Information for health care providers

General background: disease-specific metabolic emergency protocols

To prevent catabolism and subsequent metabolic decompensation, the key measure in many inborn errors of metabolism (IEM) emergency protocols is the promotion of anabolism (Dixon and Leonard, 1992; Prietsch ea. 2002; Van Hove, 2009). Information about disease-specific emergency protocols is available at multiple online resources, such as the New England Consortium of Metabolic Programs, British Inherited Metabolic Diseases group, and INVEST (in Dutch: Internisten voor volwassenen met een erfelijke stofwisselingsziekte). Scientific publications are available for urea cycle defects (Rodan ea. 2018), maple syrup urine disease (Rodan ea. 2018), organic acidemias (Aldubayan ea. 2017), fatty acid oxidation disorders (FAOD; Aldubayan ea. 2017), or incorporated in guidelines for glutaric aciduria type I and subtypes of hepatic glycogen storage diseases (GSD), such as GSD Ia (Rake ea. 2002; Kishnani ea. 2014), GSD Ib (Visser ea. 2003; Kishnani ea. 2014), GSD III (Kishnani ea. 2010), and GSD VI and IX (Kishnani ea. 2019).

The CONNECT MetabERN project: towards personalized emergency letters

Emergency situations are an important burden for many families with IEMs, amongst which 'carbohydrate, fatty acid oxidation and ketone bodies diseases', that are represented by the specific MetabERN subnetwork. The question 'How should sickness and emergency situations be managed for patients with liver GSD?' has recently been ranked as top priority for research in the international priority setting partnership for liver glycogen storage disease (Peeks ea. 2020).

An initial version of a website to automatically generate emergency letters for patients with hepatic GSD is mentioned previously (Hoogeveen ea. 2018). Metabolic specialists from many countries world-wide have collaborated in the CONNECT MetabERN project to improve the emergency letters and it's communication. Some elements of this emergency protocol are generic, i.e. regardless of the IEM (such as the approach to prevent catabolism), whereas other items are personalized based on body weight and specific IEM.

By using www.emergencyprotocol.net, personalized emergency letters can be automatically generated for (families and) patients with the following fatty acid oxidation disorders (FAOD) and glycogen storage diseases (GSD):

- Glycogen storage disease type 0 a
- Glycogen storage disease type Ia
- Glycogen storage disease type Ib
- Glycogen storage disease type III*
- Glycogen storage disease type IV
- Glycogen storage disease type VI
- Glycogen storage disease type IXa**
- Glycogen storage disease type IXb**
- Glycogen storage disease type IXc**
- Fanconi-Bickel syndrome
- Medium - chain acyl CoA dehydrogenase deficiency
- Multiple acyl-CoA dehydrogenase deficiency DH#
- Electron transfer flavoprotein α subunit deficiency#
- Electron transfer flavoprotein β subunit deficiency#
- Very long - chain acyl CoA dehydrogenase deficiency
- Isolated deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase##
- Trifunctional protein α subunit deficiency##
- Trifunctional protein β subunit deficiency##

The hyperlinks direct to specific IEMbase information.

* divided into type IIIa and IIIb
** summarized as GSD IX
# summarized as MADD
summarized as LCHADD/MTP

Assumptions regarding www.emergencyprotocol.net

General:

- For IEM families, emergency measures start at home. Subsequently, given the geographical distance between metabolic centers of expertise and IEM patients' home addresses, local or

regional physicians are often the first healthcare providers proceeding the emergency treatment. The emergency letters facilitate the communication until expert metabolic support can be sought.

- The emergency letter describes a two-phase (i.e. pre-hospital and in-hospital) care pathway to prevent metabolic emergencies. Phase one can be executed by families at home, when the sick-day dietary regimen is not tolerated. Phase two is executed in the emergency department or initial hospitalization, controlled by health care professionals, before expert metabolic support can be sought. Phase two should end with consulting the expert metabolic center and does not replace disease-specific, in-hospital, expert metabolic treatment.
- The emergency letter is generated based on the IEM and patient's body weight. Therefore, it is important to ensure that this information is accurate and that the body weight is regularly updated.
- IEM patients' medical care depends on shared care and good communication between families, metabolic experts and local health care providers. It is important that the emergency letter contains contact details of both the local health care providers and the metabolic center of expertise.
- The emergency letter will refer to the following generic and IEM-specific risk moments for catabolism and subsequent metabolic decompensation:

IEM group	**Risk moments**
FAOD	• Fever • Decreased gastro-intestinal intake; fasting • Increased gastro-intestinal loses • Surgery • Stress • Exercise (for MADD, VLCADD and LCHADD) • Alcohol intake (for young adults)
Hepatic GSD	• Fever • Decreased gastro-intestinal intake; fasting • Increased gastro-intestinal loses • Surgery • Stress • Exercise (for GSDIIIa) • Alcohol intake (for young adults) • Preparation phase colonoscopy (for GSD-Ib)

Phase 1:

- Regular oral rehydration salt (ORS) does not contain enough calories and carbohydrates for metabolic patients. Therefore, this protocol makes use of an emergency solution that consists of maltodextrin added to an ORS solution. The amount of maltodextrin depends on the body weight, as described elsewhere (Van Hove ea. 2009), with slight, simplifying modifications. For children with a body weight < 12 kg, 75 grams of maltodextrin should be added to 500 mL of ORS. For patients > 12 kg, 110 grams of maltodextrin should be added to 500 mL of ORS.
- The volume of this emergency solution depends on the following fluid requirements:

< 10 kg	100 mL/kg/day
10-20 kg	1000 mL + 50 mL/kg/day for each kg after 10
> 20 kg	1500 mL + 20 mL/kg/day for each kg after 20
> 70 kg	2500 mL

- We assume that the energy requirement (and hence) and carbohydrate requirement increases by 10% for each degree Celsius increase of body temperature. Fever is defined as a body temperature ≥ 38.0° Celsius (twice measured with one-hour interval) or ≥ 38.5° Celsius (once measured).
- Analgetics are advised for fever-management.

- The estimated, calculated carbohydrate requirements per kg body weight are based on experimental data (Bier ea. 1977), in which:
  Y=0.0014x3 – 0.214x2 + 10.411x – 9.084. [Y] = mg/min. [x] = kilograms.
- The initially calculated volume of the emergency solution aims at meeting the carbohydrate requirements up to 40.0° Celsius.
- The table below can be used to check the volumes of the emergency solution and dextrose 10% infusion (in phase 2).

Body weight (kg)	Estimated, calculated EGP (mg/kg/min)	Emergency solution (mL / 3h)	Emergency solution (mL / h)	dextrose 10% - 37ºC (mL / h)	dextrose 10% - 38ºC (mL / h)	dextrose 10% - 39ºC (mL / h)	dextrose 10% - 40ºC (mL / h)
5	7,6	63	21	23	25	27	30
6	7,7	75	25	28	30	33	37
7	7,7	88	29	32	35	39	43
8	7,7	100	33	37	40	44	49
9	7,6	113	38	41	45	50	55
10	7,5	125	42	45	50	54	60
11	7,4	131	44	49	54	59	65
12	7,3	138	46	52	58	63	70
13	7,2	144	48	56	61	68	74
14	7,0	150	50	59	65	72	79
15	6,9	156	52	62	68	75	83
16	6,8	163	54	65	72	79	87
17	6,6	169	56	68	75	82	90
18	6,5	175	58	70	77	85	94
19	6,4	181	60	73	80	88	97
20	6,2	188	63	75	82	91	100
21	6,1	190	63	77	85	93	102
22	6,0	193	64	79	87	95	105
23	5,8	195	65	81	89	97	107
24	5,7	198	66	82	90	99	109
25	5,6	200	67	84	92	101	111
26	5,4	203	68	85	93	103	113
27	5,3	205	68	86	95	104	115
28	5,2	208	69	87	96	106	116
29	5,1	210	70	88	97	107	117
30	4,9	213	71	89	98	108	119
31	4,8	215	72	90	99	109	120
32	4,7	218	73	90	100	109	120
33	4,6	220	73	91	100	110	121
34	4,5	223	74	92	101	111	122
35	4,4	225	75	92	101	111	122
36	4,3	228	76	92	101	112	123
37	4,2	230	77	92	102	112	123
38	4,1	233	78	93	102	112	123
39	4,0	235	78	93	102	112	123
40	3,9	238	79	93	102	112	123
41	3,8	240	80	93	102	112	123
42	3,7	243	81	93	102	112	123
43	3,6	245	82	93	102	112	123
44	3,5	248	83	92	102	112	123
45	3,4	250	83	92	101	112	123
46	3,3	253	84	92	101	111	122
47	3,3	255	85	92	101	111	122
48	3,2	258	86	91	101	111	122
49	3,1	260	87	91	100	110	121
50	3,0	263	88	91	100	110	121
51	3,0	265	88	91	100	110	121
52	2,9	268	89	90	99	109	120
53	2,8	270	90	90	99	109	120
54	2,8	273	91	90	99	109	119
55	2,7	275	92	89	98	108	119
56	2,7	278	93	89	98	108	119
57	2,6	280	93	89	98	108	118
58	2,6	283	94	89	98	107	118
59	2,5	285	95	89	98	107	118
60	2,5	288	96	89	97	107	118
61	2,4	290	97	88	97	107	118
62	2,4	293	98	88	97	107	118
63	2,3	295	98	89	97	107	118
64	2,3	298	99	89	97	107	118
65	2,3	300	100	89	98	107	118
66	2,2	303	101	89	98	108	118
67	2,2	305	102	89	98	108	119
68	2,2	308	103	90	99	109	119
69	2,2	310	103	90	99	109	120
70	2,2	313	104	91	100	110	121

