

METABOLIC DISORDERS

Facilitators Guide

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Duration **1-2h**

Facilitator level **Senior trainee/ANP and above**

Learner level **Junior trainee/Staff nurse and Senior trainee/ANP**

Equipment required **None**

OUTLINE

- Basics (15 mins)
- Main session (5x 20 minutes) case discussions covering key points
- Quiz (10 mins)
- Take home tips

PRE-READING FOR LEARNERS

It's helpful for the learners to have read something about the basics of metabolic disorders before the session - these are some suggested resources for them to use

<https://dontforgetthebubbles.com/spotting-the-zebras/>

https://www.rch.org.au/clinicalguide/guideline_index/Hypoglycaemia/

https://www.rch.org.au/clinicalguide/guideline_index/Metabolic_disorders/

<https://www.peminfographics.com/infographics/the-anion-gap>

Additional learning material

<https://pemplaybook.org/podcast/the-undifferentiated-sick-infant/>

<https://www.evelinalondon.nhs.uk/resources/our-services/hospital/south-thames-retrieval-service/metabolic-disorders-jan-2018.pdf>

<https://www.rcemlearning.co.uk/foamed/metabolic-babies-in-the-ed-easy-as-1-2-3/>

<https://dontforgetthebubbles.com/low-can-go-neonatal-hypoglycaemia-hypoexit-trial/>

<http://www.emdocs.net/inborn-errors-of-metabolism/>

Also include your department / region's guidelines for managing children with suspected metabolic conditions and hypoglycaemia.

BASICS

This module presents an approach to acute metabolic presentations, how to identify potential problems and emergency treatment in the ED. You don't need to make a diagnosis (bonus points if you do) but do need to remember that spotting the zebra will lead to more favourable outcomes. Metabolic diseases / disorders are also called inborn errors of metabolism (IEM).

How common are they?

Individually, metabolic conditions are rare, most having an incidence of less than 1 per 100,000 births. However, when considered collectively, the incidence may reach 1 in 800 to 1 in 2500 births (Applegarth et. al, 2000; Sanderson et.al, 2006).

Remember: some symptoms can be unspecific and can mimic sepsis; or a child with an undiagnosed metabolic condition can decompensate with an intercurrent infection.

An easy-to-understand classification by Saudubray divides the IEM in three groups of disorders, depending on how they present.

'Intoxication' disorders

An acute or progressive intoxication from the accumulation of toxic compounds, usually small molecules.

These usually present with a symptom-free interval and clinical signs of 'intoxication', which may be acute, although can be intermittent.

- disorders of **amino acid catabolism**: e.g. phenylketonuria, maple syrup urine disease, homocystinuria, tyrosinemia
- most **organic acidurias**: e.g. methylmalonic, propionic, isovaleric acidaemia
- **urea cycle defects**: e.g. Ornithine transcarbamylase deficiency (OTC deficiency), Citrullinemia type I (ASS1 deficiency).
- **sugar intolerances**: galactosemia
- **metals**: Wilson's, Menkes, hemochromatosis
- **Porphyrias**.

Disorders involving energy metabolism

A deficiency in energy production or utilization, within the liver, myocardium, muscle, brain or other tissues.

Common symptoms include hypoglycemia, hyperlactatemia, hepatomegaly, failure to thrive and cardiac failure.

- **Mitochondrial defects:** congenital lactic acidemias (defects of pyruvate transporter, pyruvate carboxylase, pyruvate dehydrogenase, and the Krebs cycle), mitochondrial respiratory chain disorders and the fatty acid oxidation defects (MCAD deficiency).
- **Cytoplasmic energy defects: disorders of glycogen metabolism** (collectively known as glycogen storage diseases), hyperinsulinism.

Complex molecules disorders

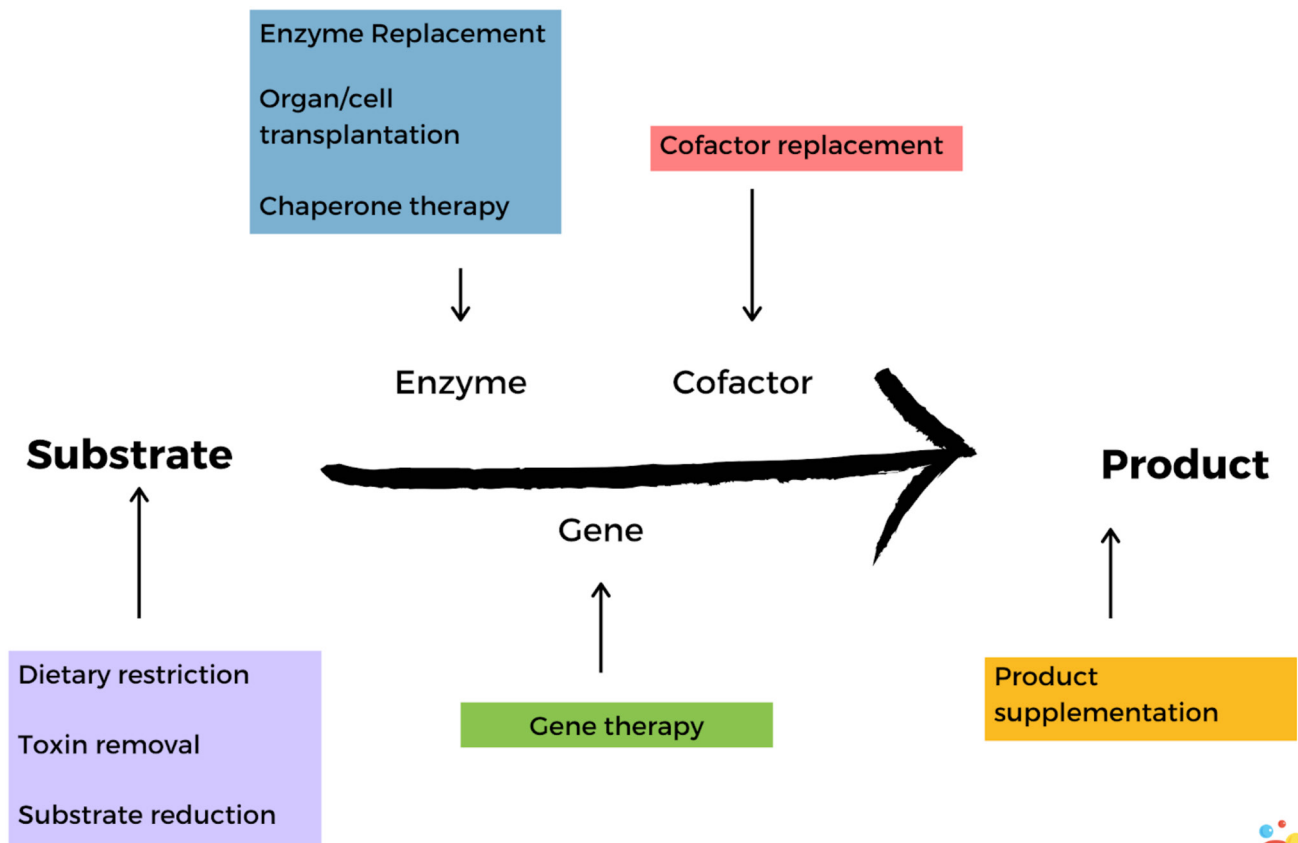
Problems in the synthesis or catabolism of complex molecules, leading to storage of big molecules.

