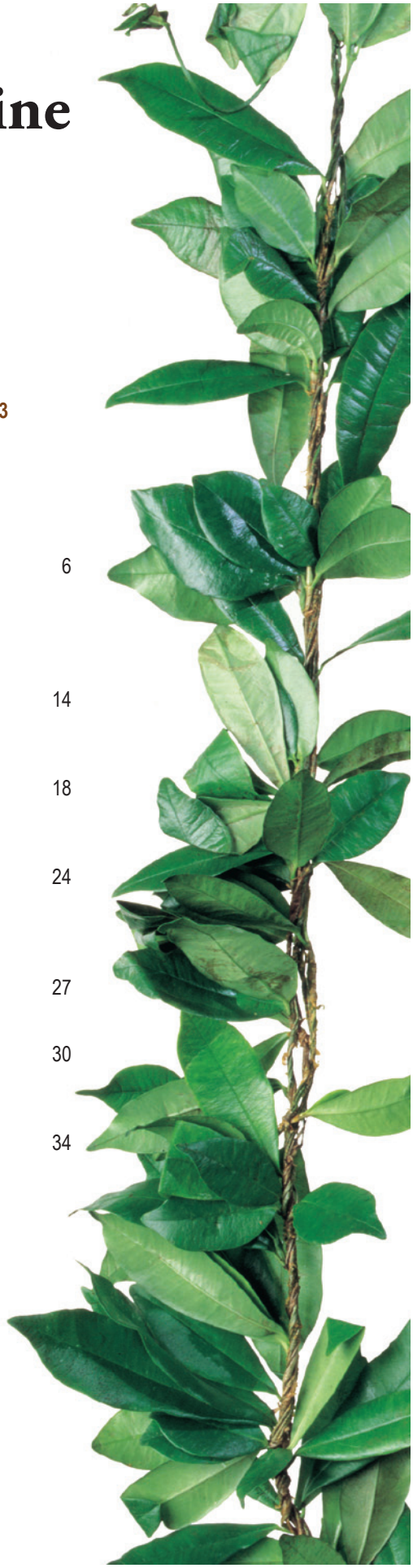
Hawai‘i Journal of Medicine & Public Health

A Journal of Asia Pacific Medicine & Public Health

September 2013, Volume 72, No. 9, Supplement 4, ISSN 2165-8218

American College of Physicians, Hawai‘i Chapter; Annual Meeting 2013

Original Research



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ISSN 2165-8218 (Print), ISSN 2165-8242 (Online)

The Journal's aim is to provide new scientific information in a scholarly manner, with a focus on the unique, multicultural, and environmental aspects of the Hawaiian Islands and Pacific Rim region.

Published by University Clinical, Education & Research Associates (UCERA)

Hawai‘i Journal of Medicine & Public Health
677 Ala Moana Blvd., Suite 1016B
Honolulu, Hawai‘i 96813
http://www.hjmph.org
Email: info@hjmph.org

The Hawai‘i Journal of Medicine & Public Health was formerly two separate journals: The Hawai‘i Medical Journal and the Hawai‘i Journal of Public Health. The Hawai‘i Medical Journal was founded in 1941 by the Hawai‘i Medical Association (HMA), which was incorporated in 1856 under the Hawaiian monarchy. In 2009 the journal was transferred by HMA to University Clinical, Education & Research Associates (UCERA). The Hawai‘i Journal of Public Health was a collaborative effort between the Hawai‘i State Department of Health and the Office of Public Health Studies at the John A. Burns School of Medicine established in 2008.

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Guest Editors' Message: American College of Physicians, Hawai'i Chapter, Annual Meeting 2013

Donald Helman MD and Gurdev Singh MD; Co-Guest Editors

The American College of Physicians (ACP) was founded in 1915 to promote the science and practice of medicine. Dr. Archibald N. Sinclair of Honolulu was a nationally recognized expert on tuberculosis and because of his numerous contributions to the medical literature, he was honored by being admitted as a Fellow of the ACP. In 1927, he became the first Governor of the Hawai'i Chapter of the ACP.

The second Governor of the ACP Hawai'i Chapter was Dr. Harry L. Arnold, Sr. His son, Dr. Harry L. Arnold, Jr., was the first editor of the Hawai'i Medical Journal, a publication of the Hawai'i Medical Association, from 1941 and remained in that position for over forty years. The aim of "the Journal" was to provide new scientific information in a scholarly manner, with a focus on the unique, multicultural, and environmental aspects of the Hawaiian islands and Pacific Rim regions. Dr. S. Kalani Brady is the current and fifth editor of "the Journal" and has presided over the transition to the Hawai'i Journal of Medicine and Public Health. He is also the immediate past Governor of the ACP Hawai'i Chapter and thus continues the strong relationship between the ACP and "the Journal".

The ACP Hawai'i Chapter has been encouraging medical students and residents to submit and present original research at the Annual Chapter Meeting for over 30 years now. The quality and quantity of submissions have increased each year and at the January 2013 Meeting we had 66 abstracts submitted. All the peer reviewers agreed that the selection process was extremely difficult for those accepted for presentation at the Annual Meeting. Of these, selecting the winners in each category was, again, a very difficult process.

It was at a subsequent Council Meeting of the Chapter that Dr. Brady suggested that, with all the excellent material being presented at the Annual Chapter Meeting that we should share the work of these young future leaders of Medicine with the wider medical community by publishing a supplement to "the Journal". This was enthusiastically and unanimously accepted. It was decided that the authors of the top ten highest scoring abstracts would be offered an opportunity to submit full-length manuscripts for publication. Some had already submitted their work to other publications and declined. We then made the offer to the next highest scoring abstract. In this way, seven were finally selected to be peer-reviewed and published in this supplement. The remaining abstracts are published in their original form.

And so, it is with the mission of the American College of Physicians "to promote the science and practice of medicine" and of the Hawai'i Journal of Medicine and Public Health "to provide new, scientific information in a scholarly manner, with a focus on the unique, multicultural and environmental aspects of the Hawaiian islands and Pacific Rim regions," that we present this Supplement.

Conflict of Interest
None of the authors report a conflict of interest.

Editors' Affiliation:
American College of Physicians, Hawai'i Chapter

New Triple Therapy for Chronic Hepatitis C: Real Life Clinical Experience in a Community Setting

Matthew J. Akiyama MD, MSc; Joy I. Piotrowski; Marina M. Roytman MD; Siu M.A.Chan FNP-BC; Leena K. Hong PA-C; Leslie Huddleston PA-C, RN; Ruby Trujillo APRN; and Naoky C.S. Tsai MD

Abstract

Recent advances in treatment of chronic hepatitis C virus have improved significantly due to the introduction of two new protease inhibitors—telaprevir and boceprevir. In combination with the previous standard of care, peginterferon and ribavirin, telaprevir and boceprevir have demonstrated improved sustained virologic response rates for HCV genotype 1 patients by approximately 30%. The purpose of this study was to assess the validity of large clinical trial data with respect to efficacy and side effects in a community setting in Honolulu, Hawai'i. This retrospective study was performed by reviewing the charts of 59 chronic HCV patients who were started on triple therapy from July 1, 2011 to July 7, 2012. Sustained virologic response was attained by 73% of patients treated with telaprevir and 46% of patients treated with boceprevir respectively. Our clinical experience with telaprevir demonstrates that SVR rates are compatible with published literature values. Rates of SVR in our cohort were also similar to those reported in cirrhotic patients — about 50%. Due to small number of patients treated with a boceprevir-based regimen, it is difficult to compare our experience with pivotal trial experience. The side effect profiles for the two protease inhibitors were similar to the literature values except for more rectal irritation and a higher incidence and severity of anemia on telaprevir therapy in the clinical setting. While not intended to be conclusive, our study demonstrates that clinical trial data are largely compatible with the outcomes obtained in our community setting.

Keywords

HCV, triple therapy, telaprevir, boceprevir, Incivek, Victrelis, real clinical setting, community experience

Introduction

Hepatitis C virus (HCV) is the most common chronic blood borne infection in the United States.[1] It is also the leading cause for liver transplants[2] and liver cancer related death in the United States.[3] It has been estimated that the number of people infected with chronic HCV (CHC) in the United States is 3.2 million.[4] It has also been estimated that fewer than half of those living with HCV are aware that they are infected.[5] In an effort to improve this discrepancy, the CDC has recently recommended screening everyone born from 1945 through 1965.[6]

Two new direct-acting antivirals—telaprevir (TVR) and boceprevir (BOC)—have reinvigorated treatment options for CHC. These protease inhibitors (PIs) have significantly improved outcomes for genotype 1 HCV patients when administered in combination with the previous standard of care—peginterferon (pegIFN) and ribavirin (RBV). The American Association for the Study of Liver Disease (AASLD) has therefore revised its recommendations for treatment of HCV genotype 1 patients to include triple therapy (TT).[7]

TVR and BOC have both been studied in large clinical trials. The ADVANCE[8] and REALIZE[9] trials demonstrated improved outcomes for TVR in treatment of naïve and experienced patients respectively. Similarly, the SPRINT-2[10] and RESPOND-2[11] trials demonstrated improved outcomes for BOC in treatment of naïve patients as well as prior relapsers and partial responders.

Few studies have been performed to assess the external validity of clinical trial data for TVR and BOC in a real clinical setting.[12] Comparisons with real world data are important in verifying the validity and generalizability of large clinical trials.[13] The purpose of this study is to compare reported data from clinical trials with outcomes in a community referral center in Honolulu, Hawai'i.

Methods

In this retrospective study, the charts of the 59 CHC patients who were started on TT from July 1, 2011 to July 7, 2012 were reviewed. Prior to commencing therapy, patients underwent a stringent selection process. Treatment candidates were assessed for family support, current employment (to minimize potential impact of side effects on their work), insurance coverage (to aid with patient assistance program applications if required), and willingness to undergo TT. In addition, ophthalmologic, cardiac, and psychiatric consults were obtained for clearance. If psychiatric care was deemed necessary, this was managed by the consultant during and after treatment. Patients were treated with standard regimens for TVR[14] and BOC[15] and standard futility rules were applied.[7] Adverse reactions were monitored and documented during clinical interviews. In cases where serious adverse events were encountered, treatment was withheld. Only those who reached the end point of SVR at the time of evaluation were included in the analysis of virologic outcomes, however all patients were included in the analysis of side effects.

Age, gender, ethnicity, biopsy documented cirrhosis, treatment response, and side effects were collected. Data from the ADVANCE and REALIZE trials for TVR and SPRINT-2 and RESPOND-2 trials for BOC as well as the product inserts for each agent[14,15] were retrieved and used to compare with our clinical experience. Standard definitions for prior treatment categories including relapser, partial, and null responder were used, and the usual definitions for rapid virologic response (RVR), early virologic response (EVR), extended rapid virologic response (eRVR), and sustained viral response (SVR) were applied.[16] Cirrhosis was defined as stage 4 fibrosis on liver biopsy.

Results

Fifty-nine CHC patients were started on TT in the study period—45 on TVR and 14 on BOC. One patient on the TVR-

based regimen developed pneumonia and stopped treatment of her own accord despite having an undetectable viral load at week 4. Three patients on TVR and 1 on BOC are still on treatment or awaiting SVR. Since these patients did not meet the end point of SVR at the time of evaluation, a total of 41 patients on TVR and 13 on BOC were included in the analysis of virologic outcomes.

Table 1 displays baseline patient characteristics. In the TVR group, the median patient age was 55 years old, 71% were male and 29% were female. By self-reporting, there were 4 black patients (9%), 21 Caucasians (47%), 4 Hawaiians (11%), 13 Asians (29%), and 2 other (4%). In the BOC group, the median age was 53, 64% were male and 36% were female. There were 9 Caucasians (64%) and 5 Asians (36%). Overall, there were 13 patients with cirrhosis (22%) in our cohort—11 out of 42 in the TVR group (24%) and 2 out of 14 in the BOC group (14%).

Key virologic end points are displayed in Table 2. The RVR rates—defined as an undetectable viral load at week 4—for patients treated with TVR and BOC were 88% and 54%, respectively. The eRVR rates—defined as undetectable viral load at weeks 4 and 12—for TVR and BOC were 85% and 54%, respectively. Of those who achieved eRVR, 77% of patients treated with TVR and 71% of patients treated BOC went on to attain SVR (Figure 1).

The SVR rates for TVR and BOC were 73% and 46%, respectively (Figure 2). When broken down by prior treatment category, 71% of treatment naïve, 92% of relapsers, 50% of partial responders, and 56% of null responders attained SVR in the TVR group. These results were comparable to the SVR rates observed in the ADVANCE and REALIZE trials (Figure 3). There were not enough data for BOC to meaningfully compare clinic with trial data therefore they are not shown.

Figure 4 displays the viral kinetics for the two PI regimens for those who attained SVR. Patients treated with BOC exhibited a slower viral decline due to the standard 4-week lead-in with pegIFN/RBV without a PI. For TVR, the three-drug regimen is initiated from the outset of therapy.

Overall, 18 patients had virologic failure or experienced serious adverse events that required terminating treatment—11 (27%) in the TVR group and 7 (54%) in the BOC group (Table 3). In the TVR group, 1 patient was a null-responder, 4 patients had virologic breakthrough, 4 patients relapsed, and 2 termination events occurred. One patient was cirrhotic and a Jehovah's Witness and developed severe pancytopenia and renal insufficiency, that led to the only hospitalization in our cohort. The other treatment termination was due to severe thrombocytopenia

Table 1. Baseline Characteristics of the Study Participants

	Telaprevir	Boceprevir	Total
N	45	14	59
Median Age – yr	55	53	
Gender – no. (%)			
Male	32 (71)	9 (64)	41 (69)
Female	13 (29)	5 (36)	18 (31)
Ethnicity – no. (%)			
Black	4 (9)	0	4 (7)
Caucasian	21 (47)	9 (64)	30 (51)
Asian[§]	13 (29)	5 (36)	18 (31)
Hawaiian	5 (11)	0	5 (8)
Other	2 (4)	0	2 (3)
Cirrhosis – no. (%)	11 (24)	2 (14)	13 (22)
Prior treatment category – no. (%)			
Treatment Naïve	18 (45)	7 (50)	25 (42)
Prior relapsers	14 (31)	5 (36)	16 (27)
Prior partial responders	3 (7)	1 (7)	4 (7)
Prior null responders	10 (22)	1 (7)	14 (24)

[§]Asian ethnicity comprised Filipino, Japanese, Korean, and Vietnamese.

Table 2. Key Virologic End Points and Number of Cirrhotics, According to Previous Treatment Category.*

Telapravir					
Prior treatemtn category – no. (%)	**Treatment Naïve**	**Prior relapsers**	**Prior partial responders**	**Prior null responders**	**All**
N	17	13	2	9	41
RVR	16 (94)	12 (92)	2 (100)	7 (78)	37 (88)
eRVR	14 (82)	12 (92)	2 (100)	8 (89)	35 (85)
SVR	12 (71)	12 (92)	1 (50)	5 (56)	30 (73)
Cirrhosis	4 (24)	2 (17)	1 (50)	1 (11)	8 (20)
Boceprevir					
Prior treatemtn category – no. (%)	**Treatment Naïve**	**Relapsers**	**Partial responders**	**Null responders**	
N	7	3	1	2	13
RVR	4 (57)	2 (67)	1 (100)	1 (50)	7 (54)
eRVR	4 (57)	2 (67)	1 (100)	0	7 (54)
SVR	3 (43)	2 (67)	0	1 (50)	6 (46)
Cirrhosis	1 (14)	1 (33)	0	0	2 (5)

*Data are for all patients who received at least one dose of a triple therapy regimen and reached SVR at time of analysis.

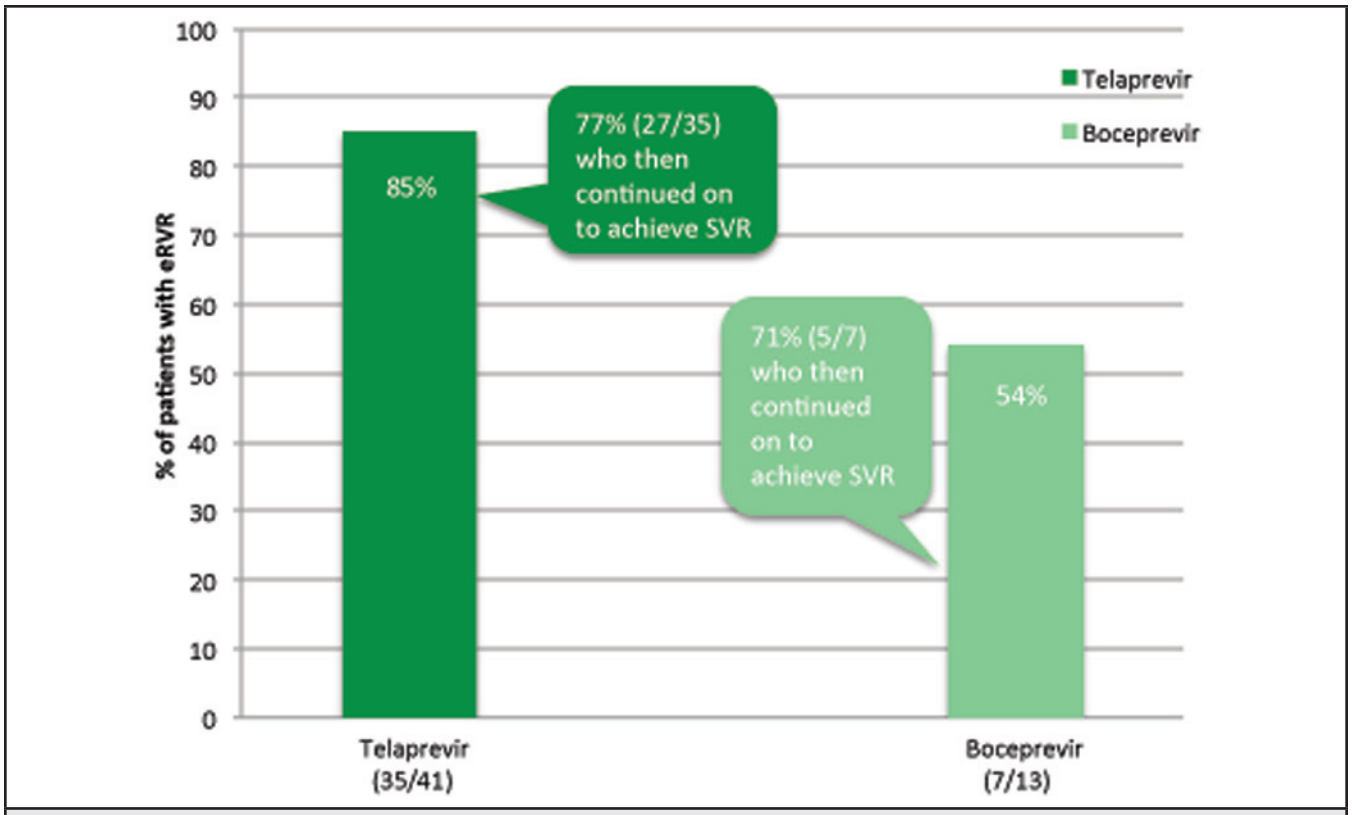

Figure 1. Percentage of patients on each protease inhibitor who achieved eRVR with annotation of those who continued on to achieve SVR.

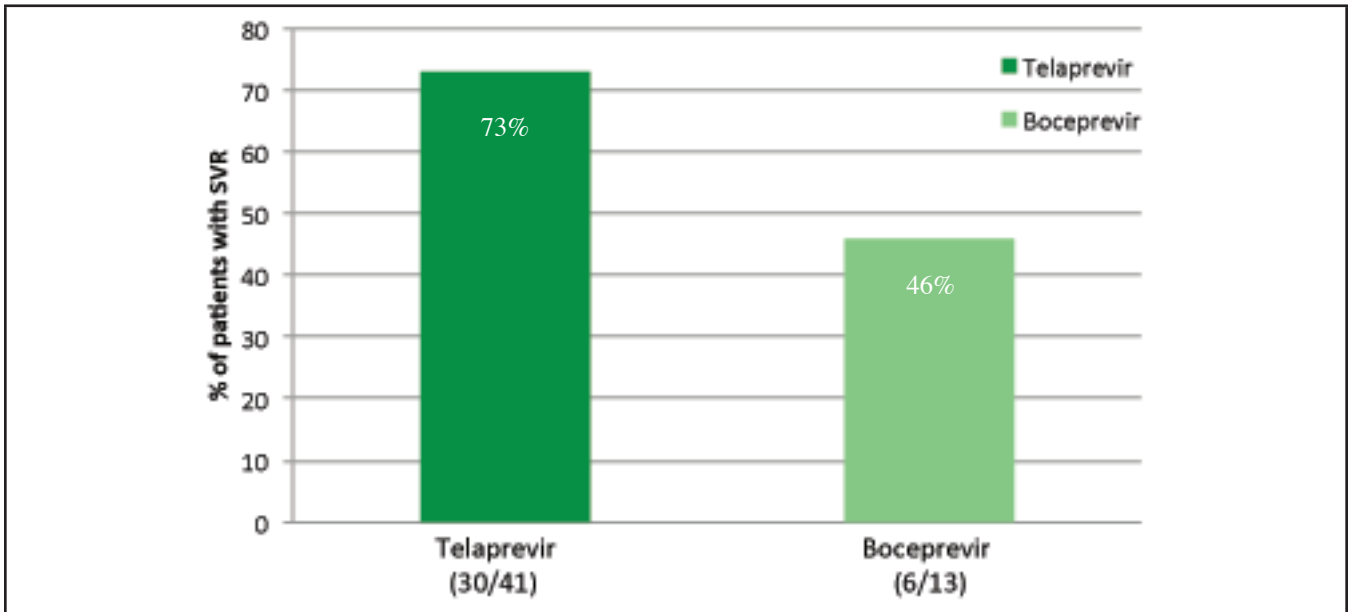

Figure 2. Percentage of patients treated with protease inhibitor that achieved SVR.

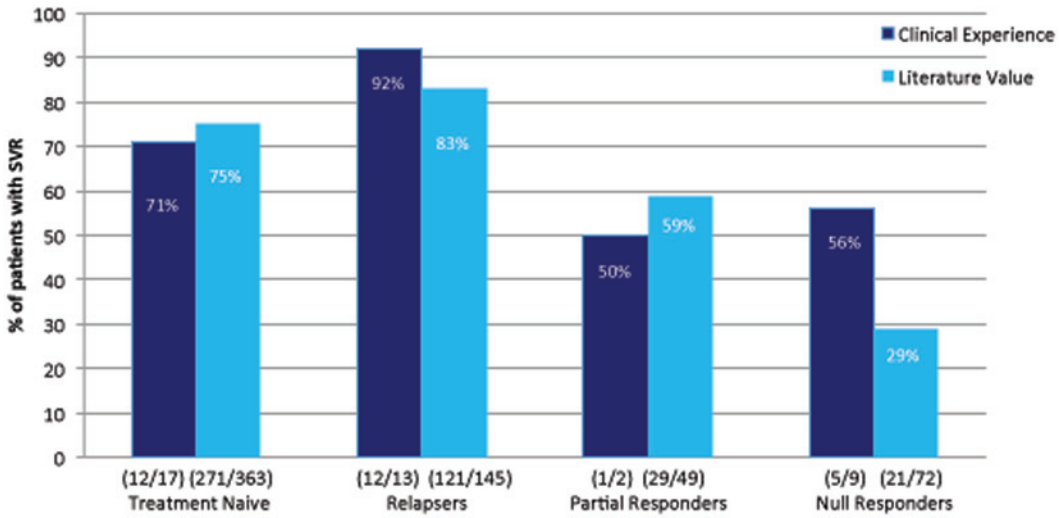

Figure 3. Percentage of patients on TVR who attained SVR. Comparison by prior treatment category between our clinical experience and published literature values in the ADVANCE and REALIZE trials.

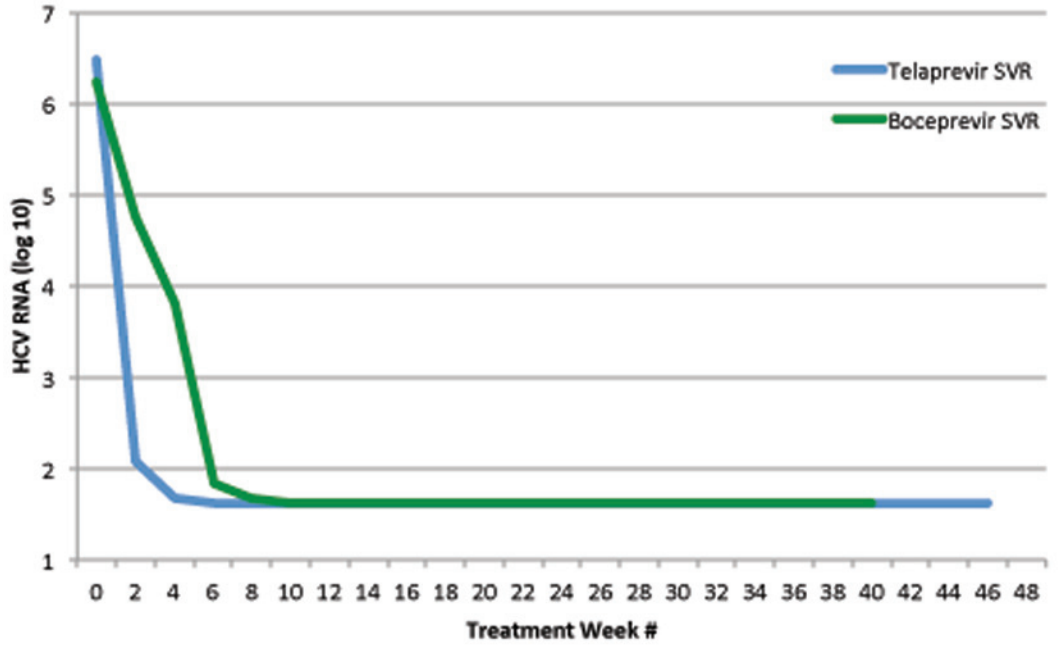

Figure 4. Changes in HCV RNA levels. Shown are changes in mean log10 HCV RNA levels over the study period for patients on TVR and BOC who attained SVR.

