Hyperammonemia and inborn errors of metabolism (IEMs):

Known and novel applications for differential diagnosis

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Point of discussion

- **Introduction**
  - Definition
  - Primary vs. secondary hyperammonemia
- **Clinical presentation**
- **Biochemical background**
- **Hyperammonemia and inborn errors of metabolism**
- **Differential diagnosis of Hyperammonemia**
- **Treatment options**
- **Summary**

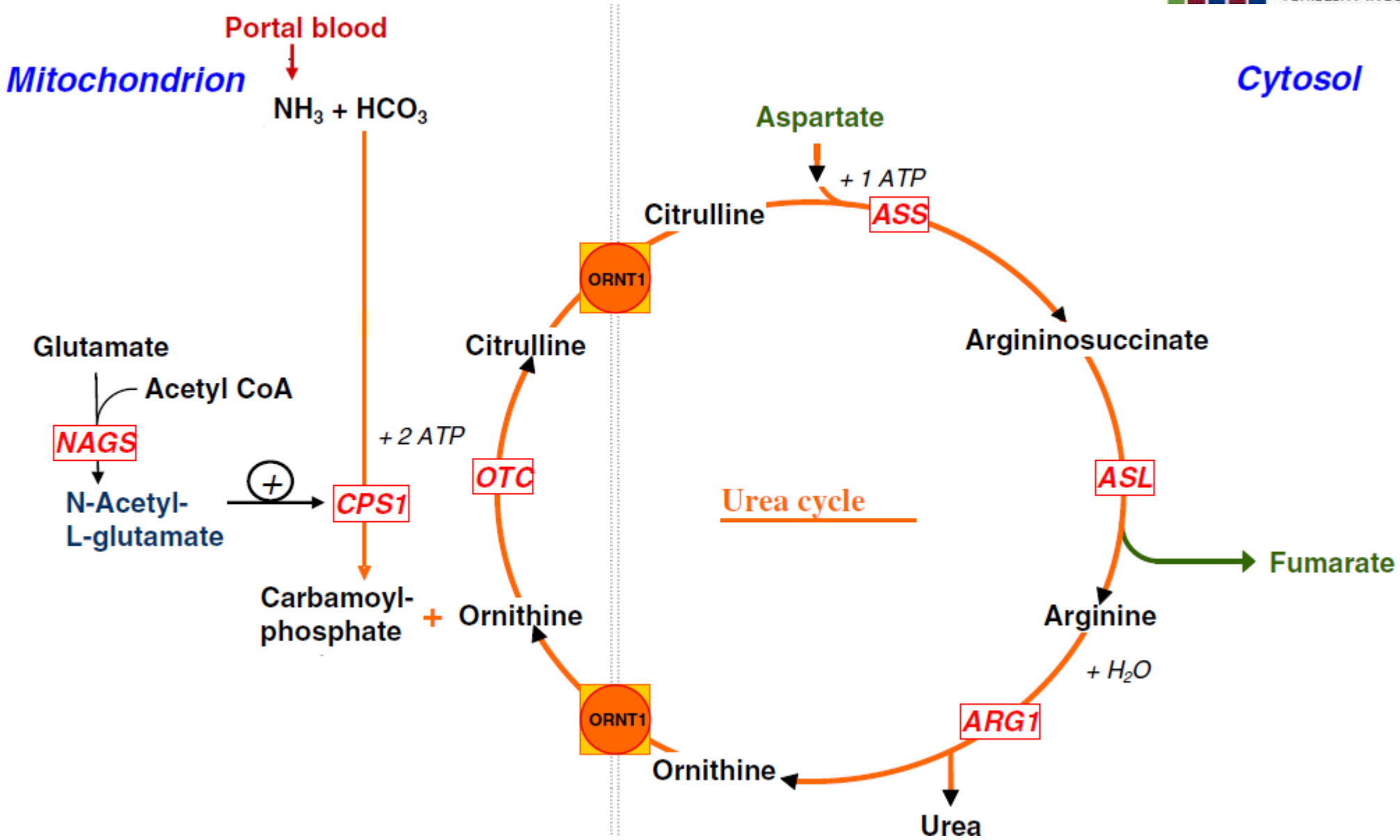
Introduction