Symptoms are chronic, progressive and independent of intercurrent events or food intake.

- **Mucopolysaccharidosis** (I-IV, VI and VII). The eponymous names are used less frequently now, particularly in the literature, but you might come across them in clinical practice (MPS I, Hurler's Syndrome; MPS II, Hunter's Syndrome; MPS VI, Maroteaux-Lamy)
- **Gaucher disease**
- **Peroxisomal disorders:** e.g. X-linked adrenoleukodystrophy (X-ALD) and Zellweger's Syndrome.

Treatment strategies

Remember your biochemistry: a substrate is transformed by an enzyme into a product .



If there is a problem with the enzyme, there will be more substrate.

If accumulation of the substrate is the problem, we remove it (like avoiding protein in the diet). Or, if the problem is the lack of the product, we can supplement it. And for some diseases the enzyme can be “corrected” (by organ transplantation, enzyme replacement).

A bonus on smells

Due to accumulation of “unusual” products in their body fluids, people with certain metabolic conditions have distinctive odours (better observed in urine, for practical reasons):

- Maple syrup, burnt sugar, curry: Maple syrup urine disease
- Sweaty feet: glutaric aciduria type II, isovaleric acidemia
- Cabbage: tyrosinemia
- Mousy, musty: Phenylketonuria
- Rotting fish: Trimethylaminuria
- Swimming pool: Hawkinsinuria

INTOXICATION' DISORDERS: CASES 1 TO 3

CASE SCENARIO 1

It's early morning in the ED and you are enjoying your coffee. You're called in to see a neonate with a history of irritability and seizures. You enter the room and are told the following: "Emma is a 3 day old, term baby who has been refusing feeds and crying excessively. There has been no history of fever or cough. At home she had seizure-like activity with tonic posturing".

First pregnancy, no antenatal or perinatal problems. Birth: Weight: 2950g, Apgar 9/10. Discharged home on day 2. Irritability since birth. Vomiting after feeds (mixed: breast and formula).

Examination: Awake, extremely irritable, upper limbs flexed, lower limbs extended, global hyperreflexia. No dysmorphic features. Otherwise no positive findings.

Weight: 3050g

Vitals: Temp 36.8°C, HR 155, RR 48, O2 sats 99%, BP wasn't checked.

What are the red flags in Emma's story?

What tests do you want to send?

Discussion points (part 1)

What are the red flags?

- Irritability and excessive crying
- Acute onset of seizures, without any obvious trigger.

What tests do you want to send?

- Blood gas, glucose, U&E, LFTs, CRP, blood culture, urine ketones and MC&S, metabolic screen. Consider CT brain.

**You send some bloods:
FBC, CRP, U&E, LFTs - normal**

Venous blood gas:

- pH: 7.33
- pCO₂: 3.1 kPa*
- HCO₃⁻: 14 mmol/L
- Na⁺: 142 mmol/L
- K⁺: 4 mmol/L
- Chloride: 100 mmol/L

Glucose: 5 mmol/L

Ketones: 2.1mmol/L

Ammonia 184

Urine: Ketones +2, and smells of sweaty feet.

Metabolic screen: plasma amino acids, urine organic acids, acylcarnitine profile sent

***1kPa = 7.5mmHg**

What do you think about these results? (encourage discussion about normal ranges for ammonia, ketones and anion gap)

What treatment will you start in the ED?

For bonus points - can you suggest a diagnosis?

Discussion points (part 2)

What do you think about these results?

- This baby has an acute neurological presentation, with **metabolic acidosis, increased anion gap and mildly elevated ammonia** - suggestive of an **organic acidemia**

- **Ammonia:**

- A normal ammonia level is <50 mol/l but mildly raised values are common, up to 80 mol/l.
- Artificially high values can be caused by muscle activity, haemolysis or delay in separating the sample. Capillary samples are often haemolysed or contaminated and therefore should not be used.
- In neonates, any illness may be responsible for values up to 180 mol/l.
- There's debate as to whether a level of >100 or 200 should be discussed with a metabolic specialist, but if in doubt, follow the RCPCH DeCon guideline and seek advice for any patient presenting with a level >100 .

- **Anion gap (AG)**

- The AG is raised at 32mEq/L $[(Na + K) - (Cl + HCO_3)]$.
- $(142 + 4) - (100 + 14) = 146 - 114 = 32$
- [PEMinfographics](#) have a nice infographic explaining interpretation of anion gaps in children. In the context of a sick neonate with a raised AG, a normal lactate and normal ketones, think organic acids.

- Urine organic acids and blood

acylcarnitines will also be sent as part of this baby's metabolic work-up.

Although the results won't be available to us in ED, the urine organic acid profile will confirm a diagnosis of an organic acidemia, while the blood

acylcarnitine profile will support

the diagnosis as the organic acids conjugate with carnitines creating compounds such as isovalerylcarnitine.

ANION GAP IN BLOOD GAS ANALYSIS

THE DIFFERENCE BETWEEN MEASURED CATIONS (POSITIVELY CHARGED IONS) & ANIONS (NEGATIVELY CHARGED IONS) IN PLASMA



HELPFUL WHEN DETERMINING THE CAUSE OF METABOLIC ACIDOSIS

NORMAL ANION GAP
6-16 MMOLS/L

FORMULA TO CALCULATE AG
 $AG = (Na + K) - (Cl + HCO_3)$

RAISED ANION GAP RESULTS FROM IMPAIRED EXCRETION OF HYDROGEN IONS OR ACCUMULATION OF ORGANIC ACIDS

CAUSES OF A RAISED ANION GAP:
LACTIC ACIDOSIS
KETOACIDOSIS
RENAL FAILURE
RHABDOMYOLYSIS
TOXINS/POISONS
ORGANIC ACIDAEMIA

NORMAL ANION GAP RESULTS FROM LOSS OF BICARBONATE

CAUSES OF A NORMAL ANION GAP:
DIARRHOEA
RENAL TUBULAR ACIDOSIS
TPN
ADDISON'S DISEASE

What treatment will you start in the ED?