Table 3. Virologic Failure and Treatment Termination.*

	Telaprevir n = 11	Boceprevir ns = 7	Total = 18
Null-response	1	2	3
Breakthrough	4	1	5
Termination	2	1	3
Relapse	4	3	7

*Virologic failure was based on either viral breakthrough or discontinuation of a study drug because of meeting a virologic stopping rule. Treatment terminations occurred in the setting of serious adverse events.

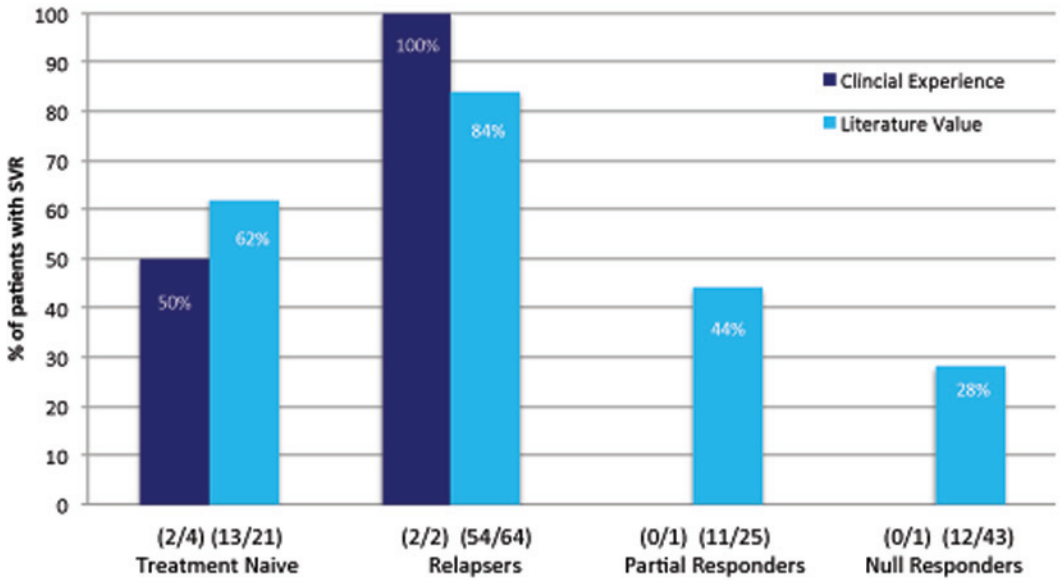

Figure 5. Percentage of cirrhotic patients on TVR who achieved SVR. Comparison between our clinical experience and published literature values found in ADVANCE and REALIZE trials.

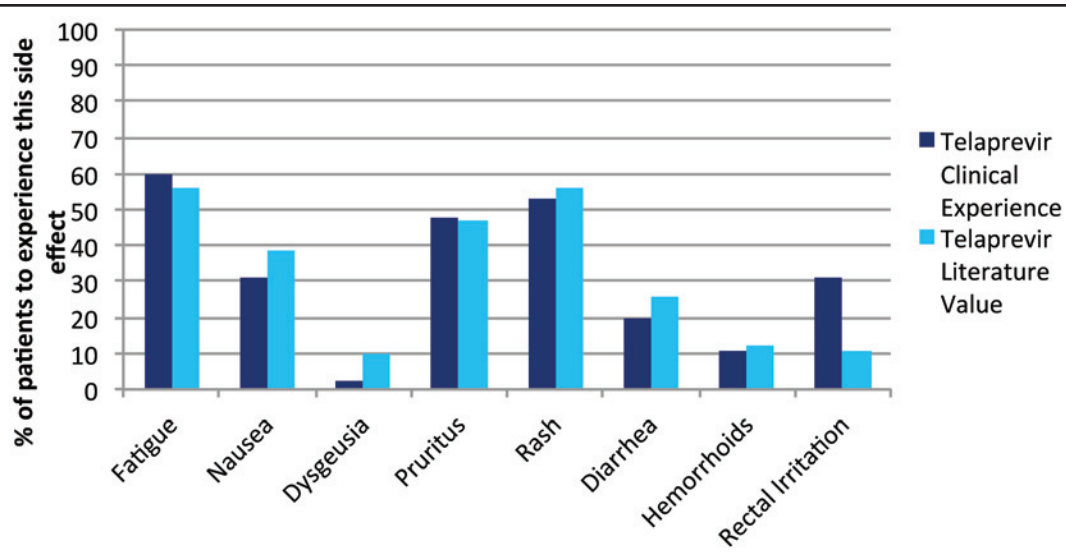

Figure 6. TVR patient side effects in comparison to the published literature values found in the ADVANCE and REALIZE trials.

in a patient with baseline thrombocytopenia and neutropenia. In the BOC group, 2 patients were null responders, 1 had virologic breakthrough, 3 relapsed, and 1 underwent treatment termination due to severe neutropenia.

In our clinical experience, the SVR rates for patients with cirrhosis on TVR were compatible in each prior treatment category with those in the published literature (Figure 5). Data in the partial and null responder categories were limited and therefore not suitable for comparison.

Side effects profiles in the trial data were largely similar to our clinical experience (Figure 6). Some key differences, however, were rectal irritation and anemia in the TVR group. Thirty-one percent from our cohort and 11% of clinical trial participants experienced rectal irritation. As for anemia, 47% of TVR-treated patients in our cohort had clinically significant anemia requiring treatment with either growth factors or therapeutic blood transfusions whereas the literature rate was 36% (Figure 7). Side effects for BOC including anemia were comparable.

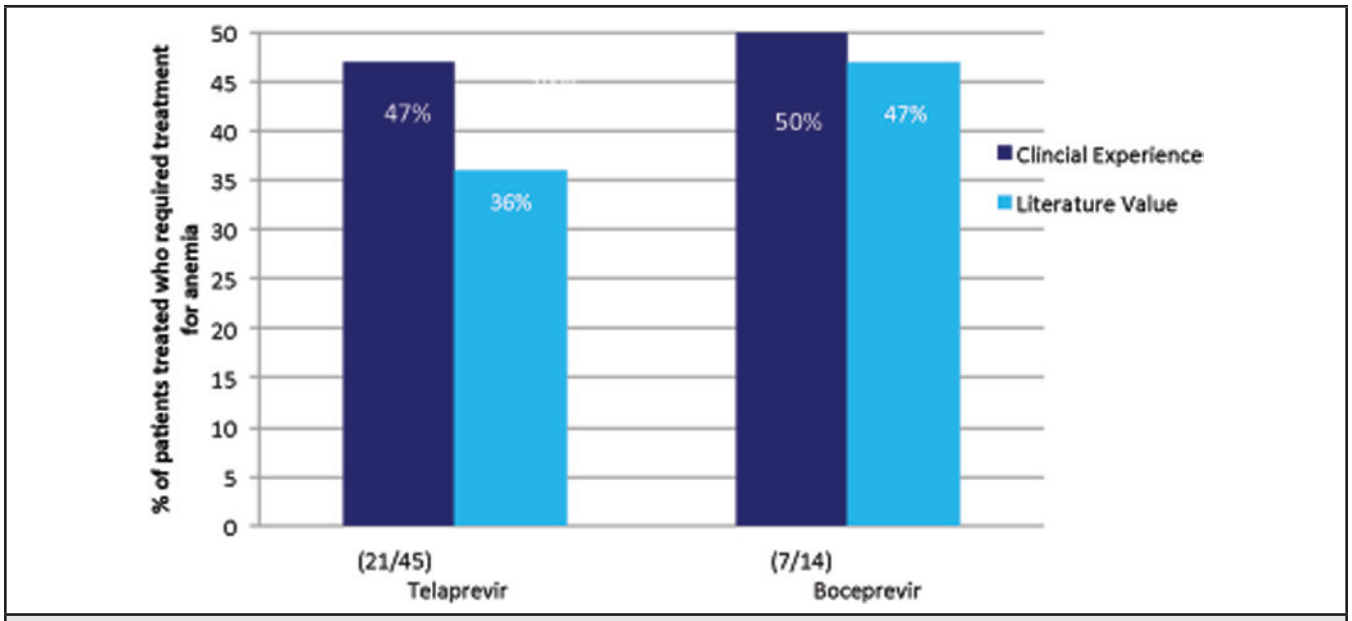

Figure 7. Percentage of patients treated with each drug that required treatment for anemia (prescribed growth factors or blood transfusions) in comparison to the published literature value for telaprevir and boceprevir.

Discussion

Virologic Outcomes

Our study demonstrates that responses to treatment and side effects profiles for TT in the community setting were largely compatible with clinical trial data. In terms of virologic end points, eRVR has been demonstrated to be a predictor of SVR. This has led to reductions in treatment duration for treatment naïve patients and prior relapsers from 48 weeks to 24 weeks—a concept known as response-guided therapy.[17] For treatment naïve patients on TVR, the ILLUMINATE trial demonstrated that of the 65% of patients who attained eRVR, 92% went on to achieve SVR. In a subset analysis of the treatment naïve patients in our cohort, the eRVR rate for on TVR was 82% (Table 1); and of those 86% when on to attain SVR (data not shown). Our study was likely not powered well enough due to a small sample size to detect the extent of this predictive relationship, however the trend is similar.

In terms of SVR, the rates for TVR were compatible with published literature values in all prior treatment categories (Figure 3), which suggests the virologic outcomes obtained in the ADVANCE and REALIZE trials are valid in our clinical setting. One difference that emerged was the magnitude of the difference in SVR between null responders in our community setting versus the REALIZE trial. Generally null responders have the lowest response to therapy since they were previously refractory to pegIFN/RBV, however 56% achieved SVR in our clinical setting, the reason for which remains unclear.

Our clinical experience with BOC was limited due to the small number of patients in this group, however comparison with the published literature values in the SPRINT-2 and RESPOND-2 trials shows that the SVR rates for treatment naïve and prior partial responders were lower, while the SVR rates for prior relapsers and null-responders were near or above the literature values (data not shown).

Cirrhosis

Patients with cirrhosis represent a special subset of patients when considering CHC treatment. The FDA has approved usage of TT for cirrhotic patients, however response-guided therapy has not been recommended since historically this group has been more refractory to therapy.

The SVR rates for patients with cirrhosis in the treatment naïve and relapser categories in our clinical experience were comparable with those in the ADVANCE and REALIZE trials (Figure 5). The single cirrhotic patients in the partial and null responder categories in our cohort experienced treatment failure due to virologic relapse and breakthrough, respectively. Limited data for these groups in our cohort makes comparison with clinical trial data difficult, however the REALIZE trial also demonstrates that the stage of liver fibrosis effects outcome significantly, particularly among partial and null responders. In clinical practice, cirrhotic patients tend to develop more profound side effects, particularly bone marrow suppression necessitating dose reductions leading to decreased therapeutic efficacy. In our cohort, the two partial and null responders required RBV and pegIFN dose reductions, respectively, which may have contributed to their therapeutic failures. Recent reports also indicate high morbidity and mortality in this group of patients.[18]

Our clinical experience in treating cirrhotic patients with BOC again was limited. Only two patients with a fibrosis score of 4 were treated. One was treatment naïve and had a null response; the other was a relapser and achieved SVR.

Side Effects

Anemia is an important and serious side effect in the treatment of HCV. Interferon and RBV both lead to bone marrow suppression, however when combined with PIs this effect is exacerbated.[19] In cirrhotic patients this effect is worsened even further since they are prone to anemia at baseline.

The number of patients treated for anemia on TVR-based regimens in our cohort was dramatically higher than the literature data.[14] We postulate that this was because the combined number of patients with bridging fibrosis and cirrhosis in our cohort was higher than the ADVANCE and REALIZE trials. Cumulatively, in our TVR cohort there were 25 patients (56%) with stage 3 and 4 fibrosis compared with 20% and 50% in the ADVANCE and REALIZE trials respectively. Another possibility may have been a lower threshold for administering epoetin alpha in the clinical setting than in clinical trials. In our clinical setting, a cut off of either 10 grams or a drop of greater than 4 grams in the first 4 weeks of therapy was used as a threshold. Blood transfusions were administered when epoetin alpha did not improve hemoglobin to baseline within 1 to 2 weeks or if patients became symptomatic. Reductions in RBV doses were less aggressively applied in our clinical setting due to past experience of lower SVR rates using this strategy in the era of dual therapy.

Rectal irritation was more common in our clinical experience with TVR than in the literature. The reason for this is unclear, however it may have been due to increased provider awareness of this side effect and therefore an increased rate of self-reporting.

Other adverse side effects in our patient population were observed in a similar percentage to the literature, with the most significant side effects being fatigue, pruritus, and rash for TVR and fatigue, nausea, and dysgeusia for BOC.

In summary, this study demonstrates that outcomes in a real clinical setting were comparable to clinical trial data with some notable exceptions. The major limitation of our study was the small sample size, particularly in the BOC group, cirrhotics, and certain prior treatment categories. In addition, the influence of viral subtypes 1a and 1b and host genotype IL28B could not be analyzed in a meaningful way since, commensurate with the setting in which data were obtained, this information was not collected for all patients prior to starting therapy.

Beyond verifying compatibility between large trial and local data, this study sheds light on treatment trends in a real clinical context. Specific to the unique ethnic context in Hawai'i, a subset analysis of Asians on TVR revealed comparable outcomes with 9 of 13 (69%) attaining SVR (data not shown). An unforeseen trend that emerged was the preponderance of patients treated with TVR. While there is no evidence to suggest that TVR or BOC offer a therapeutic advantage above the other,[20,21] our experience reflects the reality that differences in utilization exist. Factors influencing PI selection include ease of administration, patient and provider discussions about side effect profiles, compliance, as well as staff training and comfort level with each regimen. Given the absence of superiority data, we propose PI preference is guided by a combination of the above factors. Another important trend that emerged was the low rate of discontinued treatment and loss to follow up. Retention is a complex issue, however, we suspect that the vast majority of patients met therapeutic endpoints in our study due to rigorous patient selection as well as close-knit relationships with community support staff ensuring individualized patient care.

Conflict of Interest

None of the authors identify any conflict of interest.

Acknowledgements

The authors would like to acknowledge the contribution of our patients and their families for entrusting us with their medical care and our staff for their valuable support. Also, we would like to thank the Queen's Medical Center for supporting this research project.

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Anti-Gliadin Antibodies Identify Celiac Patients Overlooked by Tissue Transglutaminase Antibodies

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Abstract

For patients with suspected celiac disease, the American Gastroenterological Association recommends initial screening with anti-tissue transglutaminase antibody (tTG) and confirmation testing with small bowel biopsy. However, at Tripler Army Medical Center we routinely screen patients with both tTG and anti-gliadin antibodies (AGA) in combination. The purpose of this study was to evaluate whether this dual screening method adds to the evaluation of patients with suspected celiac disease or results in more false-positive results than tTG screening alone. A retrospective chart review of all tTG and AGA screening serologies at Tripler Army Medical Center between September 2008 and March 2012 was performed. For patients with positive serologic testing, small bowel biopsy results or reasoning for deferring biopsy were investigated. tTG was found to have a higher positive predictive value for celiac disease than AGA, however AGA identified 5 patients (19% of biopsy confirmed celiac disease) that had a negative tTG and would not have been identified by tTG screening alone. Using AGA in combination with tTG should be considered if the goal of screening is to identify all patients with celiac disease, with the understanding that this strategy will generate more false positive tests and result in additional patients undergoing small bowel biopsy.

Introduction

Celiac disease is a disorder of the small bowel characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia which occurs upon exposure to dietary gluten and has an estimated prevalence in the United States of 1:100.[1-4] Celiac disease has a wide range of clinical presentations. Classically, patients with celiac disease present with gastrointestinal symptoms such as diarrhea, malabsorption, or weight loss. However, celiac disease may be diagnosed in many patients only after they are found to have a nutritional deficiency, such as iron deficiency, or another condition associated with celiac disease, such as delayed puberty, recurrent fetal loss, or premature osteoporosis.

For patients with suspected celiac disease, the American Gastroenterological Association recommends initial serologic testing with anti-tissue tranglutaminase antibody (tTG) and confirmed with a small bowel biopsy.[5] At our facility, we routinely screen with a combination of tTG and anti-gliadin antibody (AGA). The reported sensitivities of tTG, AGA IgA, and AGA IgG are 90 to 98%, 80 to 90%, and 75 to 85% respectively. The reported specificities of tTG, AGA IgA, and AGA IgG are 95 to 97%, 85 to 95%, and 75 to 90% respectively (Table 1).[6,7]

We aimed to test our hypothesis that using AGA and tTG in combination rather than tTG alone would result in more false positive tests while failing to increase identification of patients with celiac disease.

Methods

A retrospective chart review was performed of all celiac serologies at Tripler Army Medical Center between September 2008 and March 2012. No patients were excluded from the study. All celiac serologies were analyzed at the same laboratory and used the same cutoff values for negative, equivocal, and positive results. For the purpose of this study, all equivocal results were treated as positive. In patients with positive serologic testing, medical records were reviewed to determine small bowel biopsy results or the reason for deferring biopsy. A positive biopsy was defined by the presence of any of the following: increased intraepithelial lymphocytes, crypt hyperplasia, and/or villous atrophy; Marsh staging of biopsies was not defined in pathology reports and not included in analysis. Patients that screened positive but did not undergo a small bowel biopsy were categorized into three groups: those that were not referred to the gastroenterology service, those that were seen by the gastroenterology service and not biopsied, and those that were referred to the gastroenterology service but lost to follow-up. Positive predictive values for each of the serologic assays were calculated according to the formula: positive predictive value = true positives / total positive screening. True positives were defined as patients with small bowel histological evidence consistent with celiac disease as defined above. Each screening serology was used for calculation of positive predictive value in patients that underwent small bowel biopsy. Investigators adhered to the policies for protection of human subjects as prescribed in 45 Code of Federal Regulation 46.

Results

During the specified time period, 2,733 patients were evaluated with a total of 5,268 AGA and tTG antibody tests. 232 patients had at least one positive screening serology, including 34 tTG, 120 AGA IgA, and 119 AGA IgG. Of the 232 patients with positive screening serologies, 87 (38%) underwent a small bowl biopsy and 26 were found to have celiac disease (Figure 1). The positive predictive value of tTG was calculated to be 100%, AGA IgA was 36%, and AGA IgG was 16% (Table 2). 5 of 26 patients (20%) with biopsy-proven celiac disease during our specified period had a positive AGA IgA or IgG and a negative tTG. Of patients with at least one positive serologic screening antibody, 145 (62.5%) did not undergo a small bowel biopsy. Of the 145 patients with positive screening serologies who were not biopsied, 73 (50.3%) were never referred to the Tripler gastroenterology service, 49 (33.8%) were seen by the gastroenterology service but never biopsied, and 23 (15.9%) were referred to the gastroenterology service but lost to follow-up.

Discussion

The first celiac serology, AGA IgA, was developed in the early 1980s and revolutionized the diagnostic process of celiac dis-

Table 1. Reported sensitivities and specificities of celiac screening antibodies			
	tTG IgA	**AGA IgA**	**AGA IgG**
Reported Sensitivity	90-98%	80-90%	75-85%
Reported Specificity	95-97%	85-95%	75-90%

Table 2. Positive predictive value calculations for each screening serology				
Test	**Positive or Equivocal Serology**	**Number Biopsied**	**Positive Biopsy**	**Positive Predictive Value**
tTG IgA	34	21	21	100%
AGA IgA	120	40	18	45%
AGA IgG	119	45	7	16%

Figure 1. Flow chart of all studied patients

ease.[8] Prior to serologic studies, there was no screening test for celiac disease other than clinical suspicion, which was confirmed by small bowel biopsy. Shortly after the development of AGA, other serologic tests were introduced including tTG, antideaminated gliadin peptide antibodies, and antiendomysial antibodies.[9] Although we recognize the significance of antiendomysial and antideaminated gliadin peptide antibodies, they are not routinely performed at our institution and were not included in the study.

Screening for celiac disease is recommended by the Amercian Gastroenterologic Association only for symptomatic patients. Although the prevalence of celiac disease has been estimated to be 1% in the general population, there is insufficient evidence to recommend celiac screening in the general population.[10] Patients that are at high risk of celiac disease, such as those with first degree relatives of celiac disease, children or adolescents with short stature, patients with dermatitis herpetiformis, delayed puberty, type 1 diabetes mellitus, Down syndrome, persistent iron deficiency anemia, or osteoporosis should also be considered for serologic screening.[11]

There is a clear genetic predisposition for the development of celiac disease. Approximately 97% of patients with celiac disease share the major histocompatibility complex II class human leukocyte antigen DQ2 or DQ8 haplotype. Testing for these antigens may be considered in patients with equivocal small bowel histological findings.[12] Ordering of human leukocyte antigens is not routinely performed and the results of this testing were not evaluated in this study.

The most significant finding in our study was the identification of five patients with biopsy confirmed celiac disease that had negative tTG but positive AGAs. Had these patients been screened using the American Gastroenterology Association's recommendation for tTG alone, they would have tested negative and would not have been referred for small bowel biopsy. However, positive AGA IgA and IgG antibodies with either negative tTG or untested tTG led to 61 negative small bowel biopsies and, therefore, screening with AGA will increase the number of small bowel biopsies performed. It has been reported that AGAs have a higher clinical significance in the pediatric population. Several studies have identified pediatric patients with celiac disease who were found to have positive AGA and negative tTG or antiendomysial antibodies, suggesting AGA may still be appropriate when screening this population.[13,14] Of the five patients identified in our study, only one was under the age of 18 at the time of diagnosis. False negative tTG IgA testing has also been reported due to selective IgA deficiency. 1.7% of patients with celiac disease also has selective IgA deficiency and thus will have negative IgA screening antibodies.[15] Of the five patients our study identified, 3 of them had normal IgA levels and thus their false negative tTG could not be attributed to a selective IgA deficiency; the other two patients were not tested for IgA deficiency.

Patients that had positive serologic testing that did not undergo small bowel biopsy were investigated to better determine the reason for not undergoing small bowel biopsy. We found that only 87 of 232 (38%) patients with positive serologic testing went on to have biopsy. While this percentage seems quite low, similar rate of biopsy have been described at other institutions; one study reported that only 39% of patients that screened positive in serologic testing had a small bowel biopsy.[16] We further analyzed the 145 patients that did not undergo biopsy and determined that a little more than half (50.3%) were not referred to the gastroenterology service. This may represent primary care physicians treating empirically with a trial of gluten-free diet, patient refusal of referral, or failure to follow up on laboratory results. We also found about a third of patients (33.8%) that were seen by gastroenterology did not receive small bowel biopsy. This was due to a variety of reasons including patient refusal of biopsy, current treatment with gluten free diet (which may result in a false negative biopsy), or the sentiment among gastroenterologists that AGAs generate high number of false positive tests; the deferral of biopsy was often recommended in the pediatric population.

We acknowledge the limitations of our study. The retrospective nature of the study limits the information to that contained in patient medical records and does not reflect the number of patients placed on gluten-free diet without small bowel biopsy. Additionally, we are unable to determine whether serologic testing was performed on a gluten-free diet and thus impacted the results of these screening tests. It is also unclear how many primary care physicians and gastroenterologists discussed the benefits of small bowel biopsy but patients refused the procedure and opted for a trial of dietary modification.

Conclusions

While tTG has a significantly higher positive predictive value than AGA antibodies, AGA antibodies do increase the number of patients identified with celiac disease compared to tTG alone. Based on the results of this study, we reject our initial hypothesis. Screening with tTG in combination with AGA appeared beneficial if the goal of serologic testing is to maximize the number of patients discovered with celiac disease. Close follow-up of patients with positive celiac serologies is needed to ensure that they have the opportunity to undergo small bowl biopsy.

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Disclosure Statement

The authors have no disclosures and no conflicts of interest to declare. This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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Success Using Tacrolimus in Patients with Proliferative and Membranous Lupus Nephritis and Refractory Proteinuria

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Abstract

Standard treatment for class III, IV, and V lupus nephritis (LN) is a combination of oral corticosteroids and mycophenolate mofetil (MMF). There is an estimated failure rate of 16%. Several small studies have looked at the use of tacrolimus in class III, IV, and V LN, both as induction treatment and as maintenance in patients refractory to other treatments. The majority of these studies were conducted in Asian patients. We discuss a cohort of eight female patients of various ethnicities with biopsy proven LN. All patients were evaluated retrospectively. Six were started on tacrolimus after failing to respond to MMF and corticosteroids, and one was started on tacrolimus alone because treatment options were limited by pregnancy. Five were Caucasian, one African American, one Hispanic, and one Vietnamese. Mean tacrolimus dose was 3.3 mg daily (range 2–5 mg) titrated to a mean level of 3-6 ng/dl (range 3- 6.6 ng/dl) for a mean of duration of 16 months (range 2–54 months). Six patients experienced complete remission (proteinuria <0.33g/day), and two patients had a partial remission (minimum of 50% reduction in baseline proteinuria). Albumin increased an average of 32%. Average C3/C4 levels were 64/15 mg/dL, respectively, prior to treatment, and 95/25 mg/dL following treatment. No treatment-limiting adverse effects were reported. Our case series supports the growing body of evidence that tacrolimus is an effective therapy in LN patients with refractory proteinuria. Further studies are required to establish the long-term safety and efficacy of tacrolimus.