- **Hyperammonemia: clinical condition associated with ↑ ammonia levels → neurological complications**
- **Plasma ammonia exceeds:**
  - 100 µmol/L in newborns
  - 50 µmol/L in older individuals
  - > 100 µmol/L SUSPECT AN IEM
- **Primary → enzyme/transporter deficiencies in the urea cycle**
- **Secondary / acquired → conditions affecting urea cycle indirectly**
  - Organic acidemia, Fatty acid oxidation disorders
  - Drug induced and hepatic illness/dysfunction not related to an IEM

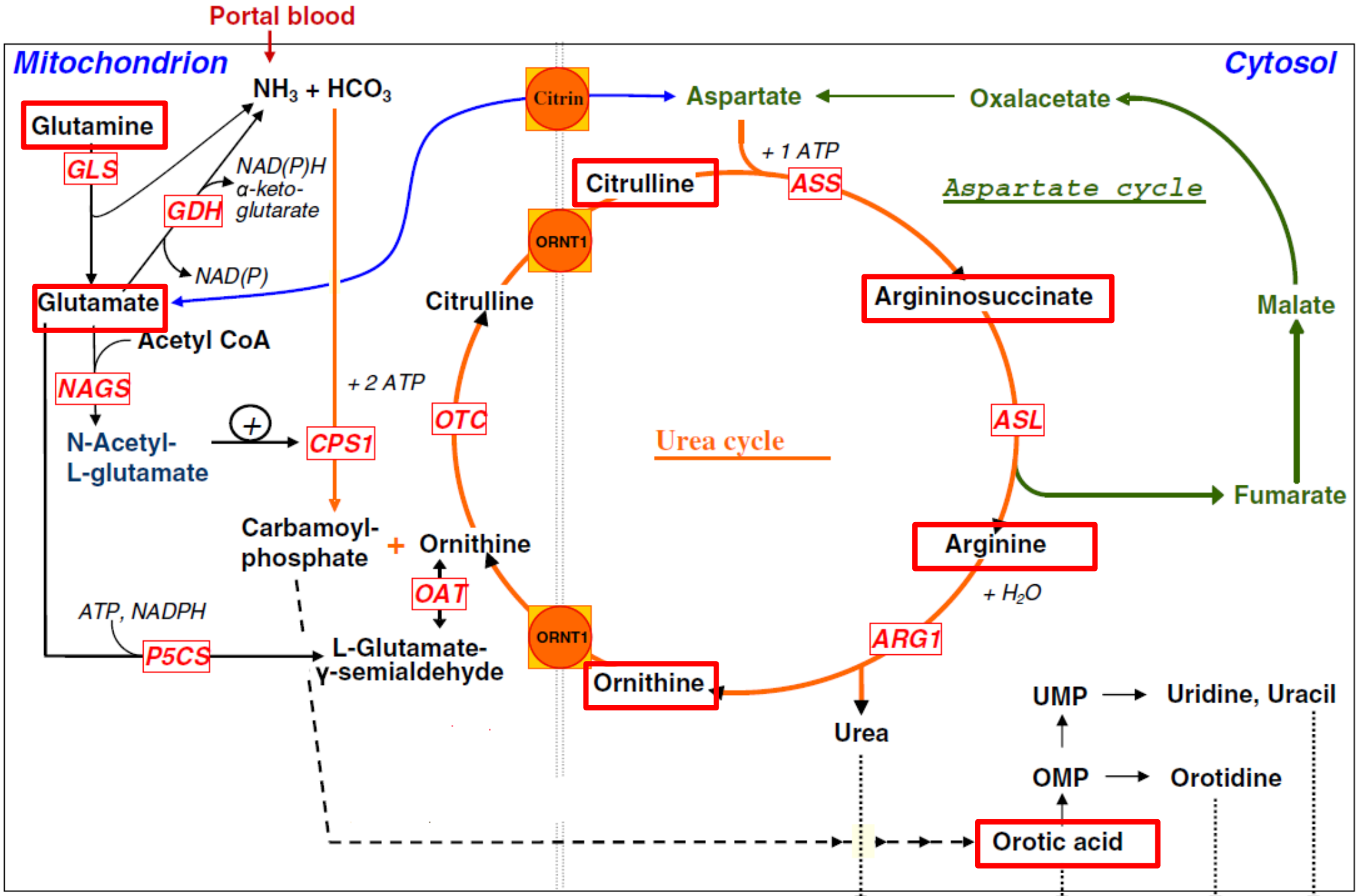
The lost clue for differential diagnosis of an IEM

