Inborn Errors of Metabolism in Infants - Guidelines for Investigation

Guideline Responsibilities and Authorisation

Department Responsible for Guideline	Newborn Intensive Care Unit (NICU)
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Target Audience	NNPs, CNSs, Registrars, SMOs and Nurses
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Guideline Review History

Version	Updated by	Date Updated	Summary of Changes
3	Nadia Wright		Evidence review, reference links added for management

Contents

1 Overview

Inborn errors of metabolism are a group of rare, usually inherited, disorders where any of a variety of metabolic pathways can malfunction at any point in the pathway. This can be through the absence or abnormality of an enzyme, or its co-factor, or the impaired transport of a biochemical. This disruption can cause toxic metabolite build up or a lack of essential proteins or enzymes required for normal body function. Undiagnosed and without management these disorders can cause acute and progressive metabolic decompensation and subsequent long-term disability or death. Some metabolic conditions have no known treatment.

1.1 Purpose

Investigation recommendations for infants where an inborn error of metabolism is acutely suspected.

Note: This guideline does not provide a comprehensive guide to acute emergency management of inborn errors of metabolism. Please see point 3 for hyper-links to acute management guidelines.

1.2 Scope

Waikato hospital staff working in the Newborn Intensive Care unit inclusive of Senior Medical Officers, Fellows, Registrars, Nurse Practitioners, Clinical Nurse Specialists and Registered nurses.

1.3 Patient / client group

Neonates and infants born in, or transferred to, Waikato Hospital.
Neonates born in the midlands region referred to the Waikato Hospital newborn team.

1.4 Exceptions / contraindications

Due to the non-specific presentation of metabolic conditions and common triggers for acute decompensation other differentials should also be concomitantly considered including but not limited to sepsis.

1.5 Definitions and acronyms

NP	Nurse Practitioner – referring in this context to those who are neonatal specialised.
Medical staff	In NICU this includes Neonatal specialised Nurse Practitioner, Clinical Nurse Specialist, Registrar, Fellow and SMO Paediatricians.
SMO	Senior Medical Officer
IEM	Inborn error of metabolism
Newborn metabolic screening	Screening recommended for all infants at 48 hours of age screening for many major inborn errors of metabolism.

2 Clinical management

2.1 Roles and responsibilities

All Staff:
Identification to the SMO when inborn errors of metabolism are suspected that may require investigation.

Medical staff:
Identification of required investigations, ordering of investigations including appropriate request forms, interpretation of investigations and documentation in clinical notes.

Nursing staff and/or phlebotomists:
Collection of investigation samples, appropriate labelling and appropriate completion of request forms with sample collection details.

2.2 Competency required

- Familiarity with this guideline
- If the course of investigation or interpretation is unclear consult with SMO on duty.

2.3 Referrals and admission

Community:
When IEM is suspected from a community referral urgent transfer/retrieval and admission of the patient should be arranged.

Secondary neonatal units:
When IEM is suspected from a secondary neonatal unit refer to the SMO for urgent phone advice regarding investigation and acute management with consideration of retrieval.

Acute admission:
Contact the SMO for urgent review if an IEM is suspected in an acutely unwell admission to ensure rapid and appropriate investigation and management.

2.4 Equipment and testing guide

Required test tubes and collection process:
Refer to Waikato Hospital laboratory guide or LabLink laboratory guide (http://testguide.adhb.govt.nz/EGuide/) for tube type and transport and/or storage requirements for all samples not commonly requested.

Urgent tests:
If the test is urgent phone the lab to discuss requirements prior to collection as some tests are performed off-site or require the on-call specialist.

2.5 Clinical Presentation: Signs and symptoms

There are three broad categories of IEM: Disorders of intermediary metabolism, Disorders of biosynthesis and breakdown of complex molecules and Disorders of neurotransmitter metabolism (See Appendix A for basic list)

Disorders of intermediary metabolism are more likely to present acutely and be potentially life-threatening, in particularly organic acidemias, urea cycle disorders, maple syrup urine disease, and fatty acid oxidation disorders.

Disorders of neurotrasmitter metabolism can present with severe metabolic encephalopathy.

Disorders involving complex molecules tend to progress more slowly and do not typically cause acute metabolic decompensation, rather presenting with symptoms such as failure to thrive and developmental delay or regression.

2.6 Guideline of investigation

Initial investigations provide a beginning rule-in/rule-out for the wide range of potential differentials, however abnormal results will then commonly require subsequent more in-depth diagnostic testing.

Considerations:

- In some IEM investigation abnormalities may only occur during acute presentation, therefore previous normal results should be repeated before being considered appropriate to rule-out a differential diagnosis.
- In infants greater than three days of age Newborn metabolic screening results may aid diagnosis. Call LabPlus to request urgent results but do not delay diagnostic testing and/or treatment while waiting for results as these are screening tests only.

Initial investigations include:

- Unless otherwise indicated tests require individual samples
- CSF is not a first line test, send these tests only if collecting CSF as part of a septic screen or as indicated by preliminary results.

