

FRONT COVER

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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 <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>					
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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 9/30/2018-9/29/2019. 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 third-year goals include finalizing recruitment of patients and controls and final analysis.

3.2. **What was accomplished:** Enrollment of patients has continued to increased, however continues to be challenging. By the end of year three the goals were to have enrolled an additional 140 for a total of 280 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:** Our system of communication with the lab has remained strong. We get notification with the results from all elevated lipases that are identified in the main hospital laboratory. Over the duration of the study we have identified 210 abnormal lipase results. We screen all these patients using the

electronic medical record for possible pancreatitis. Out of the 210 identified, 43 were potential subject and 23 had successful enrollment. Listed below is the information regarding all the patients who have been screened for elevated lipase:

- 23 Veterans were enrolled in both Groups 1 and 2 (pancreatitis patients)
- 2 missed opportunity – missed because of rapid discharge/weekend
- 39 Veterans ruled out for history of pancreatitis
- 99 Veterans captured due to elevated lipase did not have pancreatitis (cardiac issues, sepsis, e-coli ESBL UTI, lymphocytic colitis, bradycardia, dental pain, GI bleeding, ventral hernia, dizziness, vertigo, migraine HA, HTN, groin pain, dehydration, ampullary CA, N and V, etc.)
- 10 Veterans discharged without formal diagnosis of pancreatitis
- 1 Veteran transferred to another hospital w/o formal work-up or diagnosis of pancreatitis (? gastritis)
- 2 Veterans diagnosed with pancreatitis but left AMA
- 1 Veteran with high lipase but left AMA before work-up could be done
- 4 Veterans declined study participation
- 5 Veterans fell out of window of greater than >24 hour for labs and ECHO (d/t holidays and weekends)
- 11 Veterans were outpatient lab results
- 1 Veteran ruled out for CHF (CPRS documented)
- 3 Veteran ruled out for too many comorbidities
- 4 Veterans ruled out due to Pancreatic cancer
- 4 Veterans >80 years of age

3.2.2. Recruitment of alcoholic patients: We have been continually 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: Data was not unblinded for analysis this year.

- 3.3. **Opportunities for training and professional development:** Dr. Vela attended Digestive Disease Week 2019 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.
- 3.5. **Plan for the next reporting period to accomplish goals?** The plan to accomplish goals is to be continuing aggressive approach 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.

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. **Impact 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 this year has primarily been patient presentation. 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 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. We have had limitation with echocardiograms in the past but overall this has improved. The echo service has improved availability and also we have recruited some patients with protocol deviation to allow for echos to be completed within 48hours of presentation. In order to increase awareness of the study and to obtain more referrals for both patient in the alcohol group and control group, a flyer was approved by IRB in 3/2019 which enabled us to advertise in the out patient satellite clinics.

- 5.2. Actual or anticipated problems or delays and actions or plans to resolve them:** Given the slow recruitment, we have requested a no-cost extension of 1 year for the study. This will allow for additional recruitment of patients and subjects. While I don't anticipate reaching the planned goal, I do believe we will be able to get closer to the goal with an additional year.
- 5.2.1. Inability to perform echocardiograms in timely manner:** Overall this is improved and we have, in the few cases necessary, enrolled patients even if the echos fall out of 24 hour range.
- 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. Our current limitation is mostly the number of potential patients presenting.
- 5.2.3. Changes that had a significant impact on expenditures:** Our initially hired statistician, Dr. Richard Gerkin still does not have privileges to VA patient data. We are looking into internal candidates for the study statistics. Because of the above we have not had significant expenditures for statistician salary. We added a second Research Coordinator to the study with minimal financial impact.
- 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

7.1.3. Research Coordinator added 8/2019: Bryan Remuto

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