Clinical presentation

Age group	Gastro-intestinal	Neurological	Psychiatric
Neonates	**+++** Poor feeding, gastroenteritis	**+** Coma/death	**-**
Infants to children	**++** Feeding problem → poor weight gain	**+++** Seizures, intellectual impairment, headaches/migraines	**+** Irritability, hyperactivity, sleep disturbances
Adolescents to adults	**+** Protein avoidance	**+** Intermittent ataxia, intellectual impairment, headache/migraines	**+++** Irritability, hyperactivity, manic episodes, psychosis, sleep disturbances



Modified figure: Häberle *et al*. Orphanet Journal of Rare Diseases 2012, 7:32



Modified figure: Häberle *et al*. Orphanet Journal of Rare Diseases 2012, 7:32

Mechanism of ammonia toxicity in the brain

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X **Urea cycle function**

NH^3

NH^3

↓ **2-ketoglutaric acid** → **Glutamate** → ↑ **Glutamine** (osmotic property) → H_2O inward transport – swelling of brain cells

↓

Impaired Kreb cycle function

↓

Low energy production in the brain

↓

1. ↓ energy production and impaired function in the brain

2. Activation of NMDA receptors → ↑ ROS → damage astrocytes in brain

Common IEMS associated with Hyperammonemia

Organic acidemias

- Short chain organic acids has a direct influence on NAGS and CPS1 activity
- NH^3: ↑-↑↑↑ (Dercksen et al 2014).

Hyperinsulinemia-Hyperammonemia (HIH) syndrome

NH^3: ↑-↑↑↑ with hypoglycaemia

Urea cycle disorders (UCDs)

- Defective conversion of NH^3 to Urea
- Enzyme disorder NH^3 : ↑-↑↑↑
- Transporter and secondary enzyme defect NH^3: n-↑↑

Fatty acid oxidation and carnitine transporter disorders

- mitochondrial and hepatic dysfunction
- NH^3: n-↑↑

IEMS resulting in secondary hepatic dysfunction:

- NH^3: n-↑
- Tyrosinemia, galactosemia, α_1-antitrypsin deficiency

Non-IEMS resulting in hyperammonemia

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Illness and infection

Increased Ammonia Production	Decreased Ammonia Elimination
Infection	Liver failure
Urease producing bacteria (Proteus, Klebsiella)	Fulminant hepatic failure
Herpes infection	Trans-hepatic, intrajugular Shunt
Protein load and increased catabolism	Portosystemic shunt (TIPSS)
Severe exercise	
Seizures	
Trauma or burns	
Steroid administration	
Chemotherapy	
Starvation	
Gastric bypass	
GI hemorrhage	
Increased renal ammonia production	
Increased splanchnic ammonia production	
Increased peripheral catabolism due to deficiency of essential amino acids	
TPN	
Other	
Cancers (multiple myeloma)	

*TIPSS = transjugular intrahepatic portosystemic shunt.

Medication

Drugs Associated With Fulminant Hepatic Failure	Drugs Associated With UCDs
Acetaminophen	Glycine
Lipid-lowering agents: atorvastatin	Salicylates
Antiinflammatories: ibuprofen, celecoxib, diclofenac	Valproate
Anesthetics: halothane	Carbamazepine
Antibiotics: amoxicillin, amoxicillin clavulonate, flucloxacillin, telithromycin, moxifloxacin, levofloxacin, trovafloxacin, minocycline, sulfamethoxazole, trimethoprim	Sulfadiazine
	Pyrimethamine
	TPN
HIV medications: indinavir, nevirapine	
Antifungals: fluconazole, terbinafine	
Anti-tuberculous medications: isoniazid, rifampin, rifabutin, pyrizinamide	
Antiparasitic: dapsone	
Anti-epileptics: carbamazepine, valproate, phenytoin, phenobarbital	
Anti-depressants: nefazadone, sertraline, duloxetine, buproprion	
Other psychoactive: lamotrigine, donepezil, disulfiram	
Illegal drugs: MDMA (ecstasy)	

*MDMA = 3,4 methylenedioxymethamphetamine.