Source	Investigations:	Testing guide:
Blood	1. Blood gas, glucose, lactate	Capillary blood gas tube or arterial gas syringe
	2. Liver function tests: SBR total and conjugated, ALP, AST, GGT, ALT	Paediatric micro-heparin (light Green) 0.5ml *combined sample for investigations 2&3*
	3. Urea, creatinine and electrolytes (U&E)	
	4. Ammonia	Paediatric micro-EDTA (Purple) 0.5ml on ice
	5. Free Fatty acids	Paediatric micro-EDTA (Purple) 0.5ml on ice
	6. Alanine	Paediatric micro-heparin (light green x2) 1ml on ice
	7. Ketones (β-Hydroxybutyrate)	Paediatric micro-heparin (light green) 0.5ml
	8. Acylcartinine profile	Paediatric micro-heparin (light green) 1ml or single blood spot on newborn metabolic screening card
Urine	Ketones - β-Hydroxybutyrate, acetoacetate)	requires minimum 5ml of urine total for all tests
	Organic acids screen	
	Amino acid screen	
	Glycosaminoglycan (GAG) screen (if lysosomal disorder suspected)	
CSF	Lactate	
	Amino acids	0.5ml on ice -must not be bloodstained

See Appendix B for basic interpretation of biochemical findings

Specific testing and management:
For management or testing of specific inborn errors of metabolism please refer to:

- British Inherited metabolic diseases group guidelines. https://bimdg.org.uk/store/guidelines/Hyperammonaemiaand_manage_2016_415469_09092016.pdf
- Vademecum Metabolicum online resource www.evm.health2media.com/#/menu

2.7 Guideline of investigation in the event of demise without diagnosis

Discuss with the coroner regarding if jurisdiction will be taken for a post-mortem. If jurisdiction is taken these investigations will be completed during the post-mortem. If jurisdiction is not taken the following studies are recommended to aid in post-mortem diagnosis. If death is considered imminent and/or unpreventable these investigations may be commenced prior to death.

1) Blood: on filter paper (may be cardiac if not otherwise available)
2) Plasma: 3-5ml lithium heparin sample (Request lab to separate and freeze sample)
3) Whole blood: 3-5ml EDTA for DNA testing to be refrigerated
4) Urine: 5ml sample in sterile container (Lab to freeze)
5) Blood spots for acylcartinine profile: 2-3 spots on the newborn metabolic screening card
6) Skin biopsy for fibroblast culture: 5mm ^{3} sample in sterile container in transport media from cytogenetics lab. Alternatively can use sterile saline. Kept at room temperature.

7) Muscle/liver/kidney biopsy for enzymology, histology and DNA analysis: 1-3cm sample wrapped in clean tinfoil and frozen in liquid nitrogen or dry ice to -70C; one piece preserved in glutaraldehyde for electron microscopy.
8) Consider: CSF – 1ml sample to be frozen to -70C

Considerations:

- If parents do not want a post-mortem and the coroner declines jurisdiction SMO to discuss this testing with parents prior to collection. Parents may make an informed decision to decline testing.
- Biopsy samples should be collected as soon as possible after death
- If it may take some time to obtain post-mortem samples consider obtaining needle biopsy samples soon after death in discussion with the coroner.
- See LabLink laboratory guide (http://testguide.adhb.govt.nz/EGuide/) for any questions regarding sample collection, storage and transport process.

2.8 Potential complications

In the context of unfamiliar, rare or complex conditions the SMO on duty will consult with the on-call Metabolic Paediatrician at Starship Hospital.

2.9 Follow up

In the event of diagnosis of an IEM that is compatible with life:

- Refer to metabolic paediatric services for follow up +/- general paediatrician follow up
- Consider neurological follow up prior to discharge including GMA and MRI
- Consider requirement for CDC follow up
- Refer to the paediatric dietician for conditions requiring a specialised diet
- Ensure the patient has a registered GP
- Discuss with the family genetic testing re: carrier status and future family planning

In the event of diagnosis of an IEM that is incompatible with life:

- Discuss with paediatric metabolic services starship regarding specific requirements
- Consider discussion with family re: organ/tissue donation
- Please see guideline "Withdrawal of care..."
- Consider referral to Rainbow Place for home or out of hospital palliative care
- Discuss with the family genetic testing re: carrier status and future family planning

3 Links to guidelines for management of inborn errors of metabolism

3.1 Acute management metabolic emergencies

www.bimdg.org.uk/guidelines/guidelines-start.asp

Please follow the link to access British Inherited Metabolic Diseases Group guidelines for emergency management of metabolic conditions. This includes the following categories broken down into specific conditions:

- Emergency management for children
- Undiagnosed problems
- Prospective management for neonates at risk of metabolic diseases

Consider use of Vademecum Metabolicum online resource
www.evm.health2media.com/#/menu

