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2004 Annual Meeting - Part II
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Maika’i
A legend from Maui involving a large stone.
Editorial

What's Old and Still on the Horizon
History of the ACP - HAWAII

Journalism on the Slopes of Haleakala

Norman Goldstein MD, FACP
Editor, Hawaii Medical Journal

What's Old and Still on the Horizon
History of the ACP - HAWAII

The Hawaii Chapter of the American College of Physicians received its Articles of Incorporation on December 23, 1984. According to Joy Christ of the national A.C.P. office, the Hawaii Chapter actually dates back to 1927 when A. N. Sinclair was its first Governor.1

After Dr. Sinclair stepped down in 1931, there was a void for several years prior to Harry L. Arnold, Jr.’s service from 1937-1949. Senior readers of the Journal remember the name Harry L. Arnold, Jr. very well as Editor of the Hawaii Medical Journal. Following Harry in A.C.P. leadership were:

1949-58 Nils P. Larsen
1958-64 Hasings H. Walker
1964-70 Morton E. Berk
1970-73 John L. Bell
1973-77 Bernard W. D. Fong
1977-81 James L. Ball
1981-85 Robert A. Nordyke
1985-89 Irwin J. Schatz
1989-93 Nadine C. Bruce
1993-97 Vincent S. Aoki
1997-01 S. Y. Tan
2001-05 Patricia Blanchette

References
1. Christ, J. Personal Correspondence, 8/13/04

Journalism on the Slopes of Haleakala

Ten years ago, when Fred Reppun MD gave up the helm of the Journal, Harry L. Arnold Jr., Editor for more than 40 years, encouraged me to accept his position. Now, Inam Rahman, M.D., President of the Hawaii Medical Association, has invited me to continue to serve as your editor.

Because of my very busy practice on Oahu, my wife Ramsay sought and found an “upcountry” home where I could find more time to reflect and to write. As I sit on my lanai facing the West Maui mountains, I overlook the peaceful vistas of the Valley Isle with the ocean on both sides of the valley, Lanai, Molokai and Molokini. At this elevation, there are few distractions; our rooster awakens me and occasionally a cow finds its way onto our acreage. It’s then that I realize that I too am out to pasture. Maui No Ka Oi!

This new schedule, half country/half city, gives me the opportunity to read, not just dermatology journals and books, but manuscripts submitted to the Journal, and the opportunity to work more with our Peer Review Panel on submitted manuscripts.

Larry Parish, MD, Editor of the International Journal of Dermatology, has asked me to serve on their Editorial Board. The present Editor of the International Journal of Dermatology, Larry E. Gibson, MD, suggested reading an article in the British Journal of Dermatology in July 2004 by Richard Smith, Editor of the BMJ. In the manuscript, Traveling but never arriving: Reflections of a retiring Editor - 25 years of adventure, discovery and conserving, he stated “we are still in the journal equivalent of the early days of film: the talkies have yet to appear, the sight being free to all has, I think, hugely increased the influence and usefulness of the Journal.” He goes on to discuss authorship stating, “authorship is another issue with which we seem little progress. It long ago became clear that many studies included authors who had done little or nothing, and excluded people who had done a great deal of work. Attempts to separate authors and non-authors have been based more on power than contribution. The arguments of contributor-ship rather than authorship seem to me unanswerable. But most Journals have stuck with authorship.”

When Dr. Smith discusses his experience with the British Journal of Medicine, his words are apropos to our Journal:

“It took me many years to realize that I completely misunderstood what journals did. I imagined that doctors opened their BMJ’s on Friday mornings, read of some innovation, and used it on the next relevant patient. Many still seem to cling to this naive view of the function of journals. In fact, words on paper rarely lead directly to change.”

“What journals do best is what the rest of the media do best: stir up, prompt debate, upset, probe, legitimize, and set agendas. They are good at telling readers what to think about, but not what to think, and theme issues may be particularly successful in putting important but neglected subjects to doctors. Increasingly, I wonder as well if there isn’t something fundamentally misguided in sending ordinary clinicians, who are not scientists, piles of original papers that they mostly don’t read, often aren’t relevant to them, and they are not trained to appraise.2 If we were clearer about the purpose of journals, then we might redesign them completely.”

References
Letters to the Editor

Dear Norman:
I recently visited the Hue Medical College, which provides medical education for physicians, nurses, and allied medical personnel for the central region of Vietnam as well as parts of Laos and Cambodia.

I visited the library and the shelves were quite empty. They would appreciate it very much if recent copies of Journals and textbooks could be sent to the library.

The address would be Medical Library, Hue Medical College, 06 Ngo Quyen, Hue, Vietnam.

Sincerely,
James R. Langworthy, M.D.

Dear Jim,
Mahalo for your letter to the Editor.
Sitting at my desk, I turned around and looked at my library shelves, and collected two stacks of books I thought the Hue Medical College Library could use. Some may be dated (Current Therapy 2000), but this collection still has a lot of good, basic information. I also culled the past two months issues of Skin & Allergy News, Dermatology World, and Dermatology Times as well as some of my monthly Journals, including the International Journal of Dermatology, The Archives of Dermatology, The Journal of the American Academy of Dermatology, Skin & Aging, Cutis, Cosmetic Dermatology, and Practical Dermatology.

These publications should serve as the beginning of the Dermatology section of the Hue Medical Library.

Now, dear reader, why not send your no longer needed texts and Journals off to Viet Nam? According to Jim Langworthy, they really do need help augmenting their library. It may cost you a few dollars (there is no international book rate) but please do consider Jim’s request.

Norman Goldstein, M.D., Editor

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Letter to the Editor:

Aloha Norm,
I wanted to thank you for the Mango Dermatitis article in the August HMJ. Ironically, we have two 100+ year old mango trees in our yard, and my two year old son got some mango sap on his cheek. It opened an ugly red lesion that had us worried for a while. It has now healed 80% and is just a little red mark.

Reading how prevalent it is in Hawaii was reassuring we were not alone.

Keep up the good work.

M.R., a grateful reader

Dear Norman,
I received the July issue of your HMJ and am writing to both thank you and compliment you on a very nice journal. As you know, I suggested to Tom Kosasa that the HMJ be made a benefit of membership in the PPSA; I do think it would be an added attraction. Presuming that you agree, I think we should publicize that you would have the first right of refusal for all presentations at the biannual meeting. Perhaps you could request that you be handed a copy at the time of presentation.

On another note, I enjoyed your editorial on Osler. One of my avocations is the history of medicine. I don’t know if you have ever read the Flexner Report. I have a copy and found it a fascinating read. You referred to some of Flexner’s recommendations in your 3 bullets under, “...a new era of American medicine began:” As you probably know, Flexner visited something like 120 medical schools, many of which had essentially no entrance requirements, no laboratories, not even anatomy labs etc. etc... He concluded that John Hopkins was an excellent model for what a medical school should be.

I interned at Philadelphia General Hospital shortly after Osler was there and your editorial reminded me of a beautiful painting of him lecturing students there on the lawn.

Thank you again for that issue; I look forward to future copies.

With warm regards,
Jerome Goldstein, M.D.

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Dear Dr. Goldstein,
I was delighted on my return from vacation this week, to find a copy of the Hawaii Medical Journal with your excellent editorial complementing my paper on Osler. You ably filled in the history of this man who has so much influenced modern medicine. I am very grateful.

I am, of course, also pleased that you published my piece. I hope to continue furnishing you with other topics of interest.

With a sincere Mahalo,
R.S. Weeder, M.D.
Management of Patients with Chronic Kidney Disease Presenting with Acute Coronary Syndrome

Jeremy J. Lum MD, James R. Madison DO, Todd B. Seto MD, MPH, and Christian Spies MD

Abstract
We evaluated the treatment pattern of patients with chronic kidney disease presenting with acute coronary syndromes. In a retrospective chart review of 400 patients with and without kidney disease presenting with angina pectoris we found that patients with chronic kidney disease have longer hospital stays, receive fewer diagnostic angiographies, and have a delay in therapy.

Introduction
Chronic kidney disease is a significant morbidity in the United States with approximately 1,400 people per million of the population affected with this disease.1 Cardiovascular disease is a major cause of death in patients with chronic kidney disease (CKD) accounting for approximately 45% of all deaths in this population.1 This increased prevalence of cardiac disease in CKD patients is thought to be due to multiple factors including a high incidence of cardiac risk factors in patients with CKD.2,3 Past studies have shown a large percentage of dialysis patients have traditional cardiac risk factors including hypertension, diabetes, dyslipidemia, as well as increasing age.2 In addition, patients with CKD have other cardiac risk factors unique to renal disease including increased calcium intake, hyperhomocysteinemia, anemia, and increased oxidant stress secondary to uremia.4 Together, these multiple factors create a vasculopathic state leading to accelerated atherosclerosis and may influence mortality rates in patients with CKD.4,5

In addition to increased risk factors for cardiac disease, there may also be differences in the management of acute coronary syndromes (ACS) in patients with CKD as compared to patients with normal renal function. Previous studies have shown an under use of therapies for CAD in patients with CKD, including aspirin therapy, beta-blockers, thrombolytics and revascularization procedures.4 There is a paucity of data examining the use of these therapies during an acute presentation of ischemic cardiac disease. Furthermore, it is unknown if differences in treatment between patients with and without renal disease affect length of hospital stay. The goal of this study was to evaluate the utilization of cardiac testing and length of stay in patients with CKD presenting with ACS.

Methods
After approval by the appropriate institutional review boards, an analysis of computerized discharge diagnosis was performed at two major hospitals in Honolulu, Hawaii from January 2001 until June 2003. Patients carrying an ICD9 code for acute coronary syndrome and chronic renal failure as primary or secondary diagnosis were included. Patients with a creatinine of less than 1.5 mg/dl on admission were excluded from the analysis. The second group of patients with ACS without CKD was identified during the same period of time. In both groups, patients with acute renal failure were excluded from analysis.