Clay et al 2007, Hyperammonemia in the ICU. CHEST 2007, 132:1368-1378

Initial establishments of hyperammonemia

- **Should be included if IEM is suspected**
  - Challenges: Instability issues → Delayed analysis result in falsely elevated ammonia value
    - Collection without tourniquets
    - Sample should be put and transported on ice immediately after collection
    - Analyze immediately (no more than15-30 min after collection)
- **Point-of-care device is available**
  - Small/mobile clinics and home support for families with IEMS

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EMERGENCY BLOOD AMMONIA MEASUREMENT

Routine Chemistry

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Occurrence/ Parameter	UCD #	OA	FAO disorder *	HIH syndrome
Acidosis	-/+	+ - +++	-/+	-
Ketonurie	-	+ - ++	-	-
Hypoglycaemia	-	+/-	-	+
Lactate	-	+ - ++	+	-
Liver function (AST/ALT)	Mostly +	-	-/+	-
Creatine Kinase	-	-	+	-

*During fasting/metabolic crisis
Urea cycle transporter disorders may have normal routine chemistry
Note: Additional conditions resulting in hyperammonemia may include: mitochondrial disorder, pyruvate carboxylase deficiency, ornithine amino transferase deficiency, LPI, liver related IEMs

Modified table: Häberle *et al*. Orphanet Journal of Rare Diseases 2012, 7:32

Specialized metabolic testing

Metabolic testing	UCD	OA	FAO disorders	HIH syndrome
Amino acids (Specifically glutamine and citrulline)	√√ (B and U)			
Organic acids		√√ (U)	√ (U)	
Orotic acid	√ (U)			
Free carnitine and Acylcarnitines		√ (U)	√√ (B and U)	
DNA	√			√

- Additional tests to excluded galactosemia, tyrosinemia, ornithine amino transferase deficiency, and α_1-antitrypsin deficiency is also recommended
- NB: Exclude non-IEM hyperammonia

Enzyme and DNA testing

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- **Unexplained hyperammonemia without significant abnormality in metabolite profile may require Enzyme and DNA testing**
- **Example NAGS and CPS1 deficiency**

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Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com

A novel UPLC-MS/MS based method to determine the activity of *N*-acetylglutamate synthase in liver tissue

Marli Dercksen [a, b, *], Marinus Duran [a], Lodewijk IJlst [a], Wim Kulik [a], Jos P.N. Ruiter [a], Arno van Cruchten [a], M. Tuchman [c], Ronald J. A Wanders [a]