3.2 On-going management of Inborn errors of metabolism

- Genetic metabolic dietitians International https://gmdi.org/Members/Clinical-Practice-Tools/Nutrition-Guidelines
- Management Guidelines Portal https://southeastgenetics.org/ngp/ - Nutritional management guidelines
- British Inherited Metabolic Diseases Group guidelines **www.bimdg.org.uk/guidelines/guidelines-start.asp**
- Consider use of Vademecum Metabolicum online resource www.evm.health2media.com/#/menu

4 Family information

Resources:

1) Human Genetics Society Of Australasia – Resources for parents and families:
This includes TEMPLE resources educational tools to help simply disorder education.
https://www.hgsa.org.au/resources/asiem-resources-for-parents-and-families

5 Evidence base

5.1 Inborn errors of metabolism: Classifications

Within the categories described in *Appendix A* there are various methods for classification for IEM. Common classification categories are listed below, follow the hyperlink for further information regarding each class of IEM.

- 'Amino acid disorders'
  'Organic acidemias'
- 'Urea cycle disorders'
- 'Carbohydrate disorders'

- 'Fatty acid oxidation disorders'
- 'Mitochondrial disorders'
- 'Peroxisomal disorders'
- 'Lysosomal storage disorders'

5.2 Epidemiology and genetics

Conditions are individually rare but when considered together have an incidence of 1:800 to 1:2500 births.

5.3 Bibliography

- Tangye, S., Al-Herz, W., Bousfiha, A., Chatila, T., Cunningham-Rundles, C., Etzioni, A., Franco, J., Holland, S., Klein, C., Morio, T., Ochs, H., Oksenhendler, E., Picard, C., Puck, J., Torgerson, T., Casanova, J., Sullivan, K. (2020). Human inborn errors of immunity: 2019 update on classification from the international union of immunological societies expert committee. Journal of Clinical Immunology, 40(2020), 24-64. Retrieved from: https://link.springer.com/content/pdf/10.1007/s10875-019-00737-x.pdf
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- UpToDate - Metabolic Emergencies in suspected inborn errors of metabolism: presentation, evaluation and management. Retrieved from: https://www.uptodate.com/contents/metabolic-emergencies-in-suspected-inborn-errors-of-metabolism-presentation-evaluation-and-management?search=inborn%20errors%20of%20metabolism&topicRef=2936&source=see_link

Appendix A

Types of inborn errors of metabolism

Disorders of intermediary metabolism
Amino acid metabolism and transport
Fatty acid oxidation and ketogenesis
Carbohydrate metabolism and transport
Vitamin related (cobalamin, folate)
Peptide metabolism
Mineral metabolism
Mitochondrial energy metabolism
Disorders of biosynthesis and breakdown of complex molecules
Purine and pyrimidine metabolism
Lysosomal storage
Peroxisomes
Isoprenoid and sterol metabolism
Bile acid and heme metabolism
Glycosylation
Lipoprotein metabolism
Disorders of neurotransmitter metabolism
Glycine and serine metabolism
Pterin and biogenic amine metabolism
Gamma-aminobutyrate metabolism
Other (eg, pyridoxine-dependent or folinic acid-dependent seizures, sulfite oxidase deficiency)

Source: Hoffman GF, Nyhan WL, Zschocke J, et al. Inherited metabolic diseases, Lippincott Williams & Wilkins, Philadelphia 2002. UpToDate®

Appendix B

Distinguishing biochemical findings of inborn errors of metabolism*

Findings	Maple syrup urine disease	Organic acidemias	Urea cycle defects	Disorders of carbohydrate metabolism	Fatty acid oxidation disorders	Mitochondrial disorders	Peroxisomal disorders	Lysosomal storage disorders
Metabolic acidosis	±	++	-	±	±	±	-	-
Respiratory alkalosis	-	-	+	-	-	-	-	-
Hyperammonemia	±	+	++	-	±	-	-	-
Hypoglycemia	±	±	-	+	+	±	-	-
Ketones	A/H	H	A	A/H	A/L	A/H	A	A
Lactic acidosis	±	±	-	+	±	++	-	-

-: usually absent; ±: sometimes present; +: usually present; ++: always present; A: appropriate production of ketones for the degree of hypoglycemia (eg, ketones are appropriately absent in peroxisomal disorders because hypoglycemia is not a feature of these disorders); H: inappropriately high (eg, 4+ ketones are inappropriately high in the setting of a normal glucose level); L: inappropriately low (eg, ketones are inappropriately low if the blood glucose is <20 mg/dL and the urine ketones are only 1+ or 2+ because they should be significantly elevated in the setting of such extreme hypoglycemia).

* Within disease categories, not all diseases have all findings; for disorders with episodic decompensation, clinical and laboratory findings may be present only during acute crisis; for progressive disorders, findings may not be present early in the course of disease.

Adapted from: Weiner DL. Metabolic Emergencies. In: Textbook of Pediatric Emergency Medicine, 5th ed, Fleisher GR, Ludwig S, Henretig FM (Eds), Lippincott, Williams & Wilkins, Philadelphia 2006. p.1193.