REVIEW ARTICLE

Asparaginase-associated hyperammonemia

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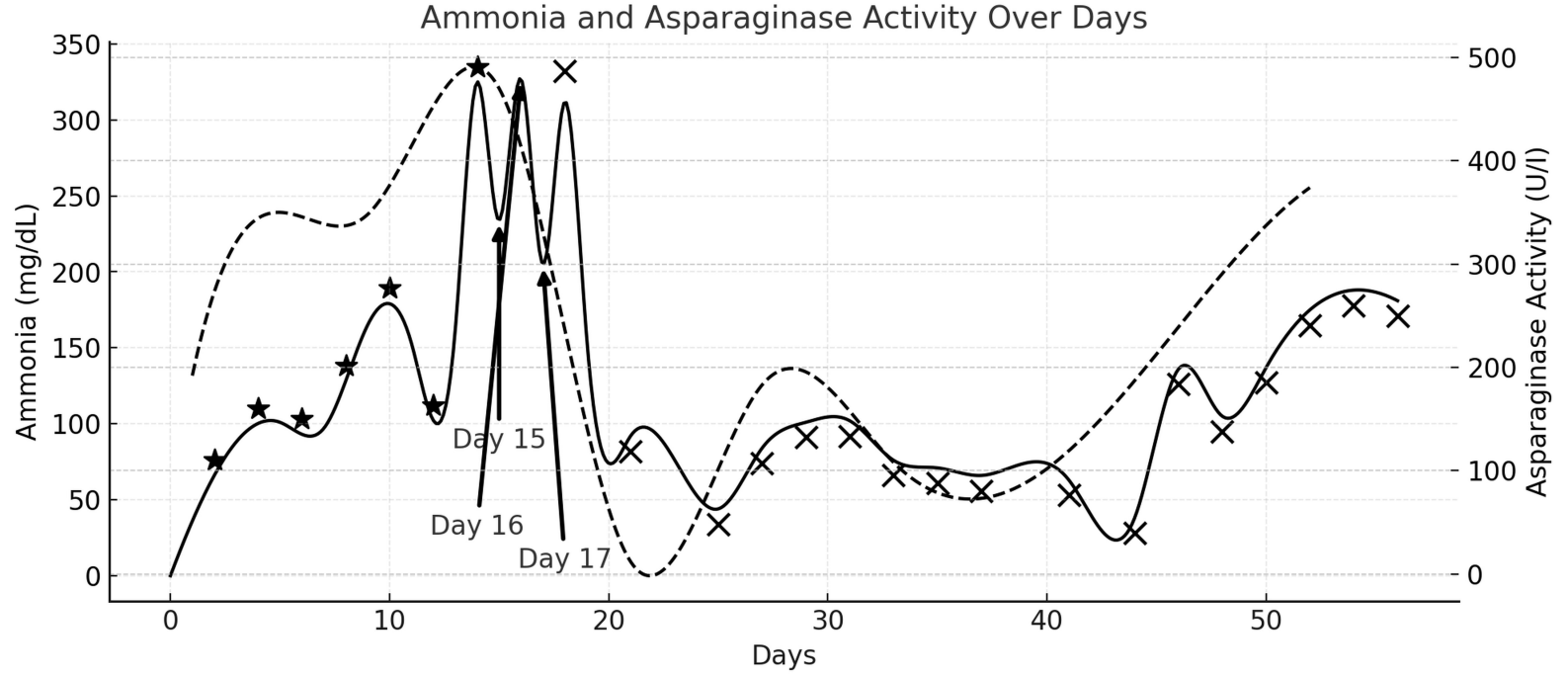

Ammonia Levels (solid line)
Asparaginase Activity (dashed line)
Erwinase 20.000 IU/m² (★)
Erwinase 15.000 IU/m² (X)
Arrow Day 15: Addition of protein restriction, 10% glucose infusion, and sodium benzoate
Arrow Day 16: Reduction of Erwinase dosing and cessation of protein restriction
Arrow Day 17: Cessation of 10% glucose infusion and sodium benzoate