Introduction

Renal complications are a major source of morbidity and mortality in patients with systemic lupus erythematosus (SLE) and are present in 25-75% of patients.[1] Deposition of circulating immune complexes and recurrent flares lead to chronic glomerular scarring, and poorly controlled glomerulonephritis is a major risk factor for renal deterioration and poor long-term outcome.[2] Histopathologic diagnosis and staging by International Society of Nephrology/ Renal Pathology Society (ISN/RPS) classification, guides therapy with a goal of normalizing renal function and preventing progressive loss by inducing and maintaining remission. [3] Treatment of classes III, IV, and V LN remains a management challenge in many cases. Established therapies include glucocorticoids plus pulsed intravenous cyclophosphamide (IVC) or oral mycofenolate mofetil (MMF). Cyclophosphamide has been commonly accepted as standard therapy since studies done through the National Institutes of Health in the 1980s reported that pulse therapy with cyclophosphamide improves the prognosis of LN compared with glucocorticoid therapy alone.[4] Unfortunately it has an unfavorable side effect profile, with adverse effects including hemorrhagic cystitis, carcinoma of the bladder, and bone marrow suppression, some of which can be fatal. It can also result in permanent sterility in young female patients.[5,6]

Mycophenolate mofetil (MMF) is an alternative to cyclophosphamide, and studies have demonstrated non-inferiority as well as a lower incidence of adverse effects when used as maintenance therapy.[7] Azathioprine has also been explored, but was shown to be less efficacious in treatment of LN when compared to MMF with a similar side effect profile.[8,9]

Evidence has accumulated to support MMF as the preferred treatment in conjunction with steroids. However, a significant proportion of patients have persistent proteinuria despite this regimen, with estimated failure rates of 16 -20%.[9-11] Continued proteinuria is predictive of poor outcome in most studies with no remission leading to high rates of chronic kidney disease and eventual progression to end stage renal disease. Even a partial remission in lupus nephritis is associated with a significantly better patient and renal survival compared with no remission. We defined partial remission as decrease in proteinuria by greater than 50%, and complete remission as reduction in proteinuria to <0.33g/day based on spot protein/creatinine ratio.[12]

More recently a group of small studies, mostly performed in Asian patient populations, have looked at tacrolimus in patients with class III, IV, and V LN. Tacrolimus is currently employed in transplant medicine to control rejection after kidney, liver, heart, and bone marrow transplantation, and is known as a safe and effective immunosuppressant. It is a macrolide calcineurin inhibitor and interferes with both T-lymphocyte signal transduction and IL-2 transcription. Known side effects and complications of tacrolimus use include tacrolimus nephrotoxicity, infections, dyslipidemias, tremor, low magnesium, new onset hypertension, and new onset diabetes mellitus, which can manifest as diabetic ketoacidosis.[13] However, unlike many other immunosuppressives, tacrolimus has been shown to be relatively safe in pregnancy.[14] MMF is associated with increased risk of facial malformations and first-trimester pregnancy loss.

Studies in murine models have demonstrated a decrease in intraglomerular cellular proliferation and normalization of affected podocytes.[15] This effect has been confirmed in humans as well, Nonaka reports a case of membranous LN in which a young female patient showed histologic improvement of subepithelial deposits after tacrolimus therapy.[16] This mechanism is thought to be independent of its immunosuppressive function, a theory supported by similar findings when it is used in other proteinuria inducing disease states, such as IgA nephropathy.[17] Tacrolimus is postulated to alter levels of the protein synaptopodin and thereby stabilize the podocyte cytoskeleton. It has now been used successfully both as multi-target therapy using a combination of steroids, MMF, and tacrolimus, and as primary induction monotherapy with steroids. For the period 2005-2012, there were approximately 10 open label trials, case series, or randomized controlled trials, and two meta-analyses investigating tacrolimus as a treatment for LN.[18-28] Available evidence suggests higher rates of remission when added to MMF, also that tacrolimus alone is an option for induction therapy. The

existing evidence reviewing side effects varies, some studies observed severe effects including severe infection and new onset diabetes, while others demonstrated a benign side effect profile for tacrolimus.

Several questions remain unanswered in the small group of existing studies on tacrolimus in LN. Optimal dosing and duration of therapy still needs to be determined. Many studies lack long-term follow up. Also, racial discrepancies are not well addressed. We present data from eight female patients with biopsy proven class III, IV, or V LN and persistent nephrotic range proteinuria in a retrospective case series.

Case Series

We retrospectively discuss eight female patients who met the diagnostic criteria for SLE according to the American College of Rheumatology definition, had a renal biopsy confirming class III, IV, or V LN, and were treated with tacrolimus. Five were Caucasian, one Vietnamese, one Hispanic, and one African American. Mean age was 27 (range 20-44). There were two patients with class IV LN, two with class IV/V LN, two with class III/V LN, and two with pure class V LN. Details regarding patient demographics and treatment history are presented in table 1.

For each patient described here, the decision to start tacrolimus was based on clinical data at the time and failure to respond to well-established immunosuppressive regimens. All were started at 0.15-0.20 mg/kg body weight taken either once daily or broken into twice daily dosing, depending on patient preference, and titrated to a goal trough of 4-6 ng/ml, the established therapeutic dose studied in transplant medicine. Troughs were measured anywhere from monthly to every three months, depending on stability of the dose. Patients were followed on a monthly basis with serial measurements of spot protein/creatinine ratio to quantify proteinuria, serum albumin, serum creatinine, and serum complement levels. Serum electrolytes, blood pressure, fasting lipid profiles, and random glucoses were monitored as well. We also report percent reduction in proteinuria and percent increase in albumin for each patient and if they meet the criteria for complete or partial remission (table 2). Any adverse effects were assessed with careful review of systems questioning at monthly visits.

Patients 1, 2, 3, 5, and 6 were similar in that they had a long-standing diagnosis of lupus nephritis with biopsy performed in the past, and had varying levels of proteinuria on a combination of immunosuppressives, but had not yet experienced a clinically significant remission. These four patients had been on relatively high doses of prednisone (30-60mg daily) and MMF for several months. All were on an ACE-inhibitor or angiotensin receptor blocker as well. Following addition of tacrolimus, they experienced 87%, 93%, 93%, 94%, and 44% reductions in proteinuria respectively (one partial remission and four complete remissions, table 2). Patient 1 experienced an increase in proteinuria within one month after she stopped tacrolimus due to noncompliance, and eventually she was lost to follow up (figure 1).

Patient 4 also failed the standard MMF and prednisone but she was relatively early in the LN disease course. She was diagnosed only two months prior to starting tacrolimus. She had nephrotic range proteinuria after two months of MMF and prednisone, even while taking 60mg of prednisone daily. Tacrolimus was added only after a short trial of standard therapy due to severe edema and nephrotic syndrome. She experienced a complete remission after nine months of treatment.

Table 1. Patient Characteristics prior to addition of tacrolimus

Patient	Age	Race	Sex	Duration of lupus	ISN Class	Time since renal biopsy	Prednisone dose at time of tacrolimusaddition	Time on MMF	Previous immunosuppressive regimens/other immunosuppressive medications	Additional relevant medications
1	27	Caucasian	F	4 years	III/IV	3 years	30mg	3 years	MMF, prednisone	Lisinopril, simvastatin
2	28	Caucasian	F	10 years	IV	8 months	60mg	10 months	hydroxychloroquine, prednisone, cyclophosphamide, rituximab, azathioprine, MMF	Lisinopril
3	28	Caucasian	F	14 years	V	2004	20mg	5 months	MMF, prednisone, hydroxychloroquine	Losartan, metoprolol
4	20	Vietnamese	F	2 years	IV/V	2 months	60mg	2 months	prednisone, MMF	Lisinopril, Mg oxide
5	29	African American	F	11 years	IV/V	11 months	40mg	3 months	Cyclophosphamide, Prednisone, Hydroxychloroquine, MMF	Lisinopril
6	44	Caucasian	F	4 years	III/V	2 months	Prednisone 40mg	2 years	hydroxychloroquine, MMF, prednisone	Lisinopril
7	21	Caucasian	F	8 months	V	N/A - pregnant	50mg daily	N/A - deferred due to pregnancy	Prednisone, Azathioprine	None
8	22	Hispanic	F	3 months	IV	1 month	Methylprenisolone 48mg QD (prednisone allergy)	2 months	hydroxychloroquine, MMF, solumedrol	Amlopdipine, furosemide, Micardis, metoprolol

Table 2. Clinical parameters before and after addition of tacrolimus								
Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Max tacrolimus dose								
	1mg bid	3mg qam/2mg qhs	1.5mg bid	2mg qam/1mg qhs	3mg BID	3mg qam/2mg qhs	3mg BID	2mg QAM/3mg QPM
Spot prot/Cr ratio								
Before	5.0	10.7	4.22	10.51	5.15	2.54	7.12	5.13
After	0.65	0.71	0.28	0.10	0.31	0.29	0.23	1.38
Duration until max remission	3 months	6 months	8 months	9 months	11 months	4 months	5 months	5 months - ongoing
% reduction in proteinuria								
	87% PR	93% CR	93% CR	99% CR	94% CR	44% CR	97% CR	73% PR
Albumin								
Before	2.2	1.76	2.7	1.8	2.9	3.1	2.4	1.7
After	3.0	3.3	3.4	3.5	3.6	3.8	3.5	3.3
Percent change	27%	47%	21%	49%	20%	18%	31%	48%
C3/C4								
Before	77/14	62/11	43/13	64/11	74/24	54/8	91/13	45/14
After	92/9	103/25	89/27	107/21	82/25	65/15	93/19	89/21
Serum creatinine								
Before	0.73	2.04	0.82	0.75	0.71	0.77	0.55	1.64
After- most recent	0.55	1.09	0.69	0.54	0.75	0.82	0.69	1.06
Average serum tacrolimus level								
	6.1	6.48	6.04	6.56	3.6	3.0	6.2	5.6
Current duration of therapy								
	4 months - noncompliant	1 year	7 months	9 months	11 months	3 months	6 months	5 months
Adverse effects								
	None reported	Otitis externa	Fine hand tremor	hypomag	hypomag	Tooth abscess	None reported	Candidiasis oral hyperglycemia
Final prednisone dose								
	20mg	stopped after 10 months	5mg	Stopped after 7 months	Stopped after 6 months	20mg	20mg	Solumderol 24mg

Patient 7 is unique because she was pregnant at time of treatment. At 12 weeks she was started on azathioprine, she had already been placed on oral prednisone, however she had continued nephrotic range proteinuria, the decision was made to start tacrolimus. Tacrolimus 1mg twice daily was started at 14 weeks. She tolerated this regimen well throughout her pregnancy. There were no fetal adverse effects noted on ultrasound, which was performed twice. This patient delivered a healthy term infant by cesarean section. She did not breast feed. She had a complete remission after 5 months of therapy. She was able to stop prednisone after 6 months of treatment, though she did take prednisone throughout her pregnancy. She underwent biopsy after delivery which demonstrated membranous LN. MMF was later added to her regimen following a transient increase in proteinuria.

Patient 8 was started on dual therapy with tacrolimus and MMF in addition to a steroid agent de novo. She had experienced some criteria for SLE in the past but had never been formally diagnosed. She was biopsied shortly after presentation with difficult to control hypertension, nephrotic range proteinuria, hypoalbuminema, and hypocomplementemia. Biopsy revealed class IV LN. Therapy was immediately initiated on steroids, MMF, and tacrolimus 1mg twice a day. Because of a prednisone allergy she was treated with solumedrol instead. She had a partial remission, currently her treatment duration is 5 months. These eight patients did not experience any treatment limiting adverse effects while taking tacrolimus. One had hypertension at baseline and was on two antihypertensives prior to addition of tacrolimus. Two had hyperlipidemia at baseline and were on a statin prior to addition of tacrolimus. One patient developed a fine hand tremor which resolved with slight decrease in tacrolimus dose, two patients developed hypomagnesemia which was corrected by oral magnesium supplementation, one patient developed otitis externa, and one patient had a tooth abscess.

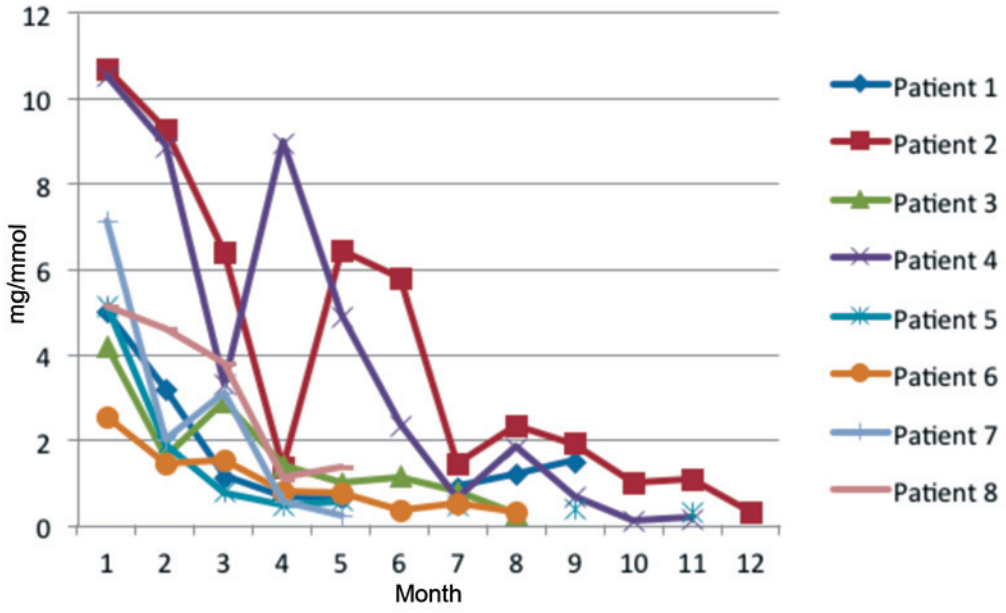

Figure 1. Spot protein/creatinine ratio (mg/mmol) following addition of tacrolimus

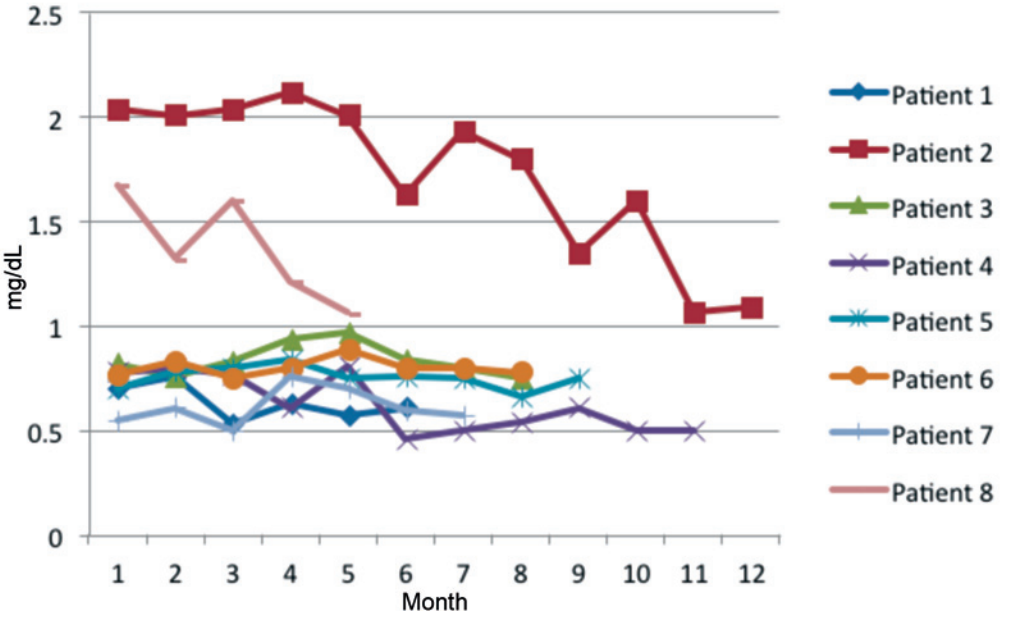

Figure 2. Serum creatinine (mg/dL) over time following addition of tacrolimus

Patient 8 had transient hyperglycemia which was managed with dietary modifications, she also had oral candidiasis. Apart from these instances clinical parameters including lipid profile, random serum blood sugar, and blood pressure remained at baseline in all eight of the patients (table 2). No patients experienced a rise in serum creatinine above baseline (figure 2).

Overall, five patients experienced a complete remission and three experienced a partial remission as defined previously (figure 1). All patients demonstrated an increase in complement (table 2). Albumin increased an average of 33% (range 18-49%, figure 3). Four patients were able to stop prednisone entirely. Average C3/C4 levels were 64/14, respectively, prior to treatment, and 90/20 following treatment. The mean treatment duration prior to maximum decrease in proteinuria and

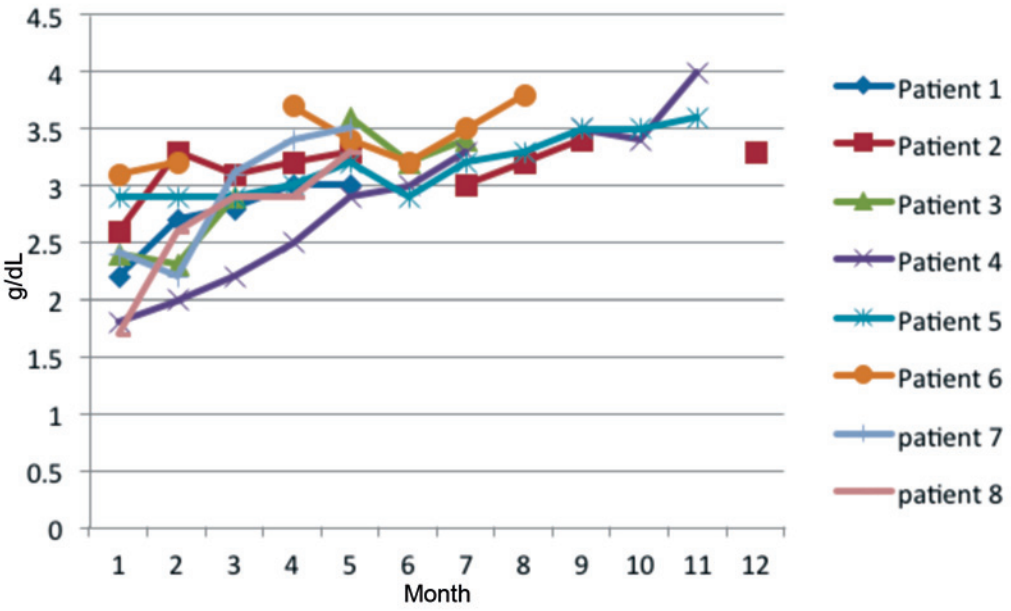

Figure 3. Serum albumin over time (g/dL) following addition of tacrolimus

improvement in serum complement levels was 8 months for the five patients who experienced a complete remission. One patient discontinued early because of medical noncompliance. The other patients described in this case series continue treatment.

Discussion

Lupus nephritis has been shown to have significant morbidity and mortality, with 10-30% of patients progressing to end stage renal disease depending on severity. Deposition of circulating immune complexes and recurrent flares lead to chronic glomerular scarring. Persistent proteinuria is directly correlated with worse clinical outcomes. Decreasing proteinuria increases time to dialysis in patients with proliferative and membranous LN. Estimated renal survival at ten years is 94% for complete remission, 45% for partial remission, and only 19% for patients with continued proteinuria.[12] Data from this case series supports the relatively new concept of treating resistant proteinuria with tacrolimus.

Few have performed direct head to head comparisons of tacrolimus and other established alternative treatments for LN. Bao, et al, performed a randomized trial of prednisone, MMF, and tacrolimus versus cyclophosphamide alone. The multi-agent therapy was found superior to cyclophosphamide at achieving complete remission at 6 and 9 months.[18] Chen, et al, looked at efficacy of tacrolimus compared to azathioprine in maintaining remission and found similar rates of relapse but significantly less leucopenia with tacrolimus. Szeto, et al, compared azathioprine to tacrolimus specifically in patients with membranous LN (class V) and found that not only did tacrolimus reduce proteinuria faster, also patients relapsed after it was stopped.[19] In a meta-analysis, Deng, et al, compared cyclophosphamide plus steroids to tacrolimus plus steroids, and determined tacrolimus is more effective as an induction therapy in Chinese patients with class III, IV, and V LN. In our patient population, we observed an added benefit when added to MMF and steroids, similar to Bao's study.

Still, the ideal use of tacrolimus in LN remains unclear. Our patient population involved mostly patients who were refractory to standard treatment, though we did have success using tacrolimus as primary induction therapy in one newly diagnosed patient. Our case series also incorporates one patient who was pregnant during her treatment. Azathioprine has also been shown safe in pregnancy, but, as discussed, is inferior to MMF. Studies in transplant medicine show tacrolimus to be safe and reliable in pregnancy; studies cite a 1% incidence of birth defects, mainly cleft palate.[29] This patient had a complete remission within five months. The average time until maximum reduction of proteinuria was 5 months, however at least four of our patients achieved a partial remission within 3 months (figure 1). The rapidity of reduction in proteinuria had a noticeable clinical benefit in these patients, with obvious reduction of edema in some. We lack long-term follow up currently.

Tacrolimus may also be a steroid sparing agent for many LN patients. All of the patients we observed were able to reduce their doses of prednisone. Some were able to stop after treatment with tacrolimus. There have been no studies performed to compare the steroid sparing ability of tacrolimus to other immunosuppressive medications, and this may be an area for future investigations.

There is a wide range of potential adverse effects, including serious hematologic complications such as severe leukopenia, anemias, transaminitis, and neurologic symptoms such as tremor and presyncope. Potential nephrotoxicity is also a concern. Some studies have found side effects to be limiting, with severe infection in particular requiring cessation of therapy prior to achievement of renal remission. Of note this was particularly observed in the Caucasian patients during the few studies that used this patient population.[25] Inherently the risk of severe infection with three immunosuppresive agents is higher than with dual or single agent therapy, but we observed only minor infections, none of which required intravenous antibiotics or hospitalization. Patient response to immunosuppressants is variable depending on ethnicity, an observation which has been described extensively for cyclophosphamide and MMF. The Aspreva lupus management study showed better response to MMF among black and Hispanic patients, and a higher prevalence of adverse effects among Asians.[30,31] Similar patterns are not yet well established for tacrolimus.

This case series augments current evidence showing tacrolimus is a viable option in LN patients who are refractory to standard treatment. Use in a pregnant patient with LN in whom other immunsupressants were not effective is a novel concept. Our observations in these patients support the growing evidence looking at tacrolimus, including its use in Caucasian patients and, in the case of one patient, pregnancy. Further exploration is needed to determine the optimal dosing, duration of treatment, and potential long-term side effects of using tacrolimus.

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Conflict of Interest

None of the authors identify any conflict of interest.

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Rapid Multiplex PCR Assay To Identify Respiratory Viral Pathogens: Moving Forward Diagnosing The Common Cold

Clifton P. Layman DO; Sarah M. Gordon MD; Diane U. Elegino-Steffens MD; Willie Agee PhD; Jason Barnhill PhD; and Gunther Hsue MD

Abstract

Upper respiratory tract infections (URIs) can be a serious burden to the healthcare system. The majority of URIs are viral in etiology, but definitive diagnosis can prove difficult due to frequently overlapping clinical presentations of viral and bacterial infections, and the variable sensitivity, and lengthy turn-around time of viral culture.

We tested new automated nested multiplex PCR technology, the FilmArray® system, in the TAMC department of clinical investigations, to determine the feasibility of replacing the standard viral culture with a rapid turn-around system. We conducted a feasibility study using a single-blinded comparison study, comparing PCR results with archived viral culture results from a convenience sample of cryopreserved archived nasopharyngeal swabs from acutely ill ED patients who presented with complaints of URI symptoms. A total of 61 archived samples were processed. Viral culture had previously identified 31 positive specimens from these samples. The automated nested multiplex PCR detected 38 positive samples. In total, PCR was 94.5% concordant with the previously positive viral culture results. However, PCR was only 63.4% concordant with the negative viral culture results, owing to PCR detection of 11 additional viral pathogens not recovered on viral culture. The average time to process a sample was 75 minutes. We determined that an automated nested multiplex PCR is a feasible alternative to viral culture in an acute clinical setting. We were able to detect at least 94.5% as many viral pathogens as viral culture is able to identify, with a faster turn-around time.

Introduction

Upper respiratory tract infections (URIs) in the population can have serious economic and public impact. URIs are the leading cause of acute illness in adults, and according to the CDC they are the leading cause of absence from work and school.[1] Each year in the United States, more than 30,000 deaths during flu season are attributed to URIs.[2]

Despite being one of the most common outpatient complaints in the United States and worldwide, pinpointing the etiology and developing an appropriate treatment plan is challenging in the clinical setting. Although the majority of URIs are viral in etiology, differentiating between the bacterial and viral etiologies can prove to be problematic because they often have an overlapping clinical presentation.[3] The overlapping presentation, combined with the genuine desire of the provider to "do something" and the frequent demand for treatment by patients and patient parents, has created a cultural expectation that can lead to the inappropriate use of antibiotics and drive up antibiotic resistance rates.[4]

A major obstacle to fast and accurate etiological diagnosis is the variable sensitivity and response time of the current method for identification of viral etiologies in URIs.[5] The current "gold standard" is viral culture, which can be a cumbersome and lengthy process. At our facility, viral identification begins with limited direct fluorescent antibody assay and viral inoculation into culture media. Some viruses require special conditions for growth, including special media, temperatures, and preparation, which requires additional technician workload and processing. Additionally, the time from media inoculation to viral growth is extremely variable, ranging from 3-14 days for most respiratory pathogens. The time and personnel constraints on viral culture prove to be large economic burdens to facilities such as ours, which runs about 2500 samples annually, the majority of which occur during flu season.

In recent years, advances in PCR methods and techniques have been harnessed in the laboratory to aid in the rapid detection of respiratory pathogens from patient specimens. PCR can differentiate and identify an expanded range of viral and bacterial targets.[6] Additionally, there are multiplex PCR modalities available with the ability to detect multiple targets in a single reaction.[7] However, traditional PCR does come with limitations. In the past, PCR has either been limited in scope of pathogenic targets or by the complexity of the test when targeting more than one pathogen.[8] Additionally, with traditional PCR there is a high risk of contamination due to the process itself, in some cases requiring specialized training and facilities. The risk of contamination and the complexity of the process, often leads to difficulty distinguishing amplification products and traditional multiplex PCR methodologies.

Recently, our facility had the opportunity to try an updated PCR platform, the FilmArray® system. In 2011, the FDA cleared the FilmArray® system, an automated nested multiplex PCR, with a sealed pouch that lowers the risk for contamination. It can run a patient sample from a nasopharyngeal swab in approximately one hour, testing for up to 20 of the most common viral and bacterial URI pathogens (see table 1).

Methods

We evaluated the feasibility of using the FilmArray® PCR in place of viral culture at Tripler Army Medical Center using a

Table 1. Viral and bacterial PCR targets

FilmArray® Automated Nested Multiplex PCR Viral and Bacterial Targets	
Viral Targets (includes multiple subtypes)	Bacterial Targets
• Adenovirus • Bocavirus • Coronavirus • Metapneumovirus • Rhinovirus • Enterovirus • Influenza A • Influenza B • Parainfluenza virus • Respiratory syncytial virus	• *Bordetella pertussis* • *Mycoplasma pneumonia* • *Chlamydophila pneumoniae*

single-blinded comparison study, comparing FilmArray® PCR results with archived viral culture results from a convenience sample of cryopreserved archived nasopharyngeal swabs from a study population. The study population consisted of acutely ill emergency department patients who presented to Tripler Army Medical Center, a tertiary care center, with complaints of URI symptoms.