• It's important to think about your differentials. Sepsis is the most common - these conditions can mimic sepsis, or decompensation can be triggered by an infection, always cover with broad spectrum antibiotics. But don't forget non-accidental injury and other differentials - the baby is likely to need a CT head if presenting encephalopathic or with seizures.



T	Trauma
H	Heart
E	Endocrine (congenital adrenal hyperplasia / thyrotoxicosis)
M	Metabolic (hypoglycaemia / hyponatraemia)
I	Inborn errors of metabolism
S	Sepsis
F	Formula
I	Intestinal
T	Toxins
S	Seizures

- Manage seizures in the usual way.
- Specific emergency treatment of her metabolic presentation requires
 - stopping sources of protein (milk)
 - avoiding catabolism (by giving glucose IV - 2mL/kg 10% glucose)
 - rehydration (IV fluids resuscitation and maintenance)

For bonus points - can you suggest a diagnosis?

- The “sweaty feet” smell is a clue to the diagnosis of Isovaleric Acidaemia. Remember that this condition can be part of the Newborn Screening in some countries (Ireland, UK, Australia, New Zealand).
- Isovaleric acidaemia is a type of organic acidemia, inherited in an autosomal recessive way. It is caused by a problem with the enzyme that usually breaks down the amino acid leucine. This amino acid accumulates and is toxic at high levels, causing an ‘intoxication’ encephalopathy. The sweaty feet smell is

stronger without treatment or during acute exacerbations.

- Maple Syrup Urine Disease (MSUD) is another organic acidaemia, associated with sweet smelling urine during decompensation. These children cannot break down leucine, valine and isoleucine. They may not have hypoglycaemia, hyperammonemia or acidosis and, if not picked up on newborn screening, can be diagnosed late, resulting in neurological sequelae.

Key take home

- **Sick neonates with metabolic acidosis, increased anion gap and mildly elevated ammonia may have an organic acidemia.**
- **Treatment is to stop feeds, prevent catabolism with 10% dextrose (and standard electrolytes for IV maintenance) and cover for sepsis with IV antibiotics, whilst considering other differentials.**

CASE 2

The next baby you see is remarkably like Emma but with a subtle difference. Lucy is a 3 day old baby, presenting with poor feeding, irritability and seizures at home. There has been no fever, cough, coryza, or sick contacts.

Examination: Awake, extremely irritable, upper limbs flexed, lower limbs extended, global hyperreflexia. No dysmorphic features. You notice that she seems tachypnoeic, although lungs are clear.

Vitals: Temp 36.8°C, HR 155, RR, O2 sats 98%, BP wasn't checked.

Glucose = 5 mmol/L Ketones = 0.1 mmol/L

VBG: respiratory alkalosis

Venous blood gas:

- pH: 7.48
- pCO₂: 3.1 kPa*
- HCO₃⁻: 24 mmol/L
- Na⁺: 135 mmol/L
- K⁺: 4 mmol/L
- Chloride: 99 mmol/L

*1kPa = 7.5mmHg

What are the key differences between Lucy's and Emma's presentations?

What is the anion gap?

What does a respiratory alkalosis make you suspicious of?

Discussion points (part 1)

What are the key differences between Lucy's and Emma's presentations?

- Lucy is tachypnoeic and has a respiratory alkalosis
- Emma, on the other hand, had a metabolic acidosis with a normal respiratory rate

What is the anion gap?

- $AG = 16 \text{ mEq/L}$
- $(Na + K) - (HCO_3 + Cl) = (135 + 4) - (99 + 24) = 139 - 123 = 16$
- Unlike Lucy's case, this baby has a normal anion gap.

What does a respiratory alkalosis make you suspicious of?

- Hyperventilation

The lab phones you with Lucy's ammonia result. It's 1250.

Why does Lucy have a respiratory alkalosis?

What do you think the diagnosis is?

What treatment do you want to start in ED?

Discussion points (part 2)

Why does Lucy have a respiratory alkalosis? What do you think the diagnosis is?

- This baby have a neurological acute presentation, with respiratory alkalosis and extremely elevated ammonia - suggestive of a urea cycle disorder
- High ammonia stimulates the brain stem respiratory centre, causing hyperventilation and, as consequence, respiratory alkalosis

What treatment do you want to start in ED?

- Overall treatment is similar to case 1: cover for sepsis, manage seizures and consider differentials.
- As with organic acidaemias, the initial (specific) treatment requires
 - stopping sources of protein (milk)
 - avoiding catabolism (by giving glucose IV - 2mL/kg 10% glucose)
 - rehydration (IV fluids resuscitation and maintenance).

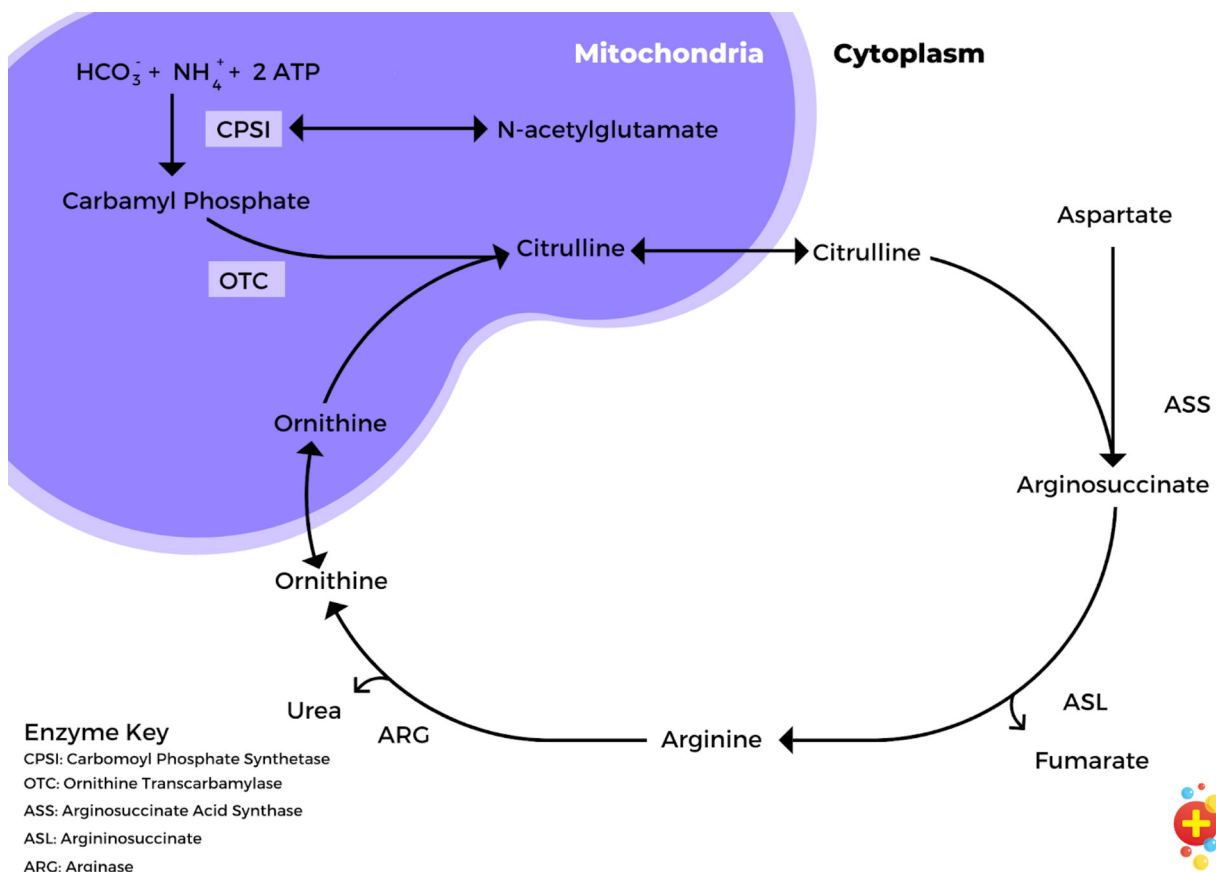
- In urea cycle disorders, the toxic metabolite is ammonia, so ammonia scavengers are used, all given intravenously:

- sodium benzoate
- phenylbutyrate
- arginine

- A nice guideline on the management of hyperammonemia secondary to an undiagnosed cause can be found on the [British Inherited and Metabolic Disease Group](#) website.

- **Urea cycle disorders** are autosomal recessive inborn errors of metabolism. A defect in one of the enzymes of the urea cycle, which is responsible for the metabolism of nitrogen waste from the breakdown of proteins, leads to an accumulation of ammonia as it cannot be metabolised to urea. The urea cycle is also the only endogenous source of the amino acids arginine, ornithine and citrulline.

- The most common urea cycle disorder is OTC deficiency. Unlike the other urea cycle disorders (which are autosomal recessive), OTC deficiency is x-linked recessive, meaning most cases occur in male infants. Female carriers tend to be asymptomatic.



- Classically, urea cycle disorders present in the neonatal period with vomiting, anorexia and lethargy that rapidly progresses to encephalopathy, coma and death if untreated. In these circumstances, ammonia accumulates leading to a very high plasma ammonia.

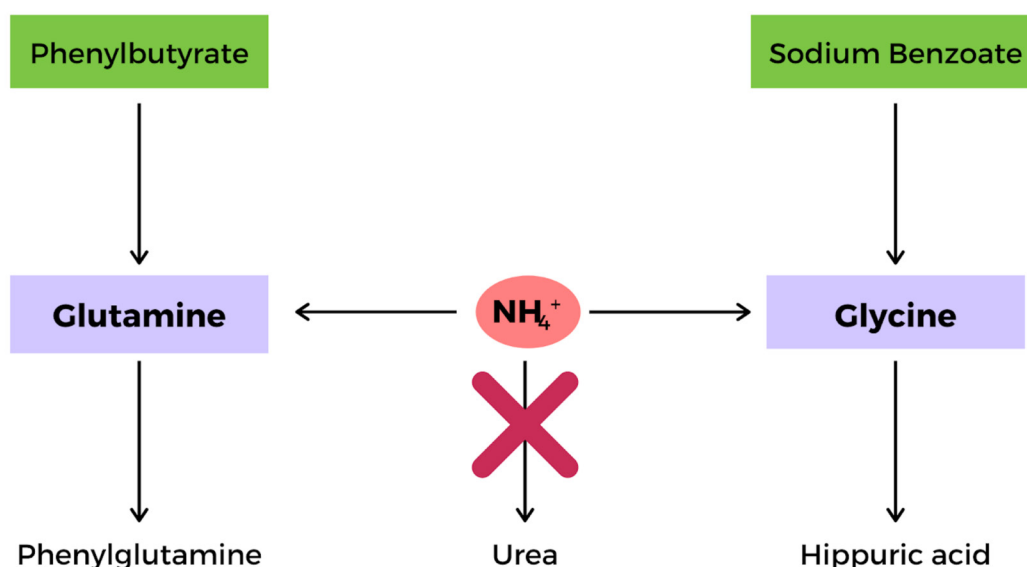
- Respiratory alkalosis is a common early finding caused by hyperventilation secondary to the effect of hyperammonemia on the brain stem, although later the respiratory rate slows as cerebral oedema develops and an acidosis is seen.

- Children presenting in infancy generally have less acute and more variable symptoms than in the neonatal period and include anorexia, lethargy, vomiting and failure to thrive, with poor developmental progress. Irritability and behavioural problems are also common. The liver is often enlarged but, as the symptoms are rarely specific, the illness is initially attributed to many different causes that include gastrointestinal disorders. The correct diagnosis is often only established when the patient develops a more obvious encephalopathy with changes in consciousness level and neurological signs.

- Adolescents and adults can present with encephalopathy and or chronic neurological signs.

- **Ammonia scavengers**

- In urea cycle defects, ammonia cannot be converted to urea so instead is converted to glutamine and glycine.
- Ammonia scavengers phenylbutyrate and sodium benzoate can be given - they offer alternative pathways for ammonia excretion through urinary pathways.
- Phenylglutamine and hippurate are produced and are excreted in urine.



Take home

- **Sick neonates with respiratory alkalosis, normal anion gap and very elevated ammonia may have a urea cycle defect.**
- **Emergency treatment is the same as for an organic acidaemia plus ammonia scavengers.**

CASE 2.1

Jane, 14 years old, is brought in by ambulance unconscious after a generalized tonic clonic seizures at home lasting at least 20 minutes. While doing the standard resuscitation steps, you talk to her mother. You learn that she has been a healthy child with no chronic conditions, no history of drug abuse, no acute illness. She's a vegetarian and enjoys dancing. It's the Coronavirus pandemic, so she has been at home for the last 3 weeks. She's started a new 'intermittent fasting diet' and yesterday, hadn't eaten since brunch. She went to bed early and this morning her mother was woken early by strange sounds coming from Jane's room and found her seizing on the floor.

Physical exam: GCS 10/15, hyperreflexia. No dysmorphic features .
You notice that she seems tachypneic, although lungs are clear.

Vitals: Temp 37.4°C, HR 112, RR 30, O2 sats 100% on supplemental oxygen (started at the ambulance), BP 110/70 mmHg.

