Hyperammonemia After Lung Transplantation: Best Practice Recommendation

Kathryn Anna Bradley

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Kathryn Bradley
Student Name (printed)

Kathryn Bradley
Student Signature

1/27/17
Date
Dedication

I would like to express my deepest gratitude to Haley Hoy, PhD, ACNP, for her support, generosity, and willingness to go above and beyond to help me on this research study. Dr. Hoy aided this study every step of the way, and for that I am indebted. I would also like to thank Ann Bianchi, PhD., RN, for her encouragement and guidance on the study. Finally, I would like to thank the nurse practitioners who completed the survey and helped contribute to my thesis.
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Abstract

Background

Hyperammonemia is a rare, often fatal, complication after lung transplantation. Hyperammonemia is characterized by increased serum ammonia levels (200 μmol/L), as well as encephalopathy, cerebral edema, seizures, coma, and even death. Current literature does not have an established standardized hyperammonemia protocol. This study seeks to identify and describe any practice protocols among lung transplant practitioners regarding the monitoring of ammonia levels after lung transplantation. This study will investigate clinical experience of diagnosing and treating hyperammonemia in the post-transplant lung setting to try to prevent, identify, and treat future cases of hyperammonemia.

Methods

Purposive Sampling was used, with required parameters of nurse practitioners who work at centers the same size as Vanderbilt Lung Transplant Center, and considered to have expert knowledge and experience. The sample consisted of twelve participants. Data were collected from the five participants who completed the questionnaire.

Results

Based on the data collected, hyperammonemia is of heightened concern after lung transplantation. With four out of the five centers monitoring ammonia levels after lung transplantation, and at least one patient diagnosed with hyperammonemia, it’s important to not only test ammonia levels post transplantation, but also to have a protocol in place. The protocols already in place varied with each response. Further research needs to be done to evaluate the patient outcomes of the different protocols. Once that research has occurred, one universal protocol needs to be established. The proposed protocol would include: a broad spectrum
antibiotic, such as Rifaximin; a bowel decontaminate agent, such as Lactulose; an amino acid supplementation, such as Arginine; and Dialysis, either Intermittent Hemodialysis (IHD) or Continuous Veno-Venous Hemodialysis (CVVHD).

**Conclusion**

All five centers were in agreement that hyperammonemia after lung transplantation is of significant concern. Four out of five centers test ammonia levels after transplantation and all five centers had a protocol in place. Yet, all five centers had completely different protocols. Thus, a universal protocol is needed for meaningful comparison.
Introduction

Hyperammonemia is a rare, often fatal, complication after lung transplantation. Hyperammonemia is characterized by increased serum ammonia levels (over 200 μmol/L), as well as encephalopathy, cerebral edema, seizures, coma, and even death. Hyperammonemia is a known complication after lung transplantation that can be augmented by the use of calcineurin inhibitors that are required for immunosuppression. Hyperammonemia is associated with a high mortality rate due to the unknown etiology, delays in diagnosis, and lack of a systematic treatment protocol. While hyperammonemia can occur in all solid organ transplantation, it occurs “predominantly in lung transplant recipients” (Krutsinger, Pezzulo, Blevins, Reed, Voigt, Eberlein, 2017). The purpose of this study is to determine if there is consensus among lung transplant practitioners regarding the monitoring of ammonia levels after lung transplantation. Hyperammonemia entails that the patient’s ammonia levels after transplantation must exceed 200 μmol/L on at least one occasion and have symptoms of encephalopathy (Chen, Bain, Iuppa, Yusen, Byers, Patterson, Trulock, Hachem, 2016). The clinical question originated from a need for a standardized protocol in the lung transplantation clinical community at Vanderbilt University Medical Center. Currently, there are no clear guidelines in practice or in the literature regarding the diagnosis and treatment of hyperammonemia. This study will assess current practices in regional lung transplant centers of similar size and will seek to determine consensus regarding current hyperammonemia practice.

