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TITLE: Severe Alcoholic Pancreatitis-Associated Acute Lung Injury in Veterans: Risks, Mechanisms, Prediction, and Therapeutic Relevance

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14. ABSTRACT

Background: Acute pancreatitis is a painful, potentially life-threatening condition of the pancreas with an unpredictable course. In this study we hope to identify and propose simple and reliable ways to predict and treat acute pancreatitis.

Hypothesis: Alcohol increases systemic bioavailability of unsaturated fatty acids(UFAs). This, along with the resulting hypocalcemia and hypoalbuminemia worsen cell injury. We propose to test a novel yet simple ratio as a reliable predictor and therapeutic target in the management of alcoholic AP.

Objective: To compare the [Serum free fatty acid/ (Serum calcium x albumin)] ratio as a predictor of severe alcoholic pancreatitis in veterans vs. other classical and proposed predictors.

Methods: Patients admitted with acute pancreatitis are enrolled and laboratory results are recorded. Total of 7 patients and controls have been enrolled to date. Serum samples are obtained and sent to Mayo Clinic, Site 1, for analysis of FFA and circulating dead inflammatory cells. Echocardiogram is done within 24 hours of admission. Control groups include patients who abuse alcohol but do not have pancreatitis and healthy patients. We plan to study the strength of associations of various risk factors for severe acute pancreatitis in comparison to the [Serum free fatty acid/ (Serum calcium x albumin)] ratio.

Conclusion: If our hypothesis is true, it would change the paradigm of managing serum calcium and albumin in acute pancreatitis. This would provide a better, novel yet simple predictor and approach to treatment for severe alcoholic pancreatitis, and potentially acute pancreatitis in general.

15. SUBJECT TERMS

Acute pancreatitis, Severe acute pancreatitis, serum free fatty acids, alcohol pancreatitis, hypocalcemia, hypoalbuminemia

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Severe Alcoholic Pancreatitis-Associated Acute Lung Injury in Veterans: Risks, Mechanisms, Prediction, and Therapeutic Relevance
Annual Report

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1. **INTRODUCTION:** This Annual Report details the accomplishments and progress of the second year of CDMRP funding of the project PR151612P1 (Severe Alcoholic Pancreatitis-Associated Acute Lung Injury in Veterans: Risks, Mechanisms, Prediction, and Therapeutic Relevance) from the time period of 9/30/2017-9/29/2018. Acute pancreatitis is a painful, potentially life-threatening condition of the pancreas with a typically abrupt onset and an unpredictable course. In this study, we will identify and propose simple and reliable ways to predict and treat acute pancreatitis. Our central hypothesis is that alcohol increases the systemic bioavailability of unsaturated fatty acids generated from visceral fat lipolysis. This, along with the resulting hypocalcemia and hypoalbuminemia, worsens cell injury, resulting in multisystem organ failure (MSOF) and converting AP to SAP. Our objective is to compare the [Serum free fatty acid/ (Serum calcium x albumin)] ratio as a predictor of severe alcoholic pancreatitis in veterans vs. other classical and proposed predictors, and test it as a therapeutic target.

2. **KEYWORDS:** Acute pancreatitis, Severe acute pancreatitis, serum free fatty acids, alcohol pancreatitis, hypocalcemia, hypoalbuminemia

3. ACCOMPLISHMENTS:

3.1. **Goals:** As stated in our statement of work (SOW), the second-year goals mainly focus on recruiting patients and controls. With the recruitment of enough patients, at the end of year two we are able to do data analysis.

3.2. **What was accomplished:** Enrollment of patients has increased, however continues to be challenging. By the end of year two the goals were to have enrolled an additional 140 for a total of 240 subjects. This was to include an additional 30 controls, 30 patients with alcohol abuse, and 80 with pancreatitis. We continue to be below our recruitment goal but we also continue to modify our techniques in identifying patients to enhance enrollment.