Unique identification numbers were assigned to each cryopreserved sample. The FilmArray® operators were blinded to the known viral culture results of each sample. Each sample was processed individually by FilmArray® operators. Only after completion of the study were the FilmArray® operators unblinded and allowed to compare the FilmArray® PCR results to the previously known viral culture results for each sample.

Results

A total of 61 archived nasopharyngeal samples were processed by the FilmArray® operators. Of those 61 samples, viral culture had previously identified 31 positive samples and 30 negative samples. The FilmArray® system identified 38 positive samples, and 23 negative samples. Additional testing proved 100% reproducibility among FilmArray® operators. Of note, average time from receipt of a sample to the result was less than 75 minutes. Previously positive viral culture results had shown an array of respiratory viruses including adenovirus, cytomegalovirus (CMV), enterovirus, influenza A and B, metapneumovirus, parainfluenza virus, and respiratory syncytial virus (RSV). The FilmArray® failed to detect 1 out of 4 parainfluenza virus samples. In two other samples, one culture-identified adenovirus and one culture-identified enterovirus, the FilmArray® PCR correctly identified the same pathogen detected by viral culture, but also detected an additional pathogen. Of the 30 negative viral culture samples, the FilmArray® PCR detected 11 additional pathogens.

Overall, the FilmArray® has a 94.5% concordance with previously positive viral culture results when identifying viral targets that are expected to be detected (excluding CMV, which is not a FilmArray® target). If CMV is included in the analysis, there is an 87.1% concordance with previously positive viral culture results. There is only a 63.4% concordance between FilmArray® PCR and previously negative viral culture results.

Table 2. Comparison of Viral Culture and PCR results

Pathogen	Viral Culture	PCR concordance [additional pathogen]	PCR discordance
Adenovirus	4	3 [1]	1
CMV*	2	0 [1]	2
Enterovirus	4	4 [1]	0
Influenza A	6	6	0
Influenza B	2	2	0
Metapneumovirus	5	5	0
Parainfluenza	5	4	1
RSV	3	3	0
Negative	30	19	11

*CMV is not a target for FilmArray®

Table 3. PCR concordance with viral culture

Viral Culture	FilmArray® PCR
Positive [Excluding CMV]	94.5% Concordance
Positive [Including CMV]	87.1% Concordance
Negative	63.4% Concordance (11 additional pathogens detected)

Discussion

Our study demonstrated that the FilmArray® automated nested multiplex PCR system is at least 94.5% as accurate as viral culture when identifying viral targets that are expected to be detected. It is our conclusion that the FilmArray® device is feasible to use in an acute clinical setting, with reproducible results. The implications of being able to identify 95% of intended viral targets in as little as 75 minutes as compared with 3-14 days are exciting. The FilmArray® device has potential to replace viral culture in an acute clinical setting due to its ease of use and rapid turnaround time. Rapid tests have the potential to directly affect clinical management in real-time[9], which may improve antibiotic stewardship and aid in local and national epidemiological surveillance.[10] Limitations of this study include the generally discordant results between culture-negative samples and the FilmArray® system, which may be a result of the enhanced ability of FilmArray® PCR to detect additional respiratory pathogens not recovered in viral culture. Because viral culture is widely accepted to have variable sensitivity, the FilmArray® should be validated in the future against other molecular based testing modalities. Other considerations for future research should be directed at whether real-time results will actually affect clinical management, and a cost-benefit analysis surrounding PCR in relation to cost effectiveness for the patient, the facility, and the payer source.

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Conflict of Interest

None of the authors identify any conflict of interest.

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A Comparison of Methods for Estimating Glomerular Filtration Rate for a Population in Hawai'i with Non-Valvular Atrial Fibrillation

Corey J. Lum DO and Steven Azuma MD

Abstract

Warfarin is the primary treatment for those with atrial fibrillation at increased risk for stroke. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) trial demonstrated that dabigatran, a direct thrombin inhibitor, was associated with lower rates of systemic embolism compared to warfarin.[1] Although individuals with a creatinine clearance of less than 30 mL/min were excluded from the trial, the FDA approved the use of dabigatran for those with creatinine clearances as low as 15 mL/min, with a lower dose of dabigatran recommended for individuals with creatinine clearances below 30 mL/min. This study calculated Glomerular Filtration Rates (GFR) via three existing formulas with varying levels of accuracy (ie, the Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) to evaluate how patient eligibility for the RELY trial may have varied depending upon the formula used. A retrospective study was performed based on a chart review conducted at a private cardiologist's office in Honolulu, Hawai'i using patients with non-valvular atrial fibrillation. Patients included were those with a BUN/Creatinine assessment within 12 months of the chart review and a CHADS2 (Congestive Heart Disease, hypertension, age greater than 75, diabetes mellitus, and stroke or transient ischemic attack) score of 1 or greater. Of 376 subjects assessed, 64 subjects who failed to meet criteria for the RELY trial when using the Cockcroft-Gault formula (ie, GFR estimates were lower than 30 mL/min) met eligibility criteria when the MDRD formula was used (ie, GFR estimates exceeded 30 mL/min). Subgroup analysis of the 64 subjects revealed that subjects were 89-years-old on average, predominantly female (76.5%), and mostly Japanese (62.5%). Nearly one in five individuals (17%) in the studied population would have received a lower dose of dabigatran if the Cockcroft-Gaunt formula was used for estimating GFRs. The authors recommend caution while dosing dabigatran in the Asian population, as the estimates of kidney functioning vary substantially depending on the formula used to estimate GFR, which may in turn lead in some cases of inadequate dosing of dabigatran.

Introduction

Atrial fibrillation increases the risks of stroke and death. For the last 50 years, warfarin has been the primary treatment for those with atrial fibrillation with an increased risk for stroke. However, a 150 mg twice per day dose of dabigatran, a direct thrombin inhibitor, was associated with lower rates of stroke and systemic embolism but comparable rates of major hemorrhage as warfarin therapy in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) trial, conducted in 2009.[1] The RELY trial excluded individuals with a creatinine clearance (CrCl), calculated via the Cockcroft-Gault (C-G) method, of less than 30 mL/min from participating.[1] However, the Federal Drug Administration (FDA) approved the use of a lower dose of dabigatran (75 mg twice per day) for those with CrCLs between 15-30 mL/min for the prevention of thromboembolic events; the lowered dosing was recommended even for those with non-valvular atrial fibrillation with an increased risk.

Both the CKD-EPI and MDRD formulas are considered superior to the C-G formula, because unlike C-G, they are corrected for body surface area (BSA).[2] Recent studies comparing the C-G, Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas to the gold-standard Glomerular Filtration Rate (GFR) measurement using 125I-iothalamate, revealed that the CKD-EPI formula gives the best estimation of GFR.[3] Furthermore, CKD-EPI provided more conservative estimates of GFR, and classified fewer individuals as having Chronic Kidney Disease (CKD).[3] However, the literature remains divided on which formula yields the best estimates, and it appears that the patient's race-ethnicity is an important factor while considering which formula to apply. According to Gerchman, et al, the MDRD may be a more accurate equation of estimating CrCl in Hawai'i, where the population is predominantly of Asian descent.[4] Consequently, most commercial laboratories in Hawai'i provide GFRs calculated via the MDRD formula.

This study was a retrospective chart review conducted at a private cardiologist's office in Honolulu, Hawai'i of patients with non-valvular atrial fibrillation. The goal was to compare GFR estimates calculated using all three formulas for patients meeting inclusion criteria in order to evaluate the extent to which the formula chosen influenced clinically relevant treatment decisions (in this case, the recommended dosage of dabigatran to be prescribed).

Methods

A retrospective chart review of records was performed to identify all patients with non-valvular atrial fibrillation. Patients who met the inclusion criteria were those with a Blood Urea Nitrogen (BUN) or Creatinine assessment within 12 months of the review, and who were assigned a CHADS2 score for atrial fibrillation stroke risk of 1 or greater. CHADS2 referred to a history of congestive heart disease, hypertension, age greater than or equal to 75 years old, diabetes mellitus and stroke or transient ischemic attack. Each one accounting for 1 point and stroke or transient ischemic attack counts as 2 points. The same laboratory values were used to calculate estimated GFRs for each subject via all three formulas (ie, C-G, MDRD and CKD-EPI). MDRD and CKD-EPI calculations were corrected for body surface area for each individual. Body surface area was calculated using a standard body surface area equation of BSA (m^2) = ([Height(in) x Weight(lbs)]/ 3131)^½.

Results

This study included 376 subjects. Based on self-reported ethnicity, the sample was 48% Japanese, 8% Chinese, 7.5% Hawaiian, 6.6% Caucasian, 5% Filipino, 1% Korean, 0.3%

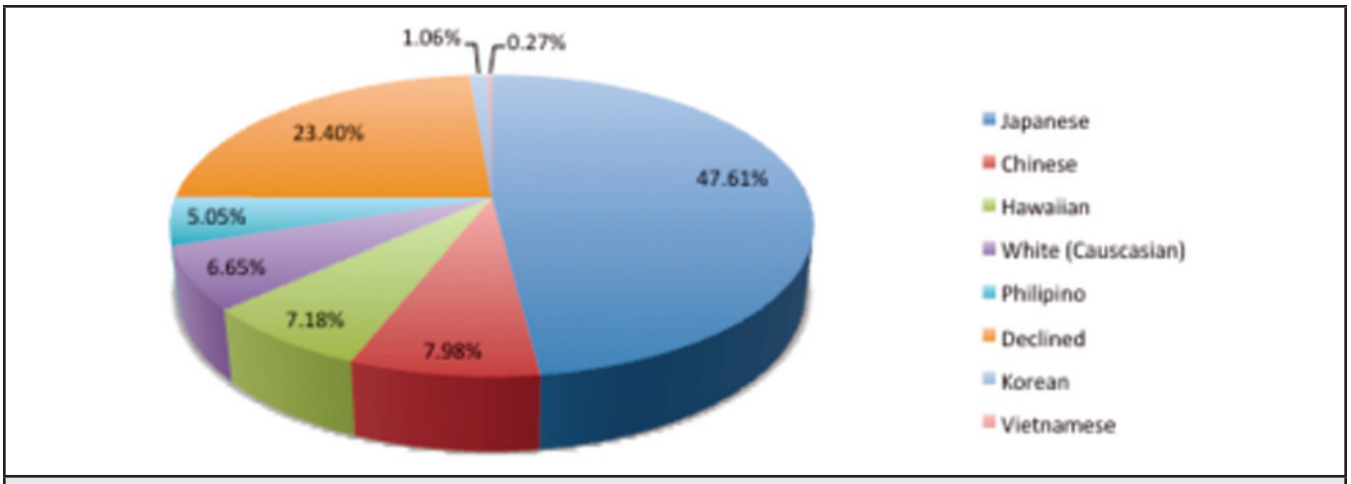

Figure 1. Percentage of ethnicities.

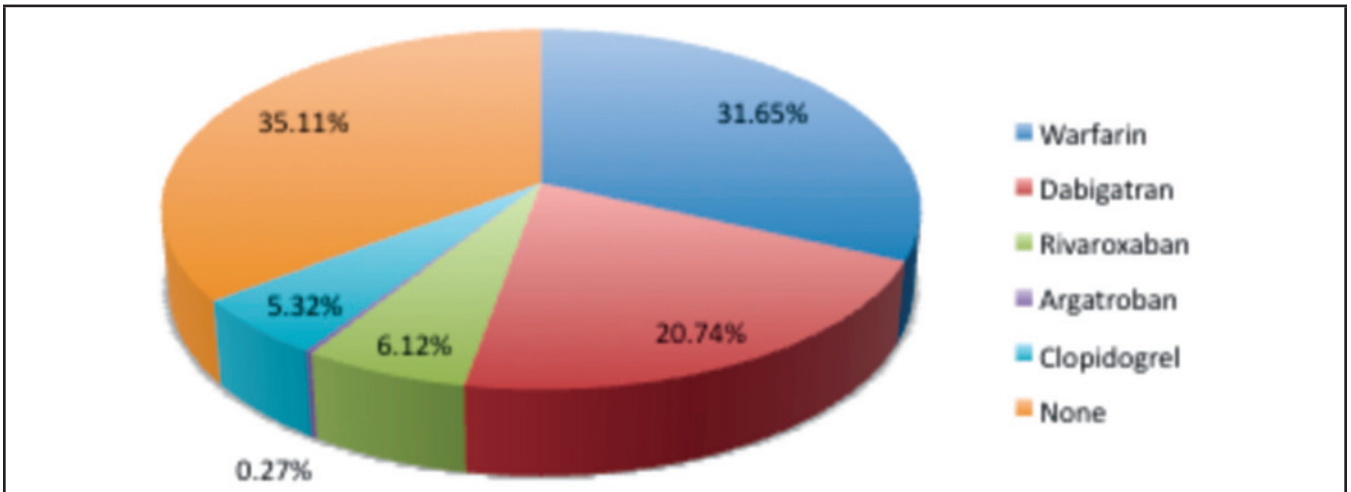

Figure 2. Percentage of population with non-valvular atrial fibrillation with a CHADS2 score of 1 or greater on anticoagulation.

Vietnamese; 24% were unknown (Figure 1). Age ranged from 36-99 with the average age of 78. Less than half (44%) were female. Average BUN and Creatinine values were 23 and 1.41, respectively. Average CHADS2 score was 2.5 with a standard deviation of 1.2. Of the 376 subjects, 32% were on warfarin, 21% on dabigatran, 6% on rivaroxaban, 0.3% on argatroban, 5.3% on clopidogrel; approximately 35% were not being treated with any anticoagulation therapy secondary to patient refusal or contraindication (Figure 2).

There were 64 (17%) subjects whose GFRs were underestimated by the C-G formula compared to the MDRD formula; the GFRs of a comparable number (n=60; 16%) were underestimated by the C-G formula when compared to the EPI-CKD formula as well. In comparison, the GFRs of 5 or fewer subjects (≤1.3%) were underestimated when the MDRD or CKD-EPI were used (Table 1).

Table 1. Patients whose kidney functioning would be differentially misclassified based on the choice of formula used for GFR calculation.

Calculated GFR is under 30 mL/min	*Calculated GFR Meets or Exceeds 30 mL/min*		
	C-G Formula	MDRD Formula	CKD-EPI Formula
C-G Formula		64	60
MDRD Formula	5		0
CKD-EPI Formula	5	4	

Table 2. Subgroup population of those with CrCl < 30 via CG but CrCl > 30 via MDRD.		
Avg. Age	89	
Females	49	76.56%
Japanese	40	62.50%
Chinese	6	9.38%
Hawaiian	0	0.00%
White (Caucasian)	0	0.00%
Filipino	2	3.13%
Declined	15	23.44%
Korean	1	1.56%
Vietnamese	0	0.00%
Average difference between GFR		0.00%

Further subgroup analysis of the 64 individuals whose GFRs were underestimated by the C-G formula compared to the MDRD formula revealed an average age of 89 years; the majority (n=49, 76.5%) were female (Table 2). Additionally, this sub-group was mostly Japanese (n=40, 62.5%), followed by Chinese (n=6, 9.4%) (Table 2). The average difference in calculated CrCl in this subgroup was 22.8 mL/min (Table 2).

Discussion

To our knowledge, no study has previously compared estimates produced by the three GFR equations using Hawai'i's culturally diverse populations. Out of 376 subjects included in this study with non-valvular atrial fibrillation with a CHADS2 score of 1 or greater, 64 subjects (17%) who would have been excluded from participation in the RELY trial (which used the C-G formula) would have met eligibility criteria if the MDRD formula was used to estimate GFR; similarly, if the RELY trial had used the CKD-EPI equation, an additional 60 subjects (16%) in this sample would have met eligibility criteria. These differences are substantial and may have influenced the outcomes of the original RELY trial. Further subgroup analysis of incorrectly excluded individuals showed that a disproportional amount was older, Japanese, and female.

According to Gerchman et al, the MDRD equation may be more accurate in estimating GFR for Japanese populations, who comprise a significant minority group in Hawai'i.[4] Also, as noted earlier it has been suggested that CKD-EPI and MDRD provide more accurate estimations of GFR compared to C-G.[3] In this study, 24% of the population had an estimated GFR < 30 mL/min using C-G, compared to only 6.8% using MDRD. The authors suspect that one explanatory factor for the large differences in estimates may be that the MDRD and CKD-EPI equations take height into consideration, whereas the C-G does not. The C-G equation is based on body weight, either ideal or actual, whereas the MDRD and CKD-EPI correct for the patient's BSA, including height.[2] The Japanese population's BSA may be different from other populations such that the C-G equation underestimate the estimated GFR compared to the MDRD and CKD-EPI. More specifically, Japanese females may have a height to weight ratio that make their BSA less favorable for using C-G for estimating CrCl. In this study, despite correcting for BSA, the C-G equation underestimated the CrCl compared to the MDRD and CKD-EPI equations. There may be other factors related to ethnicity that may be contributing to the underestimation of CrCl using the C-G equation.

The clinical implications of these findings are substantial. First, patients in Hawai'i would be overdiagnosed with Chronic Kidney Disease Stage IV (CrCl < 30 mL/min) if the C-G formula is used for GFR estimation compared to the MDRD and CKD-EPI (BSA corrected) formulas. Second, many patients with non-valvular atrial fibrillation may be under-dosed with dabigatran if the C-G formula is used; to avoid under-dosing, the authors recommend the use of the MDRD or CKD-EPI formulas for populations in Hawai'i. Finally, this study questions the generalizability of the findings of the RELY trial to Japanese populations. The authors caution the reader in dosing dabigatran in patients in Hawai'i, and recommends against the use of the C-G method for estimating CrCl, particularly in deciding upon dabigatran dosage. Using MDRD may prevent under dosing of dabigatran. Clinical correlation is advised.

Conflict of Interest

None of the authors identify any conflict of interest.

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Trial and Error: Investigational Drug Induced Liver Injury, A Case Series Report

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Abstract

This is a case report series of four patients who exhibited signs and symptoms of acute liver dysfunction during participation in a Phase I trial of a novel non-steroidal anti-inflammatory drug (NSAID) designed to inhibit microsomal prostaglandin synthase 1 (MPGES1). Within one month of trial initiation, all four patients presented with epigastric pain, fatigue, nausea, and increasing liver function tests (LFTs). Two out of four patients required hospitalization, underwent liver biopsies, and were treated with N-acetylcysteine. The remaining two patients were managed as outpatients. Liver biopsies were consistent with drug induced liver injury (DILI). Within three months of stopping the investigational drug, symptoms subsided and LFTs normalized in all patients. This case report series signifies the importance of NSAIDs and novel drug agents in general as potentially hepatotoxic substances, the need for a high level of suspicion of DILI when considering possible etiologies of acute liver failure, and the need for prompt withdrawal of the causative agent in management of patients presenting with DILI.

Introduction

Drug induced liver injury (DILI) refers to liver diseases caused by drugs and toxic substances. Not only is DILI the leading cause of acute liver failure (ALF) in the United States, it is the most common reason for drug non-approval and withdrawal by the US Food and Drug Administration (FDA).[1] Older women (> 50-60 years old) appear to be more likely to develop DILI.[2] Aside from acetaminophen, NSAIDs, along with antibiotics, top the list for causes of DILI.[3] Approximately 10% of total drug-induced hepatotoxicity is related to NSAIDs.[3] DILI can mimic all forms of liver disease, making diagnosis a challenging one. Furthermore, histology indicates the type and degree of liver injury and not the etiology of it.[4]

A high level of suspicion is necessary to make a diagnosis. The Roussel Uclaf Causality Assessment Method (RUCAM-CIOMS) is a scoring system that can aid diagnosis of DILI (Figure 1). It includes temporal relationship with drug use, exclusion of other causes, and drug's hepatotoxic potential.[4] Hy's Law is also valuable in identifying patients at heightened risk for complications of DILI. According to Hy's Law simultaneous presence of elevated serum bilirubin (>2x ULN) and elevated aminotransferases (>3x ULN) identifies patients at risk for complications.[2]

Once a diagnosis of DILI has been established, prompt removal of the causative agent, symptomatic treatment, and monitoring for ALF are paramount.[4] DILI is associated with a high level of morbidity and mortality, and thus, prompt withdrawal of the drug is necessary to prevent permanent liver damage, reduce the need for liver transplantation, and reduce mortality.[4] There are no firmly established treatment protocols for many of the causes of DILI outside of treatment for acetaminophen toxicity. Hence, the Drug Induced Liver Injury Network (DILIN), sponsored by the National Institutes of Health (NIH), is considering conducting treatment trials for severe DILI.[5]

Prostaglandin E2 (PGE2) is a principal mediator of inflammation and the most abundant prostaglandin in the human body, making it a promising target of novel anti-inflammatory therapy.[6] While relatively safe, NSAIDs are associated with gastric ulcers, pro-thrombotic events, and other adverse effects. Novel NSAIDs targeting various pathways of prostaglandin synthesis are the topic of current research in hopes of avoiding these adverse effects. Microsomal prostaglandin synthase 1 (MPGESI) is one such enzyme that selectively targets the formation of PGE2.[7] Thus, it was theorized that MPGES1 inhibition would target inflammation while minimizing gastric and pro-thrombotic side effects associated with other NSAIDs. Studies have shown that MPGES1 generated PGE2 plays a key role in inflammation, pain, fever, anorexia, atherosclerosis, stroke, and tumorgenesis.[8] It has also been shown to be up regulated in synovial tissue.[6] Inhibition of MPGES1 could theoretically reduce pro-inflammatory PGE2 while sparing other prostanoids, thus minimizing adverse side effects typical of other NSAIDs.[6,7]

Case Report

Four female patients over fifty years of age presented with signs and symptoms of acute liver dysfunction during participation in a Phase I trial of a novel NSAID inhibiting MPGES1. At the first sign of liver dysfunction, the trial's local principle investigators referred them to the Queen's Medical Center (QMC) for evaluation and notified the QMC Liver Center. Two patients were admitted, while two were managed as outpatients. The first patient was referred due to progressively worsening liver function tests (LFTs) in addition to experiencing epigastric discomfort, nausea without vomiting, and loss of appetite. The second patient presented with elevated LFTs and nausea without vomiting. These patients were admitted to QMC for further evaluation and treatment. At the time of admission, ALT and total bilirubin were 1005 and 1.5, and 1400 and 0.9, respectively. Other labs including CBC, INR, and renal function, were within normal limits. Both patients exhibited negative Hepatitis A, B, and C serologies. Temporal presentation of illness to drug exposure, exclusion of viral hepatitis, and the hepatotoxic potential of NSAIDs documented in animals supported DILI as a leading diagnosis.

Given the evidence of significant liver dysfunction provided by severely elevated LFTs, a decision was made to proceed with liver biopsy. Liver biopsies of the two patients were consistent with DILI (Figures 2, 3, 4). Figure 2 demonstrates numerous portal and lobular eosinophils. Figure 3 shows micro-granulomas. Lastly, Figure 4 highlights zone 3 cholestasis and marked lobular hepatocyte necrosis consistent with DILI. Furthermore, biopsies were negative for alpha-1 inclusions, fibrosis, and steatosis.

Figure 1. RUCAM CIOMS Scoring System for Hepatocellular DILI	
RUCAM-CIOMS for hepatocellular DILI	
Temporal Relationship of Start of Drug to ALT >2x ULN	**Points**
Initial treatment 5-90 days; subsequent treatment course 1-15 days	2
Initial treatment <5 or >90 days; subsequent treatment course >15 days	1
From cessation of drug <15 days, or < 15 days after subsequent treatment	1
After Drug Cessation – Different Between Peak ALT and ULN	
Decreases > 50% within 8 days	2
Decreases > 50% within 30 days	1
No information or decrease >50% after >30 days, or inconclusive	0
Decrease <50% after 30 days or recurrent increase	-2
Risk Factors	
No ETOH use (below recommended limit)	0
ETOH (above recommended limit)	1
Age <55 years	0
Age >55 years	1
Concomitant Drug	
No concomitant drug administered	0
Concomitant drug with suggestive or compatible time of onset	-1
Concomitant known hepatotoxin with suggestive or compatible time of onset	-2
Concomitant drug with positive re-challenge or validated diagnostic test	-3
Nondrug Causes: **- Primary: recent hepatitis A, B, or C, biliary obstruction, acute alcoholic hepatitis (AST >2x ALT), recent hypotension** **- Secondary: Underlying other disease; possible CMV, EBV, or HSV infection**	
All primary and secondary causes reasonably ruled out	2
All 6 primary causes ruled out	1
4 or 5 primary causes ruled out	0
< 4 primary causes ruled out	-2
Nondrug cause highly probably	-3
Previous Information on Hepatotoxicity of the Drug in Question	
Package insert or labeling mention	2
Published case reports but not on label	1
Reaction unknown	0
Re-challenge	
Positive (ALT doubles with drug in question alone)	3
Compatible (ALT doubles with same drugs as given before initial reaction)	1
Negative (Increase in ALT but <2x ULN, same conditions as when reaction occurred_	0
Not done	0
Total - Highly probable: >8 - Probable: 6-8 - Possible: 3-5 - Unlikely: 1-2 - Excluded: <0	

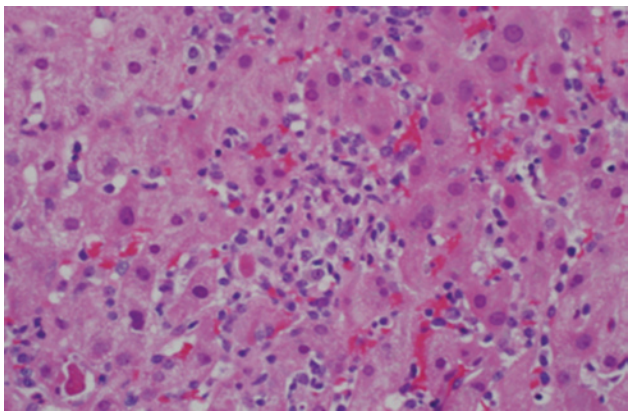

Figure 2. Intermediate power image showing eosinophils consistent with drug injury

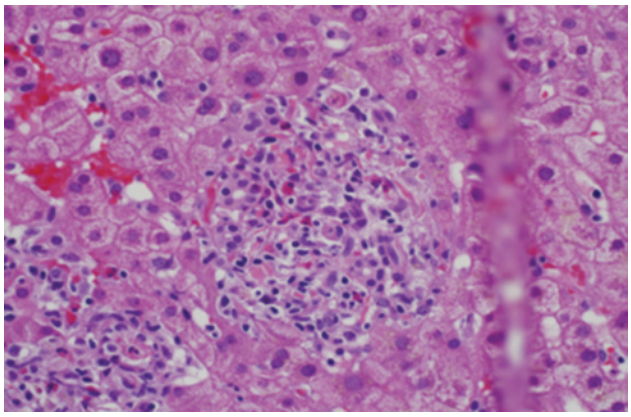

Figure 3. Intermediate power image showing granuloma consistent with drug injury

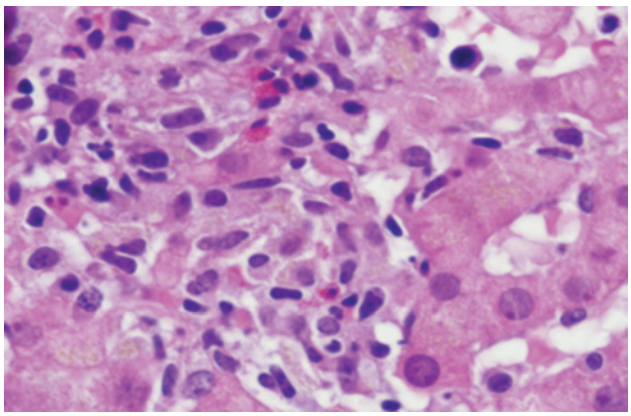

Figure 4. High power image of Zone 3 cholestasis and marked lobular hepatocyte necrosis consistent with drug injury

Although this was not a case of acetaminophen toxicity, N-acetylcysteine was administered given the critical nature of their illness and lack of alternative treatment options. LFTs began to improve immediately following cessation of investigational NSAID and normalized between six and twelve weeks of terminating the investigational drug (Figure 5). They were closely followed at the QMC Liver Center after discharge. Two additional patients were asymptomatic and were referred to the QMC Liver Center after trial investigators noticed increasing LFTs. They also recovered without complication following timely removal of investigational agent.