Demographic and clinical data were extracted as specified in the results section. Normally distributed data is reported as mean and standard deviation (±SD), non-normally dispersed data is presented as median and interquartile range. Characteristics between the two groups were compared by Chi-Square for dichotomous variables and Mann-Whitney U Test and Student’s T-test for continuous variables. To determine the independent association between time until EKG obtained and the existence of renal failure, as well for the association between length of stay and presence of CKD we used binary logistic regression analysis. Alpha-level was set at 0.05 Statistical analyses were performed with the use of SPSS version 10.0 (Chicago, IL).

Results
We identified 200 patients with and 200 patients without CKD admitted for ACS. Patients with CKD were more likely to be older, female, and more frequently had diabetes, hypertension, a history of myocardial infarction, cerebral vascular disease, and peripheral vascular disease as compared to patients with normal renal function. The patients with CKD were more likely to have atrial fibrillation, have prior congestive heart failure, and more commonly presented with heart failure compared to non CKD patients.
All patients presented at a median time of 4 hours to the ER (p=0.9). Initial EKG was obtained later in CKD-patients (pts) than non CKD-pts (29 minutes vs. 12 minutes (median), p=0.002). Regression analysis including baseline characteristics, Killip class and angina type, confirmed renal disease as being associated with >20 minute delay in obtaining initial EKG (Odds Ratio (OR)=3.91, 95% CI 2.20 to 6.94, p<0.0001). Thirty-two percent of pts with CKD and 21% of non CKD-pts underwent stress testing (p=0.007). Diagnostic angiography was performed less often in patients with CKD compared to patients with normal renal function. CKD-pts had significantly longer time intervals between admission and coronary angiography (median 2 days) than non CKD-pts (median 1 day, p=0.001).

Aspirin, Clopidogrel, GPIIbIIa-Inhibitors, Enoxaparin, and IV heparin were less frequently administered to CKD patients. CKD-pts median length of stay was seven days compared to four days in non CKD-pts (p<0.0001). Controlling for demographics, severity of disease, hemoglobin, bleeding complications, and angiographic procedures, logistic regression analysis identified chronic renal failure (OR=4.97, 95%CI 12.79 to 8.83; p=0.0001) as one of the strongest predictors for hospital stays longer than five days.

**Discussion**

Our study identified a delay in diagnostic work up in patients with CKD presenting with ACS. This included a delay in obtaining an EKG as well as delay in performing a coronary angiography. In addition to a increased length of time from admission to coronary angiography, patients with CKD also had diagnostic angiographies performed less often compared to patients with normal renal function. This finding of less aggressive evaluation is somewhat surprising given the fact that patients with CKD are known to have a higher incidence of cardiac disease and have a worse prognosis. In addition, in this high risk population sufficient therapy would make the biggest impact on survival. Based on our study we are unable to determine why there is a delay in obtaining an EKG in patients with CKD. Possible explanations include a higher incidence of atypical presentations of ACS in this population, an inadequate clinical suspicion of ACS in these patients, or an underestimation of the urgency of diagnosing ACS. Further studies would be needed to explain these findings. In addition our observations emphasize the need to further understand the reason for less aggressive evaluation and to create policies for improved diagnosis of ACS.

In addition to less frequently used diagnostic angiography, we found that patients with CKD received less medical therapy for ACS compared to patients with normal renal function. These findings are consistent with previously published studies that have found that patients with CKD receive less adjunctive medical therapies as well as reperfusion procedures. The decrease in use of anti coagulation medications may be explained by a fear of increased risk of bleeding in patients with renal insufficiency. There are no prospective studies to confirm an increase risk of bleeding in this population, since patients with CKD are excluded from studies on anti-coagulant therapy. Further prospective studies are needed to clarify outcomes of patients with CKD treated with anti coagulant therapy.

We observed that chronic kidney disease was identified as a predictor of prolonged hospital stay based on regression analysis. The association was independent of severity of disease at admission, bleeding complications, and angiographic procedures performed. This finding is in contrast to the fact that we found that these patients received less invasive testing. Possible
reasons for this decrease in use of invasive testing include a fear of worsening renal function with invasive testing or a concern of higher rates of complications in this population. Further large-scale studies are required to explain why this population has longer hospital stays. This focus on length of hospital stay has become increasingly important given the growth of managed care plans, cost containment programs, and overall emphasis on hospital economics.

Because this was a retrospective study, our study was limited by the fact that we are unable to make conclusions of cause and effect, but rather only indicate associations. In addition there is the potential for referral bias as with any observational study. Finally the ethnic diversity found in our study with a minority of Caucasian patients may limit whether this study can be applied to other populations.

**Conclusion**
Patients with CKD presenting with CKD have a delay in their diagnostic workup and receive fewer diagnostic angiographies as compared to patients with normal renal function. In addition, CKD is a strong predictor of a prolonged hospital stay.

**References**
Severity of Chronic Kidney Disease did not Influence Bleeding during Treatment of Acute Coronary Syndromes

Andrew Lee BA, Jeremy J. Lum MD, Todd B. Seto MD, MPH, Christian Spies MD, and James R. Madison DO

Abstract

We assessed the influence of CKD on bleeding in 200 patients with ACS via retrospective chart analysis. Using K/DOQI guidelines to stratify patients based on GFR, no differences in documented bleeding or antithrombotic utilization were observed among the groups. Due to increased mortality risk of patients with CKD from cardiovascular disease, assessing benefit-to-risk ratios of various medical interventions is crucial.

Introduction

Chronic kidney disease (CKD) is increasing in prevalence in the US among the adult population. Cardiovascular disease including acute coronary syndromes (ACS) accounts for nearly half of all deaths among CKD patients. Reasons for this increased risk of cardiovascular death and morbidity include a higher prevalence of cardiac risk factors in patients with renal dysfunction including smoking, dyslipidemia, hypertension, and hyperhomocysteinemia. Additionally, it has been shown that medical treatment of ACS using standard medications such as beta-blockers, aspirin, thrombolytics, as well as utilization of percutaneous revascularization techniques are less commonly implemented in patients with CKD as compared to those with normal renal function. Reported explanations for this discrepancy include concerns about bleeding complications as well as the limited available data examining the treatment and outcomes of patients with CKD. The landmark clinical trials studying the use of medical treatments and procedures after myocardial infarction have typically excluded patients with CKD or end-stage renal disease (ESRD). Further, there is no data examining the effect renal dysfunction has on the risk of bleeding in patients being treated for ACS.

The National Kidney Foundation (NKF), in an effort to improve the quality and outcomes of treatment for patients with kidney disease, launched the Kidney Disease Outcomes Quality Initiative (K/DOQI). This initiative which stratifies patients based on their glomerular filtration rate (GFR), provides criteria for evaluating and classifying kidney disease, an approach to risk stratification, and evidence-based practice guidelines for continuous care and therapy of CKD. Current work is aimed at formulating practice guidelines for the management of cardiovascular disease, especially ACS in CKD patients.

This study sought to define bleeding risks in CKD patients medically treated for ACS. Using the K/DOQI CKD guidelines to stratify patients based on their degree of kidney disease, we examined the impact of renal dysfunction on documented bleeding events and use of antithrombotic therapy.

Methods

Our study was approved by appropriate institutional review boards. Our collective was identified by a computerized search of discharge diagnoses for ACS and CKD at two major hospitals in Honolulu, HI, from January 2001 to June 2003. Medical records of these visits were accessed, and 200 patients with CKD were randomly selected from those admitted for ACS.

All patients fulfilled American College of Cardiology/American Heart Association (ACC/AHA) criteria for unstable angina or acute myocardial infarction (14). All patients were also required to fulfill criteria for CKD, defined for screening purposes as having a serum creatinine concentration of >1.5 mg/dl. Creatinine clearance was then calculated for all patients according to the Cockcroft-Gault formula: CrCl = [140 - age] * weight (kg) / [serum creatinine (mg/dl) * 72] (15). Subsequently, patients were grouped into one of four classes based on NKF/K/DOQI guidelines for CKD (13): Stage 2 (GFR 60-89), Stage 3 (GFR 30-59), Stage 4 (GFR 15-29), or Stage 5 (GFR <15). Excluded from this study were patients who underwent CABG or received thrombolytic therapy during their hospitalization, as well as those presenting with acute renal failure.

Baseline characteristics and clinical data were extracted from all charts meeting the above criteria. Using TIMI criteria, they were evaluated for bleeding complications, both major and minor events (16).
Table 1.— Baseline Characteristics of Chronic Kidney Disease Patients with Acute Coronary Syndrome, Based on K/DOQI Stage

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stage 2 (GFR 60-89)</th>
<th>Stage 3 (GFR 30-59)</th>
<th>Stage 4 (GFR 15-29)</th>
<th>Stage 5 (GFR &lt;15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>11</td>
<td>38</td>
<td>59</td>
<td>92</td>
</tr>
<tr>
<td>Male (%)</td>
<td>6 (55)</td>
<td>32 (84)</td>
<td>32 (54)</td>
<td>42 (46)</td>
</tr>
<tr>
<td>Hemoglobin (mg/dl)</td>
<td>13.8 ± 1.9</td>
<td>12.6 ± 2.4</td>
<td>11.1 ± 1.9</td>
<td>11.2 ± 1.8</td>
</tr>
<tr>
<td>Platelets (103/ul)</td>
<td>294.5 ± 15.4</td>
<td>226.3 ± 79.6</td>
<td>249.8 ± 103</td>
<td>232.7 ± 71.9</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>11 (100)</td>
<td>30 (79)</td>
<td>55 (93)</td>
<td>77 (84)</td>
</tr>
<tr>
<td>IDDM (%)</td>
<td>2 (18)</td>
<td>10 (26)</td>
<td>21 (36)</td>
<td>29 (32)</td>
</tr>
<tr>
<td>NIDDM (%)</td>
<td>2 (18)</td>
<td>8 (21)</td>
<td>14 (24)</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Prior History of MI (%)</td>
<td>2 (18)</td>
<td>11 (29)</td>
<td>32 (54)</td>
<td>38 (41)</td>
</tr>
</tbody>
</table>

Continuous data is presented as mean ± SD.
All p-values were non-significant, except for number of females (p=0.003) and baseline hemoglobin (p<0.001).
No one of the patients in this cohort had any documented history of bleeding disorders.

