin
CDG	congenital disorders of glycosylation
CK	creatine kinase
CoA	coenzyme A
Compl.(s)	complication(s)
Confirm.	confirmatory studies
CPT	carnitine palmitoyltransferase
CSF	cerebrospinal fluid
DBS	dried blood spot
DD	differential diagnosis
DH	dehydrogenase
Diagn.	diagnosis
FA	fatty acids
FFA	free fatty acids
Fru	fructose
GABA	γ-aminobutyric acid
GAG	glycosaminoglycans
Gal	galactose
GALT	galactose-1-phosphate uridyltransferase
GC	gas chromatography
Glc	glucose
HMG	3-hydroxy-3-methylglutarate
HPLC	high performance liquid chromatography
IEM	inborn error of metabolism
i.m.	intramuscular
Indic.	indication
i.v.	intravenous
IVA	isovaleric aciduria
Lab.	laboratory
Manif.	manifestation
MCAD	medium-chain acyl-CoA DH
Metab.	key metabolites
MMA	methylmalonic aciduria
MPS	mucopolysaccharide(-osis)
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MS	mass spectroscopy
mth(s)	month(s)
n	normal
NH_3	ammonia
NMR	nuclear magnetic resonance
OA	organic acids
OH-	hydroxy-
OTC	ornithine transcarbamylase
P	phosphate
PA	propionic aciduria
PALP	pyridoxal phosphate
PC	pyruvate carboxylase
PDH	pyruvate dehydrogenase
PKU	phenylketonuria
Progn.	prognosis
SCAD	short-chain acyl-CoA DH
SCHAD	short-chain hydroxyacyl-CoA dehydrogenase
SIDS	sudden infant death syndrome
Tx	transplantation
Var.	variant
VLCAD	(very)-long-chain acyl-CoA dehydrogenase
wk(s)	week(s)
yr(s)	year(s)

Amino acids

Ala	alanine
Arg	arginine
Asa	argininosuccinic acid
Asn	asparagine
Asp	aspartate
Cit	citrulline
Cys	cysteine
Gln	glutamine
Glu	glutamate
Gly	glycine
Hcy	homocysteine
His	histidine
Ile	isoleucine
Leu	leucine
Lys	lysine
Met	methionine
Orn	ornithine
Phe	phenylalanine
Pro	proline
Ser	serine
Tau	taurine
Thr	threonine
Trp	tryptophan
Tyr	tyrosine
Val	valine

Diagnosis and management of metabolic disorders

Essential basic laboratory tests

The following basic laboratory tests should be performed in every child with an acute illness in whom a metabolic disorder is a possibility:

Blood glucose
Hypoglycaemia is a presenting feature of several disorders particularly of carbohydrate and energy metabolism. Appropriate blood and urine samples should be obtained in the acute phase to make the correct diagnosis. *For details see page 5.*

Ammonia
Ammonia is highly neurotoxic and hyperammonaemia carries a high but in principle avoidable mortality and morbidity. Urgent analysis of the plasma ammonia concentration is mandatory in all acutely ill neonates and all patients with undiagnosed encephalopathy. Facilities to determine ammonia at any time of the day should be available in all hospitals. Hyperammonaemia due to a primary urea cycle disorder is among the most urgent emergencies in metabolic paediatrics and will be missed if ammonia is not measured. *For details see page 7.*

Acid-base status
Many metabolic disorders cause alterations in the acid-base status, both acidosis and alkalosis. Blood gas measurements need to be available at any time in every hospital. *For details see page 10.*

Lactate
Elevated lactate is an important sequel of hypoxia and compromised energy metabolism and may be the cause of metabolic acidosis. A primary metabolic disorder should be considered if there is no convincing secondary cause such as shock, asphyxia or cardiac disease or in particular a difficult venepuncture. *For details see page 11.*

Urinary ketones (test strip)
Ketonuria due to the ketone bodies 3-hydroxybutyrate and acetoacetate is normal during fasting but is pathological in the fed state and in the neonate where it may indicate a disorder of intermediary metabolism. Absence of ketones during fasting is suggestive of a fatty acid oxidation disorder. Ketone levels measured by non-specific tests (e.g. test strips) may be high due to the presence of interfering compounds. *See also page 11.*

Other laboratory tests
Organ dysfunction caused by metabolic disorders may be recognised in routine investigations such as blood counts, liver function tests, coagulation studies or creatine kinase levels. Uric acid is elevated in several disorders with increased cellular turnover or decreased urinary clearance. *See also page 28.*

Specific triggers of metabolic decompensation

Triggers	*Groups of disorders*
Vomiting, fasting, infection, fever, vaccination, surgery, accident/injury	Disorders of protein, energy or carbohydrate metabolism or hormone homoeostasis
High protein intake and/or protein catabolism	Disorders of protein metabolism: aminoacidopathies, organic acidurias, urea cycle defects, hyperinsulinism-hyperammonaemia syndrome
Fruit, table sugar (sucrose), liquid medicines	Fructose intolerance
Lactose, milk products	Galactosaemia
High fat intake	Lipoprotein lipase deficiency, glycerol intolerance, fatty acid oxidation disorders
Drugs	Porphyrias, Glc-6-P-dehydrogenase deficiency
Extensive exercise	Disorders of fatty acid oxidation, glycolysis, muscle glycogenolysis, purine and pyrimidine metabolism, respiratory chain