Review of Literature

Literature for this research study was identified using electronic sources of databases. The literature search was limited to articles published in the English language from 2013 onwards. The databases of PubMed and CINAHL were independently searched using
combinations of the key word phrases: Hyperammonemia, lung, lung transplant, lung transplantation, ammonia, treatment, and protocol.

Chen et al. presented a case series of hyperammonemia after lung transplantation and proposed a treatment protocol (2016). The researchers “conducted a retrospective cohort study of patients who underwent lung transplantation at Barnes-Jewish Hospital in St. Louis, MO between January 1, 2000 and December 31, 2013” (Chen et al., 2016). Patients who developed hyperammonemia syndrome, defined as encephalopathy and ammonia levels exceeding 200 µmol/L on at least one occasion, were included in the study (Chen et al., 2016). The case series revealed that out of the 807 lung transplant procedures performed, eight patients, or 1%, developed hyperammonemia syndrome (Chen et al., 2016). Six out of the eight patients who developed hyperammonemia syndrome died (Chen et al., 2016). Chen et al. state that “median time to onset was 9.0 days, and median peak ammonia level was 370 µmol/L. All 8 patients were treatment with hemodialysis, 7 of 8 patients were treatment with bowel decontamination, and 5 of 8 patients were treated with nitrogen scavenging agents. Six of the 8 patients died” (2016). This study developed a protocol which focuses on minimization of ammonia production and accelerated nitrogen removal (Chen et al., 2016). The protocol includes: bowel decontamination agent, nitrogen scavenging agent, amino acid supplementation, Renal Replacement Therapy (RRT), and an antimicrobial. The patient’s ammonia levels (33-75 µmol/L or >75 µmol/L) determine which treatment protocol will be utilized. The more aggressive treatment option adds caloric supplementation and amino acid replacement. This study’s limitations include the restricted ability to generalize the results since the study only looked at case studies from one hospital in Missouri. Additionally, the study has not determined the efficacy of the proposed protocol. Chen et al. note that “further investigations into the pathophysiology, diagnosis, and
treatment of hyperammonemia are necessary to prevent, identify, and treat this life-threatening condition” (2016).

Krutsinger et al. understand that idiopathic hyperammonemia syndrome (IHS) occurs most often in lung transplant recipients (2017). The researchers performed a “retrospective cohort study of all lung, heart, and kidney transplants performed at the University of Iowa between January 1, 2008 and December 31, 2015” (Krutsinger et al., 2017). A systematic review was used to identify all reported cases of IHS in non-liver solid organ transplant recipients (Krutsinger et al., 2017). The study included thirteen institutions from around the world (Krutsinger et al., 2017). Of the 32 cases of hyperammonemia among non-liver solid organ transplants, 26 were lung recipients, four were renal recipients, and two were heart-lung recipients (Krutsinger et al., 2017). Patients met the definition of IHS if they had all of the following criteria: “adult transplant recipient with postoperative ammonia level >42 μmol/L, absence of cirrhosis, liver failure, or history of liver transplantation, presence of encephalopathy” (Krutsinger et al., 2017). The median time to peak ammonia level was ten days, and the median peak level was 477 μmol/L (Krutsinger et al., 2017). The researchers found that “early initiation of dialysis, high dialysis dose, increased frequency, and high efficiency hemodialysis were associated with increased survival” (Krutsinger et al., 2017). Of the 128 lung transplants performed, five cases of IHS were reported, for an incidence of 3.9%, which is significantly greater than the 0.1% incidence rate of non-lung and liver transplants (Krutsinger et al., 2017). This systematic review is limited by the small sample size of 32 cases that met criteria, and the retrospective study design (Krutsinger et al., 2017). The proposed treatment protocol includes bowel decontamination agents, nitrogen scavenger agents, and high dose RRT (Krutsinger et al., 2017). Considering the high mortality rate of IHS, Krutsinger et al. recommend early diagnosis,
and an “aggressive, multimodal approach” to treatment (2017).