IfDM = Insulin-dependent Diabetes Mellitus, NIDDM = Noninsulin-dependent Diabetes Mellitus, MI = Myocardial Infarction.

Figure 1.— Frequency of Documented Bleeding

Finally, the in-hospital utilization of ASA, clopidogrel, GPIIbIIIa-inhibitors, enoxaparin, and IV-heparin was recorded.

Differences between K/DOQI groups were analyzed using ANOVA or chi-square test, as appropriate. Statistical analysis was performed by using the SPSS statistical package, version 10.0 (SPSS Institute, Inc., Chicago, IL). Continuous data are expressed as mean ± SD and categorical data as frequencies and percentages.

Results

We reviewed 200 patients with CKD admitted for ACS. No increased bleeding tendencies, such as known bleeding diatheses, a family history of bleeding disorders, or chronic outpatient Coumadin use, were identified in this cohort. Baseline characteristics between each K/DOQI group were similar (Table 1), except for the Stage 3 group having fewer women compared to the Stage 5 group (16% vs. 54%, p=0.003). Differences in baseline hemoglobin from Stage 2 to Stage 5 (13.8 mg/dl ± 1.9 vs. 11.2 mg/dl ± 1.8; p<0.001) were also noted. Finally, there was an increasing trend in the number of patients per K/DOQI group, from Stage 2 to Stage 5.

The overall bleeding rate was 27% for the cohort. There were no significant differences among the groups in frequency of documented bleeding (Stage 2, 3, 4, 5: 15%, 28%, 27%, 29% respectively; p=0.872 [NS]) or in mean number of PRBCs transfused (Stage 2, 3, 4, 5: 0.5, 1.0, 1.0, 1.5 respectively; p=0.5249 [NS] (Figure 1).

No significant differences were observed in the utilization of aspirin, clopidogrel, GPIIbIIIa-inhibitors, enoxaparin, or IV-heparin among the K/DOQI groups (Table 2). Finally, regression analysis did not identify K/DOQI Stage as an indicator for increased bleeding.

Discussion

Despite the event rate being higher than historic controls8,17 we were unable to identify whether the
K/DOQI Stage of CKD had any influence on bleeding risks among those receiving medical treatment for ACS. While not statistically significant, the bleeding rate of patients in Stage 2 was lower than in other stages. Possible explanations include the low number of patients within this group, or perhaps this might represent a threshold of renal dysfunction, where a transition from Stage 2 to Stage 3 may be associated with increased bleeding risk. We will need larger sample size to better evaluate the relationship. While we did observe an increasing trend in the total number of PRBCs transfused as the degree of kidney disease worsened, this may represent the slightly lower baseline hemoglobin level found in those subjects in Stage 4 and 5 being transfused to a similar goal, or perhaps this is an early sign of increased bleeding among those with more advanced kidney disease. Perhaps stronger conclusions could be drawn if specific indications for blood transfusions were known. Finally, no significant differences in the utilization of antithrombotic therapy were observed between K/DOQI groups. This is in contrast to previous studies that have reported decreased use of antithrombotic therapy with increasing renal dysfunction. This study demonstrated that similar medical therapy among patients with declining renal function did not result in an increased bleeding rate. The major implication of this finding is in the treatment of patients in Stage 4 and Stage 5. With an over-representation of cardiovascular disease occurring among those with CKD, more work is needed to improve outcomes in this population. Because our study is retrospective in design, we can make no conclusions; however it may add to the limited data that the degree of renal failure may not be a limiting factor when determining appropriate medical treatment of CKD patients with ACS.

The overall bleeding rate of this cohort was 27%, higher than reported bleeding rates among non-renal disease patients with ACS. Patients with renal dysfunction demonstrate an increased risk of bleeding, due to defects in platelet function and metabolism, defects in vascular endothelial/smooth muscle cell metabolism, and the influence of anemia on hemostasis. There is also data suggesting that CKD patients have an increased tendency towards occult gastro-intestinal bleeding while undergoing dialysis treatment. However, since our report is
retrorspective in design, direct causes of bleeding could not be determined, although it is likely that multiple metabolic or pathologic influences affect bleeding in this collective. The principal observation from this report is that while there appears to be an increased overall bleeding event rate in those with CKD, there does not appear to any difference as the degree of kidney disease worsens.

While there were no statistically significant differences in the use of various medical therapies between K/DOQI groups, the overall utilization of antithrombotic therapy was much lower than reported in patients with ACS and normal renal function.\(^7\)\(^\text{-12}\) While this study did not address mortality rates of the cohort, other studies have found a consistent and large mortality benefit with increased use of antithrombotics, regardless of the severity of renal dysfunction.\(^7\)\(^,8\)\(^,\text{11,12}\)

Several considerations should be made when interpreting this study. This cohort was derived from a retrospective chart analysis and is prone to limitations inherent to such studies. This includes the possibility of unmeasured factors influencing the data and the inability to generate cause and effect conclusions. While all bleeding events were documented, many records failed to document the location of the bleed. Thus, conclusions regarding the possible contraindications of patients not receiving antithrombotic therapy cannot be made. Additionally, potential participant bias may exist, due to large number of Stage 4 and Stage 5 patients treated at surveyed hospitals.

In conclusion, this study found that the severity of renal dysfunction did not influence bleeding risk among patients medically treated for ACS. Currently, all trials regarding treatment and outcomes after ACS have excluded patients with renal insufficiency. Large prospective clinical trials that include patients with CKD are needed to properly assess actual bleeding risks and recommend appropriate interventions in this high-risk population. Presumably, with the development of more aggressive treatment strategies both in the acute setting and in primary prevention, improvements in the quality of care of patients with CKD may be realized.

References
Gender Differences in Therapy for Patients Admitted for Unstable Angina and Myocardial Infarction with Underlying Chronic Kidney Disease

Jocelyn M. Sonson BA, Jeremy J. Lum MD, James R. Madison DO, Todd B. Seto MD, MPH and Christian Spies MD

Abstract
We examined treatment patterns of female pts with CKD admitted for ACS. In this retrospective review of 200 patients with chronic kidney disease presenting with acute coronary syndrome, we found that females patients were less likely to receive aspirin and ACE-inhibitors and there was a trend towards less frequent use of coronary angiography.

Introduction
Coronary heart disease (CHD) continues to be the leading cause of morbidity and mortality among persons in industrialized countries. In addition, patients with chronic kidney disease (CKD) have a high prevalence of cardiovascular disease and cardiac death. In the United States, cardiac disease accounts for 44% of overall mortality in chronic dialysis patients.1 Recent data support the application of proven interventions in the general population, such as angiotensin-converting enzyme inhibitors and statins to patients with CKD and ESRD.2,3 Each year more than 1 million American women and men are diagnosed with acute myocardial infarction (AMI) Previous studies looking at sex differences in management of acute coronary syndromes (ACS) found that women were less likely to undergo more invasive treatments than men.4,5,6 Other studies also report that women are less likely to undergo both diagnostic and revascularization procedures than men.7,8,9

There is a lack of data evaluating gender differences in the management of ACS in patients with CKD. The purpose of this study is to evaluate gender differences in treatment patterns of patients with CKD presenting with ACS.

Methods
Demographic and clinical data were extracted as specified in the results section. Bleeding was defined as either minor or major bleeding episode following the TIMI bleeding criteria (reference). We categorized participants into two groups based on the existence of chronic renal failure. Normally distributed data is reported as mean and standard deviation (SD), normally data is presented as median and interquartile range. Characteristics between the two groups were compared by Chi-Square for dichotomous variables and Mann-Whitney U Test and Student’s T-test for continuous variables. To determine the independent association between incidence of bleeding and other cofactors including CKD we used binary logistic regression analysis to calculate odds ratios. The study was a retrospective analysis of patients with CKD who presented to two major hospitals in the metropolitan area of Honolulu, Hawaii from January 2001 to June 2003. Patients carrying an ICD 9 code for ACS and CKD as a primary or secondary diagnosis were included.

Patients with a Creatinine less than 1.5 were excluded from the study. Criteria for diagnosis of ST-segment elevation AMI includes ischemic-type chest discomfort of > 30 minutes with electrocardiogram evidence of ST-segment elevation ≥0.2 mV in ≥2 contiguous precordial leads of ST-segment elevation ≥0.1 mV in ≥2 limb leads and an elevated serum creatine kinase-MB level (> 10%) or an elevated serum cardiac specific troponin I level (> 2 ng/ml). Non-ST-segment elevation AMI was diagnosed by ischemic-type chest discomfort of > 30 minutes without ST-segment elevation but with an elevated serum creatine kinase-MB or a cardiac-specific troponin I level.10 Unstable angina was diagnosed by ischemic-type chest discomfort of > 30 minutes with normal serum creatine kinase-MB and cardiac-specific troponin I levels. Data on demographics, cardiac risk factors, presenting symptoms, diagnostic tests and therapeutic interventions were gathered from the patient’s medical records. Killip classification was defined using the collected data in order to assess symptoms of heart failure. Statistical analyses was done using chi-square, Student’s t-test and Mann-Whitney U test to determine differences in management between the two treatment groups.
Table 1.— Baseline Characteristics for Women and Men

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n=97)</th>
<th>Men (n=104)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [mean ± SD]</td>
<td>68 ± 13.8</td>
<td>70 ± 2.8</td>
<td>NS</td>
</tr>
<tr>
<td>Comorbidities (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>42.3</td>
<td>39.4</td>
<td>NS</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>15.5</td>
<td>9.6</td>
<td>NS</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>26.8</td>
<td>27.9</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>89.7</td>
<td>86.5</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>67.0</td>
<td>43.3</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>43.3</td>
<td>36.5</td>
<td>NS</td>
</tr>
<tr>
<td>Obesity *</td>
<td>7.2</td>
<td>7.7</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>5.2</td>
<td>10.6</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>25.8</td>
<td>14.4</td>
<td>0.044</td>
</tr>
<tr>
<td>Troponin I max (ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [interquartile range]</td>
<td>2.3 [0.26-19.77]</td>
<td>2.7 [0.27-16.75]</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine kinase-MB max (U/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [interquartile range]</td>
<td>8.4 [3.6-18.8]</td>
<td>8.3 [4.7-20.8]</td>
<td>NS</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>45% ± 16.6</td>
<td>42% ± 14.3</td>
<td>NS</td>
</tr>
<tr>
<td>Killip class (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>36.1</td>
<td>50</td>
<td>0.03</td>
</tr>
<tr>
<td>II</td>
<td>38.1</td>
<td>33.7</td>
<td>NS</td>
</tr>
<tr>
<td>III</td>
<td>25.8</td>
<td>14.4</td>
<td>0.044</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>2.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; PCI, percutaneous coronary intervention; LV, left ventricular

*Obesity defined as BMI≥25.