Given the temporal relationship of presentation to trial participation and improvement upon cessation, age over 55, exclusion of other causes of potential ALF including viral hepatitis, alcoholic hepatitis, and other infections, and knowledge of the hepatotoxic potential of NSAIDs, a diagnosis of DILI was made. The RUCAM-CIOMS scale was used to determine the likelihood of DILI as a diagnosis in these four women. All four women received a score between 6 and 8, corresponding to a "probable" diagnosis of DILI. Patients were not re-challenged with the drug in question to avoid the possibility of further liver damage. Thus, they each had the potential to earn 3 additional points on RUCAM-CIOMS scale if they had experienced worsening of symptoms and LFTs with re-introduction of drug in question. This would have made a diagnosis of DILI "highly probable."

Discussion

Though FDA approved NSAIDs are widely used and report of DILI is rare, it should always be in the differential diagnosis in the clinical setting of acute liver injury. Older women may be at increased risk for NSAID induced liver injury as shown previously and again illustrated in our case series.

While targeting MPGES1 sought to reduce gastric and prothrombotic side effects associated with other NSAIDs, the high incidence of acute liver injury nationwide prompted the sponsor to immediately terminate the trial. High clinical suspicion played a key role in prompt diagnoses and treatment of the patients who were referred to the QMC Liver Center. Nonetheless, it took up to three months for their LFTs to normalize. DILI can quickly deteriorate into fulminate liver failure necessitating liver transplantation if not diagnosed and treated early in the course of disease. RUCAM-CIOMS scoring system and Hy's Law are helpful when considering a diagnosis of DILI and determining the risk of complications. Clinicians should not hesitate to obtain liver biopsy early in the course of the disease as it will aid in establishing diagnosis and will be more technically difficult to obtain when disease progresses and coagulopathy develops. One must keep in mind that biopsy indicates type and degree of liver injury, not etiology (not a specific drug that caused the injury). Prompt removal of the offending agent and supportive treatment remain the corner stone of DILI treatment. There is some data to indicate that acetylcysteine is helpful in other types of DILI and should be considered given relatively benign nature of this therapy.

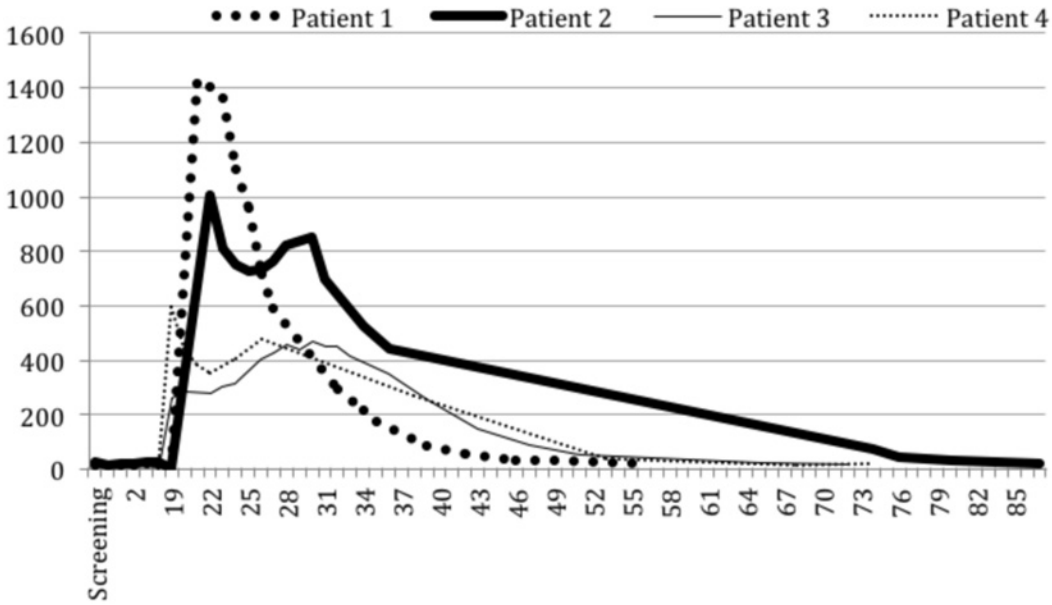

Figure 5. ALT values over time from start of treatment to normalization. Patients 1 and 2 stopped experimental treatment, were admitted, and treated with N-acetylcysteine on Day 19. Patients 3 and 4 stopped treatment on Day 12.

Future research is being directed at possibly identifying individuals susceptible to DILI by specific drugs. NSAIDs are metabolized by the liver's cytochrome P450 system. Various genes encode for members of the cytochrome P450 superfamily of enzymes. It has been hypothesized that allelic variation in one or more members of the P450 superfamily could explain why certain people are more susceptible to NSAID induced liver injury.[2] It is conceivable that the women in our case series were slow metabolizers of the investigational drug, making them susceptible to drug induced liver injury. Pharmacogenetics based investigation of allelic variation of various P450 enzyme polymorphisms coupled with knowledge regarding how various drugs are metabolized could serve as a possible screening method to reduce the number of cases of DILI in the future and represents a topic of current DILI research.[9]

The search remains for the development of a novel and safe target of inflammation. While MPGES1 appears to be a novel target of inflammation, the most recent Phase I trial has failed to prove its safety. As research pursues other enzymatic targets of inflammation, this case demonstrates the need for DILI to remain high on the differential when presented with severe liver dysfunction of unknown etiology.

In conclusion, we have presented a case series of four patients with DILI due to a novel investigational NSAID. Our case report series highlights the potential for NSAID induced hepatic toxicity, the importance of recognition of drug induced liver injury, use of the RUCAM-CIOMS scoring system in aiding diagnosis, and prompt withdrawal of offending agent. Additionally, it calls to attention the need for awareness that early phase clinical trials are being conducted here in Hawai'i and that patients presenting with acute liver failure may have been exposed to an investigational agent with unknown toxicities.

Conflict of Interest

The authors report no conflict of interest.

Acknowledgement

We would like to thank and acknowledge the Queens Pathology Department and Dr. Peter Bryant Greenwood for their contribution to this work.

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Albuminuria as a Marker of Cardiovascular Risk in HIV-Infected Individuals Receiving Stable Antiretroviral Therapy

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Abstract

Albuminuria (urinary excretion of more than 30 milligram of albumin per gram of creatinine) serves as an indicator of microvascular injury, which has been associated with atherosclerosis and cardiovascular disease in HIV-seronegative individuals. Albuminuria has been reported to be prevalent among HIV-seropositive individuals, however, the relationship between albuminuria and risk for cardiovascular disease in this population has not been well-studied. We examined the relationships between albuminuria and parameters of atherosclerosis including carotid intima-media thickness and traditional cardiovascular risk assessment among HIV-seropositive individuals receiving stable antiretroviral therapy. We utilized a cross-sectional baseline data from the Hawai'i Aging with HIV-Cardiovascular Study cohort.

Results: *Data was available on 111 HIV-infected patients (median age of 52 (Q1,Q3: 46, 57), male 86%; diabetes 6%; hypertension 33%; dyslipidemia 50%; median CD4 count of 489 cells/mm^3 (341, 638); HIV RNA PCR < 48 copies/ml of 85%). Eighteen subjects (16.2%) had microalbuminuria, and two subjects (1.8%) had macroalbuminuria. Albuminuria was significantly associated with increased Framingham Risk Score (P=.002), insulin resistance by HOMA-IR (P=.02), diastolic blood pressure (P=.01), and carotid intima-media thickness (P =.04). The correlation between the amount of albuminuria and carotid intima-media thickness remained significant even after adjusting for age, gender, ethnicity, current smoking status, diabetes mellitus, diastolic blood pressure, fasting insulin level, CD4 count, and HIV-RNA viral load.*

Conclusion: *Albuminuria is prevalent among HIV-infected patients receiving stable antiretroviral therapy. It is significantly related to previously defined markers of cardiovascular disease and metabolic syndrome among HIV-infected patients receiving stable antiretroviral therapy.*

Keywords

HIV, albuminuria, CD4 count, HIV viral load, atherosclerosis, aging, cardiovascular disease

Introduction

Albuminuria is recognized to be associated with renal progression in type 1 diabetes. In type 2 diabetes patients, however, albuminuria is a stronger predictor for cardiovascular disease (CVD) than kidney function. Albuminuria has become a marker of early stage of systemic atherosclerosis.[1,2] Meta-analysis studies have revealed that albuminuria is associated with increasing cardiovascular events in high risk populations including patients with diabetes, hypertension, and metabolic syndrome. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recognized albuminuria as a major CVD risk factor.[3] The correlation of CVD appears to be strongly related to the amount of albuminuria, even at levels of albuminuria lower than 30 mg/g.[4] The prevalence of microalbuminuria (30-300 mg of urine albumin per gram of creatinine) varies from 10-30% in diabetic, 5-25% in hypertensive, and 5-10% in the non-diabetic, non-hypertensive population.[5] However, albuminuria has not been well-studied in HIV-seropositive individuals. A previous study reported an 11% rate of albuminuria in HIV-seropositive individuals compared to 2% among control individuals. Several cardiovascular risk factors including insulin resistance and elevated blood pressure were noted to be associated with higher albumin-to-creatinine ratio in HIV-infected patients.[6]

Ultrasonographic imaging of carotid intima-media thickness (cIMT) is a non-invasive method of assessing systemic atherosclerosis. It was used as a surrogate endpoint in several clinical intervention studies,[7,8] with higher levels of cIMT observed among HIV-seropositive individuals. Hsue, et al, suggested that this may be secondary to an interplay between hemodynamic shear stresses and HIV-associated inflammation.[9] We examined the relationships between albuminuria, risks for cardiovascular disease, and carotid intima-media thickness among HIV-seropositive individuals receiving stable antiretroviral therapy using cross-sectional baseline data from the Hawai'i Aging with HIV-Cardiovascular Study cohort.

Methods

Study Population

The Hawai'i Aging with HIV-Cardiovascular Study, a natural history longitudinal study of the role of oxidative stress and inflammation in HIV cardiovascular risk, enrolled 158 HIV-infected adults age ≥ 40 years old, living in the state of Hawai'i. Inclusion criteria included documented HIV-seropositive status and having been on the same regimen of antiretroviral therapy for at least six months. IRB approval was obtained from the University of Hawai'i and all subjects provided informed consent prior to entry into the study.

Clinical Parameters

General medical and HIV-specific histories, and medication history were obtained. Clinical parameters assessed included height, weight, waist-to-hip ratio, blood pressure, and ankle-brachial index. An EKG was obtained. Blood parameters assessed included fasting lipids, glucose and insulin as well as results from an oral glucose tolerance test. The Framingham Risk Score was calculated using ATP III guideline.[10] HIV-specific laboratory measurements included CD4 count and plasma HIV-RNA viral levels.

Urine Albumin

The level of urine albumin was determined by Immunoturbidimetric assay using a Roche/Hitachi MODULAR P analyzer. Albuminuria was defined as urine albumin-to-creatinine ratio (ACR) of more than 30 mg/g, as assessed from random urine collection. Microalbuminuria was defined as urine ACR between 30 and 300 mg/g and macroalbuminuria as urine ACR more than 300 mg/g.[11]

Common Carotid Artery Intima-Media Thickness (cIMT)

cIMT is an ultrasonographic measurement of the thickness of intima-media of the common carotid artery. High-resolution B-mode ultrasound images of the right common carotid artery (CCA) were obtained from each patient using previously described techniques.[12-15] Centralized reading services were provided by the University of Southern California Atherosclerosis Research Unit Core Imaging and Reading Center. A single reader measured the intima-media thickness of the far wall of the distal common carotid artery along a 1-cm length just distal to the carotid artery bulb with automated computerized edge detection.

Statistical Analysis

Differences in clinical and laboratory characteristics between subjects without and with albuminuria were compared using non-parametric Wilcoxon rank test for continuous variables and Chi-squared test for categorical variables. Albuminuria was characterized as both a categorical and a continuous variable. Categorically, albuminuria was defined as ACR of more than or equal to 30 mg/g versus less than 30 mg/g. As a continuous variable, albuminuria including measures below 30 mg/g was normally distributed. The cIMT was logarithmically transformed due to a skewed distribution. Multivariable linear regression analysis was employed to relate cIMT with albuminuria. Multivariable linear regression was adjusted for covariates found to be significant on univariate analysis. A two-sided probability of $P < .05$ was used to determine statistical significance. Statistical analyses were performed using the JMP statistical program (SAS Institute Inc., Cary, NC).

Results

Demographic and baseline clinical characteristics of the 111 participants are detailed in Table 1. The majority of participants were men (86%) and Caucasian (56%) with a median age of 52 years (Q1,Q3: 46,57). Baseline renal function with glomerular filtration rate was 81.9 ml/min (Q1,Q3: 72.8,93.5) by MDRD (Modification of Diet in Renal Disease) formula and was 85.4 ml/min (Q1,Q3: 73.6,96.5) by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. Participants had a median CD4 count of 489 cells/mm^3 (Q1,Q3: 341,638). The majority of participants had undetectable HIV viral load (85%). All participants were receiving highly-active antiretroviral therapy with 75% receiving a tenofovir-based regimen.

The rate of albuminuria in this study group was 18% (20/111), 16.2% (18/111) with microalbuminuria and 1.8% (2/111) with macroalbuminuria. There were significant differences in age, Framingham risk score, diastolic blood pressure, fasting insulin level, HOMA-IR (Homeostatic model assessment index of insulin resistance),[16] and common cIMT between those individuals without and with albuminuria (Table 2). There were no differences in ethnicity, history of diabetes, history of hypertension, body mass index (BMI), systolic blood pressure, Glomerular filtration rate (GFR) by MDRD or CKD-EPI formula, lipid profile, CD4 count, and proportion of subjects receiving a tenofovir-based antiretroviral regimen between groups.

When albuminuria was analyzed as a continuous variable, age, fasting insulin, diastolic blood pressure, HIV-RNA viral load,

Table 1. Demographic and baseline clinical characteristics of 111 participants. Continuous variables as listed a median (Q1, Q3).

Baseline Characteristics	Values, N=111
Age, years	52 (46, 57)
Male gender, n (%)	95 (86)
Ethnicity, n (%)	
Caucasian	62 (56)
Asian and Pacific Islander	23 (21)
African American	5 (5)
Others	21 (19)
Past Medical History	
History of diabetes, n (%)	7 (6)
History of hypertension, n (%)	37 (33)
History of dyslipidemia, n (%)	55 (50)
Current Smoker, n (%)	29 (26)
Framingham score	0.07 (0.04, 0.10)
BMI, kilogram/m2	25.7 (23.7, 28.0)
Waist-hip ratio	0.93 (0.89, 0.98)
GFR	
MDRD, ml/min	81.9 (72.8, 93.5)
CKD-EPI, ml/min	85.4 (73.6, 96.5)
Fasting Lipids	
Total cholesterol, mg/dl	176 (151, 199)
HDL, mg/dl	40 (32, 50)
LDL, mg/dl	108 (83, 127)
Triglyceride, mg/dl	122 (53, 168)
HbA1c, %	5.5 (5.4, 5.7)
Fasting glucose, mg/dl	104.5 (87.5, 135)
Fasting insulin, mg/dl	15.3 (4.2, 33.9)
HOMA-IR	1.37 (0.80, 2.56)
HIV Laboratory Parameters	
Current CD4 count, cells/mm^3	489 (341, 638)
Nadir CD4 count, cells/mm^3	135 (29, 253)
Undetectable viral load, n (%)	94 (85)
Currently Receiving ART	
Tenofovir-based regimen, n (%)	83 (75)

Table 2. Comparison of HIV-seropositive participants with and without albuminuria. Continuous variables as listed a median (Q1, Q3).			
Characteristics	**Patients with Albuminuria (n=20)**	**Patients without Albuminuria (n=91)**	***P*-value**
Age, years	57 (49, 62)	51 (46, 56)	.01
Male gender, n (%)	18 (90)	77 (85)	.52
Ethnicity, n (%)			
Caucasian	13 (65)	49 (54)	.19
Asian and Pacific Islander	3 (15)	21 (23)	
African American	1 (5)	4 (4)	
Others	3 (15)	17 (19)	
Past Medical History			
History of diabetes, n (%)	3 (15)	4 (4)	.11
History of hypertension, n (%)	10 (50)	27 (30)	.11
History of dyslipidemia, n (%)	12 (60)	43 (47)	.33
Current Smoker, n (%)	6 (30)	23 (26)	.78
Framingham Score	0.10 (0.08, 0.16)	0.07 (0.04, 0.10)	.002
BMI, Kilograms/m²	25.9 (22.4, 28.4)	25.8 (23.9, 27.9)	.86
Waist-hip Ratio	0.96 (0.91, 0.99)	0.92 (0.89, 0.97)	.07
Systolic Blood Pressure, mmHg	126 (120, 140)	129 (112, 129)	.05
Diastolic Blood Pressure, mmHg	83.8 (75.3, 83.8)	74 (68, 80)	.01
GFR			
MDRD, ml/min	71.41 (65.92, 95.96)	83.40 (74.42, 93.40)	.10
CKD-EPI, ml/min	72.82 (65.91, 99.57)	86.76 (76.24, 96.49)	.08
Lipids			
Total cholesterol, mg/dl	184 (144.3, 260)	175 (153, 195)	.22
HDL, mg/dl	36 (32, 53)	41 (32, 50)	.66
LDL, mg/dl	119 (73.8, 169)	107 (84, 125)	.44
Triglyceride, mg/dl	139 (94, 198.8)	116 (82, 166)	.21
HbA1c, %	5.7 (5.4, 5.9)	5.5 (5.3, 5.7)	.43
Fasting glucose, mg/dl	91.5 (82.5, 100.3)	88 (81, 94)	.25
Fasting insulin, mg/dl	10.1 (5.1, 14.8)	5.9 (3.7, 10.1)	.02
HOMA-IR	2.54 (0.97, 3.47)	1.19 (0.79, 2.19)	.02
HIV Laboratory Parameters			
Current CD4 count, cells/mm*	470 (394.3, 545.8)	502 (333, 660)	.57
Nadir CD4 count, cells/mm*	92 (35.3, 193.8)	160 (27, 266)	.40
Undetectable viral load, n (%)	17 (85)	77 (84.6)	.96
HIV viral load, copies/mm*	69 (53, 77)	59 (50, 282)	.94
Currently on ART			
Tenofovir-based regimen, n (%)	17 (85)	66 (73)	.39
cIMT, mm	0.83 (0.70, 0.91)	0.70 (0.65, 0.81)	.04

*HIV viral load among participants with a detectable HIV viral load

Table 3. Multivariable regression model of common carotid intima-media thickness*			
Variable	**β**	**SE**	***P*-value**
Age, years	0.000990	0.001061	.3540
Gender, female	- 0.013163	0.011208	.2445
Ethnicity	0.003819	0.002743	.1684
Smoking status, current	0.006758	0.009304	.4702
Diabetes	0.011243	0.024816	.6520
CD4 count, cells/mm^3	0.000602	0.000731	.4138
HIV-RNA viral load, copies/ml	0.000034	0.000011	.0027
Fasting insulin, mg/dl	- 0.000408	0.000469	.3874
Diastolic blood pressure, mmHg	0.000671	0.000934	.4753
Albuminuria, mg/g	0.000092	0.000045	.0451

*Dependent variable was log (cIMT)

and albuminuria all significantly correlated with log (cIMT) by univariate analysis. The correlation between the amount of albuminuria and log (cIMT) remained significant even after adjustment for age, gender, ethnicity, current smoking status, diabetes mellitus, CD4 count, HIV-RNA viral load, fasting insulin, and diastolic blood pressure (Table 3).

Discussion

In diabetic patients, microalbuminuria is recognized as one of the earliest indicators for diabetic nephropathy. The association between microalbuminuria and cardiovascular disease is also well recognized in the general population. Microalbuminuria is a key indicator of a need for intensified treatment with angiotensin converting enzyme inhibitor or angiotensin II receptor antagonist. In HIV-seropositive individuals, the data on albuminuria and risk for cardiovascular disease is limited and not well understood. Previous studies suggested higher rate of cardiovascular disease and higher rate of albuminuria in this population. Among a cohort of women with HIV infection, 39% of African-American and 25% of Caucasian women had clinically significant albuminuria.[17] These levels of albuminuria have subsequently been demonstrated to be associated with poorer outcomes including an increased risk of hospitalization and mortality.[18,19] From our study, we found the rate of albuminuria among HIV-seropositive individuals receiving stable antiretroviral therapy was 18%.

Several hypotheses have been proposed to explain mechanisms that can cause an increase in albuminuria in the HIV-seropositive population. Albuminuria has been hypothesized to be due to HIV directly damaging the glomeruli causing HIV nephropathy (HIVAN), to deposition of immune complexes generated as an immune response to the HIV, to opportunistic infections that lead to glomerular damage,[20] and/or to the side effects of highly-active antiretroviral therapy that may directly affect the kidneys such as tenofovir or cause higher rates of hyperlipidemia and an increased tendency towards atherosclerotic change.

Our study found associations between albuminuria and markers of subclinical atherosclerosis and CVD such as Framingham risk score, HOMA-IR, and cIMT in our HIV-seropositive participants. This data also supports the finding from previous studies that found associations between albuminuria in HIV-seropositive individuals and insulin resistance, and elevated systolic blood pressure.[4] Our study is limited by its cross-sectional nature and lack of a HIV-seronegative control. Our results demonstrate an association between albuminuria and clinical and laboratory markers of subclinical atherosclerosis, while correlation indicates that future prospective studies relating albuminuria and CVD clinical outcomes are an important area for future investigation.

Conclusion

Albuminuria is prevalent among HIV-infected patients receiving stable antiretroviral therapy. It is significantly related to cardiovascular and metabolic parameters among HIV-infected patients receiving stable antiretroviral therapy. As albuminuria increases morbidity and mortality, routine urine albumin assessments as part of HIV care, particularly among patients with CVD risk factors, are warranted.

Conflict of Interest

The authors report no conflict of interest.

Disclosure Statement

- Dr. Cecilia M. Shikuma has received research support from NIH (U54MD007584, U54NS43049, P20RR011091, and R01HL095135), Pfizer, Merck, and Gilead Pharmaceuticals, and has served on an advisory board for Glaxo Smith Kline.
- Dr. Beau K. Nakamoto has received research support from NIH (U54MD007584).
- Dr. Kalpana J. Kallianpur has received research support from NIH (U54MD007584, U19MH081835, U54MD007584).
- Dr. Dominic C. Chow has received research support from NIH (K23HL088981).
- No other authors reported any financial disclosures.

Acknowledgement

We thank our study participants and community physicians for their roles in this study.

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Association of Vitamin D Deficiency with Functional Disability and Chronic Diseases Among Veterans Entering a Nursing Home

Anna Tamai MD; Gotaro Kojima MD; Kamal Masaki MD; James Epure MD; Craig China MD; G. Webster Ross MD; Helen Petrovitch MD; and Marianne Tanabe MD

Abstract

Background: Nursing home residents are at high risk of vitamin D deficiency. There has been only one previous study about vitamin D status on admission to the nursing home, and limited data are available about associations with functional disability and chronic diseases.

Methods: Data were collected by retrospective chart review of electronic medical records and Minimum Data Set (MDS) for all veterans admitted to a VA nursing home in Honolulu, Hawai'i, between January 2011 and June 2012. All veterans had a comprehensive geriatric assessment and measurement of serum 25-hydroxyvitamin D level within 7 days of admission. Females, hospice patients, vitamin D supplement users, and those transferred from other nursing homes were excluded, leaving a final analytic sample of 104 patients. Vitamin D deficiency was defined as serum 25-hydroxyvitamin D level <20 ng/mL. Baseline data collected included age, ethnicity, BMI, functional disability (mobility, bathing, dressing, toileting, continence, and feeding) and prevalent chronic diseases to study cross-sectional associations of vitamin D deficiency using logistic regression.

Results: Prevalence of vitamin D deficiency on admission to the nursing home was 49.0% (51/104) among male veterans not taking supplements. The mean age was 70.6 years (range 35-95), with ethnicity as follows: 51 (49.0%) White, 34 (32.7%) Asian, and 6 (5.8%) Black. In multiple logistic regression models adjusted for age, ethnicity and BMI, vitamin D deficiency was significantly associated with number of ADL disabilities (OR = 1.36 for each increase in ADL disability, 95%CI = 1.03-1.78, $P = .03$) and prevalent diabetes (OR = 2.99, 95%CI = 1.12-7.99, $P = .03$). When all six ADL disabilities were entered separately into the multivariate logistic regression model instead of total number of ADL disabilities, only the disability in feeding (OR = 4.74, 95%CI = 0.97-23.23, $P = .05$) and prevalent diabetes (OR = 2.92, 95%CI = 1.03-8.24, $P = .04$) remained significant. There were no significant associations between vitamin D deficiency and prevalent hypertension, hypercholesterolemia, coronary artery disease, stroke, cancer, depression or dementia.