3.2.1. **Recruitment of patients with pancreatitis**: We have refined our technique to identify patients who may potentially have pancreatitis. We have an excellent relationship with the laboratory technician who sends us the results from all elevated lipases that are identified in the main hospital laboratory. Over the past year we have

identified 92 abnormal lipase results. We screen all these patients using the electronic medical record for possible pancreatitis. Out of the 92 identified, 10 have qualified for enrollment into the study. Listed below is the information regarding all the patients who have been screened for elevated lipase:

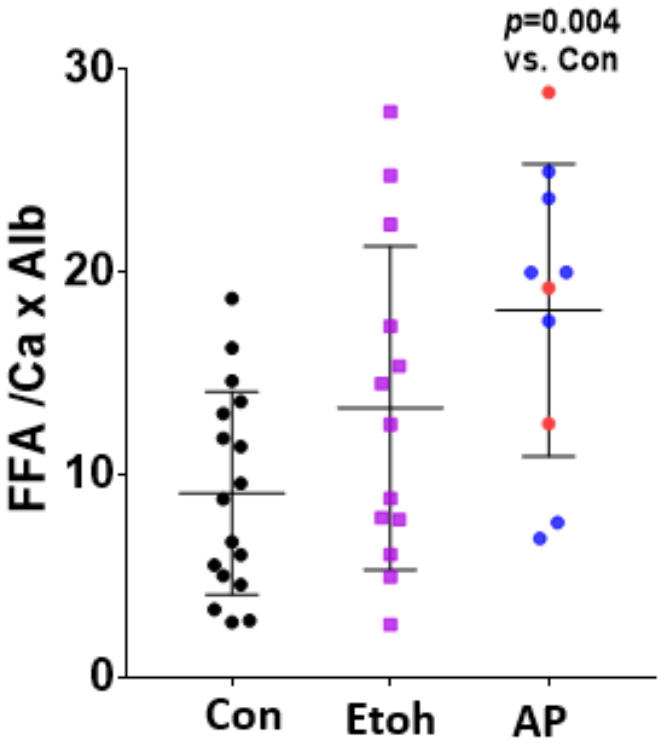
- 10 Veterans were enrolled in both Groups 1 and 2 (pancreatitis patients)
- 23 Veterans did not qualify because of history of pancreatitis
- 34 Veterans did not have pancreatitis (admitted for cardiac or other medical issues)
- 8 Veterans discharged from ED without formal diagnosis of pancreatitis w/ two later admitted to hospital
- 1 Veteran diagnosed with pancreatitis left ED against medical advice
- 3 Veterans declined study participation
- 5 Veterans could not be enrolled within the time frame of the study, i.e. labs and echocardiogram completed within 24 hours of admission (due to holidays and weekends)
- 5 Veterans were outpatients and not diagnosed with acute pancreatitis
- 1 Veteran did not qualify due to history of CHF (CPRS documented)
- 2 Veterans did not qualify due to comorbidities, including pancreatic cancer

3.2.2. Recruitment of alcoholic patients: We have been successful in refining the process of identifying these patients for potential enrollment. As with the elevated lipase levels, we are notified by the laboratory for every elevated alcohol level. These patients often get admitted to the psychiatry floor for management. This inpatient stay allows for relative ease of access to the patient for discussion and consent, blood draw, and echocardiogram.

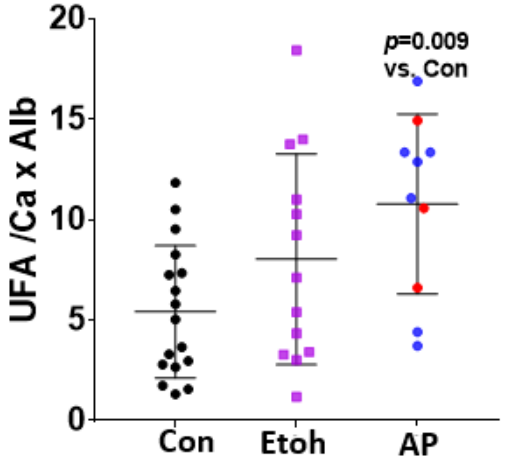
3.2.3. Recruitment of controls: With advertising during the Phoenix VA Research week, and intermittently holding recruitment booths we have been successful in recruiting normal control patients for the study. The main limitation of recruiting more control patients is the availability of echocardiograms.