**Results**

The study included 97 women, mean age 68 ± 14 years (range 35 to 98), and 104 men, mean age 70 ± 13 years (range 29 to 100) (p=NS). Table 1 shows the prevalence of coronary risk factors in women versus men. Family history of coronary artery disease was statistically more prevalent in women (25.8%) than men (14.4%) (p=0.44). There was no statistically significant difference in severity of disease between women and men. Both groups presented with similar maximum serum creatine kinase-MB and cardiac specific troponin I. In addition, both men and women had similar left ventricular ejection fractions. However, women tended to present with worse Killip classification than men. (Table 1)

There were no significant differences in the rates of non-invasive testing. Both women and men had similar rates of lipid panel evaluation and stress testing (Table 2). Despite these differences in stress testing rates, women were less likely to undergo coronary angiography. Aspirin and ACE-inhibitors were used significantly less frequently in women compared to men. In contrast to these findings, more women were treated with ARBs. (Table 2) The rates of PCI and CABG were similar across both gender groups.

**Discussion**

Previous studies that assessed gender differences in ACS within the normal population found that women were older than men and had more risk factors and more comorbid conditions.4,11,12,13 Our study found no age differences between women and men with CKD presenting with ACS, nor were there more risk factors or comorbidities. Despite women presenting with worse symptoms of heart failure, this study found that women with CKD presenting with ACS were less likely to receive aspirin and ACE inhibitors compared to men. Our findings are consistent...
Table 2.— Diagnosis and Treatment of Acute Coronary Syndrome in Chronic Renal Failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n=97)</th>
<th>Men (n=104)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive testing (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipids</td>
<td>75.2</td>
<td>76.9</td>
<td>NS</td>
</tr>
<tr>
<td>Stress test</td>
<td>32.2</td>
<td>29.4</td>
<td>NS</td>
</tr>
<tr>
<td>Invasive testing (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>26.8</td>
<td>39.4</td>
<td>0.058</td>
</tr>
<tr>
<td>Medication (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>37</td>
<td>53</td>
<td>0.025</td>
</tr>
<tr>
<td>ARB</td>
<td>37</td>
<td>20</td>
<td>0.008</td>
</tr>
<tr>
<td>Aspirin</td>
<td>69</td>
<td>83</td>
<td>0.041</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>71</td>
<td>72</td>
<td>NS</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>36</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>24</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>GPIIb/IIIa</td>
<td>8.3</td>
<td>6.7</td>
<td>NS</td>
</tr>
<tr>
<td>IV Heparin</td>
<td>20.6</td>
<td>15.3</td>
<td>NS</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>51</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>Statin</td>
<td>52</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>Reperfusion therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>14.4</td>
<td>11.5</td>
<td>NS</td>
</tr>
<tr>
<td>CABG</td>
<td>6.2</td>
<td>9.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

with previous studies looking at gender differences in patients presenting with ACS. These studies found that women were less likely to be treated with aspirin, heparin, or beta-blockers.\textsuperscript{14} In contrast to our study, these previous studies did not look specifically at patients with CKD. Based on our results we are unable to explain why there is a difference between the treatment of men and women presenting with ACS. Possible explanations include a lack of knowledge of how prevalent heart disease is in women and a lack of emphasis of treating heart disease in women as compared to men. Further larger studies are needed to determine how significant a difference there is between genders and why this occurs. Of particular interest would be what impact this decreased use of therapy for ACS has on outcomes among the female population presenting with CKD.

In addition to differences in medical therapy between men and women, our study found a decreased utilization of coronary angiography in the female population. These findings are similar to previous research that found that women in all age groups were less likely to undergo diagnostic catheterization than men.\textsuperscript{15} In addition, previous studies have found that women were less likely to undergo more aggressive diagnostic evaluation and treatment than men.\textsuperscript{16} Reasons for treatment differences between men and women may include a bias towards more conservative therapy in the female population or an under estimation of how large an impact heart disease has on this gender group. Further larger studies are needed to determine how significant a difference there is between genders and why this occurs.

Harrold et al. examined gender differences and trends over time in the management of patients with AMI.\textsuperscript{4} These investigators noted that overall, women were less likely to undergo cardiac PCI and CABG. In this study, however, there was no significant difference between revascularization rates among both groups. Possible reason for the difference in our findings compared to other studies may be the overall low incidence of CKD patients undergoing revascularization secondary to comorbidities.

In general this study found that patients with CKD are less likely to undergo revascularization compared to patients without renal insufficiency. This is consistent with previous studies which found that patients with CKD presenting with ACS receive less aggressive treatment.\textsuperscript{16,17,18} Perhaps patients with CKD may have more contraindications to aspirin, beta-blockers, and ACE inhibitors. In addition, patients with CKD may have poorer outcome after interventional therapy.
There were several limitations inherent in this study. This study was a small, retrospective, observational, chart review study done at 2 metropolitan Honolulu hospitals, and therefore may not be representative of other hospitals nationwide. In addition, as a retrospective study there is the potential for referral bias.

Conclusions
The results of this study demonstrated that although women with CKD had similar baseline characteristics compared to men with CKD at time of presentation for ACS, women were treated less aggressively. Women were less likely to receive aspirin and were evaluated with cardiac catheterization less often than men.

References
Case Report: A Common Presentation of a Rare Disease-Hepatosplenic T-Cell Lymphoma

CPT Jamalah A. Munir MD, LTC Glenn Preston MD, and MAJ Roger Polish MD

Abstract
Hepatosplenic T-cell lymphoma is a rare neoplasm characterized by systemic B-symptoms, hepatosplenomegaly, no lymphadenopathy, and lymphomatous infiltrates in the splenic red pulp, hepatic sinusoids, and bone marrow sinuses. The team presents the case of a healthy 30 year old man, active duty Marine, who presented with classic symptoms, yet obtaining a diagnosis took over three months from the onset of symptoms. This clinical entity, initially described in 1990, is elusive, with vague and misleading symptoms. Despite aggressive conventional therapy with anthracycline-based regimens and stem cell transplant, prognosis is poor and median survival is less than one year.

Introduction
Hepatosplenic T-cell lymphoma (HSTCL) is a rare lymphoid neoplasm only recognized as a distinct entity in 1990. This neoplasm is characterized by lymphomatous infiltration of the hepatic and splenic red pulp sinuses resulting in splenomegaly and hepatomegaly without peripheral lymphadenopathy. Since the initial classification, approximately 80 cases have been described in the literature.

Case Report

History/Physical exam
A 30 year old Caucasian man who is an active duty Marine Corps officer stationed in Okinawa, Japan without significant past medical history initially presented to his local clinic with complaints of back and abdominal pain with associated intermittent fevers and diaphoresis. He was given NSAIDs and told to keep himself well hydrated. He continued to fulfill his active duty responsibilities for about two months, while his symptoms gradually worsened, with increasing abdominal and back pain, and daily fevers. At this time, he also complained of frequent loose dark stools, malaise, anorexia, and mild nausea. The abdominal pain was described as a generalized cramping without any aggravating or relieving factors and a sensation of “rock-hard abs”. He was admitted to the Naval Hospital in Okinawa for massive hepatosplenomegaly and abdominal guarding.

Physical examination revealed a firm abdomen with mild diffuse tenderness to palpation, liver palpable 5 cm below the costal margin, spleen palpable to the level of the umbilicus, and no peripheral lymphadenopathy. Initial laboratory evaluation revealed: white blood cell count 4.2 x 10^9/L with normal differential, normal hematocrit, platelets 98 x 10^9/L, aspartate aminotransferase (AST) 152 IU/L, alanine aminotransferase (ALT) 118 IU/L, γ-glutamyl-transpeptidase (GGT) 110 IU/L, alkaline phosphatase 182 IU/L, total bilirubin 0.9 mg/dL, INR 1.2, and lactate dehydrogenase (LDH) 3343 U/L. Given his presentation, there was concern for malignancy vs. severe infectious etiology, and the patient was air-evacuated to Tripler Army Medical Center for further evaluation.