**Methods**

**Design**

A purposive sample consensus survey analysis was completed. The survey consisted of four multiple choice and open ended questions entered into an electronic survey database to determine the consensus among lung transplant practitioners regarding the monitoring of ammonia levels after lung transplantation.

**Sample**

The purposive sample was obtained by convenience method when selecting the sample size of twelve nurse practitioners who work at centers the same size as Vanderbilt Lung Transplant Center. The nurse practitioners were considered to have expert knowledge and experience. The questionnaire was sent out to twelve participants, but only five nurse practitioners responded.

**Setting**

The electronic study was conducted online by sending out the instrumentation of a four question survey through the website Survey Monkey.

**Procedure**

The university institutional review board approvals were obtained (Appendix A). Participants were recruited by the Research Advisor. Participants provided consent to participate in the study as part of an electronic survey and then provided their responses to the four multiple choice and open ended questions (in a discussion format). The responses were documented and accessed anonymously.

**Instrument**

The participants filled out an electronic online survey consisting of four multiple choice
and open ended questions (Appendix B). The IP address tracker was disabled.

**Results**

**Data**

Electronic surveys were sent out through a known electronic survey tool to twelve nurse practitioners. Five nurse practitioners responded, which was a response rate of 42%. The respondents answered all four questions. A qualitative study was conducted using an electronic survey. All five participants stated there was a strong level of concern for hyperammonemia after lung transplantation in their program (Appendix C). Four centers currently monitor ammonia levels after transplantation, with one participant stating that ammonia levels are not monitored after transplantation (Appendix C). The responses for frequency of monitoring ammonia levels included daily, every other day for twelve days, at no specific interval, and pre, initial, and PRN (Appendix D). The number of patients with hyperammonemia after lung transplantation ranged from zero to five (Appendix D). The participants all indicated that their centers had treatment protocols; however, no two centers had any similar factors listed in their treatment protocol (Appendix D). Most centers treated hyperammonemia with only antibiotics, and the antibiotics all differed between the centers. One participant reported that their center used Arginine, Levocarnitine, and CVVHD, which treats the source of hyperammonemia.

**Discussion**

The results from the electronic survey solidified the need for guidelines regarding the diagnosis and treatment of hyperammonemia. Additionally, a standardized protocol should be developed to treat hyperammonemia. The survey results emphasize the significance of testing for hyperammonemia after lung transplantation. Yet, only 80% of the participants’ centers tested for hyperammonemia and 80% had treatment options in place. The centers all had completely
different protocols. None of the treatment plans included similar components and the timelines for testing ammonia levels post-transplantation all varied. To combat the lack of treatment protocol and guideline for testing of ammonia, this study will propose both factors to be tested. Early diagnosis is key for treatment of hyperammonemia. Thus, ammonia levels should be tested with the routine lab work post-transplant, and then six days post-transplant, since the median time to peak ammonia level was nine to ten days post-transplant (Chen et al., 2016). Additionally, ammonia levels should be tested as needed if any signs and symptoms of hyperammonemia occur, such as altered mental status or seizures.