3.2.4. Interim analysis of data: Despite the low numbers of patient recruitment, we have identified some exciting trends in our data. Our hypothesis that the Serum free fatty acid/ (Serum calcium x albumin) ratio may be a predictor of severe pancreatitis cannot yet be tested due to our low enrollment numbers of patients with acute pancreatitis to date. Preliminarily, however, we are seeing a trend suggesting that this may indeed be an important marker. There is a significant difference in this ratio between our study groups. As noted in the following graph, there is a clear trend that this ratio is

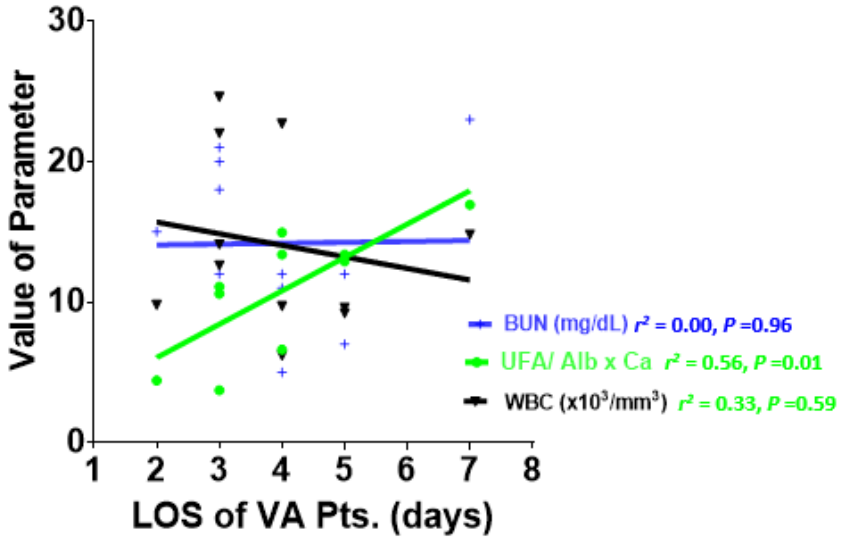
higher in those with alcohol use compared with normal controls and an even higher ratio in those with acute pancreatitis.



The P value for this trend was even stronger when comparing the *unbound* fatty acids/(Ca++ x Albumin) to in patients vs. controls as can be seen in the graph below.



These trends support the idea that alcohol can cause the release of free fatty acids from visceral lipolysis and that calcium and albumin are critical to neutralize these. Patients with acute pancreatitis of any cause have lipolysis as well and this will contribute the cascade of worsening organ failure in these patients. As can be seen from the graph below, we can see a clear linear correlation between the UFA/(Ca x Alb) and length of stay.



While we clearly need more patients to support this, the trend is significant. Even with the small numbers, the linear correlation is much stronger with the novel UFA/Alb x Ca than with traditional markers including the WBC and BUN.

The echocardiogram results from all our patients have been normal in respect to ejection fraction. As Dr. Singh has noted in his animal data, the ejection fraction in these patients with both alcohol use or with acute pancreatitis may have a falsely normal ejection fraction. This may be because of a decreased end diastolic volume and stroke volume. We are in the process of adding this information to our collection data forms so that we may be able to analyze these trends soon. This may involve cardiology re-entering the information from prior echocardiograms performed and previously read.

3.3. **Opportunities for training and professional development:** Dr. Vela attended Digestive Disease Week 2018 which allowed for knowledge expansion in the field of pancreatology.

3.4. **How were the results disseminated to communities of interest?** Our data is still limited due to the small number of patients enrolled to date. We do plan to submit our data in abstract form for presentation at Digestive Disease Week 2019.

3.5. **Plan for the next reporting period to accomplish goals?** The plan to accomplish goals is to be aggressive in increasing enrollment in all groups. While we are at the mercy of patients being diagnosed with pancreatitis in groups 1 and 2, groups 3 and 4 we can recruit. We are limited by the number of outpatient echocardiograms that can be performed but will be working with the cardiology group to increase this as well.

4. IMPACT

4.1. **Impact on the development of the principal discipline of the project:** Recognizing that our data is limited given low numbers at this point, there are several interesting trends that may impact the evaluation of acute pancreatitis. The FFA/Ca x Alb and UFA/Ca x Alb differences between groups is promising even with our low numbers. These may become another useful tool in identifying patients early on as potentially having longer length of stay or poor outcome. As we obtain more data points we will have the ability to validate this trend and compare it to traditional scoring systems.

4.2. I**mpact on other disciplines:** Nothing to report.

4.3. **Impact on technology transfer:** Nothing to report.