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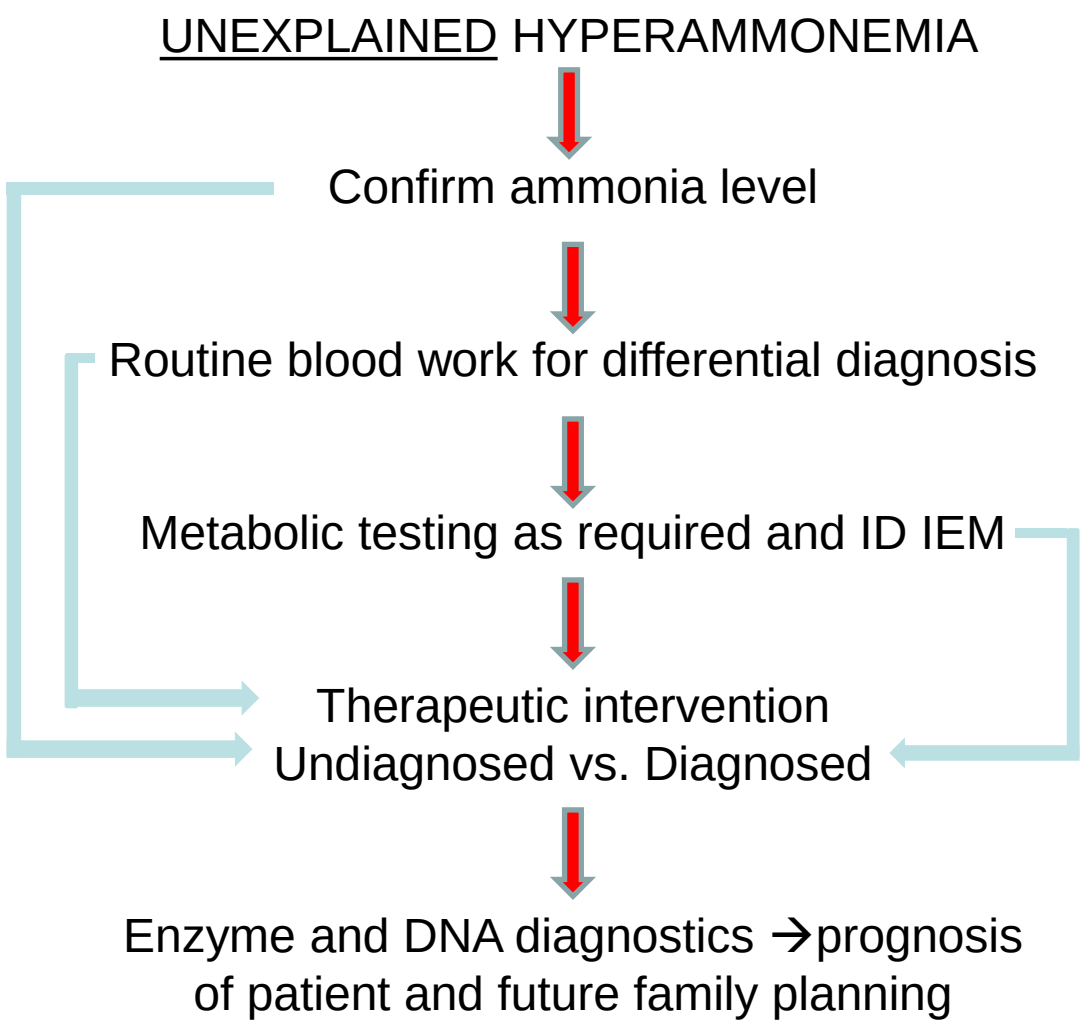
Therapeutic intervention

Ammonia level (µmol/l)	Undiagnosed	Diagnosed*
Above upper limit of normal	Limit/stop protein intake	Same as for undiagnosed
	IV glucose, avoid fasting	
>100 but < 250 (neonates) >150 but < 250 (older patients)	Same as above	Same as above
	Nitrogen scavengers (sodium benzoate and phenylbutyrate)	Start supplementation and nitrogen scavengers according to the protocol of each disorder • UCD disorders: Carbaglu ®, L-Citrulline, L-Arginine • OA disorder: L-Carnitine and Glycine for IVA • FAO disorders: +/- MCT feeding/L-Carnitine • HIH: Diazoxide
	Intermediate/detoxifier and cofactor administration: (L-arginine, L-carnitine, biotin and Vit B12)	
250-500	Same as above	Same as for undiagnosed
	Prepare for dialysis	
	Begin dialysis, if no rapid drop of ammonia within 3–6 hours	
500	Same as above	Same as for undiagnosed
	Dialysis	

* Treatment plan should be revised according to specific diagnosis and adjusted according to acute vs. chronic presentation

Modified table from Alfadhel *et al*., 2016. Guidelines for acute management of hyperammonemia in the Middle East region. Therapeutics and Clinical Risk Management 12:479–487

SUMMARY


UNEXPLAINED HYPERAMMONEMIA
Confirm ammonia level
Routine blood work for differential diagnosis
Metabolic testing as required and ID IEM
Therapeutic intervention
Undiagnosed vs. Diagnosed
Enzyme and DNA diagnostics →prognosis
of patient and future family planning

Thank you

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