Conclusions: Almost half the male patients entering a nursing home in Hawai'i had vitamin D deficiency. A high number of ADL disabilities, disability in feeding, and prevalent diabetes were independently associated with vitamin D deficiency. Future studies should focus on targeting these patients for screening and intervention with supplementation to possibly prevent adverse health outcomes of vitamin D deficiency.

Conflict of Interest

The authors report no conflict of interest.

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Factors Associated with 30-Day Hospital Readmission Among Nursing Home Residents

Gotaro Kojima MD; James Davis PhD; Kamal Masaki MD; and Christina Bell MD

Abstract

Background: Hospital readmissions within 30 days are increasingly targeted as a quality parameter. Frail nursing home patients are at high risk for hospitalization. The purpose of this study was to examine baseline prevalent chronic diseases associated with hospital readmission within 30 days.

Methods: We collected data on demographics and prevalent diseases for all patients admitted to one hospital-affiliated nursing home between January 2003 and December 2006, with follow-up data on pneumonia episodes and hospitalizations through June 2011. Multivariable logistic regression models identified baseline prevalent chronic diseases associated with hospital readmission within 30 days of nursing home admission.

Results: Of 238 patients (mean age 83.4, range 45-103) admitted to the nursing home, 156 (65.5%) originally came from hospitals, 54.6% were female, 92.4% were Asian, 43.6% were on Medicaid, and 76.5% were first admitted for intermediate care and 23.5% for skilled nursing care. Although recent pneumonia was the factor most strongly associated with hospital readmission (OR = 14.5, $P < .0001$), in the model without pneumonia, chronic diseases associated with 30-day hospital readmission included pulmonary disease (OR = 2.2, 95%CI = 1.1-4.3, $P = .019$) and congestive heart failure (OR = 1.8, 95%CI = 1.0-3.4, $P = .055$). There were no significant associations between hospital readmission and myocardial infarction, stroke, cancer, diabetes, and dementia.

Conclusions: Among nursing home patients, although recent pneumonia was the strongest risk factor for 30-day hospital readmission, those with baseline chronic pulmonary disease and congestive heart failure were at especially high risk for hospital readmission within 30 days of nursing home admission. These patients may benefit from care focused on preventing hospital readmissions.

Conflict of Interest

The authors report no conflict of interest.

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Prevalence and Factors Associated with Percutaneous Endoscopic Gastrostomy (PEG) Tube Feeding Among Nursing Home Patients

Anna Tamai MD; Christina Bell MD; James David PhD; Karen Lubrimir MD; and Kamal Masaki MD

Abstract

Background: Unnecessary percutaneous endoscopic gastrostomy (PEG) tube feeding in nursing homes (NH) is a growing concern and an important area of research. Hawaii has one of the highest rates of PEG tube feeding in NH patients in the US, yet has lower rates than many NHs in Asian countries. We examined prevalence and factors associated with PEG tube feeding in NH patients in Hawaii.

Methods: We conducted an observational cohort study of all patients admitted between 2003 and 2006 to an urban 180-bed hospital-affiliated NH in Honolulu, Hawaii. Data were collected from time of admission until discharge or death through 6/30/2011, from electronic and paper medical records and Minimum Data Set (MDS). Data included demographic characteristics, baseline medical conditions, functional status, cognitive status and code status. We created a Charlson Comorbidity Index (CCI) score based on baseline medical conditions on admission, and a disability score (ADL score) and Cognitive Performance Score (CPS) using baseline MDS data. Multivariable logistic regression was used to analyze factors associated with PEG tube feeding.

Results: Of 238 NH patients aged 45-104 years (mean 83 years), 35 (14.7%) had PEG tube feeding. Of the NH cohort, 130 (54.6%) were female, 218 (92.3%) were Asian, 123 (51.9%) had a prior stroke and 163 (72%) had dementia based on CPS score. Among the 35 PEG tube fed patients, 23 (66%) had PEG placement prior to NH admission, 12 (34%) had PEG placement after NH admission, and 26 (74%) patients had PEG tube feeding until death or the end of follow-up (61 days to 8.4 years, mean 2.4 years). Prior stroke was associated with increased likelihood of PEG tube feeding (aOR = 2.52, 95%CI = 1.03-6.17, *P* = .04); with borderline increased likelihood for high comorbidity index (aOR = 2.21, 95%CI = 0.89-5.52, *P* = .09) and high ADL disability score (aOR = 2.03, 95%CI = 0.87-4.73, *P* = .10). DNR status was inversely associated with PEG tube feeding (aOR = 0.31, 95%CI = 0.11-0.85, *P* = .02). Age, dementia, Medicaid status, previous speech or physical therapy, and weight loss were not significantly associated with PEG tube feeding.

Conclusion: In this predominantly Asian-American NH cohort with high prevalence of PEG tube feeding, prior stroke was strongly associated with PEG tube feeding, while dementia was not. Further study is needed to examine ways to identify and reduce unnecessary tube feeding in this population.

Conflict of Interest

The authors report no conflict of interest.

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Computed Tomography Abdomen/Pelvis in the Emergency Department: Can Clinical Parameters Guide the Appropriate Use of Imaging?

Taylor Choy MD and Hyo-Chun Yoon MD, PhD

Abstract

Introduction: Computed tomography (CT) has revolutionized the management of abdominal pain by providing swift and effective diagnosis of abdominal pathology. As a result, CT utilization has dramatically increased over the past decade, particularly in emergency departments. This is concerning, both from a cost perspective, and also because of radiation exposure. This study aims to assess whether it is possible to create an appropriateness criteria for patients with nontraumatic abdominal pain by attempting to correlate clinical parameters with patients with positive CT results.

Materials and Methods: We identified 300 consecutive abdominal-pelvic CT scans of patients age 60 or younger presenting to the emergency department with nontraumatic abdominal pain. The medical records of the patients were reviewed for the following: age, gender, pain location, past medical history, associated symptoms, physical findings, and WBC count. We eliminated 2 cases in which a complete blood count was not obtained. From the chart analysis, we extracted six variables which are commonly described and utilized in clinical evaluation of abdominal pain; nausea/vomiting, fever, age > 35, gender, peritoneal signs, and leukocytosis. This information was used to form a predictive model that we examined by logistic regression analysis.

Results: Of the 298 patients in the study, 150 (50.3%) had a CT scan showing intraabdominal pathology that could explain abdominal pain. "Significant positive results on CT" were found in 106 patients (35.6%), indicating that the CT finding would directly affect management of the patient; including 29 cases of appendicitis, 17 of diverticulitis, 10 of pancreatitis, 14 of small bowel obstruction, and 8 of urinary stones. Positive CT scans correlated positively with age > 35 (OR 2.67, 95% CI 1.60-4.45) and leukocytosis (OR 3.17, 95% CI 1.90-5.29). Clinically significant CT results (ie, appendicitis, diverticulitis, SBO, pancreatitis, etc.) correlated with age > 35 (OR 2.88, 95% CI 1.67-4.96), male gender (OR 2.095, 95% CI 1.24-3.53), peritoneal findings on exam (OR 2.56, 95% CI 1.07-6.11), and leukocytosis (OR 2.56, 95% CI 1.51-4.32).

Discussion: Predicting CT results in patients with abdominal pain based on clinical parameters is a complex issue. However, our analysis produced four variables which correlate positively with significant findings on CT. Our model predicts that a female patient, whose age is equal to or below 35, with a normal white count, and who has no peritoneal findings on exam is 70.8% less likely to have a significant positive finding on CT than the average patient in our study.

Conflict of Interest

The authors report no conflict of interest.

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Is the Rising Incidence of Non-Tuberculous Mycobacteria (NTM) in Respiratory Specimens from the United States Associated Pacific Islands (USAPI) Associated with Respiratory Disease?

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Abstract

Introduction: The United States Associated Pacific Islands (USAPI) comprise six jurisdictions, which have formal relationships with the United States. Our laboratory has provided culture and anti-mycobacteria susceptibility testing (AST) for the USAPIs for MTB, but have also identified NTM in the process. NTM are frequently grown from these samples, but there has been no data on their incidence to date. The objective of this epidemiological study is to access incidence and provide a baseline for further study on the association of NTM with respiratory disease.

Methods: Data on all respiratory specimens submitted for TB culture from August 2007 to December 2011 was extracted from a comprehensive database. Cases were identified if a subject had at least one NTM positive respiratory culture. Specimen integrity was carefully monitored in the collection process and may account for an absence of NTM recovery in multiple specimens. Multinomial regression was used to determine if the rates of NTM were increasing in the USAPIs. Rates of TB were used for comparison as rates of sample collection increased during the entire study period. Subjects with negative sputum sample(s) were used as the reference category.

Results: A total of 15,811 respiratory specimens from 5,804 patients were submitted for AFB culture and AST from August 2007 to December 2011. A total of 998 patients had at least one AFB positive sputum culture, where 67.5% (675) were positive for TB and 32.3% (323) were positive for NTM. A total of two patients had both TB and an NTM isolated from the respiratory samples collected from them on the same date. The odds of a patient with a positive NTM respiratory culture compared to the previous year was 1.63 ($P < .001$). In comparison, the odds of a patient with a positive TB respiratory culture compared to the previous year was not statically significant (OR: 0.98, $P = .69$).

Conclusions: The incidence of patients with positive NTM respiratory cultures in the USAPI is rising, which may be of medical concern in contributing to respiratory disease along with TB. Further studies will be required to ascertain if these cases represent actual respiratory disease, that requires multiple, quality specimens showing NTM positive respiratory cultures associated with clinical and radiological correlation supporting NTM disease.

Conflict of Interest

The authors report no conflict of interest.

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Is Ace Inhibitor/Angiotensin-Receptor Blocker Associated with Acute Kidney Injury Post-Coronary Artery Bypass Grafting in a Mixed Ethnicity Population in a Community-Based Hospital in Hawai'i?

Ma Clarisse Toledo MD; Ekamol Tantisattamo MD; Dorothy Shigaki MD; and Roland C.K. Ng MD

Abstract

Background: Acute kidney injury (AKI) after coronary artery bypass grafting (CABG) is common, and preoperative risk factors are well-established. Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker (ACEI/ARB) therapy has shown cardio-protective effects in coronary artery disease patients. However, there were concerns that preoperative use of ACEI/ARBs in cardiac surgery could cause extreme vasodilatation in the post-operative period thereby posing a risk to patients for the development of AKI post-surgery. The association between therapy with ACEI/ARB and acute kidney injury after cardiac surgery remains controversial. In this study, we aim to determine whether the preoperative use of ACEIs/ARB is associated with AKI post CABG in a mixed ethnicity population in Hawaii.

Methods: This was a retrospective study of 101 adult patients undergoing CABG between January 2009 and December 2011 in a single community-based hospital in Honolulu, Hawai'i. Baseline data collection included patients' characteristics, peri-operative variables, and postoperative complications. The incidence of AKI was likewise obtained. Postoperative AKI was defined as an increase of 0.3 mg/dL or more in the serum creatinine from baseline in the first 48 hours after surgery.

Results: Of the 101 patients, AKI occurred in 34 patients (34%). The incidence of stage 1 and 2 AKI was 94% and 6%, respectively. There was no incidence of stage 3 AKI. Of all of the variables, only advanced age (≥=65 years old) (P=.0357) and preoperative cardiac catheterization (P=.0024) were significantly associated with an increased incidence of AKI. Otherwise, there was no significantly increased incidence of AKI with the following variables: gender (P=.3147), ethnicity (P=.4198), those who underwent both CABG and valve repair (P=.2611), insulin-dependent diabetes mellitus (P=.714), hypertension (P=.2539), hyperlipidemia (P=.805), COPD (P=.6011), preoperative use of ACEI/ARB (P=.6738), furosemide (P=.223), postoperative use of aspirin (P=.1598), and postoperative atrial fibrillation (P=.4367). Japanese accounted for the majority of the population (51%), followed by Filipino (18%), mixed ethnicity (8%), and others (23%).

Conclusions: The incidence of AKI post CABG in this mixed ethnicity population in Hawai'i is not different from other published studies. In addition, ACEI/ARB therapy is not associated with an increased risk of AKI post CABG, and our study suggests that preoperative discontinuation of ACEI/ARB may not be warranted.

Conflict of Interest

The authors report no conflict of interest.

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The European System for Cardia Operative Risk Evaluation (Euroscore) II as a Predictor of Prolonged Extubation in Patients Undergoing Valvular Surgery

Chunrong Lin MBBS; Jacqueline King MD; Jamie Rubin MD; and Samuel Evans MD

Abstract

Introduction: The EuroSCORE II was updated from the EuroSCORE I and validated this year as a predictor for in-hospital mortality after cardiac surgery. The EuroSCORE I was previously shown in multiple studies to be a good predictor of delayed extubation in patients undergoing coronary artery bypass graft (CABG) surgery. In contrast, very few studies have been conducted on predictors of delayed extubation in patients undergoing valvular surgery. Identifying risk factors and predictors of prolonged intubation in patients undergoing valvular surgery will allow clinicians to address any modifiable risk factors, and optimize a high-risk patient's chances of a favorable outcome. The aim of this study is to evaluate the newly developed EuroSCORE II as an indicator for prolonged extubation following valvular surgery. The most common causes of delayed extubation in patients undergoing valvular surgery were also tabulated and analyzed.

Methods: We conducted a retrospective chart review on all patients in Queens Medical Center (QMC) from 1/1/2011 to 12/31/2011 who underwent any form of valvular surgery, either as a single procedure or in combination with another cardiothoracic procedure. The factors for patients who were intubated post surgery for 6 hours or more were identified and analyzed. Statistical analysis of the EUROscore as a predictor for the duration of intubation was performed.

Results: A total of 186 patients with a median age of 65, (39.8% females) were found to have had valvular surgery during the time period specified for our study. Forty-two (22.6%) patients were extubated within 6 hours, which is the definition of early extubation, in most studies. Strictly valve procedures comprised 66% with the rest being combinations (including CABG and aortic dissection repair). Procedures involving the aortic valve comprised 59%, involving the mitral valve, 46%; involving the tricuspid valve, 10% involving the pulmonary valve, 2%. Minimally invasive procedures were 7%. The most common causes of delayed extubations were hypoxia and bleeding. Statistical analysis of the EuroSCORE II showed that it correlated well with extubation times ($P < .01$).

Conclusion: The majority of the patients undergoing valvular surgery in QMC are not extubated within the recommended time frame. The EuroSCORE II is a good predictor for prolonged extubation in patients following valvular surgery and may be useful in identifying patients at high risk for prolonged extubations, allowing clinicians to mitigate any modifiable risk factors in this group of patients.

Conflict of Interest

The authors report no conflict of interest.

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mTOR is Localized to Both the Mitochondria and Cytosol at Comparable Levels in the Heart

Genia Taitano MPH; Toshinori Aoyagi PhD; and Takashi Matsui MD, PhD

Abstract

Introduction: Recently our study using cardiac-specific transgenic mice (Tg) reported that cardiac mechanistic target of rapamycin (mTOR), a key downstream molecule in insulin signaling, suppresses myocardial cell death in both in vivo and ex vivo ischemia-reperfusion (I/R) injury. Previous reports suggest that mitochondria are the center of cardiomyocyte cell death subsequent to I/R injury. Therefore, we hypothesized that mTOR is co-localized with key molecules that contribute to mitochondrial meditated cell death. In this study, we explored the physical relationship between mTOR and the mitochondria in the heart.

Methods: Hearts were harvested from 12 week-old mTOR-Tg and littermate control wild-type (WT) mice. Ventricular cardiac muscle was homogenized and membrane fractions were isolated serially with different g-forces. Centrifugation at 750g yielded the nuclear fraction; 12,500g the heavy-mitochondrial (HM) fraction (presumed to contain larger protein-complexes associated with the mitochondrial membrane); 100,000g the S100 (presumed to contain smaller protein-complexes associated with the mitochondrial membrane); the cytosolic fraction was obtained from the supernatant of the S100 pellet. Samples from the fractions were subjected to Western blot analysis to identify proteins, including mTOR. Upwards of three independent experiments were completed.

Results: Immunoblotting for the Voltage-Dependent Anion Channel (VDAC) and an anti-apoptotic protein Bcl-xL, both mitochondrial proteins, confirmed that the HM and S100 fractions, but not cytosolic fraction, contain similarly substantial amounts of mitochondrial proteins. No difference in VDAC and Bcl-xL expression was observed between mTOR-Tg and WT mice. Hemagglutinin (HA), a marker protein tagged to mTOR in mTOR-Tg mice, was expressed in varying degrees in all membrane fractions. Interestingly, the expression level of HA was highest in S100 and 6 fold greater than the HM fraction ($P<.01$). Anti-mTOR blotting showed that mTOR was present in both mitochondrial fractions of both WT and mTOR-Tg mice, with the densest bands again attributed to S100. mTOR expression in WT S100 was 4 fold greater than that of WT HM fraction ($P<.001$). Although there was no statistically significant difference, total mTOR in both WT and mTOR-Tg mice was dominantly expressed in S100 compared to the cytosolic fraction. mTOR expression in mTOR-Tg S100 was 1.5 times that of WT S100 ($P<.01$) and highest overall.

Conclusion: This study demonstrates that mTOR is localized in the mitochondria, particularly with smaller protein-complexes associated with the mitochondrial membrane, in addition to the cytosol. Smaller mitochondrial protein-complexes are known to be composed of critical proteins involved in cell death regulation. mTOR may interact with these proteins to limit or prevent cell death in the heart. We are pursuing research to uncover the role of cardiac mTOR in mitochondria-mediated cell death.

Conflict of Interest

The authors report no conflict of interest.

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Colonic Angioectasia Related Hemorrhage: The Importance of Evaluation During Active Bleeding

John Bonnes Jr. DO and Jeffrey Laczek MD

Abstract

Introduction: Colonic angioectasia is a common source of lower gastrointestinal bleeding and can be challenging to identify when active bleeding is not present. We present a case that illustrates the utility of evaluating patients with suspected angioectasia-related hemorrhage during episodes of active bleeding.

CaseReport: A 79-year-old woman on chronic anticoagulation secondary to mitral valve replacement presented with recurrent lower gastrointestinal bleeding over the past three years. She had recurrent episodes of hematochezia in 2009 during which no source was identified despite multiple upper and lower endoscopies. A tagged red blood scan showed active hemorrhage in the ascending colon. Angiography showed non-bleeding angiodysplasia in the cecum and ascending colon and the ascending branch of the right colic artery was prophylactically embolized. She had a recurrent episode of hematochezia in 2010 and no source was identified on EGD, colonoscopy or wireless capsule endoscopy. In 2012, she developed recurrent hematochezia associated with a drop in her hemoglobin level from 10.8g/dL to 6.2g/dL over a two-week period. Her hemodynamics remained normal and she was admitted to our facility. She received a blood transfusion and then underwent colonoscopy while still actively bleeding. Active bleeding was seen in the ascending colon adjacent to which was a very subtle angioectasia which was treated with argon plasma coagulation. She had no further bleeding during her hospital stay.

Discussion: Direct visualization during colonoscopy is the preferred method to diagnose colonic angioectasia and these lesions often have a distinctive "coral reef" appearance. However, as the images in this case show, the appearance of colonic angioectasia can be subtle with the aberrant vasculature almost indistinguishable from normal vascular patter of the colonic mucosa. Performing colonoscopy during active angioectasia-related bleeding greatly helps to identify and treat these lesions. The management of patients on anticoagulation with obscure gastrointestinal hemorrhage is very challenging. In these patients, the typical management of lower gastrointestinal hemorrhage involves delaying endoscopy until the patients anticoagulation is reversed. This management strategy is very appropriate for unstable patients, patients with undifferentiated lower gastrointestinal bleeding or suspected diverticular bleeding. However, stable patients with suspected angioectasia-related hemorrhage may be better served with an expedited evaluation while their bleeding is ongoing.

Conflict of Interest

The authors report no conflict of interest.

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Post-Transplant Opportunistic Infection: Case of Mycobacterium Haemophilum Masquerading as Leprosy in a Renal Transplant Patient

Nathanial Copeland MD; Tomas Ferguson MD; Troy Denunzio DO; and Navin Arora DO

Abstract

Introduction: Immunosuppression following solid organ transplantation (SOT) predisposes patients to the development of opportunistic infections that manifest in many ways including cutaneous infection. Skin lesions in immunosuppressed patients have a broad differential including both infectious and non-infectious etiologies. Skin infections by mycobacteria are relatively rare and most are due to nontuberculous mycobacterium (NTM). One such NTM, Mycobacterium haemophilum, is generally reported in opportunistic skin infections often associated with water exposure. Very rarely, M. leprae also has been reported as a cause of opportunistic skin infections in SOT recipients. Both pathogens may be difficult to distinguish both clinically and pathologically, but culture can distinguish between the two because M. haemophilum will grow and M. leprae will not. We present a case of M. haemophilum cutaneous infection in a renal transplant recipient that was initially felt to be due to M. leprae based on biopsy appearance.

Case Report: A 67-year-old Asian man with a history of renal transplant in 2006 presented to an outside facility with a 4 month history of swelling and rash over his right lower extremity. Examination revealed multiple non-pruritic, painless, erythematous plaques and edema over the right residual limb. Treatment with anti-fungal cream was unsuccessful and steroid cream resulted in worsening of rash. Biopsy showed tuberculoid granulomatous dermatitis with no visualized acid fast bacilli (AFB) but neuronal invasion that was concerning for leprosy. He was referred to the Infectious Disease service. The patient's history was also significant for DM, PVD status post right below the knee amputation, and travel or residence in Thailand, Vietnam, and Panama. Patient had been on immunosuppression since 2006 with cyclosporine, mycophenolate, and low dose prednisone. Due to the concern for leprosy, a tissue sample was obtained at our facility for pathology and AFB culture. Biopsy was notable for granulomatous dermatitis and presence of AFB consistent with borderline tuberculoid leprosy. Culture, however, was positive for AFB and final identification revealed M. haemophilum by PCR. Patient was treated initially with clarithromycin then ciprofloxacin was added based on results of susceptibility testing. The patient has had a good clinical response with significant improvement of the rash.

Discussion: NTM are known to cause skin infections in SOT patients. M. leprae is a very rare pathogen whereas other NTM such as M. haemophilum are more common. Nerve involvement is a common feature of M. leprae and is considered to be highly suggestive of leprosy in the appropriate clinical setting. This case was unique as the initial biopsy showed neuronal invasion, leading to the suspicion for leprosy, but the culture subsequently grew M. haemophilum. This is the first known case describing neuronal invasion caused by M. haemophilum.

Conflict of Interest

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Chronic Inflammatory Demyelinating Polyneuropathy with Reversible Dementia: A New Clinical Entity?

Christine Dorman DO and Jorge Samaniego MD

Abstract

Introduction: Classic chronic inflammatory demyelinating polyneuropathy (CIDP), an acquired demyelination of peripheral nerves and nerve roots presents with symmetric motor and sensory involvement, weakness in proximal and distal muscles, globally diminished or absent reflexes, painful dysesthesias, and back pain with no brain involvement. In this case, a highly functional lawyer presents with reversible dementia and motor and sensory symptoms consistent with CIDP. This case may represent a new clinical entity of CIDP with reversible dementia.

Case Report: A 60-year-old man presented with progressive weakness, and cognitive dysfunction in the form of dementia over the last 8 weeks. Sensory and motor weakness continued to progress affecting upper and lower extremities with both proximal and distal muscle groups to the point where the patient was unable to move without assistance. The patient had word finding difficulty, short-term memory impairment, and was disoriented, despite his comprehension being intact. Initial Montreal Cognitive Assessment (MoCA) was 12/30. Initial neurologic exam was notable for muscle strength 3/5, globally depressed deep tendon reflexes. Lumbar puncture revealed elevated protein with no pleocytosis and no serum paraprotein. EMG/NCS demonstrated mixed sensorimotor axonal and demyelination peripheral polyneuropathy. CIDP was diagnosed based on clinical history according to Koski criteria. He was started on a 5-day treatment of IVIG, after which he had marked cognitive improvement after just one dose and improvement in weakness after the second dose of IVIG. Three weeks after IVIG treatment, the patient's cognitive function was back at baseline with MoCA score 29/30; no further word finding difficulty, and no short term memory impairment. At discharge, the patient's weakness had significantly improved to the point where he was able to walk with only the aid of a walker. His neurologic exam had improved as well as his muscle strength 4/5 and 2/4 deep tendon reflexes. Left sural nerve biopsy would eventually reveal moderate peripheral neuropathy with axonal degeneration, moderate loss of large and small myelinated nerve fibers, confirming diagnosis of CIDP.

Discussion: CIDP encompasses several different variants, including Lewis-Sumner syndrome, distal acquired demyelinating sensory neuropathy, sensory predominant CIDP among other variants. However, none of the variations of CIDP have a reversible cognitive impairment component. Patient met diagnosis of CIDP according to Koski criteria, as he had chronic polyneuropathy progressive for at least 8 weeks with no serum paraprotein, no genetic abnormality, and symmetric exam revealing weakness in all four limbs and proximal weakness in both lower extremities. Potentially, the patient could have had simultaneous diagnosis of dementia and CIDP, but the marked improvement in cognitive function after just one dose of IVIG makes that theory unlikely. PubMed search yielded no single case of CIDP with supratentorial manifestations in a patient with normal brain MRI. This case may represent a new clinical variant: CIDP with cognitive impairment.

Conflict of Interest

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Knowledge and Perceptions Regarding Community-Acquired Staphylococcal Infections Among Health Care Workers in Hawai'i

Brandyn S. Dunn MPH; Alan Katz MD MPH; Eric Hurwitz PhD, and Alan Tice MD

Abstract

Introduction: Since the early 1990s, national rates of methicillin-resistant Staphylococcus aureus (MRSA) infections have increased dramatically. Initially identified in health care settings, community-acquired MRSA is now a major public health concern. With Hawai'i's strikingly high incidence and prevalence of MRSA infections, a high level of knowledge and awareness among health care workers is essential to successfully controlling this evolving epidemic.