You send some bloods:

Glucose = 5 mmol/L Ketones = 0.1

VBG: respiratory alkalosis

Ammonia = 650 (normal <40)

Anion gap = 15 (normal)

LFTs: slightly above reference levels

FBC, U/E, CRP normal


What are your differential diagnoses?

What key points in this case point you towards a metabolic disorder?

Discussion points

What are your differential diagnoses?

- This adolescent has an acute onset of neurological symptoms. The differential diagnoses are broad but a red flag for a metabolic condition is that her encephalopathy was precipitated by prolonged fasting.
- The RCPCH decon guideline lays out an approach to the child with a decreased conscious level, including differentials, investigations and management (take a look at the DeCon poster and summary guidance).



Royal College of Paediatrics and Child Health
Leading the way in Children's Health

THE MANAGEMENT OF CHILDREN AND YOUNG PEOPLE WITH AN ACUTE DECREASE IN CONSCIOUS LEVEL (DECON)

Population: Children aged from 4 weeks up to 18 years who have a decreased conscious level†

IDENTIFY DECON

1

Identify DeCon

GCS ≤ 14
AVPU = P or U

See 'Neurological assessment' box

2

Perform DeCon specific ABCD

A • Intubate if GCS <9, AVPU = U or if there is suspected/proven raised intracranial pressure* See 'Signs of raised ICP' box

B • 100% Oxygen if oxygen SaO₂ <95%

C • If circulation compromised give 10 ml/kg isotonic fluid bolus if DeCon associated with either signs of raised intracranial pressure (ICP) or ketoacidosis (as opposed to 20 ml/kg)*

D • Perform a capillary glucose test ≤15 minutes of presentation* if capillary blood glucose <3 mmol/L give 2ml/kg of 10% dextrose and consider a hypoglycaemia screen

• In a child with a clinical diagnosis of raised ICP, before imaging consider sedation, intubation and ventilation to maintain the PaCO₂ between 4.5 and 5.0 kPa

*Based on consensus methodology or weaker evidence

3

Take core investigations

Point of care tests Capillary blood glucose, Blood gas (arterial, capillary or venous) for pH, PCO₂, BE, Lactate & Urine dipstick

Laboratory tests Glucose, U&Es, LFTs, FBC, Blood culture, Ammonia (venous or arterial only)

Saved samples 10ml of urine for later analysis including toxicology

4

Start observations

Record hourly:
HR, RR, SaO₂, BP, Temp, physical state/appearance

Continuously monitor:
SaO₂, ECG

Consider differential diagnoses

DIFFERENTIAL DIAGNOSIS

1

Hypertensive encephalopathy

Investigation • Look for signs of raised ICP + papilloedema
• Do 4 limb BP
• Urinalysis for blood/protein + U&Es

PICU and NEPHROLOGY • Discuss when DeCon + Hypertension (BP >95th centile for age)

2

Intracranial infection

Differential • Bacterial meningitis
• Herpes Simplex Encephalitis (HSE)
• Intracranial abscess
• TB meningitis

Investigation • LP including CSF HSV PCR if no contraindications
See 'LP WARNING' box

Treatment • Bacterial: www.nice.org.uk/guidance/ig102
• HSE: Acyclovir (Duration decided by local ID experts)
• TB: www.nice.org.uk/guidance/ig107

3

Metabolic

Hypoglycaemia • Hypoglycaemia screen if lab Glucose <3mmol/L
• 2ml/kg bolus 10% Dextrose
• Treat infusion of 10% Dextrose (Target 4-7mmol/L)

Hyperammonaemia • If plasma level >100micromol/L
• Send a free flowing venous (or arterial) sample of ammonia to the laboratory, which should be informed it is coming. Samples should be transported on ice in case of a delay before analysis which might affect the interpretation
• SEEK EXPERT METABOLIC ADVICE

DKA www.ksped.org.uk/media/7629/bsped-dka-aug15.pdf

4

Raised ICP

Diagnosis See 'Signs of raised ICP' box

Treatment • Refer to the NICE Bacterial meningitis and meningococcal septicaemia guideline for recognition and fit
www.nice.org.uk/guidance/ig102

PICU • Discuss acute management with local PICU
• Position head in midline
• 20° head up tilt
• Avoid internal jugular CVCs
• Isotonic fluids (restricted)
• Manual or hyperventilate saline
• Intubate and ventilate to a PaCO₂ of 4.5-5.0 kPa BEFORE IMAGING

5

Prolonged fits/Post convulsive

Investigation Mg²⁺ and Ca²⁺ and Na⁺

PICU **Discuss treatment if:**
• Na⁺ <125 mmol/L
• Ionised Ca²⁺ <0.75 mmol/L
• Mg²⁺ <0.65 mmol/L
and the convulsion is ongoing despite anticonvulsant treatment

6

Cause unclear

Consider additional tests and involvement of specialists e.g. Neurologist or Metabolic expert

Investigation **Additional tests:**
• CT/MRI
• LP
• Urine Toxicology
• Urine organic and plasma aminoacids
• Plasma lactate/EEG

7

Sepsis

Diagnosis T>38°C or <35.0°C or T101 or T102
WCC >12x10⁹/L or <4x10⁹/L or a purpuric rash

Investigation • CRP
• Blood PCR (meningococcus/pneumococcus)
• Clotting
• Skin swabs (from areas of inflammation)
• Joint aspiration (if septic arthritis)
• Thick and film film (for malarial parasites if foreign travel to endemic area)

Treatment Broad spectrum antibiotics <1 Hour + Follow 'Sepsis 6 pathway'
https://www.survivingsepsis.org/RunDrs/Pages/default.aspx
• EARLY SENIOR REVIEW

8

Alcohol intoxication

Investigation Consider blood alcohol test when suspected as a cause of DeCon

Treatment • ABCD/PLS
• Treat hypoglycaemia with iv glucose + maintenance Dext/Saline
• Treat severe and if present treat respiratory failure/aspiration pneumonia and hypothermia
• Other concurrent ingestions
• And avoid emetics (in case of aspiration)

Consideration • Consider all other likely contributory drugs
• Consider contacting local poisons unit

9

Shock

Diagnosis Mottled, cool extremities or diminished peripheral pulses + systolic BP <5th centile for age or urine output <1ml/kg/hr

Differential Sepsis, trauma, anaphylaxis, heart failure

Treatment 20 ml/kg isotonic fluid bolus (10 ml/kg if raised ICP or ketoacidosis)

Reassessment ↓ HR
↓ Capillary refill time
↓ Level of consciousness See 'Neurological assessment' box
↓ Blood pressure (to normal level for age)
↓ Lactate concentration and/or improvement in base excess
↑ in urine output

PICU Consider for intubation/ventilation/nitroglycerin if >40ml/kg fluid given

10

Neurological assessment

GLASGOW COMA SCORE (GCS)