The treatment protocol should include an aggressive multimodal approach. The protocol should include a bowel decontamination agent, an antibiotic, an amino acid supplementation, and renal replacement. The amino acid supplementation, Arginine, helps excrete ammonia by stimulating the ammonia molecules to break down into urea, which is removed from the body through the urine. “Arginine supplementation is thought to be essential to prevent further protein catabolism and minimize toxicity by facilitating conversion of ammonia to less toxic metabolites” (Chen et al., 2016). Protein catabolism increases ammonia levels. The amino acid supplementation, Arginine, also serves as a nitrogen scavenging agent (Krutsinger et al., 2017). Subsequently, a bowel decontamination agent, such as lactulose, binds to the ammonia and traps in it the stool, making it easier to excrete out of the body. Since the etiology of hyperammonemia is unknown, treatment with an antibiotic, such as Rifaximin, removes the bacterial load, while also eliminating ammonia producing colonic bacteria. Rifaximin acts an antibiotic and bowel decontamination agent. Renal replacement therapy (RRT) lowers the amount of ammonia in the blood through filtration. RRT can either be continuous veno-venous hemodialysis (CVVHD) or intermittent hemodialysis (IHD), however, “aggressive ammonia removal via IHD may be
associated with improved survival” (Krutsinger et al., 2017). Chen et al. also agree that “IHD is a more effective ammonia-reducing modality” (2016). It’s imperative that all components of the treatment protocol are used. Each part serves a vital role in removing ammonia from the body. According to Chen et al., out of the eight patients who were treated with portions of the suggested protocol, six patients died (2016). Krutsinger et al. list other agents in their proposed protocol (2017). For example, Azithromycin and Doxycycline are listed for antibiotics, Levocarnitine and Sodium Benzoate + Sodium Phenylacetate are listed in addition to Arginine as nitrogen scavenger agents (Krutsinger et al., 2017). Lung transplant centers can use other forms of antibiotics. The protocol is meant to be followed as a guideline, with health care providers choosing the specific medications individualized for their patients, as long as the patient is being treated with all four parts of the protocol. Krutsinger et al. even suggest that “possible prevention of hyperammonemia may provide further rationale to start azithromycin prophylaxis early” (2017). To objectively assess the effect of the treatment protocol on patients with hyperammonemia after lung transplantation, the patients should be treated with the same antibiotic, the same nitrogen scavenger, the same bowel decontaminate, and IHD. This study has developed a protocol for future lung transplant recipients that develop hyperammonemia; however, the efficacy of the protocol has yet to be established. By investigating clinical experience of diagnosing and treating hyperammonemia in the post lung-transplant setting, this study has developed a protocol for prompt diagnosis and treatment of this rare, but fatal disease.

**Limitations**

One limitation of the findings is that the results of the study are not generalizable to all lung transplant centers. This is due to the small sample size (n=5). Another limitation is that the number of patients reported by the participants to have developed hyperammonemia after lung
transplantation cannot be compared to the number of lung transplants performed at the center because the number of lung transplants is not known. The significance of the number of patients with hyperammonemia after lung transplantation is not identified in the centers surveyed. Additionally, the outcomes of the treatment patients received from each center is not known. Future research should include a larger sample size, the number of lung transplantations performed, as well as the results of the treatment protocol.

**Conclusion**

Based on the clinical findings from the electronic survey, it is vital that a standardized diagnosis and treatment regimen is created and established for hyperammonemia after lung transplantation. Given the fact that hyperammonemia occurs in 1% of lung transplants with a 75% mortality rate with current treatment methods, hyperammonemia is of heightened concern (Chen et al., 2016). Lung transplant centers are in need of a consistent diagnosis and treatment protocol, thus this study created both. With increased awareness for hyperammonemia, prompt identification and implementation of the treatment protocol, hopefully hyperammonemia will not result in as many fatalities.
References


Appendix A

July 13th 2017

Kathryn Bradley
College of Nursing
University of Alabama in Huntsville

Dear Ms. Bradley,

The UAH Institutional Review Board of Human Subjects Committee has reviewed your proposal, What is the current practice regarding the measurement of ammonia levels after lung transplantation?, and found it meets the necessary criteria for approval. Your proposal seems to be in compliance with this institution’s Federal Wide Assurance (FWA) 00019998 and the DHHS Regulations for the Protection of Human Subjects (45 CFR 46).

Please note that this approval is good for one year from the date on this letter. If data collection continues past this period, you are responsible for processing a renewal application a minimum of 60 days prior to the expiration date.

No changes are to be made to the approved protocol without prior review and approval from the UAH IRB. All changes (e.g. a change in procedure, number of subjects, personnel, study locations, new recruitment materials, study instruments, etc) must be prospectively reviewed and approved by the IRB before they are implemented. You should report any unanticipated problems involving risks to the participants or others to the IRB Chair.