Methods: Health care and related workers were surveyed to assess their knowledge and perceptions about staphylococcal and MRSA infections. Knowledge was estimated by demonstrated ability to correctly identify risk factors including diabetes, obesity, pets, and seawater exposure as well as understanding the seriousness of antibiotic resistance. Perceptions were estimated by demonstrated awareness of the severity and elevated incidence and prevalence of *S. aureus* and MRSA infections.

Results: This study identified that occupation (advance clinical practitioner, nurse, public health professional, athletic trainers, and non-medical workers) as well as work location (community vs hospital) influence knowledge and perceptions regarding the epidemiology, severity, and risk factors of *S. aureus* and MRSA infections. Additionally, despite a well-documented global crisis with antibiotic resistance, Hawai'i's community health care workers were less inclined to correctly identify the threat of antibiotic resistance as compared to their hospital-based colleagues.

Conclusion: Trends were observed in knowledge and perceptions with level of medical education. Differences were also noted according to work location. Overall, health care and related workers in the community were less likely to understand basic principles associated with *S. aureus* infections as well as misperceive this imminent threat. These findings provide compelling evidence for focused educational interventions targeting community health care and related workers to improve awareness of staphylococcal infections in order to successfully address and combat this emerging epidemic.

Conflict of Interest

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Ten Year Outcomes of Percutaneous Coronary Intervention in a Low Volume Military Treatment Facility

Emilio Fentanes MD and Thomas Wisenbaugh MD

Abstract

Background: Quality assurance of a percutaneous coronary intervention (PCI) program is particularly important when the center volume of procedures is low (<400/yr).

Methods: We searched for predictors of 30-day and long-term incidence of stent thrombosis, myocardial infarction, need for repeat revascularization, and death from any cause for all PCIs performed at Tripler Army Medical Center from January 2002 through June 2012. The New York State Registry (NYSR) regression model was used to compute expected mortality rate based on patient risk factors. Review of electronic medical records, phone, and mail correspondence was used for follow-up. Long-term results were benchmarked against several large registries.

Results: PCIs were performed 929 times in a total of 795 patients, for an average PCI volume of 88/yr. Follow up data was obtained on 99.8% of the patients at 30 days, with a median follow-up of 59 months. Eighteen deaths occurred prior to hospital discharge or during the first 30-days after PCI, for an unadjusted observed morality rate (OMR) of 2.26%. Based on the NYSR model our expected mortality was 2.19% (*P*=.88, NS). There was a higher incidence of acutely ischemic and unstable patients compared to NY State patients. Multivariate logistic regression identified independent predictors of death at 30 days: stent thrombosis (definite or probable, Odds Ratio 96), acute MI, hemodynamic instability (OR 47), emergent (OR 17) or salvage (OR 28) PCI, and need for pre-procedural balloon pumping (OR 27). The 30-day incidence of definite or probable stent thrombosis was 2.6% and the cumulative Kaplan-Meier estimates were 3.0% at 6 months, 3.4% at 1 year and 4.2% at 3 years, all higher than benchmarks. Furthermore, since stent thrombosis was such a powerful risk factor for death at 30 days, we searched for and identified multivariate predictors of stent thrombosis: renal insufficiency (OR 7.15), emergent (OR 6.6) or salvage (OR 10.3) PCI, proximal LAD stenosis (OR 4.1), number of stents (OR 13.8), and operator (OR 3.7). Long-term survival Kaplan-Meier estimates were 94% at 1 year, 89% at 3 years, comparable to benchmarks.

Discussion: Actual 30-day mortality was similar to expected mortality based on risk factors in the NYSR model, and long-term survival was comparable to that reported in large registries. Major adverse cardiac outcomes including stent thrombosis are known to be higher in low volume centers. In our facility, stent thrombosis was higher than predicted by patient-specific risk factors. Operator-related factors and the number of stents used per procedure may be modifiable, and have the potential of improving short-term outcomes.

Conflict of Interest

The authors report no conflict of interest.

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Review of 18 Deaths Thirty Days Following Percutaneous Coronary Intervention at a Low Volume Military Treatment Facility: Decade of Experience

Emilio Fentanes MD and Thomas Wisenbaugh MD

Abstract

Background: Quality assurance of percutaneous coronary intervention (PCI) is particularly important at programs where the volume is low (<400 yr/center) as in all Military Treatment Facilities. In addition to statistical analysis of all cardiovascular outcomes, a detailed review of individual deaths is an important part of quality assurance.

Methods: We analyzed multiple risk factors used in regression analysis of outcomes in two large registries, as well as procedural, operator and other variables to attempt to determine what we might do differently to achieve better outcomes after PCI. Furthermore, each individual death within 30 days of the index procedure underwent a detailed chart review to assess other risk factors and variables that were not addressed within our database.

Results: PCIs were performed 929 times in a total of 795 patients, for an average PCI volume of 88/yr. The 30-day and long-term outcomes are reported separately. Eighteen patients died within 30 days of a PCI. Whereas the 30-day risk of death after PCI was high for some patients (up to 97% by NY State regression model), mortality expected on the basis of risk factors was low for others (as low as 0.5%; mean 35%). While some were very elderly (up to 89 years), others were not (as young as 41 years old; mean age 70). Twelve had current heart failure prior to PCI, 11 had acute STEMI as the indication for attempted PCI; 14 had multi-vessel disease, and more than 5 had prior CABG. Six developed multi-organ failure leading to death of which 2 occurred prior to PCI. In 5 patients who died, a decision was made to withdraw support, and in 3 it was determined that anoxic brain injury occurred prior to PCI, raising the question of whether they were candidates for aggressive therapy in the first place. Two patients died after failed attempts at PCI for acute STEMI. Half the patients who died had definite or probable stent thrombosis after PCI; three fourths of those were still on clopidogrel. Two died from massive pulmonary embolism. Two had PCI in the immediate post-op state.

Discussion. We need to: (1) identify why young patients and patients with low pre-procedural risk subsequently die; then try to improve procedural technique and operator expertise to reduce the risk of stent thrombosis and other complications; (2) treat heart failure before performing non-emergent PCI; (3) sustain and improve management of patients with acute STEMI which is a high risk subgroup undergoing PCI; (4) defer or avoid invasive management of cases which may be near end-of-life prior to their acute coronary event; (5) remember pulmonary embolism as a cause of death after PCI, and (6) remember that patients are in a prothrombotic state immediately after major surgery, and (7) continue diligence in respect to long-term antiplatelet therapy. Perhaps we should make greater use of prasugrel in lieu of clopidogrel.

Conflict of Interest

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Seasonal Variation of 25-Hydroxyvitamin D Levels in HIV-Infected Patients in Hawai'i

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Abstract

Introduction: Lack of sun exposure is widely accepted as a cause of low 25-hydroxyvitamin D (25[OH]D) levels. The effect of season on 25(OH)D has been extensively studied among patients in high-latitude regions, where shorter days during winter months lead to decreased cutaneous vitamin D production. However, data regarding the effect of season specifically on 25(OH)D levels within the tropical zone is scarce. We examined the influence of seasons on 25(OH)D levels among subjects enrolled into the Hawai'i Aging with HIV Cardiovascular Cohort (HAHC-CVD).

Methods: Entry criteria into the HAHC-CVD cohort required subjects to have documented HIV infection, be at least 40 years old, and to be on stable antiretroviral therapy for at least six months. After informed consent, fasting blood samples were collected, stored in EDTA tubes, frozen at -140 degrees Celsius and forwarded to LipoScience Inc. (Raleigh, NC). Chemiluminescent immunoassay (DiaSorin) was used to determine 25(OH)D levels. Low 25(OH)D was operationally defined in our study as having serum 25(OH)D<30 ng/ml. Patients were grouped by whether 25(OH)D was collected in summer (May 1 - September 30) or winter (October 1 - April 30). Multiple regression and logistic regression were used to investigate factors associated with 25(OH)D. *P*-value less than .05 was considered significant.

Results: Of 158 patients enrolled from March 2009 to July 2011, 88 (56%) and 70 (44%) were enrolled in winter and summer, respectively. There were 57.6% whites and 88% men. Over-all median (interquartile range) age was 51 (46, 57) years. Forty-three percent had 25(OH)D<30 ng/ml. Median body mass index (BMI) of winter and summer patients were 26.4 (24.3, 29.8) kg/m^2 and 25.5 (23.4, 27.1) kg/m^2, respectively ($P = .03$). Median 25(OH)D levels were 29.6 (22.0, 38.0) ng/ml in winter and 36.9 (25.0, 44.5) ng/ml in summer ($P = .01$). By simple linear regression, 25(OH)D was significantly associated with winter visit (ß = -0.0737, $P = .01$), ethnicity (white versus non-white, ß = 0.1194, $P < .01$), BMI (ß = -0.0111, $P < .01$) and current use of zidovudine (ß = -0.1233, $P = .03$). In multiple linear regression, ethnicity (ß = 0.1044, $P < .01$) and BMI (ß = -0.0079, P =v.02) retained significance but winter visit (ß = -0.0519, $P = .07$) was marginal. Similar results were found on logistic regression. Subgroup analysis of non-obese patients showed that 25(OH)D levels were significantly lower in winter (37.2 ng/ml in summer and 31.3 ng/ml in winter, $P = .04$).

Conclusion: Seasonal variation in 25(OH)D levels was observed in our cohort of HIV-infected patients in Hawai'i. Although BMI and ethnicity were better predictors of 25(OH)D levels than season in multivariate analysis, the importance of season in influencing 25(OH)D levels in the tropics cannot be conclusively ruled out.

Conflict of Interest

The authors report no conflict of interest.

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Hepatitis B Surveillance in Adult Chemotherapy Patients

Sarah Gordon MD; Jacquelyn Mitchell MSN, AOCNS; Tomas Ferguson MD; and Jeffrey Berenberg MD

Abstract

Introduction: Due to a high prevalence of hepatitis B virus (HBV) in Hawai'i and the Pacific Islands and the deaths of two chemotherapy patients from reactivation, a screening protocol was created to identify chronic HBV in new chemotherapy patients. The goal of this quality improvement project was to formally assess internal compliance with screening between 2009 and 2011.

Methods: Our screening protocol requires testing all new chemotherapy patients with hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBc), and hepatitis B surface antibody (HBsAb). HBsAg positive patients are treated with antivirals. HBc positive patients are monitored with serial hepatic function tests. We evaluated if screening tests had been performed in each patient seen between 2009 and 2011, and determined the percentage of effectively screened patients. A positive screening result includes only HBsAg positive patients and patients who are HBc positive/HBsAb negative since these individuals have the highest reactivation rate. A positive serology result includes all of the above tests. We monitored if the patients were treated or followed with serial laboratory evaluation if indicated. We also characterized our patient population by ethnicity.

Results: 329 patients received chemotherapy (94, 109, and 126). Among HBsAg positive patients (5, 1.5%), all were referred to Infectious Disease for treatment. The HBc positive patients (55) were followed with serial hepatic function tests for the duration of chemotherapy. 13 of these were HBsAb negative (4% of all patients). A total of 5.5% of all patients had a positive screening result as defined above. Overall compliance was 98%, six patients were not screened. Of individuals with a positive serology result, 85% self-identified as either Asian or Pacific Islander.

Discussion: Reactivation of chronic HBV in individuals exposed to immunosuppressive treatments has a mortality rate of 4-41%. The American Society of Clinical Oncology's stance is equivocal regarding screening all patients receiving chemotherapy, though they do endorse selective screening for patients at increased risk for HBV reactivation. Hawai'i has a higher prevalence of chronic hepatitis B (defined by positive HBsAg) compared to the mainland US population (3.6% vs 0.4% respectively). Our current screening is effective; however our management is limited by the lack of a clear duration of monitoring for HBc patients post chemotherapy. None of the HBsAg positive patients treated with antivirals developed evidence of reactivation. No deaths due to hepatitis B reactivation at Tripler Army Medical Center have been observed since surveillance began. Based on the high proportion of patients with a positive screening result that we encountered, we propose that screening at risk populations should continue to be standard practice.

Conflict of Interest

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Atypical Presentation of Hepatic Sarcoidosis

Robert Greenwood DO; Rodger Stitt MD; and John Garvie, MD

Abstract

Introduction: Sarcoidosis is a multisystem inflammatory disease characterized by noncaseating granulomas. It affects approximately 34 in 100,000 African Americans. Hepatic involvement is rare and is typically subclinical with only 0.1% to 0.9% of patients with clinically significant GI symptoms. We present a case of previously undiagnosed sarcoidosis with initial presentation of nausea, vomiting, pruritus, and severe abdominal pain with a cholestatic pattern of liver injury.

Case Presentation: A 42-year-old African American woman with prior cholecystectomy and a history of diabetes mellitus, type 2 was admitted with severe right upper quadrant pain, nausea, vomiting, pruritus and a 45 pound weight loss over the course of 3 months. Physical exam showed diffuse abdominal pain without peritoneal signs worse in the RUQ and epigastric region with positive Murphy's sign. Labs revealed cholestatictransaminitis with elevated direct bilirubin and dramatically elevated alkaline phosphatase. RUQ ultrasound and MRCP were normal. An infectious workup was negative and the patient was not taking any hepatotoxic drugs. Serum anti-mitochondrial antibody was negative and subsequent biopsy revealed a large number of noncaseating granulomas with notable autoimmune biliary pathology on initial pathology read. Although a chest x-ray was normal, a chest CT revealed mediastinal lymphadenopathy. A fine needle aspiration showed noncaseating granulomatous lymphadenitis. ACE level was elevated at 101 U/L. Diagnosis of multisystem sarcoidosis was made. Prednisone was started and the patient was discharged several days later with nearly complete resolution of her symptoms.

Discussion: Sarcoidosis is a rare inflammatory disease identified most commonly in African American patients. Hepatic involvement is typically subclinical and found on routine blood work in 10%-30% of patients with pulmonary sarcoidosis. In this atypical case the patient presented with a clinical picture mimicking acute biliary pathology and no symptoms or classic pulmonary findings of pulmonary sarcoidosis. A few rare cases of symptomatic GI sarcoidosis with a biliary obstructive picture are noted in the literature, however, these patients are exclusively males and also presented with fever and hepatosplenomegaly, so sarcoidosis was not high on the initial differential. Infectious etiologies of granulomatous hepatitis including HIV, TB and fungal infection were ruled out. She was not on any drugs reported to cause granulomatous hepatitis. Primary biliary cirrhosis became the initial working diagnosis. However, the patient's AMA negative status and a pathology addendum that noted only minimal biliary tree involvement prompted a reevaluation and workup for sarcoidosis. In this atypical case of hepatic sarcoidosis the patient presented with a clinical picture consistent with acute biliary pathology and no symptoms of sarcoidosis. However, demonstration of a granulomatous hepatitis without other apparent cause and negative AMA in a high-risk demographic patient led to a correct diagnosis.

Conflict of Interest

The authors report no conflict of interest.

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Pathological Views of Injured Myofibers After Myocardial Infarction in a 3D Reconstruction Obtained from Multiple Tissue Sections

Monica Katz MS; Hiroko Aoyagi BS; Toshinori Aoyagi PhD; Scott Lozanoff PhD; and Takashi Matsui MD, PhD

Abstract

Adverse left ventricular (LV) remodeling after acute myocardial infarction, characterized by LV dilatation and fibrosis, is a critical factor for prognosis in the subsequent development of heart failure. Though myofiber organization is a key component of cardiac structure, pathological views of injured myofibers during LV remodeling have not been characterized well. In our previous study using ischemia-reperfusion (I/R) injury models in mice, histological assays demonstrated the formation of a broad fibrotic scar extending from the initial infarct zone to a remote zone along mid-circumferential myofibers. However, the fibrosis was contained and did not extend into longitudinal myofibers within the internal and external aspects of the myocardium. We hypothesized that myocyte injury after I/R extends along myofibers but not coronary vessels. However, a histological analysis of tissue sections does not adequately indicate myofiber injury distribution throughout the entire heart. To address this, we investigated patterns of scar formation along myofibers using 3D images obtained from multiple tissue sections of the heart following I/R. Mice were subjected to surgical I/R (30 min-ischemia followed by reperfusion) injury by ligation of the left anterior descending coronary artery (LAD) and examined at 1 week after I/R. Each heart was fixed with 4% polyformaldehyde and cut serially into sections 5-μm thick from base to apex. In total, more than 100 sections were stained with Masson's trichome to identify regions of tissue fibrosis. Of those, 31 representative tissue sections were selected in equal distribution along the base to the apex. To generate the 3D model, digital images of the sections were outlined to highlight fibrotic areas, realigned for anatomic accuracy, and reconstructed using WinSurf v 1.0. The 3D model clearly delineates scar formation along myofibers beginning at the anterior wall of the base and extending inferiorly to the posterior wall of the apex. The pattern was consistent with distribution of the mid-circumferential myofibers. The data suggest that myocyte injury after temporal coronary ligation extends along myofibers rather than coronary vessels. Interestingly, recent clinical reports of patients with post-myocardial infarction evaluated with gadolinium-contrast MRI showed late enhancement of scar tissue limited only to the mid-myocardium in some cases. The same technique could be used to confirm the pattern of scar formation using autopsy samples. Computerized 3D images of histological assays are useful tools for visual analysis of myocardial architecture in I/R models and in the evolution of fibrosis in clinical settings.

Conflict of Interest

The authors report no conflict of interest.

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Wellen's T Waves and U Waves in Acute Coronary Syndrome

Mark Lebehn MD; Osamu Fukuyama MD; and Mark Joven MD

Abstract

Introduction: The most common electrocardiographic (EKG) finding suggestive of acute severe ischemia is development of the ST segment depression. Although this is the most sensitive EKG marker for transient ischemia, ST segment depression cannot reliably identify the location of the ischemia in most cases. In contrast, T wave inversion, especially so-called "ischemic T wave" is not as common as ST depression, however, it is more specific for location of the ischemia on the surface EKG.

Wellen's Syndrome, ie, deeply and symmetrically inverted T wave in the anterior lead (Type A), and biphasic T wave with positive initial deflection and negative terminal deflection (Type B), has been well-known for identifying the presence of severe anterior ischemia due to proximal LAD stenosis. The development of U wave inversion in the precordial lead has also been noted to be a specific marker of the proximal LAD stenosis.

We present a case of acute coronary syndrome (ACS) in a patient who demonstrates both EKG findings serially and who subsequently was found to have severe proximal LAD stenosis.

Case description: A 52-year-old man with a 20 pack smoking history and hypertension presented with chest pain. He was initially noted to have inverted U waves in leads V_3 and V_4 which subsequently evolved into deep and symmetric T wave inversion in leads V_2 through V_4 on EKGs taken during chest pain free periods. Troponin I peaked at 1.11 ng/L. He was treated with standard ACS medications. Coronary angiography showed a subtotally occluded proximal LAD which was subsequently stented. He had an uneventful hospital course and was later discharged.

Discussion: Although described separately in literature, EKG changes seen in Wellen's Syndrome and the lesser-known inverted U wave can identify the high risk patient population with proximal LAD stenosis. We will review the literature regarding Wellen's Syndrome and inverted U wave and raise physician awareness in recognizing the implication of these EKG changes for instituting early therapy and providing timely intervention in these high-risk patients.

Conflict of Interest

The authors report no conflict of interest.

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The Effects of Extended Release Niacin on Lipoprotein Sub-Particle Concentrations in HIV-Infected Patients

Chunrong Lin MBBS; Andrew Grandinetti PhD; Cecilia Shikuma MD; Scott Souza PharmD; Nisha Parikh MD, MPH; Beau Nakamoto MD, PhD; Kalpana J. Kallianpur PhD; and Dominic Chow MD, PhD

Abstract

Introduction: With the advent of highly active antiretroviral therapy (HAART), Cardiovascular Disease (CVD) has emerged as the leading cause of death in Human Immunodeficiency Virus (HIV) infected patients. An atherogenic lipoprotein phenotype has been described in HIV-infected patients with a predominance of small, dense LDL (SLDL) particles with accompanying elevated triglycerides and reduced high density lipoprotein cholesterol. This randomized controlled pilot study was conducted to evaluate the efficacy of Extended Release Niacin (ERN) in reversing the atherogenic lipoprotein phenotype.

Methods: A total of 17 HIV positive subjects on HAART therapy with High Density Lipoprotein Cholesterol (HDL-c) levels below 40mg/dl and Low Density Lipoprotein Cholesterol (LDL-c) below 130mg/dl were enrolled. Nine were randomized to be treated with ERN titrated from a starting level of 500mg/night and titrated to a level of 1500mg/ night. Eight patients were assigned to the control arm. No placebo was used. Lipoprotein profiles of the subjects were analyzed at baseline and at the end of 12 weeks with Nuclear Magnetic Resonance (NMR) spectroscopy. Results At the end of 12 weeks, NMR spectroscopic analysis revealed a significant increase in overall LDL size (1.22% in ER Niacin treated subjects vs -1.96% in control patients, $P = .04$) and a decrease in small LDL particle concentration (-17.02% in ERN treated subjects vs 21.42% in control patients, $P = .03$) in subjects receiving ERN as compared to those in the control group. Only 1 subject receiving ERN developed serious flushing which was attributed to an accidental overdose of the drug.

Conclusions: This pilot study demonstrates that ERN therapy in HIV-infected patients with low HDL-c is safe and effective in improving the lipoprotein profile in these patients.

Conflict of Interest

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Moyamoya Disease as Potential Contributor to Recurrent Stroke in a 57-Year-Old Man

Erin Liu MS; Thomas Deleon MD; and Kuo-Chiang Lian MD

Abstract

Learning Objectives: Moyamoya disease is a rare cerebrovascular disease characterized by stenosis or occlusion of the arteries around the circle of Willis with arterial collateral circulation. Patients with Moyamoya have significant risk for brain hemorrhage. Recognition of this disease in the patient with recurrent strokes requires a high degree of clinical suspicion.

Case Presentation: A 57-year-old man with a past history ofdiabetes, hyperlipidemia and hypertension presented to the emergency department with right-sided weakness and aphasia. A head CT on admission without contrast showed a small left frontal gyrus stroke with no acute hemorrhage and he was managed medically. Laboratory testing on admission was remarkable for elevated hemoglobin A1c and LDL cholesterol. The patient's neurologic symptoms improved initially, however on Day 3 of hospitalization, the patient developed worsening of his symptoms. Physical examination was notable for a right-sided facial droop, hemiparesis in his right upper extremity, decreased strength in lower right extremity and mixed aphasia. Repeat head CT without contrast revealed a large left middle cerebral artery infarction and CTA of the neck showed multiple intracranial stenoses, specifically occlusion of the left M1 artery and moderate stenosis of the right M1 artery. Multiple collateral vessels reconstituting M2 segments were also noted, which were suspicious for Moyamoya disease. His proximal right upper extremity weakness improved mildly, but on Day 4 the patient again developed worsening right-sided weakness and a repeat head CT showed an evolving left middle cerebral artery infarction. Other stroke workup including transthoracic echocardiogram and carotid duplex ultrasound were unremarkable. He was medically managed with aspirin, atorvastatin, lisinopril, and insulin. He continued to receive speech, occupational, and physical therapy throughout his hospital stay and was transferred to an inpatient rehabilitation facility for further care after stabilization of his neurologic symptoms.

Discussion: This case illustrates the clinical presentation of recurrent strokes, which is common in the context of Moyamoya disease. The diagnosis of Moyamoya disease is made with MRA or CTA which shows significant stenosis or occlusion of the cerebral arteries with a prominent collateral circulation. It is important to consider this disease in a patient with recurrent strokes because of the progressive nature of the disease and increased risk for cerebral hemorrhage.

Conflict of Interest

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A Case of Erythema Nodosumleprosum in a 23-Year-Old Marshallese Man Presenting with Rash

Erin Liu MS; Chunrong Lin MD; and Kuo-Chiang Lian MD

Abstract

Learning Objectives: Lepromatous leprosy is a rare disease affecting the skin and peripheral nerves that should be considered in patients from endemic areas who present with a rash. Rarely, leprosy may present with erythema nodosum. Early recognition of this disease is important as early leprosy treatment is essential to avoid complications.

Case Presentation: A 23-year-old man presented to the emergency department with evolving rash over two weeks. The rash was non-pruritic and started on his lower limbs and gradually spread upwards to the rest of his body, including his face and ears. One week after the rash appeared, he developed fever and generalized pain in his hand and foot joints.

The patient had no allergies and no family history of skin disease. He was born in the Marshall Islands but had been living in the United States for the past five years. He had no known history of STDs. He had no recent history of international travel and none of his close contacts had had a similar rash.

Physical examination revealed multiple erythematous nodules and papules on the head and neck, disseminated brown and erythematous macules and papules on trunk and limbs, including hands. Palpable purpura and hyperpigmented patches were present on his lower anterior legs. Mild synovitis of his finger joints and bilateral inguinal lymphadenopathy were present. There was no mucosal involvement.

Diagnostic testing revealed a white blood cell count of 3.0x109/L and erythrocyte sedimentation rate of 80mm/hr. A skin biopsy was performed and was histologically diagnostic of lepromatous leprosy. Cytology also demonstrated neutrophilic infiltrate and karyorrhectic debris consistent with erythema nodosumleprosum. Fite stain demonstrated numerous intracellular acid-fast bacilli. A modified treatment protocol consisting of dapsone, rifampin, and moxifloxacin was initiated. In addition, the patient was treated with prednisone for inflammatory symptoms.

Discussion: This case describes erythema nodosum with systemic symptoms as an atypical presentation of lepromatous leprosy. It illustrates the importance of maintaining a high clinical suspicion for leprosy in a patient who presents with a disseminated erythematous nodular and maculopapular rash. Although it is rare, it should be included in the differential for an unexplained rash in a patient from an endemic area.

Conflict of Interest

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Involvement of Visit Companions in Internal Medicine Resident Ambulatory Clinic Visits: Perspectives of Patients, Companions, and Internal Medicine Residents

Yvonne Lum MS; Jessica L. Colburn MD; and Colleen Christmas MD

Abstract

The purpose of this study is to understand the role and perspectives of visit companions during medical visits with resident physicians. Surveys were administered in person to patients and visit companions, if present, attending a medical resident continuity clinic. Residents were asked to complete an online survey on their experiences with visit companions.

The average age of patients without companions was 55 years. The most common reason these patients did not bring a visit companion was that they did not feel it would be helpful. In the past, 52% of these patients had brought a companion, reporting that they had previously done so for support and company, to ask the physician questions, and for help remembering the physician's instructions.