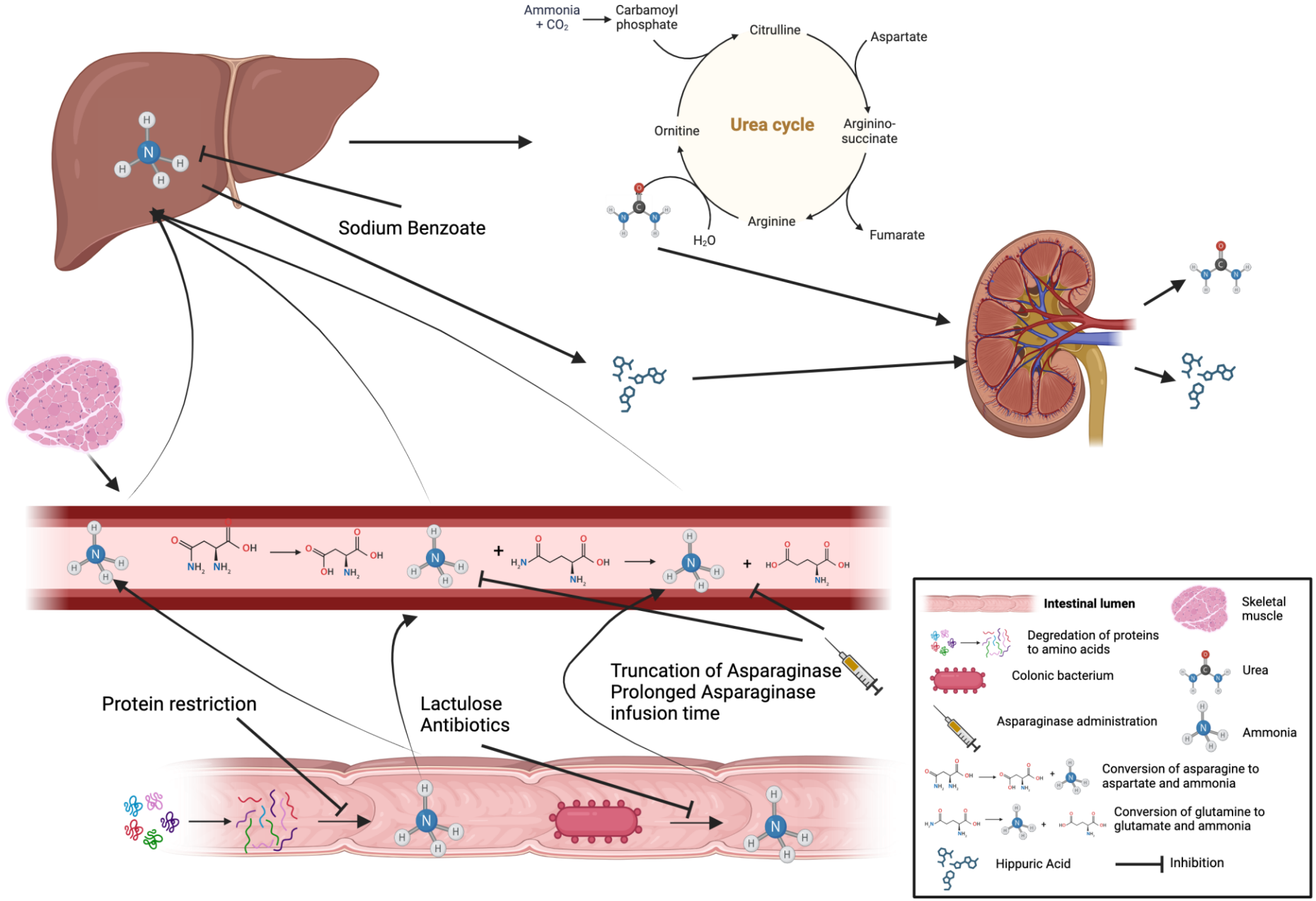
Ammonia + CO_2
Carbamoyl phosphate
Citrulline
Aspartate
Urea cycle
Ornitine
Arginino-succinate
Arginine
Fumarate
H_2O
Sodium Benzoate
Protein restriction
Lactulose
Antibiotics
Truncation of Asparaginase
Prolonged Asparaginase infusion time
Intestinal lumen
Skeletal muscle
Degredation of proteins to amino acids
Colonic bacterium
Urea
Asparaginase administration
Ammonia
Conversion of asparagine to aspartate and ammonia
Conversion of glutamine to glutamate and ammonia
Hippuric Acid
Inhibition

Figure and table legends:

Figure 1:

Shows possible interventions according to CTCAE grade of encephalopathy.

Table 1:

Studies assessing Asparaginase associated hyperammonemia

Supplemental Figure S1:

Depiction of ammonia levels and Erwinase activity in a 10-year-old boy with a late, isolated ALL relapse. Due to hypersensitivity, he was treated with Erwinase 20.000 IU/m² with a total of 28 doses planned.

After the sixth dose, he became increasingly lethargic, and after the seventh dose, he briefly lost consciousness. Seizures and thrombosis were excluded, and treatment with Erwinase 20.000 IU/m² continued. Due to persistent lethargy, protein restriction, 10% glucose infusion, and sodium benzoate were introduced on day 15 (black arrow). On day 16 (black arrow), the Erwinase dose was reduced to 15.000 IU/m² and protein restriction was stopped, and on day 17 (black arrow), protein restriction, 10% glucose infusion, and sodium benzoate were stopped. The patient continued on Erwinase 15.000 IU/m², and symptoms subsided, although ammonia levels remained elevated.

Ammonia levels (smooth solid line), **Asparaginase activity levels** (smooth dashed line), **Timing of Erwinase doses; 20.000 IU/m²** (★), **15.000 IU/m²** (X).

Days shown on the x-axis represent days after the initiation of Erwinase treatment.

Supplemental Figure S2:

Shows ammonia metabolism when Asparaginase is administered. In the intestines ammonia is a by-product of bacterial metabolism during the digestion of proteins. In skeletal muscle ammonia is a result of the breakdown of amino acids. When asparaginase is administered, ammonia is produced from the hydrolyzation of asparagine and glutamine to aspartate, glutamate, respectively as well as ammonia.

Ammonia is transported to the liver where it enters the urea cycle and is incorporated into urea, which is excreted through the kidneys.

Interventions administered in patients with AAH are also highlighted. Lactulose and antibiotics inhibit the absorption/production of ammonia in the intestines. Sodium benzoate leads to synthesis of hippuric acid via conjugation with glycine, thus reducing nitrogen to be catabolised in the urea cycle and thus reducing ammonia production. Hippuric acid is excreted from the kidneys. Withdrawal of Asparaginase or prolonging Asparaginase administration time decreases the ammonia produced from the hydrolysis of glutamine and asparagine.