Eyes	Motor	Voice
4 Open	6 Obeys commands	5 Oriented
3 To command	5 Localises pain	4 Confused
2 To pain	4 Flexion withdrawal	3 Inappropriate words
1 No response	3 Abnormal flexion	2 Incomprehensible
	2 Abnormal extension	1 No response

GCS MODIFICATIONS IN CHILDREN UNDER 5 YEARS

Motor	Voice
6 Normal spontaneous movements	5 Alert, babble, coo, words or sentences to usual ability
5 Localises to unpleasant pain (SOP) or withdraws from touch	4 Less than usual ability, intubate cry
4 Withdraws from noxious pain	3 Cries to pain
	2 Moans to pain

AVPU SCALE

A = Alert V = Responds to voice P = Responds to pain U = Unresponsive

11

Observation - normal ranges

Age	Respiratory Rate	Heart Rate	Systolic BP
Neonate	30	100	70
<1 year	35-45	100-160	75
1-5 years	25-35	95-140	80-90
5-12 years	20-25	80-120	90-100
>12 years	adult	adult	100-120

12

Signs of raised ICP

BRADYCARDIA (Heart rate <60 bpm) OR HYPERTENSION (MAP >95th centile for age)

Pupillary dilation (unilateral or bilateral) OR loss/impairment of reaction to light

Abnormal breathing pattern OR posture

! LP WARNING

Do not attempt an LP if...
• There are signs of raised ICP (Even if GCS is 15)
See 'Signs of raised ICP' box
• GCS <8 or deteriorating OR focal neurological signs OR GCS <12 after a seizure lasting >10 minutes.
• CT/MRI suggesting CSF pathway obstruction
• Clinical evidence of circulatory shock/meningococcal disease

†This does not include: Children with a previously diagnosed condition which may decompensate causing a decreased conscious level (e.g. epilepsy, ventriculo-peritoneal shunt, previously diagnosed metabolic condition), who already have an agreed management plan for acute illness. OR Children who on a day to day basis score 14 or less on the Glasgow Coma Scale or Modified Glasgow Coma Scale (e.g. children with epileptic encephalopathy, minimally responsive state following accepted brain injury).

- **All** children presenting with a decreased conscious level, regardless of age, should have an ammonia sent as part of their initial investigation in ED.
- In late onset urea cycle defects, acute metabolic encephalopathy develops following metabolic stress precipitated by a rapid increase in nitrogen load from
 - infection, trauma, rapid weight loss and auto-catabolism, increase in protein turnover from steroids, surgery, childbirth or other precipitants of protein catabolism.
- Adolescents and adults with an undiagnosed urea cycle defect may be completely fit and well, but may have chronic symptoms such as headache, cyclical vomiting, behavioural difficulties, psychiatric symptoms or mild learning difficulties.
- They may be selective vegetarians, restricting their protein intake.
- Between episodes patients are relatively well. However, acute presentations can be fatal or patients may be left with a neurological deficit, so the learning point is to always send an ammonia in any child presenting with an acute encephalopathy.
- Two cases reports your team may find interesting
 - <https://jmedicalcasereports.biomedcentral.com/articles/10.1186/s13256-015-0741-2>
 - <https://www.mja.com.au/journal/2015/203/11/initial-presentation-urea-cycle-disorder-adulthood-under-recognised-cause>

Key take home

- **Send ammonia as part of your investigation of adolescents presenting with a decreased conscious level**

CASE 3

It's 11am on Easter Monday in Dublin. Ellie-Mae is a 6 day old baby, born at 37 weeks via SVD, in Wales while her mother was visiting some friends.

When Ellie-Mae was 3 days old her mother returned to Ireland to stay with her own mother, for some early baby support. Since day two of life Ellie-Mae has been vomiting after feeding. She is bottle fed and since yesterday she has only been accepting half of each bottle, but mother thought it was tiredness from the long trip.

Ellie-Mae's mother brought her to the ED this morning because she has been quiet, hasn't been crying as usual with nappy changes and seemed too sleepy to take this morning's bottle.

Pregnancy: Mother 21 years old, G1P1, no problems.

Birth: SVD at 37/40, BW 2.9kg, no resus, no NICU. She was jaundiced on the second day of life, but below phototherapy levels.

Family history: healthy parents from the Irish Traveller Community.

Physical exam: Weight 2.45kg (16% below birth weight), jaundiced, lethargic. Anterior fontanelle is sunken, and Ellie-Mae looks dehydrated. You can palpate the liver 2 cm below the right costal margin. No spleen palpable. Otherwise no positive findings.

Vitals: Temp 37°C, HR 185, Capillary refill time 3 seconds, RR 55, BP systolic = 102 mmHg (crying), O2 sats 97%

What are the red flags in Ellie-Mae's case?

Discussion points (part 1)

What are the red flags in Ellie-Mae's case?

- History: vomiting and lethargy
- 16% weight loss by day 6 of life
- Examination: jaundice and a palpable liver

You take some bloods:

Glucose 2.0mmol/L

Ketones = 6 mmol/L

VBG metabolic acidosis - hyperchloremic

Venous blood gas:

- pH: 7.32
- pCO₂: 4 kPa
- HCO₃⁻: 20 mmol/L
- Na⁺: 135 mmol/L
- K⁺: 3.5 mmol/L
- Chloride: 95 mmol/L

When you see Ellie-Mae's low glucose level you send a hypoglycaemia screen.

You also send FBC, U&E, LFTs, clotting, ammonia and blood culture

LFTs: AST 70U/L, ALT 75U/L, Bilirubin total 255 µmol/L, direct 60µmol/L, Alkaline phosphatase 270U/L

INR 1.8

Ammonia 47

How do you investigate hypoglycaemia?

What treatment do you want to start in ED?

Do these tests make you suspicious of any diagnoses?

Discussion points (part 2)

How do you investigate hypoglycaemia?