If you have any questions regarding the IRB’s decision, please contact me.

Sincerely,

Bruce Stallsmith
IRB Chair
Professor, Biological Sciences
Exempt

☐ Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (a) research on regular and special education instructional strategies, or (b) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. The research is not FDA regulated and does not involve prisoners as participants.

☐ Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interviews, or observation of public behavior in which information is obtained in a manner that human subjects cannot be identified directly or through identifiers linked to the subjects and any disclosure of the human subject’s responses outside the research would NOT place the subjects at risk of criminal or civil liability or be damaging to the subject’s financial standing, employability, or reputation. The research is not FDA regulated and does not involve prisoners as participants.

☐ Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement) survey procedures, interview procedures, or observation of public behavior if (a) the human subjects are elected or appointed public officials or candidates for public office, or (b) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter. The research is not FDA regulated and does not involve prisoners as participants.

☒ Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. The research is not FDA regulated and does not involve prisoners as participants.

☐ Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs. The protocol will be conducted pursuant to specific federal statutory authority; has no statutory requirement for IRB review; does not involve significant physical invasions or intrusions upon the privacy interests of the participant; has authorization or concurrent by the funding agency and does not involve prisoners as participants.

☐ Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. The research does not involve prisoners as participants.

1 Surveys, interviews, or observation of public behavior involving children cannot be exempt.
Appendix B

INSTRUMENT with informed consent in the body of the survey

This study involves research, the purpose of which is to obtain the transplant clinician's perspective on monitoring of hyperammonemia after lung transplantation. The survey takes about 10 minutes to complete. You must be 19 years of age or older to participate. If you agree to participate, you will be asked 5 short questions. Voluntary completion of the survey serves as your consent. There are no foreseeable risks or discomforts to participating in the study. Your name will not be associated with your responses and strict confidentiality of records will be maintained. Participation is voluntary, and refusal to participate will involve no penalty or loss of benefits. There are no costs to participate, you may withdraw at any time. There will be approximately 12 participants. If you any questions about the research and research participant's rights, you may contact the Principal Investigator, Haley Hoy PhD, haley.hoy@uah.edu, 256-824-6669, or (Bruce Stallsmith, IRB Chair, <irb@uah.edu>, 256.824.2339). Your voluntary completion of this survey serves as your consent to participate.

1. What is your program's level of concern for hyperammonemia after lung transplantation?
   Strongly concerned
   Medium level of concern
   Low level of concern
   No concern

2. Do you currently monitor ammonia level after lung transplantation?
   No
   I don't know
   Yes (Please specify at what interval)

3. How many patients with hyperammonemia have been detected after lung transplant in your program?

4. Do you have a treatment protocol for hyperammonemia after lung transplant?
   No
   I don't know
   Yes- (please specify)
Appendix C

Q1 What is your program's level of concern for hyperammonemia after lung transplantation?

Q2 Do you currently monitor ammonia levels after lung transplantation?

Q3 How many patients with hyperammonemia have been detected after lung transplant in your program?

Answered: 5  Skipped: 0

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<td>5</td>
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Q4 Do you have a treatment protocol for hyperammonemia after lung transplant?
### Appendix D

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<th>Do you currently monitor ammonia levels after lung transplantation?</th>
<th>How many patients with hyperammonemia have been detected after lung transplant in your program?</th>
<th>Do you have a treatment protocol for hyperammonemia after lung transplant?</th>
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<td><strong>Participant 1</strong></td>
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<tr>
<td><strong>Participant 2</strong></td>
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<tr>
<td><strong>Participant 3</strong></td>
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<tr>
<td><strong>Participant 4</strong></td>
<td>Pre, initial, PRN</td>
<td>1 RHC</td>
</tr>
<tr>
<td><strong>Participant 5</strong></td>
<td>No specific interval. Monitor in patients with mental status changes, especially with hypoactive delirium</td>
<td>4, 3 recently</td>
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