Diagnostic evaluation
Computed tomography scan of chest, abdomen, and pelvis demonstrated (Figure 1): massive splenomegaly with a splenic index of 5400cc, (normal 460cc); hepatomegaly without intrahepatic or extrahepatic ductal dilatation; inflammatory changes of the descending and
sigmoid colon with focal areas of bowel wall thickening; and no significant lymphadenopathy. Given the colon-related findings and the patient’s symptoms of loose dark stools coupled with nausea and anorexia, we pursued endoscopic evaluation to further delineate these findings/symptoms. Both esophagogastroduodenoscopy and colonoscopy were normal without pathologic findings. Although a malignant etiology was likely, the patient had significant travel history and thus a concurrent infectious workup was performed. At time of evaluation, he was stationed in a remote/field location on the outskirts of Okinawa, Japan. He had recently traveled to remote regions in Australia, and had previously been stationed or traveled to Korea, Kuwait, and Norway. Tests performed to rule out infection included: serologic test for hepatitis A, B, and C; thick and thin smears for malaria; blood, urine, and sputum cultures; monospot testing for Ebstein Barr virus (EBV); HIV; human T-cell lymphotropic virus type I (HTLV-1), PPD testing for tuberculosis; cytomegalovirus (CMV) serologic testing; brucella, coxiella, cryptococcus, coccidioides, histoplasma, lyme disease, and typhus. The thorough infectious evaluation only revealed IgG positivity to CMV and was otherwise negative.

During the diagnostic evaluation, he continued to suffer from daily fevers and mild abdominal discomfort, with persistent transaminitis. A bone marrow biopsy with aspiration and peripheral blood analysis was subsequently performed. The findings included: peripheral blood analysis - a mild and normochromic/normocytic anemia, with mild lymphopenia and thrombocytopenia, without circulating blasts or otherwise atypical/dysmorphic elements; bone marrow/aspirate - cellular and hematopoietically active bone marrow with megakaryocytic hyperplasia; flow cytometry - subpopulation of CD2+, CD3+, CD7+, CD5+, CD4+, and CD8+ lymphocytes. This subpopulation of aberrant lymphocytes was of undetermined significance. B-lymphocytes showed heterogeneous surface immunoglobulin expression. There were also viral, bacterial, fungal, and AFB cultures obtained from the bone marrow, which eventually returned negative. Chromosomal analysis demonstrated 46, XY normal male, without abnormalities.

Following the non-diagnostic bone marrow biopsy, the search for a tissue diagnosis led us to an ultrasound guided liver biopsy, and then possibly a splenectomy for symptomatic relief and diagnostic value. The liver biopsy demonstrated diffuse infiltration of an atypical lymphoid population within the hepatic sinusoids. Lymphocytes were positive for LCA (Leukocyte Common Antigen) and UCHL-1 (specific for T-cells), and negative for CD20 (B-cell receptor). These features were consistent with hepatosplenic T-cell lymphoma. Further genetic characterization was limited due to the small tissue sample obtained on initial biopsy. Subsequent evaluation and immunohistochemical staining revealed that the small subpopulation of T-cells with the aberrant phenotype (CD4+, CD5+, and CD8+) was consistent with 10% bone marrow involvement with lymphoma. Staining showed UCHL-1 positive cells distributed intrasinusoidally throughout the marrow clot sections. Given the final diagnosis and severity of illness, the patient was transferred to a medical facility closer to his family for definitive treatment. He is undergoing a protocol at the National Institutes of Health with EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin). With chemotherapy, his spleen decreased in size and he is currently awaiting allogeneic stem cell transplant.

**Discussion**

The clinical features described in the case report are characteristic of hepatosplenic T-cell lymphoma. This rare neoplasm only accounts for 5 percent of all peripheral T-cell lymphomas (Table 1) and PTCLs are only a small portion of all non-Hodgkin lymphomas (15%)². Since Facet described this condition as a distinct entity in 1990 by, there have been approximately 80 cases reported in the literature. This uncommon lymphoma primarily affects young males with a median age of about 35 years. Patients typically present with marked splenomegaly and most often hepatomegaly, without lymphadenopathy. Most will have systemic B-symptoms including fever, night sweats, fatigue and weight loss. Predominant laboratory findings include reduced peripheral blood counts (especially thrombocytopenia), elevated LDH, and abnormal liver associated enzymes. The diagnosis of HSTCL can be difficult, as occurred with the described patient, and can easily be missed at the outset. Reports of initial misdiagnosis include

<table>
<thead>
<tr>
<th>Table 1.— WHO/REAL Classification of Mature T-Cell and NK-Cell Neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemic</td>
</tr>
<tr>
<td>• T-Cell prolymphocytic leukemia</td>
</tr>
<tr>
<td>• T-Cell Large Granular lymphocytic leukemia</td>
</tr>
<tr>
<td>• Aggressive NK-cell leukemia</td>
</tr>
<tr>
<td>• Adult T-cell leukemia/lymphoma (HTLV-1+)</td>
</tr>
<tr>
<td>Nodal/Lymphoma</td>
</tr>
<tr>
<td>• Peripheral T-cell lymphoma, unspecified</td>
</tr>
<tr>
<td>• Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>• Anaplastic Large-cell lymphoma (ALCL)</td>
</tr>
<tr>
<td>Extra nodal/cutaneous</td>
</tr>
<tr>
<td>• Indolent:</td>
</tr>
<tr>
<td>• Mycosis Fungoides/Sezary Syndrome</td>
</tr>
<tr>
<td>Primary Cutaneous ALCL</td>
</tr>
<tr>
<td>• Aggressive:</td>
</tr>
<tr>
<td>• Extranodal NK/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>Enteropathy-type T-cell lymphoma</td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
</tr>
<tr>
<td>Subcutaneous Pantoculis-like T-cell lymphoma</td>
</tr>
<tr>
<td>Blastic NK-cell lymphoma</td>
</tr>
</tbody>
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viral hepatitis, autoimmune hepatitis, chronic myelomonocytic disorder, and idiopathic thrombocytopenic purpura, are evidence of the difficulty characterizing this uncommon disease.  

The majority of cases are diagnosed at splenectomy. Less commonly, the diagnosis may occur at liver biopsy, as in our case. The typical histopathologic findings on biopsy show a pattern of infiltration of abnormal, homogenous, medium-sized lymphocytes of the hepatic sinusoids and splenic red pulp. HSTCL usually arises from a CD4+/CD8- T-cell, and in ~15% of cases CD4+/CD8+ T-cell. It is uncommon to diagnose HSTCL on bone marrow biopsy alone due to the often subtle involvement. Bone marrow involvement can range from subtle infiltrates only detected by immunostains to 70% marrow involvement. The initial marrow biopsy specimens are commonly hypercellular with trilineage hyperplasia that may be confused with a myelodysplastic or myeloproliferative syndrome.  

Splenomegaly and lymph node enlargement are common findings on physical examination. Hepatosplenomegaly mimicking acute hepatitis may be seen in up to 6 months. The initial presentation is usually a CD4- CD8+ T-cell lymphoma. It may also present with fever, weight loss, and hepatosplenomegaly. The disease progression is often rapid, with lymphadenopathy, hepatomegaly, and extramedullary disease. The prognosis is poor, with a median survival of 6 months. Treatment options include chemotherapy, radiation, and stem cell transplant. In those few patients with chronic lymphocytic leukemia, there is typically early relapse. There may be an increase in median survival of up to 6 months for those patients who undergo splenectomy (either diagnostic or therapeutic) but ultimately all reported cases have died within 1-2 years despite varied therapeutic options. This case report of hepatosplenic T-cell lymphoma described the characteristics of a young man presenting with massive splenomegaly and hepatomegaly without lymphadenopathy. This case’s elusive findings make diagnosis challenging, and should be included in the differential diagnosis of hepatosplenomegaly.

References
Bleeding Risk in Patients with Underlying Chronic Kidney Disease Admitted for Acute Coronary Syndromes

Kyoko S. Yamada MD, Jeremy J. Lum MD, James R. Madison DO, MS, Todd B. Seto MD MPH, and Christian Spies MD

Abstract
A retrospective review of 200 patients with acute coronary syndrome (ACS) and chronic kidney disease (CKD) was compared to 200 patients without CKD to investigate the incidence of bleeding. Logistic regression analysis identified CKD as an independent risk factor for bleeding (OR 1.82, 95% CI 1.02 - 3.25). CKD patients with ACS appear to have more bleeding complications.

Introduction
There are approximately 300,000 people with end stage renal disease (ESRD) and 2 million with chronic kidney disease (CKD) in the United States. 4 Forty-one percent of patients with ESRD will succumb to cardiovascular disease and more than one in five of these deaths will be as a result of an acute myocardial infarction. 2 The inferior outcomes of patients with end stage renal disease following myocardial infarctions have been attributed to a variety of causes including higher prevalence of comorbidities in patients with renal disease, certain vascular characteristics, higher levels of homocysteine and differences in management. 3,4,5 These differences in management include less frequent beta-blocker or aspirin therapy, less utilization of thrombolytics and infrequent percutaneous revascularization procedures in patients with acute myocardial infarctions and CKD compared to patients with normal kidney function. 6,7,8,9

Medical therapy for acute coronary syndromes (ACS) heavily relies on anticoagulant and antiplatelet therapy. 10 However, due to fear of bleeding complications secondary to uremic platelet dysfunction, patients with CKD commonly do not receive these blood thinning agents, although differences in bleeding complications in patients presenting with ACS with or without CKD have never been evaluated outside a post-hoc analysis of a randomized controlled trial. 11,12

Thus, the goal of our study was to evaluate the incidence of bleeding complications in patients admitted with ACS and CKD.

Methods
After approval by the appropriate institutional review boards, an analysis of computerized discharge diagnosis was performed at two major hospitals in Honolulu, Hawaii, from January 2000 until June 2003. Patients carrying an ICD9 code for acute coronary syndrome and chronic kidney disease as primary or secondary diagnosis were included. Patients with a creatinine of less than 1.5 mg/dl on admission were excluded from the analysis. The second group of patients with acute coronary syndromes without CKD was identified during the same period of time. In both groups, patients with acute renal failure were excluded from analysis.