- Discuss your institution's hypoglycaemia guideline - which tests to send, where to find the bottles and Guthrie cards.
- Discuss the differential diagnoses of hypoglycaemia. Refer to the following material:
 - https://www.rch.org.au/clinicalguide/guideline_index/Hypoglycaemia/
 - <https://www.paediatricfoam.com/2017/04/neonatal-hypoglycaemia/>

Test	Expected result	Abnormal result	Causes of abnormal result
Insulin	Low	Normal/ High	Infant of diabetic mother Congenital Hyperinsulinism Islet cell adenoma Beckwith-Wiedemann Syndrome
Cortisol	High	Low	Adrenal insufficiency Pan-hypopituitarism
GH	High	Low	Pan-hypopituitarism Isolated GH deficiency
Ammonia	Normal	High	Urea cycle disorders Organic acidaemias Hyperinsulinism
Lactate	Normal	High	Glycogen storage disorders (GSD) Sepsis
3 β -Hydroxybutyrate	Mildly raised	Low High	Hyperinsulinism Fatty acid oxidation defects Organic acidaemias
NEFA	Mildly raised	Low	Hyperinsulinism
Amino acids		Abnormal profile	Ketotic hypoglycaemia Aminoacidopathies Urea cycle defects
Acyl carnitine		Abnormal profile	Fatty acid oxidation defects Organic acidaemias
Urine organic acids		Abnormal profile	Fatty acid oxidation defects Organic acidaemias
Urine ketones	Mildly raised	Low High	Fatty acid oxidation defects Organic acidaemias

Reproduced from the PaediatricFOAMed post [Sweet Nothings? Hypoglycaemia in the Neonate](#)

Do these tests make you suspicious of any diagnoses?

- Hypoglycaemia, this neonate has hepatomegaly and raised liver enzymes point towards a diagnosis of **galactosaemia**.
- Some countries screen for galactosaemia in their newborn screening programmes (Ireland, UK, New Zealand, some parts of Australia). Because of its autosomal recessive inheritance, galactosaemia is more common in some ethnic groups.
- In the Irish travelling community, for example, the incidence is higher than the rest of the populations, so babies born to parents from the travelling community are specifically screened on day 1 of life in Irish maternity hospitals. The baby's diet should exclude galactose, so newborn babies of Irish travelling families are given soy-based formula rather than breast feeds or standard formula until their screening test result is known.

What treatment do you want to start in ED?

- The initial investigation and management of hypoglycaemia: this baby needs Glucose 10% 2mL/kg IV as soon as possible. Collect blood prior to treatment.
- Management is similar to the previous cases:
 - Clinical stabilisation
 - Antibiotics
 - stop feeds
 - Correct hypoglycaemia with 2ml/kg 10%
 - Give maintenance fluids with electrolytes to maintain hydration as per your local policy

A bit about Galactosaemia

- Galactosaemia occurs due to a defect in the enzyme galactose-1-phosphate uridyl transferase (GALT). It presents after the affected patient receives the sugar galactose, present in milk. Accumulation of galactose-1-phosphate results in damage to the brain, liver, and kidney. The affected neonate presents with vomiting, hypoglycaemia due to an inability to metabolise glucose, feeding difficulty, seizures, irritability, jaundice, hepatomegaly, liver failure, cataracts, splenomegaly, and Escherichia coli sepsis. The condition presents with metabolic acidosis. Source: [Gene Reviews](#)

DISORDERS INVOLVING ENERGY METABOLISM.

ADVANCED CASE 4

Liz is a 3 year old girl from the countryside, who is visiting her grandmother in the city. She has been having diarrhea since yesterday and started vomiting last night. In the last 3 hours she hasn't been able to tolerate anything orally. There has been no fever or respiratory symptoms and she is passing urine as normal. Her 5 years old cousin has similar symptoms.

Her Grandmother informs you that Liz has MCAD deficiency and her emergency plan was tried at home, without success. Liz is not usually treated at your hospital and you don't have her chart. Unfortunately Liz's grandmother didn't think to bring the plan to hospital.

Physical exam: Liz looks tired and is mildly dehydrated, but smiles at you.

Her heart sounds are normal and her chest is clear. She has increased bowel sounds, a soft abdomen with mild diffuse pain on deep palpation and no masses or organomegaly.

Vitals: Temp 37°C, HR 165, capillary refill time 3 seconds, RR 32, BP systolic = 104mmHg, O2 sats 97% in air.

Glucose 2.5 mmol/L, Ketones 0.4 mmol/L

What is the priority in Liz's treatment?

Is her ketone response appropriate to the degree of hypoglycaemia?

Liz's grandmother told you Liz has MCAD Deficiency, but what is it?

Where can you find resources to help you manage Liz?

Discussion points

What is the priority in Liz's treatment?

- Liz has MCADD and needs extra calories when she is sick. The most important intervention is to give simple carbohydrates by mouth (e.g. glucose tablets or sweetened, non-diet beverages) or intravenously if needed to reverse catabolism and sustain anabolism. Liz is vomiting all oral intake so cannot tolerate oral carbohydrates, so the intravenous route is necessary.

Is her ketone response appropriate to the degree of hypoglycaemia?

- No, it's not. The body's response to prolonged fasting is to break down fat to create ketones to be used as an alternative source of energy. Liz has not produced ketones, because she is unable to break down fat.

Liz's grandmother told you Liz has MCAD Deficiency, but what is it?

- Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is the most common fatty acid oxidation disorder in Caucasians in Northern Europe and the United States. Most children are now diagnosed through newborn screening.
- Children with fatty acid oxidation disorders (medium, long and short chain defects) have typical **acylcarnitine** patterns. This is one of the reasons acylcarnitines are sent as part of metabolic and hypoglycaemia work-ups.
- Clinical symptoms in a previously apparently healthy child with MCAD deficiency include **hypoketotic hypoglycemia** and vomiting that may progress to lethargy, seizures, and coma, triggered by a common illness. Hepatomegaly and liver disease are often present during an acute episode.
- Children appear well at birth and, if not identified through newborn screening, typically present between three and 24 months of age, although presentation even as late as adulthood is possible.
- The prognosis is excellent once the diagnosis is established and frequent feedings are instituted to avoid any prolonged periods of fasting. Gene reviews <https://www.ncbi.nlm.nih.gov/books/NBK1424/>

Where can you find resources to help you manage Liz?

- The British Inherited Metabolic Disease Group, BIMDG, has specific guidance on their [website](#), including
 - Correct hypoglycaemia immediately with 200mg/kg glucose: 2 ml/kg of 10% glucose or 1ml/kg of 20% glucose, over a few minutes.
 - Treat shock or circulatory compromise with a bolus of 20ml/kg 0.9% sodium chloride.
 - Give maintenance fluids with potassium once the plasma potassium concentration is known and the child is passing urine.

DISORDERS INVOLVING STORAGE OF COMPLEX MOLECULES

ADVANCED CASE 5

Mike is 12 years old, presenting to the ED with cough and fever. He has been coughing for 10 days, worse progressively in the last five and febrile in the last 3 days. Since yesterday he just wants to sleep and even when afebrile he looks unwell. Appetite is poor and he has been “sipping some apple juice”. You learn from his mother that he has a condition called Mucopolysaccharidosis (MPS) type I and is on treatment with “the enzyme”. Every now and again, “he is chesty and needs to come to hospital”.

Physical exam: Pink, hydrated, but looks sick. You notice that he is shorter than an average 12 year old boy, has hand contractures and coarse facial features. Cardiovascular: systolic murmur, +2/+6. Good pulse volume. Respiratory: creps and rhonchi on the right side. Abdominal exam: mild hepatomegaly. Umbilical hernia.

