5-FU Induced Hyperammonemnic Encephalopathy
Tanvi Shah1
1 School of Pharmacy, MCPHS University, Boston, Massachusetts, USA

BACKGROUND
• Hyperammonemnic encephalopathy (HE) is a serious delayed, adverse side effect induced by 5-fluorouracil usually occurring 1.5-4 days after the start of chemotherapy.1
• 5-Fluorouracil is an antimetabolite pyrimidine analog used primarily to treat various forms of cancer, particularly in slow growing cancers like ovarian, colorectal, gastric, and breast cancers. The adverse side effects include nausea, vomiting, diarrhea, stomatitis, neutropenia, and thrombocytopenia – due to bone marrow suppression, mucositis, myelosuppression, hand-foot syndrome, rarely cardiac toxicity.2 One of the rarer side effects that can occur due to 5-FU is HE.
• Encephalopathy describes a disease affecting the function and/or structure of your brain. There are several different types, some of them are permanent and some of them are reversible/temporary.

INTRODUCTION
Pathophysiology of 5-FU Induced Hyperammonemnic Encephalopathy
• Due to these mechanisms discussed, ammonia levels increase exponentially. Astrocytes convert ammonia to glutamine, however when there is too much ammonia conversion to glutamine, the excess glutamine compromises the astrocyte structure and function, causing astrocyte swelling.
• It is important to note that the astrocytes are in charge of neurotransmitter, removal and maintenance of the blood brain barrier, and blood flow. The astrocyte swelling then causes increased intracranial pressure and encephalopathy.
• Additionally, high concentrations of glutamine and ammonia cause cerebral damage, oxidative stress and failure of neurotransmitter systems. Furthermore, the astrocyte swelling and oxidative stress leads to cell apoptosis.6

OBSERVATIONS
• 5-FU induced (HE) is a metabolic condition that manifests as altered mental status with elevated ammonia levels and no hepatic involvement. Whereas hepatic encephalopathy has a completely different etiology, by ruling out liver involvement, we can distinguish the types of encephalopathy from one another. Hyperammonemnic and hepatic encephalopathy are easily confused for one another since both of them lead to cognitive abnormalities.3
• Aggravating factors of 5-FU induced hyperammonemnic encephalopathy include renal dysfunction, dehydratation, constipation, body weight loss, 1
• Some other medications that can induce hyperammonemnic encephalopathy valproic acid, aminophylline, sulfinpyrazone, and methamphetamines.
• Signs and symptoms include psychomotor, intellectual, and cognitive abnormalities usually evolving to respiratory alkalosis and then metabolic acidosis.4

Mechanisms Resulting in Hyperammonemnic Encephalopathy
1. Fluorooacetate build up: 5-FU metabolism produces fluorooacetate which inhibits the Krebs cycle which leads to a decrease in ATP production and inhibits the glutamate dependent and nitrogen scavenging pathways.
2. Lactulose: decreases the intestinal production and absorption of ammonia.
3. After recovering from HE the patient will still need to be on chemotherapy for cancer treatment, patients can be rechallenged with:
   1. Capecitabine
   2. Lowered dose of 5-FU

METHODS
Keywords were entered into Pubmed to find papers, MeSH terms such as 5-fluorouracil and (HE) were used.

RESULTS
In order to treat the patients (HE) we need to decrease the ammonia levels which can be done by giving:
1. Branched chain amino acids (BCAA): which have shown excellent results when administered, aids with ammonia metabolism.
2. Lactulose: decreases the intestinal production and absorption of ammonia.
3. After recovering from HE the patient will still need to be on chemotherapy for cancer treatment, patients can be rechallenged with:
   1. Capecitabine
   2. Lowered dose of 5-FU

3. Tegafur-uracil (1:4) molar ratio: by taking tegafur which is an oral 5-FU prodrug with uracil which is a DPD substrate, the 5-FU is slowly released, reducing the side effects of the fluorooacetate, due to slower degradation of 5-FU.
4. Most cases of 5-FU induced encephalopathy spontaneously improve, recurrence is possible when given to the same patient. It is hard to find an alternative some medioc's that are safe as all are contraindicated, however the outcomes were disappointing.
5. If the provider attempts to rechallenge the patient with 5-FU there are several things that can be done with the 5-FU infusion which can reduce the risk of hyperammonemic encephalopathy
6. Low-protein diet: By restricting protein intake, it leads to less amino acid build up therefore reducing the risk of ammonia build up. A low-protein diet also limits the nitrogen release that occurs due to protein catabolism.7
7. Hydration with 5% glucose: Which is done to provide enough energy/ATP without overloading the deficient Krebs cycle.
8. Carbaglutamic acid: Which promotes the first step of the urea cycle in an attempt to detoxify ammonia.
9. Sodium benzoate: A nitrogen scavenger, which reduces the ammonia plasma levels.
10. Anaplerotic substrates: To prevent a cataplerotic state oral alpha ketoglutarate and ornithine are given to provide intermediates for the Krebs and urea cycle. The alpha ketoglutarate is a substrate in the Krebs cycle while the ornithine converts excess ammonia into urea, aiding with ATP production and ammonium detoxification.
11. Vitamins: Such as vitamin B1 to help with protein metabolism, riboflavin to help with nitrogen metabolism, and biotin to decrease blood ammonia.
12. Essentially the supplements provide the body with as many materials to keep the Krebs cycle going which is important since the Krebs cycle helps with ammonium detoxification. By giving these additional substances we are trying to prevent the recurrance of HE.

REFERENCES
3. Raitt M, Singson C, McAnulty J, et al. 5-FU-induced hyperammonemic encephalopathy in a case of Metastatic Rectal Adenocarcinoid Successfully Rechallenged with the Fluoropyrimidine Analog, Capecitabine

CONCLUSIONS
• 5-FU Induced HE prevention strategy recommendations
• There are currently no recommendations for management except for immediate discontinuation of 5-FU infusions associated with hydration and a low-protein diet.
• In this case ammonium chelators (sodium benzoate or sodium phenylacetate) could be used or Urea and Krebs cycle intermediates.
• More research needs to be done in order to identify potential predictive markers of cataplerosis which is indicative of 5-FU induced HE (ex. Plasma lysine)