General clinical situations

The metabolic emergency

In the neonate, the early clinical features of acute metabolic decompensation are almost always non-specific; they include "unwell", lethargy, feeding problems, vomiting, abnormal breathing, hypotonia and seizures. Disorders of glucose, protein and fat breakdown (intermediary metabolism) in the neonatal period typically have an *asymptomatic interval*, with clinical manifestations from the second day of life onwards ("intoxication type"), although hyperammonaemia in particular may present as early as day 1. The baby's general condition will usually deteriorate rapidly despite normal or non-specific findings in routine investigations (laboratory signs of infection, lumbar puncture, chest X-ray, cranial ultrasound) and antibiotic therapy. The *family history* may reveal siblings who died with similar clinical manifestations ("sepsis", "SIDS") or unexplained disorders in other family members (progressive neurological disease, maternal PKU, multiple miscarriages, HELLP syndrome, etc.). Consanguinity increases the risk of a recessive disorder.
Metabolic disorders **after the neonatal period** may present with recurrent vomiting and lethargy progressing to coma without focal neurological signs or typical patterns of organ dysfunction. Initial management may follow similar principles as in neonates. Care must be taken to identify the conditions that triggered metabolic decompensation such as vomiting and fever or changes in the diet.

A metabolic disorder should be considered, along with other diagnoses (e.g. infection, CNS pathology) ...
... in all neonates with unexplained, overwhelming or progressive disease particularly after normal pregnancy and birth;
... in all children with acute deterioration of the general condition and/or reduced consciousness, particularly when preceded by vomiting, fever or fasting;
... in all children with symptoms and signs of acidosis or hypoglycaemia.

Appropriate diagnostic and therapeutic measures must be initiated as soon as possible to avoid long-term damage.

Post-mortem investigations: see *page 25*

Phase 1: Basic metabolic emergency investigations and first line management

Stop intake of potentially toxic compounds (protein, fat, galactose, fructose)

Insert i.v. line and take blood samples for urgent analysis of:
- Electrolytes, *glucose*, CRP, CK, ALT, AST, creatinine, urea, uric acid, *acid-base status*, coagulation studies
- Ammonia, lactate
- Store plasma sample for amino acids, acylcarnitines, etc.
- Store filter paper card ("Guthrie" card for newborn screening) with dried blood spots for acylcarnitines (amino acids, possibly DNA studies)
- Store the rest of the other samples for possible additional tests (inform laboratory)

Obtain urine sample:
- Check colour and odour
- Perform standard test strip analyses (e.g. ketone bodies, glucose, protein; pH >5 during acidosis → DD renal tubular acidosis)
- Store urine sample from the acute phase for organic acids or additional metabolic tests

If lumbar puncture is performed:
- Store CSF (freeze immediately)

Start with **10% glucose infusion, 150 ml/kg/day** (10 mg/kg/min, ~60 kcal/kg/day), with appropriate electrolytes.

Glucose supply in this infusion is at the rate of normal hepatic glucose production and is usually sufficient for disorders of reduced fasting tolerance such as glycogen storage disorders or MCAD deficiency. It may not be sufficient in disorders that are exacerbated by catabolism, e.g. organic acidurias or urea cycle defects. It may be potentially dangerous in mitochondrial disorders (specifically pyruvate dehydrogenase deficiency) as a high glucose supply may enhance lactic acidosis. The benefits of the high-glucose infusion outweigh the risks but lactate and acid-base status should be checked regularly.

Order additional investigations as indicated, e.g. ECG, echocardiogram, cranial imaging. **Results of emergency investigations should be available within 30(–60) min**. At that stage, decide on specialist investigations and additional therapeutic measures.

Phase 2: Treatment and investigations according to the initial findings

If the emergency investigations show ...
... hypoglycaemia: see *page 5*
... hyperammonaemia: see *page 7*
... metabolic acidosis: see *page 10*
... elevated lactate: see *page 12*
... severe liver disease: see *page 19*

If results are inconclusive but metabolic disease remains a possibility:
- Continue glucose infusion
- Review the history and clinical signs. Phone regional metabolic centre for advice.
- After discussion, send samples for specialist metabolic investigations (results relevant to the diagnosis of treatable metabolic disorders should be available within 24 [at most 48] hrs):
  - Dried blood spots for acylcarnitines and amino acids (urgent analysis)
  - Plasma sample for amino acids and acylcarnitines
  - Urine sample for simple metabolic tests and organic acids
- Monitor electrolytes, glucose, lactate, acid-base status (keep sodium well above 135 mmol/l to avoid cerebral oedema)