Demographic and clinical data were extracted as specified in the results section. Bleeding was defined as either minor or major bleeding episode following the TIMI-bleeding criteria. 13 We categorized participants into two groups based on the existence of chronic kidney disease. Normally distributed data is reported as mean and standard deviation (SD). Characteristics between the two groups were compared by Chi-Square for dichotomous variables and Mann-Whitney U Test and Student’s T-test for continuous variables. To determine the independent association between occurrence of bleeding and other cofactors including CKD we used binary logistic regression analysis to calculate odds ratios. Alpha-level was set at 0.05, unless otherwise stated. Statistical analyses were performed with the use of SPSS version 10.0 (Chicago, IL).

Results
Baseline Characteristics
We identified 200 patients with and 200 patients without CKD admitted for ACS. Patients with CKD were older then those without CKD (69 ± 13.3 vs 66.5 ± 13.7 years, p=0.079) (Table 1). Patients in the CKD were more likely to be female and non-Caucasian, and had more diabetes, hypertension, previous history of myocardial infarction, cerebral vascular disease,
peripheral vascular disease, congestive heart failure, and atrial fibrillation (Table 2). On admission, patients with CKD more commonly presented with acute heart failure, more frequently were anemic and had a higher activated partial thromboplastin time (PTT) compared to patients without CKD (Tables 1 and 3).

Incidence of Bleeding
There was a trend towards more clinically overt bleeding in patients with CKD than in patients with normal kidney function (27.5% vs 20.5%, p=0.101) (Table 4). Patients with CKD more frequently received blood transfusions compared to patients admitted with ACS without coexisting renal disease (mean 1.3 ± 3.03 vs 0.83 ± 2.98, p=0.118).

In binary logistic analysis CKD was associated with the occurrence of any kind of bleeding complication (OR 1.82, 95% CI 1.02 to 3.25, p=0.042), as was coronary angiography (OR 3.44, 95% CI 1.87 to 6.34, p<0.0001) after exclusion of patients who underwent coronary artery bypass grafting (Figure 3). Use of Clopidogrel (OR 0.39, 95% CI 0.22 to 0.69) and higher platelet counts (OR 0.98, 95% CI 0.98 to 0.99) were associated with less frequent bleeding.

Therapeutic Interventions
Aspirin, Clopidogrel, GPIIb/IIIa-Inhibitors, Enoxaparin, and IV heparin were less frequently administered to CKD patients (Figure 1). Patients with CKD also did not receive as much invasive therapy, with less frequent utilization of diagnostic angiography procedures and percutaneous coronary interventions (Figure 2).

Discussion
This study suggests that patients with chronic renal failure are more at risk for bleeding than those without chronic renal failure. Although we documented a higher incidence of bleeding (27.5% vs 20.5%), and more frequent transfusions in the CKD patients, this was not found to be statistically significant (p=0.101). In logistic regression analysis, after accounting for anti-platelet agents, aspirin, age, and other confounding factors, we found that CKD was associated with the combined outcome of major and minor bleeding, independent of the severity of renal dysfunction. The conflicting results are likely a result of the small number of patients in our initial analysis and this is one of the limitations of our study.

Although one might expect lower bleeding rates with less anti-coagulant therapy, we saw a higher incidence of bleeding. This may be secondary to uremic platelet dysfunction and other, as yet unspecified factors.

All types of anti-coagulation and therapeutic interventions were documented as less frequently employed in CKD patients. It is likely that the pre-

<table>
<thead>
<tr>
<th>Table 1.— Baseline Characteristics</th>
<th>CKD (n=200)</th>
<th>Non-CKD (n=200)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69 ± 13.3</td>
<td>66.5 ± 13.7</td>
<td>0.079</td>
</tr>
<tr>
<td>Female</td>
<td>48%</td>
<td>29%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>58%</td>
<td>44.5%</td>
<td>0.004</td>
</tr>
<tr>
<td>Asian</td>
<td>58%</td>
<td>44.5%</td>
<td>0.004</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>24%</td>
<td>13%</td>
<td>0.074</td>
</tr>
<tr>
<td>Caucasian</td>
<td>16%</td>
<td>34%</td>
<td>0.283</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
<td>8.5%</td>
<td>0.123</td>
</tr>
<tr>
<td>Medicare Insurance</td>
<td>70%</td>
<td>32%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Killip Class*</td>
<td>56%</td>
<td>85%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Class I</td>
<td>56%</td>
<td>85%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Class II</td>
<td>36%</td>
<td>7%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Class III</td>
<td>20%</td>
<td>2%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Class IV</td>
<td>7%</td>
<td>1%</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

* demonstrating no evidence of heart failure in Class I, mild mod CHF in Class II, overt pulmonary edema in Class III and cardiogenic shock in Class IV (21)

<table>
<thead>
<tr>
<th>Table 2.— Comorbid conditions</th>
<th>CKD (n=200)</th>
<th>Non-CKD (n=200)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM using insulin</td>
<td>28%</td>
<td>8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DM not using insulin</td>
<td>19%</td>
<td>16%</td>
<td>0.372</td>
</tr>
<tr>
<td>Hypertension *</td>
<td>88%</td>
<td>63%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperlipidemia *</td>
<td>40%</td>
<td>42%</td>
<td>0.729</td>
</tr>
<tr>
<td>AML</td>
<td>41%</td>
<td>14%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CVA</td>
<td>23%</td>
<td>6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVD</td>
<td>14%</td>
<td>2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CHF</td>
<td>37%</td>
<td>3.5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All</td>
<td>15%</td>
<td>4.5%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Defined as a Creatinine of ≥1.5 mg/dl
† Defined as history of diabetes, regardless of duration of disease, need for anti-diabetic agents, or a fasting blood sugar >7 mmol/l or 126 mg/dl
‡ Defined as BP > 140/90 on 2 separate occasions
§ Defined as BP > 140/90 on 2 separate occasions
* Defined as thromboplastin time (PTT) of 60-120 seconds

<table>
<thead>
<tr>
<th>Table 3.— Baseline Laboratory Values</th>
<th>CKD (n=200)</th>
<th>Non-CKD (n=200)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>35</td>
<td>42</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Platelets</td>
<td>233</td>
<td>243</td>
<td>0.283</td>
</tr>
<tr>
<td>PTT</td>
<td>39.8</td>
<td>33.5</td>
<td>0.002</td>
</tr>
<tr>
<td>INR</td>
<td>1.4</td>
<td>1.2</td>
<td>0.074</td>
</tr>
</tbody>
</table>

1. CKD defined as a Creatinine of ≥1.5 mg/dl

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The assumed risk of bleeding complications in this group is what motivated the lack of medical interventions. However, this has never been adequately researched as CKD patients are frequently excluded from studies on anti-coagulant therapy. There are no guidelines for the use of GPIIb/IIIa inhibitors in patients with CKD and only recently has dosing information of low-molecular weight heparin in CKD patients been released. Recent studies demonstrate mixed results on the use of anti-coagulant therapy in this group. Two studies utilizing the GPIIb/IIIa inhibitor, abciximab in patients with CKD during PCI fail to demonstrate an increased risk of major bleeding. 

In the ESPRIT trial sub-group analysis, which examined the effects of the GPIIb/IIIa inhibitor eptifibatide in patients with chronic kidney disease undergoing coronary artery stent placement, patients with CKD were found to be more at risk for bleeding. However, in these studies there are limitations that prevent the application of these results to a large number of patients, including small sample sizes, problems with post-hoc analysis and lack of generalizability of the study populations. Freeman's study on the use of GPIIb/IIIa inhibitors in CKD patients presenting with ACS found a two-fold increase in major bleeding events that appeared to correlate with decreasing creatinine clearance. The implications of his findings of increased bleeding, which are similar to those here are unclear, as he also notes that the use of GPIIb/IIIa inhibitors offered a significant protective effect in decreased mortality. 

Our observation of increased bleeding events in patients with CKD signifies the need for further prospective trials to clarify the risk of bleeding in patients with CKD being treated for ACS.

In addition to uremic platelet dysfunction, the observation of increased bleeding in patients with CKD treated with anti-coagulants may be explained by alteration of the pharmacokinetics of anti-coagulants in renal insufficiency. The pharmacokinetics of GPIIb/IIIa inhibitors and low molecular weight heparins are altered in those with renal insufficiency 

It is possible that inadequate dose adjustment may partially account for the increased association with bleeding in those patients in whom they were utilized. In the future, optimal dosing of anti-coagulants following acute coronary syndrome in the setting of renal failure needs to be determined.

Our study population was ethnically diverse, with Caucasians accounting for only a minority of the patients examined as compared to other studies, which have been done largely on Caucasian and African-American populations. It is unclear what effect ethnic background may have had on our data.

The design of the study as a retrospective chart review is also limiting in that we can only note associations. In order to really establish whether there is a significant role for uremia in bleeding, we would
need to have a prospective trial. It also hinders us in our evaluation of long-term consequences for bleeding.

Conclusions
Patients with chronic kidney disease routinely receive less anticoagulant and anti-platelet treatment for acute coronary syndrome partly out of concern for bleeding complications. Given that CKD might be a risk factor for bleeding complications, appropriate management strategies must be investigated. Randomized controlled trials are needed to establish the role of uremic platelet dysfunction in bleeding complications and to determine the safety of anti-platelet and anti-coagulant medications.

References
Students entering medical school usually recognize the role of forensic pathologists like Quincy of TV fame, but have a vague or nebulous perception of what pathology really is. Students are more aware of clinical specialties like family practice, surgery, pediatrics, obstetrics and gynecology, psychiatry and medicine. They also understand that they must master basic science disciplines like anatomy, biochemistry, physiology and pharmacology to become physicians. Somehow pathology remains more elusive. Even so, students often become enthusiastic and excited when they see the vital role that pathology plays in understanding disease. As teachers such enthusiasm is not only refreshing but inspirational in showing my students how interesting and dynamic the study of disease can be.