4.4. **Impact on society beyond science and technology:** Nothing to report.

5. CHANGES/PROBLEMS:

5.1. **Changes in approach and reasons for change**:

5.1.1. The etiology of our low enrollment has been multifactorial. As can be noted from the numbers of patients with elevated lipase in 3.2.1 there are multiple reasons why patients

with elevated lipase may not qualify for our study. One of the largest groups that did not qualify were those with prior history of pancreatitis. We have included the exclusion criteria of prior pancreatitis because patients with recurrent acute pancreatitis or chronic pancreatitis have more scarring and more injury to the pancreas which may decrease the acuity of their illness in subsequent flares. We want to continue to enroll patients with first time episodes of acute pancreatitis. One minor change to protocol that may be helpful in including more patients is to increase the time window that the patient can be enrolled. Scoring systems in acute pancreatitis are most useful in the first 24-48 hours of admission to allow providers to accurately triage patients to the appropriate level of care. Our protocol demands that the patient be enrolled and all studies, including echocardiogram, be performed within the first 24 hours of admission. This strict timeline has caused us to lose some patients. At times this is due to lack of echocardiogram availability, but it also may be from patients presenting over the weekend when our services are not available. We believe we will be able to increase our enrollment if we increase the time allowed to complete evaluation to up to 48 hours. We believe this will help increase enrollment without sacrificing the important information gained from the early evaluation. We are planning to submit the change to the agency for approval early in year 3.

5.2. Actual or anticipated problems or delays and actions or plans to resolve them:

5.2.1. Inability to perform echocardiograms in timely manner: While the availability of echocardiogram technologists has improved since the last annual report, there are still some personnel challenges that have made it difficult for us to enroll patients in groups 3 and 4. We are frequently addressing and readdressing the communication plan to minimize this difficulty. We have the full support of the Chief of Cardiology who is working with us to improve this process so that we can enroll as many patients as possible without causing significant strain on the echocardiogram service. We hope over the next year we can increase our enrollment of group 3 and 4 substantially.

5.2.2. Challenge in identifying potential patients: We have improved our ability to screen for patients significantly with the ongoing partnership with the chemistry laboratory. With this, we get notifications daily, and at times multiple times per day, on abnormal lab testing

that may indicate a potential patient for our study. Even with this, we would like to try to decrease the time to notification. We are in the process of submitting new fliers to be placed in the ED advertising our study so that providers will be more likely to call when there is a potential patient.

5.2.3. **Changes that had a significant impact on expenditures**: Our initially hired statistician, Dr. Richard Gerkin did not renew privileges this year to the Phoenix VA. Because of this the IRB does not permit him to analyze our data. Basic statistical analysis was done for this report by Dr. Vijay Singh. We are in the process of adding Dr. Gerkin back onto the study in a different classification for the VA vs. looking into internal candidates for the study statistics. Because of the above we have not had significant expenditures for statistician salary.

5.3. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**: Nothing to report

5.4. **Significant changes in use or care of human subjects:** Nothing to report

5.5. **Significant changes in use or care of vertebrate animals:** Nothing to report

5.6. **Significant changes in use of biohazards and/or select agents:** Nothing to report

6. PRODUCTS

6.1. **Publications, conference papers, and presentations:** Nothing to report.

6.2. **Journal publications:** Nothing to report.

6.3. **Books or other non-periodical, one-time publications:** Nothing to report.

6.4. **Other publications, conference papers, and presentations.** Nothing to report.

6.5. **Website(s) or other Internet site(s):** Nothing to report.

6.6. **Technologies or techniques:** Nothing to report.

6.7. **Inventions, patent applications, and/or licenses:** Nothing to report.

6.8. Other Products: Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

7.1. Individuals who have worked on the project:

7.1.1. PI: Dr. Stacie A. F. Vela: no change

7.1.2. Research Coordinator: Gail Farrell: no change

7.2. Changes in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period: Nothing to report.

7.3. Other organizations were involved as partners?

7.3.1. SITE 1, Mayo clinic Arizona. Co-PI Dr. Vijay Singh: no change

8. SPECIAL REPORTING REQUIREMENTS

8.1. COLLABORATIVE AWARDS: Independent report sent by Dr. Singh

9. APPENDICES: Nothing to report