Hypoglycaemia

Glucose concentration:
1 mmol/l = 18 mg/dl
10 mg/dl = 0.55 mmol/l

Definition
Blood glucose < 2.6 mmol/l (45 mg/dl) at all ages

Consider
- *In the neonate*: evidence of non-metabolic causes?
- *History*: time since last meal (hypoglycaemia postprandial, after fasting), drugs, erratic?
- *Examination*: hepatomegaly, liver failure or cirrhosis, small genitals, hyperpigmentation, short stature?
- *Glucose requirements*: > 10 mg/kg/min indicates (persistent or transient) hyperinsulinism (*page 88*) unless there are marked losses elsewhere (e.g. urine)
- *Rule out* (in the neonate): septicaemia, severe systemic illness, small for gestational age, maternal diabetes

Laboratory investigations during symptomatic hypoglycaemia

Adequate laboratory tests must be carried out *during symptomatic hypoglycaemia* to identify the underlying cause, or else many diagnoses may be missed.

Essential
- **Free fatty acids + 3-hydroxybutyrate** (serum or plasma); ketones (test strip). A marked elevation of *free fatty acids* indicates active lipolysis and that the hypoglycaemia is associated with a fasting reaction. In this situation, "normal" (low) values of *plasma ketones* (3-hydroxybutyrate is sufficient) are strongly suggestive of a disorder of fatty acid oxidation or ketogenesis. Normal values: see *page 167*.
- **Acylcarnitines** (dried blood spots or plasma). This test is diagnostic of most (but not all) fatty acid oxidation disorders and various organic acidurias.
- **Hormones** (serum). *Insulin* (normal: insulin completely suppressed when glucose < 2.6 mmol/l [45 mg/dl]), *cortisol* (normal > 270 nmol/l).
- **Lactate** (blood, NaF tube). Elevations may indicate liver damage or impaired glycogenolysis/gluconeogenesis but may also be found after a seizure or difficult blood sampling (see *page 12*).
- **One spare tube** (serum or plasma) for anything from below or forgotten or lost
- **Organic acids** (urine) → various metabolic disorders that may cause hypoglycaemia

Others
- Blood gases, blood count, CRP, electrolytes, phosphate, liver/renal function tests, CK, uric acid, triglycerides, carnitine status, growth hormone
- Ammonia (EDTA blood) → e.g. liver damage or glutamate dehydrogenase deficient hyperinsulinism
- Amino acids (plasma)
- Consider toxicological investigations (incl. C-peptide)

Differential diagnosis

Hypoglycaemia in premature children is frequently caused by problems of adaptation and may not require extensive laboratory tests. The most frequent causes of persistent neonatal hypoglycaemia are hormonal disturbances, e.g. hyperinsulinism or hypopituitarism. Hypoglycaemia of hyperinsulinism is accompanied by low concentrations of free fatty acids and ketone bodies due to *inhibition of lipolysis*. *Regulatory disturbances* (e.g. ketotic hypoglycaemia, glycogen storage disease type III, hypopituitarism after the first year of life) result in hypoglycaemia with particularly strong ketosis. *Defects of fatty acid utilisation* (*carnitine shuttle*, *fatty acid oxidation*, *ketogenesis*) are characterised by hypoglycaemia, high levels of free fatty acids and low ketones during lipid catabolism. *Gluconeogenesis defects* (e.g. glycogen storage disease type I) show marked hypoglycaemia with lactic acidosis; ketone levels may be low or elevated.

As always: There are exceptions to every rule or simplification.

Ketones "normal" (low) or insufficiently elevated		**Free fatty acids relatively low**: hyperinsulinism, ↓ counter-regulatory hormones
		Free fatty acids greatly elevated: disorders of fatty acid oxidation and ketogenesis
Ketones elevated		"Ketotic hypoglycaemia", organic acidurias, ↓ counter-regulatory hormones (after the first year), glycogen storage disease types III and 0, ketolysis defects
Lactate elevated (>2 mmol/l)	Without **hepatomegaly**	Organic acidurias, ketolysis defects, respiratory chain defects, long-chain fatty acid oxidation disorders (especially LCHAD)
	Isolated **hepatomegaly**	Glycogen storage diseases, gluconeogenesis defects
Liver disease		Fructose intolerance, respiratory chain defects, long-chain fatty acid oxidation disorders, tyrosinaemia type I

Treatment

- Glucose i.v. 7–10 mg/kg/min (glucose 10%: 110–150 ml/kg/day), keep blood sugar ≥ 5.5 mmol/l (100 mg/dl).
  If glucose bolus is needed: Do not give more than 200 mg/kg (glucose 20%: 1 ml/kg).
- Await results of specialist investigations and treat accordingly
- High glucose requirement > 10 mg/kg/min or incompletely suppressed insulin at times of hypoglyaecemia is abnormal and suggests hyperinsulinism (see *page 82*)
- For disorders of fatty acid oxidation and ketogenesis see *page 91*