Pathology is a basic discipline that is an essential part of the broad educational experience that every medical graduate receives. Pathology is the scientific study of the nature of disease and its causes, processes, development and consequences. Pathology is a core discipline in the educational experience of every physician. Before medical students can truly understand what they need to know to be good physicians, they must understand the nature of disease.

To appreciate how pathology is taught today, past accomplishments need to be reviewed. Virchow’s *Cellular Pathology* (1858) marked the beginning of modern pathology and revolutionized the approach and understanding of disease. Virchow regarded the body as a cell-state in which every cell is a citizen, and disease as a civil war brought about by external forces among the cells. His understanding explained the evolution of a particular disease. For example, he proposed that a Charcot (neuropathic) joint was due to repeated episodes of minor trauma to joints that were unprotected by the pain response. With continued damage and inadequate repair, a Charcot joint evolved. Virchow’s approach was the beginning of integrating the available scientific information regarding anatomy and physiology to understand a particular disease process.

Standard textbooks of pathology remained largely descriptive and often did not explain the dynamics of disease processes. Dr. Stanley Robbins, a master teacher and pathologist, recognized this deficiency and believed that medical students needed to know how diseases began and progressed. He understood that basic pathophysiology was a meaningful way to approach the understanding of disease. In 1957 he published his first textbook entitled, *Textbook of Pathology, with clinical applications* to correct this deficiency. Dr. Robbins recognized that descriptions of disease were often uninspiring, not very interesting, and failed to explain the natural history of disease. His chatty writing style and prose peppered with light-hearted asides, made the study of diseases come alive for subsequent generations of medical students. He made understanding of disease practical and useful by emphasizing the mechanisms that underlie illnesses.

In 1979, Ramzi Cotran and in 1984, Vinay Kumar joined Dr. Robbins to produce the premier textbook of pathology currently used worldwide. With the passing of Stanley Robbins at age 88 in 2003 and Ramzi Cotran at the age of 67 in 1999, Vinay Kumar was left to carry on Dr. Robbin’s legacy. Vinay Kumar, with new coauthors Abul K. Abbas and Nelson Fausto, all former colleagues of Dr. Stanley Robbins, recently published the 7th edition of “Robbins and Cotran Pathologic Basis of Disease”. Review of this new edition indicates that Dr. Robbin’s legacy, as one of medicine’s great teachers, will endure. This edition, like previous editions, is written for medical students and remains the premier textbook for medical students. This edition will be treasured by medical students as much today as it was in the past. This textbook, like previous editions, will also be invaluable to upper level medical students, clinical residents and practicing physicians.

At John A. Burns School of Medicine (JABSOM), the student’s didactic experiences are coupled with practical applications that use a variety of methods and materials. The Robbins and Cotran textbook is recommended for the study of disease. This book emphasizes clinical correlations and the pathophysiology of disease. Such an approach integrates many disciplines and includes particularly anatomy, physiology, biochemistry, microbiology, cell and molecular biology, genetics and pharmacology. Such integration is helpful to students doing Problem Based Learning (PBL). Actual clinical specimens, standard x-rays and CT and MRI scans are used. Since modern imaging techniques make it feasible to see inside the body, the abnormalities seen by imaging with their gross and microscopic appearance are shown. Students can correlate a particular pathologic abnormality with its image appearance. Obviously a student must understand the diseases and their natural history to make these correlations. The combination of such didactic and practical experience provides every student with the fundamentals to understand and recognize the diseases that afflict man.

Finally, JABSOM’s educational approach introduces students to diseases and pathologic processes that they are likely to encounter in Hawaii and particularly those disorders that complement the health care problems in the PBL curriculum. The epidemiology of disease becomes a key basis for such study. The unique aspects of diseases that apply to Hawaii are included, for example, cosinophilic meningitis is caused by *Angiostrongyulus cantonensis*, and the prevalence of diseases like diabetes mellitus and hyperuricemia among Polynesian populations.

See, “Pathology” p. 353
Introduction
This paper problematizes polypharmacy, including CAM, in the context of elderly cancer patients. Further, it reviews the unique findings of studies of CAM use in Hawaii, which offer insights into both the objectives and the measure of CAM use by cancer patients, and suggests that this knowledge can be translated into integrated clinical practice.

Polypharmacies
Polypharmacy is a coherent preventive and therapeutic strategy in conventional biomedicine, and is used increasingly in the treatment of monodrug-resistant and (re)emergent infections such as malaria, tuberculosis, and cholera (Farmer 1999; Scheld et al. 1998; Scior et al. 2002). Multi-drug regimens also may be effective for disorders for which a substantial proportion of patients experience no or incomplete response to singlet drugs—e.g., cardiovascular disorders, hypertension, and epilepsy (Campos-Castello and Campos-Soler 2004; Gavras and Rosenthal 2004). Today, the term polypharmacy extends to multiple prescriptions from more than one physician, as well as to patient-crafted combinations of prescription drugs, and drugs with other therapeutic modalities. In a more conventional definition, polypharmacy is indicated for co-morbidities, for which the elderly are at especially high risk.

Polypharmacy among the Elderly
In the U.S. and western Europe the elderly comprise 15%-20% of the population but account for 30-40% of all drug prescriptions. An estimated 90% of community-dwelling older adults take at least one prescription, most take two or more; nursing-home, variably assisted-living, and hospitalized elderly typically take six to nine prescription drugs. Older adults also purchase about 50% of over-the-counter products (Clews et al. 2001; Corcoran 1997; Paille 2004; Pollock 1998). Polypharmacy among the elderly is further confounded by the use of complementary and alternative medicines, for virtually all age-associated conditions. Estimated rates of consumption range between 50% and 90%.

While polypharmacy offers benefits in some clinical contexts, it constitutes substantial risk for all patients, and especially for the elderly. Beginning at about 40 years of age, individuals experience a linear decline in a number of physiologic functions, which can affect pharmacokinetic and pharmacodynamic processes. Possible undesired outcomes of—singlet and especially multiple—drug consumption include altered drug distribution and activity, delayed and extended-duration effects, and changes in the processes of drug metabolism and detoxification. Polypharmacy significantly increases the risk and severity of adverse drug reactions (ADRs) which correlate directly and exponentially with the number, and number of kinds, of drugs taken and the number of prescribing physicians. The rate of ADRs among older adults is two to seven times higher than for other age sectors (Koda-Kimble and Young 2001).

The annual cost of age-associated drug-related problems is enormous and is compounded by psychological and social disjunctions. Polypharmacy fosters confusion: many elderly have difficulty keeping track of multiple medications, especially those with different but overlapping dosing schedules; anxiety about toxicity and ADRs increases incrementally with added prescriptions. This resonates especially for elderly whose memory of fewer medicines is more vivid than their short-term experience with current prescriptive practices. These and other concerns contribute to invoking other cultural constructions of health and healing that are discrepant with biomedical paradigms, and include actions that may be interpreted by biomedicine as “noncompliance.” One potent expression of patient-driven strategies is self- or home-treatment, including the use of complementary and alternative medicines (CAM).

Cancers, Polypharmacy, and CAM
An 11-fold greater incidence, and more than half of cancers, occur in individuals aged 65 years or older, among whom the greater likelihood of co-morbidity, coupled with the complex nature of cancer therapies, encourages polypharmacy (Al-Shahri et al. 2003; Lichtman 2003; Terret 2004), including self- or home-treatment. Like its pharmaceutical counterpart, the CAM industry maximizes profit by making available a multiplicity of products that both fill and create niches of “need.” Patients command agency in their own health care by purchasing these products, and through their social transaction create and transform the meaning of the therapeutic experience. A great variety of CAM are promoted specifically for the prevention and treatment of cancers, with estimates of CAM use by cancer patients ranging as high as 85%. CAM typically are used to supplement chemotherapies and for the treatment of side effects of cancer and cancer therapies; only a small percentage of cancer patients use CAM as an alternative to biomedical treatments.

Cancer and CAM in Hawaii
Our studies of CAM use in Honolulu, Hawaii (Etkin et al. 1999; Etkin and McMillen 2003) explored in depth the cultural constructions...
of health and healing in a demographically diverse population, and documented 346 discrete CAM products or processes. Seventy-five percent of CAM reported by study participants are botanicals, which range from treatments for specific disorders such as hypertension to more general objectives such as “general health.” We further refined the research methodology and scope in a subsequent study that focused on hospitalized and out-patients in the oncology unit of a major medical center in Honolulu (Etkin and Ross 2002).

Our research establishes that cancer patients in Honolulu use a wide range of CAM and corroborates the findings of other studies of CAM use in Hawaii and North America. Those other studies were based on surveys rather than in-depth interviews, and are largely descriptive. Our studies add ethnographic depth to reveal how the popularity of CAM is both market-driven and culturally-constructed. The commodification and aggressive marketing of contemporary culture extends to health care and CAM, and encourages consumers to “shop around.” Among the preventive and healing metaphors that guide the interpretation of illness, the idea of “holistic” (whole-body) healing extends beyond the individual to the community and the environment—healthy land, healthy community, healthy individuals. As their experience with cancers increased study participants’ concern for the toxicity of chemotherapy, they were drawn to botanical CAM on the shared perception that “natural” products are safe. Especially compelling for elderly cancer patients are commercial CAM that advertise “cleaning” and “immune boosting” properties. These and related terms (e.g., “cholesterol-lowering,” “antioxidant”) that have diffused into the vernacular through advertising and popular science media are apprehended by the public only as something healthful, without specific information about how to measure the presence or efficacy of these qualities.

No study participant used CAM as an alternative to chemo- and other biotherapies; most sought CAM to strengthen themselves and to manage the anticipated or experienced side effects of conventional treatments. Our research confirmed the image commonly projected in the CAM literature (e.g., Kelner et al. 2004; Richardson et al. 2004) that oncologists and patients have discrepant views about the efficacy and potential risk of CAM. However, while study participants were not inclined to discuss CAM with physicians, they are respectful of their advice and, significantly, would welcome health professionals in a resource role for CAM information. By now, the allied health professions have apprehended just how many patients use CAM and the diversity of products available. Biomedical professionals who do try to engage their patients on the subject of CAM come to appreciate how little reliable information is available about CAM in the context of conventional medicine; and there is growing interest in instructing teaching physicians and other health professionals about CAM (e.g., Ben-Arye and Frenkel 2004).