Vitals: Temp 37.5°C, HR 132, RR 30, BP systolic = 112mmHg, O₂ sats 88% in air.

What is Mike’s clinical diagnosis and what treatment do you want to start in the ED?

Discussion points

What is Mike’s clinical diagnosis and what treatment do you want to start in the ED?

- Patients with Mucopolysaccharidosis don’t require any emergency treatment in the ED for their underlying metabolic disease. They are, however, at increased risk of respiratory infections.
- Mike is likely to have a community acquired pneumonia and needs to be treated accordingly with oxygen and antibiotics.

A bit about mucopolysaccharidoses

- **In mucopolysaccharidosis disorders, the body is unable to break down mucopolysaccharide sugar chains. These mucopolysaccharide sugars buildup in cells, blood and connective tissue: hence the name, ‘storage disorders’.**

- In general, most affected people appear healthy at birth and experience a period of normal development, followed by a decline in physical and/or mental function.
- As the condition progresses, it may affect appearance; physical abilities; organ and system functioning; and, in most cases, cognitive development.
- Most cases are inherited in an autosomal recessive manner, although one specific form (Type II) follows an X-linked pattern of inheritance.
- Specific treatment can be provided via Enzyme replacement therapy or haematopoietic stem cell transplantation in the early stages.
- Presently, enzyme replacement therapy is available for MPS I, II and VI and is given as an intravenous infusion either weekly or biweekly, depending on the disease.
- Both enzyme-replacement and haematopoietic stem cell treatments still have gaps and few clinical trials supporting them. (rarediseases.info; Dornelles et.al, 2014).

SIMULATION (30-60 MINS)

See the APLS online sim scenario, page 54-57:

http://www.aplsonline.com/pdfs/Simulation_Scenarios.pdf

MCQS

Question 1.

A neonate presents with extreme irritability and vomiting. Which laboratory tests can be most helpful in identifying an underlying inherited metabolic condition?

- | | | | |
|---------------------|---------------------|-----------------|---------------------------------|
| A
Ammonia | B
Glucose | C
LDH | D
Coagulation profile |
|---------------------|---------------------|-----------------|---------------------------------|

Irritability and vomiting are nonspecific presentations for a broad range of neonatal conditions. An elevated ammonia can help guide you towards a metabolic condition, such as organic acidemias and urea cycle disorders.

Question 2.

Hypoglycaemia with low ketones are an _____ response, it can lead us to think of _____ diagnosis.

- | | |
|-----------------------------------|--|
| A
Appropriate, sepsis | C
Inappropriate, diabetes |
| B
Appropriate, diabetes | D
Inappropriate, fatty acid oxidation disorders. |

The body's response to prolonged fasting is to break down fat to create ketones that will be used as an alternative source of energy. So in hypoglycaemic states, high ketones will be observed. If ketones are low, it's because the body is unable to break down fat properly, such as in fatty acid oxidation disorders.

Question 3.

Which tests are part of the investigation of hypoglycemia?

- A Insulin and GH
- B Amino acids (plasma)
- C Ketones
- D All the above

The basic screen aims to identify the most common endocrine or metabolic conditions responsible for hypoglycemia. Usually it involves: glucose, ketones (Beta-hydroxybutyrate), insulin, cortisol, Growth Hormone (GH), ammonia, lactate, free fat acids, serum amino acids, acylcarnitines profile (Guthrie card) and urine for organic acids and ketones.

Question 4.

Extremely high ammonia can be usually found in which condition?

- A Hyperinsulinism
- B Phenylketonuria
- C Urea Cycle disorders
- D MSUD

Ammonia can be increased for a range of reasons (muscle activity, haemolysis, neonatal sepsis), however in urea cycle disorders these levels are the highest observed. The urea cycle is responsible for the metabolism of nitrogen waste from the breakdown of proteins, because one of these enzymes are deficient, it leads to an accumulation of ammonia as nitrogen cannot be metabolised to urea.

Question 5.

Which of the following is incorrect regarding Anion Gap (AG)?

- A The AG is the difference between primary measured cations and the primary measured anions.
- B Potassium (K⁺) is the most important cation for AG calculation.
- C Commonly measured anions are Chloride and Bicarbonate.
- D AG is useful in understanding causes of metabolic acidosis.

If not available, the anion gap can be calculated without Potassium, in this situation the reference range will be different (12 ± 4 mEq/L).

Take home tips

- 1** Common is common. Treat for common diseases while looking for rare differential diagnoses.
- 2** You don't need to make a specific diagnosis in the emergency department but don't forget metabolic conditions while investigating sick patients. The early symptoms are often non-specific and initially, therefore, the diagnosis is easily overlooked.
- 3** Have a low threshold for sending basic metabolic investigations: plasma amino acids, urine organic acids and acylcarnitines. The ammonia result will be back quickly and will help you manage the child acutely.
- 4** Hypoglycemia requests immediate action in children. Collect relevant samples and treat as soon as possible.
- 5** Atypical smells can help you with the differential diagnosis. You don't need to remember the specific condition; suspecting a metabolic disorder and collecting relevant samples is enough.
- 6** Do not panic. Patients with diagnosed metabolic disorders usually carry an emergency plan. If not, reliable online resources can help. Also, the opposite is true: patients with some metabolic disorders might not require any different acute treatment from other children with a similar presentation.

REFERENCES

Adam , HH. Ardinger, RA. Pagon, S. E. Wallis, L. J. H. Bean, K. Stephens, & A. Amemiya (Eds.), GeneReviews® [online book].

Applegarth DA, Toone JR, Lowry RB. Incidence of inborn errors of metabolism in British Columbia, 1969-1996. *Pediatrics*. 2000 Jan;105(1):e10.

Dornelles AD, de Camargo Pinto LL, de Paula AC, Steiner CE, Lourenço CM, Kim CA, Horovitz DD, Ribeiro EM, Valadares ER, Goulart I, Neves de Souza IC, da Costa Neri JI, Santana-da-Silva LC, Silva LR, Ribeiro M, de Oliveira Sobrinho RP,

Giugliani R, Schwartz IV. Enzyme replacement therapy for Mucopolysaccharidosis Type I among patients followed within the MPS Brazil Network. Genet Mol Biol. 2014

Sanderson S, Green A, Preece MA, Burton H. The incidence of inherited metabolic disorders in the West Midlands, UK. Arch Dis Child. 2006 Nov;91(11):896-9.

Saudubray J-M, Baumgartner MR, Walter JH. (editors) Inborn Metabolic Diseases. Diagnosis and treatment. 6th Edition. Springer 2016.

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