Phase 2:

- The emergency letter lists the ideal, minimal laboratory tests required to assess the metabolic state of the patient in the first critical sample. Based on the clinical condition, this list of laboratory tests can be extended. After the first sample, local healthcare providers will consult the metabolic center of expertise who can ask for additional blood tests according to the individual situation if needed. The assessment of additional laboratory tests to identify any underlying cause of acute presentation (infection, dehydration, etc.) should be the responsibility of the healthcare provider.

IEM	Laboratory tests
GSD 0	Blood: glucose, blood gas analysis, lactate, ketones
GSD Ia	Blood: glucose, blood gas analysis, lactate
GSD Ib	Blood: glucose, blood gas analysis, lactate, neutrophils
GSD IIIa	Blood: glucose, blood gas analysis, lactate, ketones, CK, myoglobin
GSD IIIb	Blood: glucose, blood gas analysis, lactate, ketones
GSD IV	Blood: glucose, blood gas analysis, lactate, ammonia, ketones
GSD VI	Blood: glucose, blood gas analysis, lactate, ketones
GSD IX	Blood: glucose, blood gas analysis, lactate, ketones
FBS	Blood: glucose, blood gas analysis, lactate, ketones, calcium, magnesium, phosphate Urine: glucose, protein
MCADD	Blood: glucose, blood gas analysis
MADD	Blood: glucose, blood gas analysis, ammonia, CK, myoglobin
VLCADD	Blood: glucose, blood gas analysis, CK, myoglobin
LCHADD/MTP	Blood: glucose, blood gas analysis, CK, myoglobin

- The dextrose 10% bolus and maintenance infusion should balance between adequate treatment of (symptomatic) hypoglycemia and prevention of iatrogenic hyperglycemia.
- The emergency letter lists the following IEM-specific considerations:

IEM	Considerations
All IEMs	• Administration of glucagon is contraindicated • Symptomatic metabolic acidosis (pH<7.25) may require active buffer treatment with sodium bicarbonate intravenously. Dose in mmol = 0,33 x body weight in kg x base deficit
GSD Ia	• Lactated Ringer's solution is contraindicated
GSD Ib	• Lactated Ringer's solution is contraindicated • Neutropenia and neutrophil dysfunction may require (increasing the dose of) GCSF
GSD IIIa	• Hyperhydration and regular checks of electrolytes are needed in case of acute rhabdomyolysis
MADD	• Specific treatment is needed in case of acute hyperammonemia • Hyperhydration and regular checks of electrolytes are needed in case of acute rhabdomyolysis
VLCADD	• Hyperhydration and regular checks of electrolytes are needed in case of acute rhabdomyolysis • Maintenance of MCT dietary treatment needs to be considered
LCHADD/MTP	• Hyperhydration and regular checks of electrolytes are needed in case of acute rhabdomyolysis • Maintenance of MCT dietary treatment needs to be considered

- First laboratory test results are usually available within an hour. These results together with the clinical presentation and the above-mentioned considerations will determine the follow-up treatment, for which consultation by the metabolic center of expertise is warranted.

Acknowledgement of contributors

The development of www.emergencyprotocol.net has been a process rather than one project….

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www.emergencyprotocol.net is a website designed to help health care providers and (families of) patients with certain FAODs and GSDs to generate a personalized emergency letter. These letters intend to support communication between patients/families, the metabolic expert team and local health care providers. Shared care is shared responsibility. The website or emergency letters should not be considered a substitute for expert metabolic advice.

www.emergencyprotocol.net will generate a personalized emergency letter that summarizes the communication and initial management, taking account of what can be regarded as the current best practice. The medical and contact information is scrutinized carefully, but the website and emergency letters may still contain errors. There may be situations when alternative management is preferable or appropriate. Health care providers are invited to communicate with patients and patient representatives, whether, when and how their emergency letters will be updated in the best way and which role patients/families may play in this process. Therefore, each emergency letter needs to be carefully checked by the person who has generated it, before use.

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