The findings of both of our studies reinforce the importance of polypharmacy. The risk of ADRs among pharmaceuticals has been amply demonstrated, and while evidence documenting the possibility of ADRs between CAM and pharmaceuticals is limited (Bielory 2004; Elvin-Lewis 2001; Sparreboom et al. 2004), the theoretical possibilities are high. Only a very small percentage of all CAM have been systematically tested in clinically meaningful ways, none of the commercial products is subjected to standardization or other regulation (contrary to what many consumers believe, CAM are not regulated by the U.S. Food and Drug Administration). Consequently, even some of the commercial products that contain botanicals that have been well characterized phytochemically are not reliable.

**Conclusion**

The subtext here is not that CAM are without benefit. Indeed, the scientific literature (ethnopharmacology, pharmacognosy, and phytochemistry) suggests significant pharmacologic potential. The point is that in the context of complex physician-driven and patient-augmented polypharmacy, the potential for ADRs is high. This statement implicates pharmaceuticals as much as it does what we might eventually know about CAM, although one could argue that pharmaceuticals will always pose a greater risk in view of the higher potency and concentration of active constituents. The documented risks of ADRs in pharmaceutical polypharmacy, in conjunction with the widespread and apparently growing use of CAM offer a compelling argument to generate clinically meaningful data on the physiologic implications of using CAM and translate that information into integrated clinical practice.

For more information on the Cancer Research Center of Hawaii, please visit our web site at www.crch.org.

**Notes**

1. Supported by funding from the National Science Foundation – DBS-9221266 – PI, Nina Etkin.

**References**


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A public service of this publication and the Consumer Information Center of the U.S. General Services Administration.
JABSOM's experience over the past 15 years indicates that the PBL curriculum makes integration of the basic understanding of pathology a natural and vital part of every case and, in turn, of every student's basic medical education. Student performance on the National Board of Medical Examiners Step 1 examinations has consistently been at or above the national average. This teaching approach is well received by most students. Nearly five percent, about double the national average, of JABSOM's graduates have sought residency training in pathology. Graduates of JABSOM and/or the Hawaii Pathology Residency Program now comprise more than half of the practicing pathologists in Hawaii.

In summary, pathology remains an essential and valuable component of every physician's education. The teaching approach used by the faculty in the Department of Pathology at JABSOM really prepares all graduates for future practice in any specialty they may choose.
Youthful Vanity Is A Disease From Which We Usually Recover.

Sometimes the eagerness to cash in on cosmetic dollars drives physicians to goofy extremes. You already know of hardware piercing the nose, the ear lobe and cartilage, the lip, the cheek, the tongue, the elbow, the nipple, the umbilicus, the eyebrow, and even the _________(fill in the blank); and now you can see your friendly eye surgeon get the “jewel eye.” Yes, the Maloney Vision Institute based in Los Angeles is offering the “jewel eye.” The office procedure involves an incision made in the conjunctiva, and a platinum star, half-moon, or heart is placed against the sclera. Never mind the chronic exudation, redness, infection, or possible foreign body rejection, it’s a great payday, and it beats hours in the operating room, doing complicated surgery for much less money. Fees run $3,900 and up, depending upon the value of the jewel implanted. And ophthalmology, once the king of specialties, looks more like a painted streetwalker.

There Is No One So Stupid As An Educated Man.

The recent annual banquet of the Hawaii Medical Association was honored by the presence of Governor Linda Lingle and American Medical Association President-elect Edward Hill. Dr. Hill gave an excellent review of recent activities by the AMA, and outlined directions for the future. Special attention to tort reform, and AMA plans for helping the uninsured. Governor Lingle gave a smashing speech with special discussion about the recent ghostly optometry bill where the Democrats overrode her veto despite the cries of alarm from the Dean of John A. Burns School of Medicine, the chief of ophthalmology at JBSOM, and the chair of the Board of Medical Examiners. It was a pure power play to embarrass Governor Lingle, and public safety be damned! Her message was a simple one - to paraphrase; you doctors are stupid. You spend your energy, your money, and your time supporting, testifying and trying to educate people who do not listen to you, who resent you, invarably ignore you, and vote for some vested interest. “Put your support and your money to work for a change in the Legislature.” Thank you, Governor, for telling it like it is.

Radical Solution For The Visually Challenged.

There is a small bloc of severely myopic people who are beyond lasik or any correction except very, very thick glass lenses. Their myopia extends far out of reach of standard correction, with negative 10s on up to 20 or more, and often they cannot tolerate contact lenses. Now they can be offered the intra-ocular implant. The Food and Drug Administration is planning to approve this option with two lenses under consideration, the Verisyse lens offered by AMO Inc. and the Vision Lens made by Starr Surgical Inc. The Verisyse lens is a rigid lens attached to the iris (called the “Worst” claw - I could think of a better name). The Starr lens is foldable and sits behind the iris. The Verisyse lens has been used in Europe for a decade, and has been implanted in about 100,000 eyes, and will probably be the first one approved. Some of us ancient dudes remember IOLs attached to the iris back in the 1970s - some did well, some did not. The put down was, “The iris is a curtain, not a curtain rod.” What goes around, comes around.

You Shouldn’t Rob Peter To Pay Pauline.

Politicians are so creative about taxes. In New Jersey, the legislature has imposed a 3.5% tax on ambulatory surgery centers, and 6% tax on cosmetic surgical procedures. The income generated from the added tax is to be directed to hospitals to help them meet expenses generated by unfunded care. (No mention is made of the physician who supplies the care. Only the hospital gets rewarded.) The idea of taxing medical care is not new, of course, since Hawaii’s physicians and medical facilities have been paying 4.17% since mammals crawled out of primordial ooze. And in Hawaii, the added tax does not go to subsidize any medical care, but goes into the “general fund” for our Democratic legislature to play with. Still, the New Jersey action is alarming because other states are certain to look at their plan and consider how it might be applied to help with their medical expenditures.

You Rarely See A Shot Glass Filled With Coffee.

For a really, really expensive cup of coffee, order a Kopi Luwak. The beans go for $1,000 a pound and are only grown in Indonesia. But wait, don’t grind them right away; first, they must be fed to a civet cat. After the beans have passed, so to speak, they are harvested from the civet drop-ings and then roasted. The partial digestion by the cat serves to break down and remove bitter proteins leaving a flavor described as “earthy, with chocolate undertones.” Right! As might be expected, production is limited to a few hundred pounds a year. Apparently, the line to apply for work as a cat-pooh-picker is limited.

Tomorrow We Have To Get Busy On This Problem.

Britain’s Environment Agency is concerned regarding the use of the popular anti-depression drug Prozac. The medication is being used in such large quantities that traces are found not just in wastewater, but even in rivers and wells being used for drinking water. Dr. Andy Croxford, spokesman for the agency, stated, “We need to determine the effects of the low-level, almost continuous discharge.” Not surprisingly, when informed of the contamination, affected residents didn’t seem to care very much.

Wealthy People Ride To The Hounds. Poor People Go To The Dogs.

In Pensacola, Florida, Jerry Bradford, age 37, had seven mixed breed shepherd puppies he couldn’t get rid of. He decided to shoot them in the head (at the Humane Society they say “euthanize” which has a nicer ring to it). After doing in three of the pups, Bradford was holding one in his hand and one in his arms. The puppy in his hand placed a paw on the trigger of the 38 caliber revolver, and shot Bradford in the wrist, which curtailed the slaughter for the day. Bradford went to the hospital and was subsequently charged with felony animal cruelty. The surviving four puppies were in good health, and placed at the animal shelter for adoption. The Florida NRA chapter is considering running the pup for lieutenant governor.

The Higher A Man Feels In The Evening, The Lower He Is In The Morning.

Three products are on the market for that chronic illness, the hangover. Those difficulties with loss of appetite, headache, nausea, fatigue, shakiness, and sometimes diarrhea and vomiting, claim to be alleviated by Chaser, or Hangover Magic, or Rebound. They purport to act on the metabolism of alcohol and prevent the toxic components from building up in the body. But, do they really work? Researchers in alcohol use don’t really know what causes hangover, and many believe that it is the result of the brain reacting to the withdrawal of alcohol. The real way to deal with hangovers is to drink coffee instead of booze the night before.

Dad’s Really Gonna Hit The Roof Over This!

A family in southwest Washington state wanted to scatter the remains of their patriarch over the countryside. Only problem was that when the urn was held out the aircraft window, the holder lost the grip and it crashed through the roof of a home in Forest Grove, Oregon. The occupants were shocked at the thunder on their roof, but no one was injured. The lady of the house said that some of old dad would probably remain in the attic. Of course, as is well known, scattering ashes from an aircraft should not be done by holding an urn in the slipstream.

**ADDENDA**

- A 22year old woman developed a brain abscess (strep viridans) four weeks after a tongue piercing which caused oral infection
- The Canadian Embassy in Mexico said that women planning to enter Canada as strippers must provide naked pictures of themselves in order to qualify for a visa
- In Enid, Oklahoma, a 27 year old man was arrested after he tried to rob a bank. He claimed that he was going to use the money to help pay the national debt
- According to the Associated Press, a construction worker in Turkey poured milk into his hand, snorted it up his nose, and blew it 9.223 feet out his left naco-lacrimal duct. He was hoping to establish a world’s record
- A line of people waiting to buy raw fish is called a sushi queue

Aloha and keep the faith —rts

*Contents of this column do not necessarily reflect the opinion or position of the Hawaii Ophthalmological Society and the Hawaii Medical Association. Editorial comment is strictly that of the writer.*
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