The average age of patients with companions was 50 years, while the average age of their companions was 40 years. Nine were family members and 10 were non-relatives, of which 7 were spouses. Nearly all companions (84.2%) accompanied the patient to the exam room, and about half (47.4%) accompanied the patient to every clinic visit. Nearly all companions (84.2%) reported satisfaction with the clinic visit. The most frequently reported roles during visits were asking the physician questions and helping to remember the physician's instructions.

Twenty-seven residents have responded to the online survey to date (55% response rate), and 74% reported feeling comfortable working with companions during clinic visits, 96% had not received any formal training in working with visit companions, and 70% reported interest in additional training. The most desired type of training was clinic mentorship and group sessions with caregivers. Residents reported involving companions during clinic visits by asking them for additional information and providing instructions to assist the patient after the visit.

When asked to rank aspects of the clinic visit they believed were most important to companions, residents reported that receiving information about the general health of the patient was the most important, followed by education about warning signs and symptoms, and the opportunity to share concerns about the patient. These rankings were consistent with the views of the companions themselves.

In this pilot investigation, half of the patients of the internal medicine clinic who brought a companion did so for every visit. These patients relied on their companions to ask questions during the visit and to help remember the physician's instructions. Residents and companions generally agreed on the roles of companions, but almost none of the residents had any formal training in interacting with visit companions.

Conflict of Interest

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Cameron's Ulcer: An Unusual Cause of Upper Gastrointestinal Bleeding

Jacob Mathew DO; Amy Stratton DO; and Jeffrey Laczek MD

Abstract

Introduction: Upper gastrointestinal bleeding is common in the adult population. Peptic ulcer disease is a common cause of gastrointestinal bleeding and is usually related to Helicobacter pylori (H. pylori) infection or nonsteroidal anti-inflammatory drugs. Patients with a large hiatal hernia are at risk for a Cameron ulcer, which has a different physiology and treatment options.

CaseReport: A 64-year-old woman presented with multiple episodes of melena followed by a syncopal episode and coffee-ground emesis. Her past medical history was notable for GERD and a hiatal hernia diagnosed on esophagogastroduodenoscopy (EGD) in 2008; she denied any NSAID use. Her GERD had been well-controlled on esomeprazole, but she stopped taking this medication two months before her presentation due to a concern over long-term side effects. On presentation, her blood hemoglobin level was 9.8 g/dL, decreased from a baseline of 14 g/dL. She underwent EGD which confirmed a large hiatal hernia and showed a 1 cm ulcer with a visible vessel located along the diaphragmatic impression, consistent with a Cameron ulcer. The ulcer was treated with epinephrine injection and bipolar cautery. Gastric biopsies were obtained, which later retuned negative for H. pylori. A proton pump inhibitor was restarted and she recovered uneventfully. Repeat upper endoscopy two months later showed complete resolution of her Cameron's ulcer. After a discussion of therapeutic options, she was referred for fundoplication and surgical repair of her hiatal hernia.

Discussion: Cameron ulcers are a mechanical phenomenon, related to extrinsic compression of the diaphragm on the stomach in patients with large hiatal hernias. These lesions should be suspected during upper endoscopy in patients with large hiatal hernias as Cameron ulcers may be overlooked due to their location along the diaphragmatic impression. Although our patient's ulcer resolved after she was restarted on a proton pump inhibitor, surgical repair of the hiatal hernia (often performed in combination with a fundoplication) is a consideration in patients who fail to respond to standard therapy.

Conflict of Interest

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Insomnia in Older Veterans: Prevalence, Self-Rated Health, and Talking to a Doctor About Sleep Problems

Sean Matsuwaka MS; Jennifer Martin PhD; and Cathy Alessi MD

Abstract

Objectives: To determine insomnia prevalence and variations in prevalence with age among older Veterans and examine the relationships among insomnia, self-rated health, and talking to a doctor about sleep problems.

Design: A cross-sectional postal survey. Setting: VA Greater Los Angeles Healthcare System - Sepulveda Ambulatory Care Center (SACC) Participants: Veterans over age 60, who received outpatient care at SACC in the prior 12 months and resided within 25 miles of SACC (n=9080) Interventions: None

Measures: Data were collected from a postal survey, which included items addressing the diagnostic criteria for insomnia (difficultly falling or staying asleep, early awakening, insufficient/non-restorative sleep, daytime symptoms, duration of sleep problems) plus demographics, self-rated health, and whether the Veteran had previously talked to a doctor about sleep problems.

Results: Of 9080 surveys 4758 were returned. Of responders 51.5% met International Classification of Sleep Disorders (ICSD) insomnia diagnostic criteria. An unadjusted logistic regression model showed that individuals in the 60-65 year age bin were at the highest risk for insomnia, with the odds of having insomnia decreasing with each successively older age group (all $P<.05$). Veterans with poor self-rated health had higher insomnia prevalence, more daytime symptoms of insomnia, and reported fewer hours of sleep compared to Veterans with good self-rated health. In a regression model, poorer self-rated health, meeting insomnia criteria, younger age, and more daytime symptoms were significant independent predictors of discussing sleep problems with a doctor.

Conclusion: Older Veterans had high rates of insomnia, but contrary to most prior work, insomnia became less prevalent as age increased. Greater efforts are needed to help older Veterans recognize and disclose sleep problems, and doctors should routinely screen for insomnia and account for comorbidities when treating insomnia patients.

Conflict of Interest

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A Rare Asian Condition

Jason Meadows MS and Jared Acoba MD

Abstract

Introduction: Hemophagocytic Syndrome (HS) is a rare condition in adults that carries a very poor prognosis. Increased cytokine levels cause excessive activation of T cells and macrophages resulting in the phagocytosis of erythrocytes, leukocytes, and platelets and their precursors.

HS in adults can occur secondary to viral illness, autoimmune disease or malignancy. Most malignant causes are T-cell or NK cell lymphoma. B-cell lymhpoma is a rare cause of HS, particularly in Western countries, and has been described almost exclusively in Asia, especially Japan.

Case: An 88-year-old Japanese-American man with chronic iron-deficiency anemia and a history of prostate cancer presented with an approximately 2 month history of progressive fatigue and generalized weakness, associated with dizziness, poor appetite, intermittent nose bleeds and weight loss of 10-15 lbs. He presented to an outside hospital 2.5 weeks prior to admission with several days of chills without fever or night sweats and was discharged after ER workup was unremarkable. Review of systems was otherwise normal. At his primary care appointment 1 week prior to admission he was encouraged to increase oral intake. Basic lab workup at that time was reported to be normal.

The patient was noted to be cachectic with pale conjunctivae and a mildly enlarged liver. Lab workup showed significantly elevated LDH, Ferritin, hsCRP as well as pancytopenia. Bone marrow biopsy showed hemophagocytosis. Diagnosis of large B-cell lymphoma with aberrant expression of CD5 and CD13 was made.

The patient became progressively dyspneic over the course of his hospitalization. Chest CT scan on hospital day 4 showed mild bilateral lower lobe consolidation and effusion. Despite empiric coverage with broad-spectrum antibiotics, the patient continued to have increasing oxygen requirements and expired on hospital day 5.

Discussion: HS is rare, particularly in association with B-cell lymphoma. Our patient met all diagnostic criteria for lymphoma-associated hemophagocytic syndrome including duration of fever >1 week. The presentation and pathologic findings pointed strongly toward this diagnosis. Timely diagnosis of the patient's lymphoma and hemophagocytic syndrome was made but still the patient succumbed to respiratory failure, possibly due to an acute pneumonia or complications of hemophagocytic syndrome.

There are no treatment guidelines for hemophagocytic syndrome in adults, although most patients reported in the literature are treated with cytotoxic chemotherapeutic regimens with or without stem cell transplantation. Some case series and case reports have shown significant survival benefit for stem cell transplantation in this setting.

Conclusions: Case reports and case series in the literature are almost exclusively from Japan. This is the first such case reported in Hawaii. While standard treatment is not well established, it likely involves chemotherapeutic agents and either allogeneic or autologous stem cell transplant.

Conflict of Interest

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A Review of Stent Thrombosis Following Percutaneous Coronary Intervention at Tripler Army Medical Center: 2002-2012

Bijan Nik Moradi MD; Emilio Fentanes MD; and Thomas Wisenbaugh MD

Abstract

Background: Stent thrombosis is a leading cause of death after percutaneous coronary intervention (PCI). Over the past decade, 929 PCI procedures were performed. We have found that half of the 18 deaths occurring within 30-days were related to stent thrombosis, and that of 32 patients who had definite or probable stent thrombosis at up to 26 months after PCI, more than half (17) died. To reduce the incidence of this often-fatal outcome, we need to identify and avoid repeating mistakes.

Methods: We reviewed records and angiograms of 12 patients with definite stent thrombosis.

Results: Technical factors possibly relevant to stent thrombosis: only half the patients were treated with drug-eluting rather than bare metal stents. Intravascular ultrasound (IVUS) was used to confirm adequate deployment in only 2 cases. Only 1 stent was <2.5mm i.d. and only 1 was longer than 24mm. None were considered to have a residual stenosis of >10% compared to proximal or distal reference vessel diameter. An untreated edge dissection was identified in only one case. In 5 cases multiple stents were used in bifurcation stenoses including one case of culotte stenting, a well-known risk factor for stent thrombosis. Patient factors possibly relevant to stent thrombosis: Four patients were still smoking at the time of stent thrombosis. One patient had discontinued clopidogrel 10 months after receiving a bare metal stent, and had thrombosis 4 months later. Two years after receiving a drug-eluting stent, 1 patient had stent thrombosis 16 days after discontinuing clopidogrel for a prostate biopsy. In two cases of subsequent, sub-acute stent thrombosis, the stents had been deployed emergently for, respectively, STEMI in the setting of hip surgery and coronary bypass surgery for myocardial infarction associated with 3-vessel disease.

Discussion: To reduce the incidence of the often-fatal complication of stent thrombosis, we need to try harder to get our patients to quit smoking and to continue diligently following their compliance with clopidogrel. Patient selection is important: those with diffuse disease downstream from important potential target stenoses, and those with complex bifurcation stenoses that will require multiple stents should be considered for alternative therapy. Operators need to practice better stent use by avoiding multiple stents in bifurcation lesions, minimizing stent overlap. When patients have acute infarction following major surgeries, the possibility of a pro-thrombotic state should be taken into consideration before resorting to stent deployment, since thrombectomy or balloon angioplasty alone may suffice. Whether more frequent use of IVUS-confirmation of adequate deployment would help is a matter of conjecture.

Conflict of Interest

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Redesigning Football Helmets to Reduce Concussion Risk: Return to the Leatherheads?

Austin S. Nakatsuka (Medical Student) and Loren G. Yamamoto MD, MPH, MBA

Abstract

Background: American football is a popular sport that has most recently brought attention to head injury/concussion severity. The current football helmet design has a rigid exterior with a padded interior. While the internal helmet design can reduce the potential for injury, the hardness of the outer portion of the helmet promotes its use as a striking force to injure other players. New helmet designs have focused on reducing the injury potential of the helmet, but most of the efforts have focused on modifying/improving the interior of the helmet. Softening the hard external layer of the helmet may reduce the incentive to use the helmet as a striking force if it can no longer be used to injure another player. Our hypothesis is that adding a soft cushion layer to the exterior of the helmet will reduce the impact potential of the helmet. The purpose of this study is to reduce the injury risk of concussions by providing additional head protection and removing the incentive to use the helmet as a striking force against opposing players.

Methods: We obtained a commercially available Riddell (Elyria, OH) football helmet that measures complex impact characteristics via accelerometer-based sensors known as HITS (high impact telemetry system). This helmet has been used in previous studies on head trauma impact sustained in football. This helmet was used to measure the impact sustained within the helmet. In the initial phase of this study, we placed the HITS helmet on a heavy duty head and torso mannequin used for boxing practice (Century BOB, Century MMA, Oklahoma City, OK), to mimic the degree of neck movement that would normally occur with a helmet strike. We then struck the upper parietal region of the HITS helmet with a conventional weighted helmet swung from a pendulum. We then applied a 1.3 cm layer of polyolefin foam to the exterior surface of the HITS helmet and then repeated the same process. The Riddell HITS software recorded the resulting linear acceleration (in G units, 1G = 9.8 meters per second squared), rotational acceleration (radians per second squared), as well as three other calculated head injury linear acceleration measures; GSI (Gadd severity index), HIC (head injury criteria), and HITsp (high impact telemetry suspect profile).

Results: All impact severity measures were significantly reduced with the application of the external foam. Five helmet strikes on the bare helmet were compared to five helmet strikes on the foam covered helmet. Mean linear acceleration decreased from 22.8±1.3 G, 95%CI 21.7-23.9 to 13.2±2.8 G, 95%CI 10.8-15.6. Mean rotational acceleration decreased from 2043±83 radian/s/s, 95%CI 1971-2116 to 1054±331 rad/s/s, 95%CI 764- 1345. HIC decreased from 5.2±0.8, 95%CI 4.5-5.9 to 1.2±0.4, 95%CI 0.8-1.6. GSI decreased from 6.8±0.8, 95%CI 6.1-7.5 to 1.4±0.9, 95%CI 0.6-2.2. HITsp decreased from 17.8±0.4, 95%CI 17.4-18.0 to 10.6±3.5, 95%CI 7.6-13.7.

Conclusion: These results support the hypothesis that adding a soft exterior layer reduces the injury potential for concussion on the football field. Further studies will include varying the foam thickness and using different densities of foam to modify the impact and injury potential of helmets on two factors: (1) Reducing the severity of the impact injury (2) Reducing player aggressiveness by removing the external hardness of the helmet.

Conflict of Interest

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Actual Body Weight Dosing of Vancomycin in Obese Patients

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Abstract

Background: Based on recent studies, the Infectious Disease Society of America (IDSA) updated its guideline to recommend that empiric vancomycin dosing should be calculated on actual body weight, rather than conventional fixed dosing. A vancomycin trough level is a surrogate for its efficacy, and sub- and supra-therapeutic levels are risks for bacterial resistance and nephrotoxicity respectively.

Objective: To determine if IDSA-recommended weight-based dosing achieves timely therapeutic vancomycin levels, and avoids sub- and supratherapeutic levels across body mass index (BMI) categories.

Methods: Retrospective study of patients who received vancomycin for a suspected or proven gram-positive infection from March-June 2012 at The Queen's Medical Center. Inclusion criteria: (1) age ≥18 years old; (2) vancomycin>3 doses; and (3) vancomycin trough level measured at appropriate time. Exclusion criteria: (1) CrCl<60 ml/min; (2) non-standard vancomycin dosing regimen and/or schedule. Patients were divided into 5 BMI (kg/m^2) groups: <20, 20-24.9, 25-29.9, 30-34.9, and ≥35. The primary outcome was the proportion of initial vancomycin trough levels that were sub-therapeutic (<10 mg/L), therapeutic (10-20 mg/L), and supra-therapeutic (>20 mg/L).

Results: We identified 171 eligible patients. Overall, only 44.4% of patients had a therapeutic trough level, 32.7%with sub-therapeutic and 22.8% supra-therapeutic. The proportion of patients with therapeutic, sub- and supra-therapeutic trough levels differed significantly by BMI group (*P*=.005). With increasing BMI category, the proportion of patients with supra-therapeutic levels significantly increased (*P*=.003). For example, among patients with BMI ≥35, 48%were supra-therapeutic and 17% were sub-therapeutic, compared with 12% and 37% respectively in patients with BMI 20-24.9. With each increase in BMI of 5 kg/m^2, the odds of being supratherapeutic increased by 35% (*P*=.005).

Conclusion: Adherence to the revised IDSA recommendations for weight-based vancomycin dosing is associated with variation in trough levels, a proxy for efficacy and safety, that is related to weight. More studies are needed to determine the optimal dosing of vancomycin in obese patients.

Conflict of Interest

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Constrictive Pericarditis: A Diagnostic Perplexity

Jared Pate MSIII and Steven Azuma MD

Abstract

Constrictive pericarditis is only diagnosed once in every 10,000 admissions. It is characterized by inflammation and fibrous scarring of the pericardium resulting in a thickened, rigid sac that impairs diastolic filling. Approximately 50% of cases are idiopathic, while post cardiac surgery and post radiation therapy account for 37% and 9% respectively. The scarcity of presenting symptoms and the rarity of diagnosis make it a challenge to recognize.

A 57 year-old man with no past medical history presented to the emergency room with progressing fatigue for two weeks and worsening lower extremity edema for one week, associated with dyspnea on exertion and decreased exercise tolerance. He was noted to be in atrial fibrillation with RVR upon admission to ER. Physical exam was significant for an 8 centimeter elevated JVP, and a Kussmaul's sign, which was noted sitting upright. Mild abdominal distention, hepatomegaly, and 3+ bilateral pitting edema to the upper thigh were also noted. Electrocardiogram showed non-specific low voltage QRS. A lateral chest x-ray showed significantly abundant calcifications along the anterior, inferior aspect of the cardiac silhouette. A subsequent tissue Doppler echocardiogram noted a septal bounce and an elevated early diastolic mitral annular velocity or E'. Cardiac catheterization showed an equalization of pressures, a dip and plateau sign, and ventricular interdependence. A phrenic-to-phrenic nerve pericardectomy was performed, removing a 5 millimeter thick, firm, calcified pericardium. A final diagnosis of idiopathic constrictive pericarditis was diagnosed as tissue pathology showed no abnormalities other than severe calcification. Five days post-operatively, significantly decreased leg edema, heart rate, dyspnea, abdominal distention, and JVP were noted. He was subsequently discharged two weeks post-operative with resolution of his symptoms.

This case illustrates the rarity of having multiple signs and symptoms associated with constrictive pericarditis as well as the new diagnostic capabilities of tissue Doppler. In constrictive pericarditis, elevated JVP is found in 86% of patients, dyspnea on exertion in 78%, edema in 54%, abdominal fullness in 68%, fatigue in 25%, a Kussmaul's sign in 21%, calcifications on chest x-ray in only 20%, and atrial fibrillation in only 10%. Newer data has also shown excellent specificity, 97%, for constrictive pericarditis when an elevated E' of greater than 12 cm/sec is noted. The presence of multiple rare signs and symptoms and the use of new diagnostic tissue Doppler signs make this case extremely unusual. Recognizing these signs and the proper use of cardiac catheterization and tissue Doppler is critical in differentiating constrictive pericarditis from restrictive cardiomyopathy and pericardial tamponade. It is also critical for the initiation of pericardectomy to prevent further deterioration or cardiac death.

Conflict of Interest

The authors report no conflict of interest.

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Are We Meeting Our Patients Needs? Performance Improvement Project to Measure Access to Care and Burden of Disability

Brendan K. Seto; Todd B. Seto MD; and Deborah Taira Juarez ScD

Abstract

Objective: To understand potential barriers to access of care and burden of disability among multi-racial/ethnic patients at a hospital-based, outpatient cardiac center.

Methods: Patients visiting The Queen's Medical Center for outpatient cardiac testing completed a 17-item survey from June-July 2012 (N = 98 patients). Questions on access to care (n = 5) and disability (n = 6) were from the RAND Visit-Specific Satisfaction Questionnaire and Census Questions on Disability. Disability was defined as "a lot of difficulty" or "cannot do at all" in any of 6 domains (seeing, hearing, walking, remembering, bathing, or communicating). Fisher's Exact and Student's t-tests were used as appropriate using Stata v11. The study was approved by The Queen's Medical Center RIRC.

Results: Native Hawaiians and Pacific Islanders (NHPI) (23%), Caucasians (22%), Japanese (20%), Filipinos (11%), and Chinese (11%) accounted for the majority of patients. Overall, 25% preferred to speak a language other than English, with significant differences between Chinese (55%, $P < .001$), Filipinos (29%, $P = .04$), Japanese (20%, $P = .02$), and NHPI (26%, $P = .02$) from Caucasians (0%). Overall Access was rated very good/excellent by 76% of patients, with 10% rating it as fair/poor. There were non-significant differences in very good/excellent ratings among Chinese (73%), Filipino (93%), Japanese (70%), NHPI (74%), and Caucasian (68%). Four other access measures – Length of Wait for Appointment; Convenience of Location; Getting Through by Phone; Time in Waiting Room – also did not vary by race/ethnicity. The Time in Waiting Room was rated fair/poor by 29%.

Overall, 66% of patients had at least some form of disability (seeing, hearing, walking, remembering, bathing, or communicating). There were no significant differences by race/ethnicity, although NHPI (83%) more often reported some level of disability than Caucasians (54%), Japanese (60%), Filipino (57%), or Chinese (73%).

Only 49% of patients knew their appointment time; 35% thought it was 15 minutes and 12% thought it was 30 minutes later than scheduled. Patients waited 27±20 minutes in the waiting room (range 0–98 minutes). NHPI (33±6 min) waited significantly longer than Caucasians (20±3 min, $P = .04$), with a slightly longer wait than Japanese (29±4 min), Filipinos (24±4 min), Chinese (26±7 min).

Conclusion: Patients at a hospital-based outpatient cardiac center face several barriers to the access of care, and may have impairments in physical function that need to be addressed. Further research is needed to better understand the reason for the significant difference in wait times and how access and outcomes differ by race/ethnicity. This research will shed light on changes needed to better suit patient needs.

Conflict of Interest

The authors report no conflict of interest.

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Cholangiocarcinoma...Or Not?

Adam Smith MD; Patrick Kenny MD; and Tamie Kerns MD

Abstract

Introduction: Cholangiocarcinoma includes all tumors originating in the epithelium of the bile duct and is the ninth most common gastrointestinal tract cancer. Metastatic disease may also rarely be present in the common bile duct. We present a case of metastatic malignant melanoma presenting as obstructive hepatitis and initially was thought to be and was almost treated as cholangiocarcinoma prior to adequate tissue sampling.

Case Report: A 76-year-old man presented with nausea, vomiting, and painless jaundice. He had a mixed hepatocellular pattern with transaminases and alkaline phosphatase greater than 1000 and total bilirubin of 12. A three-phase liver CT showed an enhancing mass within a dilated common bile duct and extension of the mass into the right and left intrahepatic bile ducts. He subsequently underwent ERCP with bile duct brushings and stent placement. Bile duct brushings showed benign reactive ductal epithelial cells. An endoscopic ultrasound with fine needle aspiration of the bile duct mass was performed. Pathology was negative for CK7, CK20, and positive for S100, Pan-melanoma, and negative for BRAF. No suspicious skin lesions were seen on close inspection by a dermatologist. However, two years prior the patient was diagnosed with cutaneous malignant melanoma in situ that was surgically resected. Thus, it was felt that this case represented metastatic melanoma to the bile duct. Due to significant comorbidities the patient was determined to be a poor surgical candidate. He has completed first line therapy for unresectable multiple melanoma with four rounds of ipilimumab.

Discussion: Pathologic diagnosis of cholangiocarcinoma is often difficult to obtain from ERCP secondary to paucicellularity of these tumors and with no imaging modality that is specific for cholangiocarcinma. The hepatobiliary tract is a possible, though relatively rare, location for metastatic focus of malignant melanoma and should be considered in a patient with a history of melanoma and no tissue diagnosis after ERCP. There are multiple case reports of metastatic melanoma to the ampula of Vater causing obstructive hepatitis, but only 10 reports of disease found in the common bile duct. This case highlights the importance of obtaining tissue from suspected malignant lesions using various forms of endoscopy to ensure proper treatment and prolonged survival.

Conflict of Interest

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Serology Improves Patient Adherence to Helicobacter Pylori Testing

Amy Stratton DO and Jeffrey Laczek MD

Abstract

Background: There are several non-invasive methods to diagnose Helicobacter pylori (H. pylori) infection. Prior to November 2010 available testing methods at our facility included serum H. pylori IgG, stool antigen, and urease breath testing. The serum H. pylori IgG was no longer offered as of November 2010 and we sought to evaluate the effect of this change on non-invasive H. pylori testing. We hypothesized that that patient adherence was better with H. pylori IgG testing than with other non-invasive tests and that the elimination of H. pylori IgG testing would reduce the overall number of patients screened non-invasively for H. pylori as well as overall adherence to non-invasive H. pylori testing.

Methods: A retrospective review was performed to evaluate the number of noninvasive H. pylori tests ordered and the number of tests resulted at our institution during two time periods. During the first time period (November 1, 2009 to October 31, 2010), H. pylori IgG, stool antigen, and urease breath test were all available. During the second time period (November 1, 2010 to October 31, 2011) only H. pylori stool antigen and urease breath testing were available.

Results: During the period in which H. pylori IgG testing was available, 2437 non-invasive H. pylori tests were ordered. During this period, the completion rate for H. pylori IgG testing was 85%, compared with 51% for the stool antigen and 53% of the urease breath test. The overall completion rate for H. pylori testing during this period was 77%. During the time period in which only the stool antigen and urease breath test were available, 1894 non-invasive H. pylori tests were ordered. During this time period, the completion rates for stool antigen and urease breath testing were 55% and 50%, respectively, with an overall completion rate of 55%.

Conclusions: The H. pylori serum IgG test cannot distinguish between previous H. pylori exposure and active H. pylori infection, whereas a positive H. pylori stool antigen or urease breath test indicates active H. pylori infection. However, this study suggests that testing for H. pylori via serum IgG has a higher patient adherence than the other two testing methods. At our institution, the number of non-invasive H. pylori tests ordered and patient adherence to testing both dropped after H. pylori IgG testing was discontinued. We feel that the improved patient adherence to serologic H. pylori testing, compared with other attractive features of this test, merit re-instituting H. pylori IgG testing.

Conflict of Interest

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It is Not Where You Die, But Who is With You When You Die: Evolving Palliative Care Practices Among Marshall Islanders in Hawai‘i

Anna Tamai MD; Lauren Okamoto MD; Sheldon Riklon MD; and Gregory Maskarinec PhD

Abstract

Introduction: Many Marshall Islanders seek healthcare services in Hawai‘i. Little is known about traditional Marshallese palliative care practices. Our purpose was to learn about traditional Marshallese palliative care practices to provide culturally appropriate care.

Methods: We performed 2 focus groups in 2011-2012 among Marshall Islanders living in or visiting the island of Oahu, Hawai‘i. Group facilitators were uniformly trained to conduct focus groups using prepared script, with a native speaking interpreter. Data were analyzed using classical thematic triangulation methods to identify specific Marshallese palliative care practices and the effect of economic and social challenges in Hawai‘i.

Results: Six females and seven males, ages 46-79 years, participated. A “good death” was defined as “peaceful and pain free,” occurring naturally with avoidance of artificial life prolongation. Factors associated with a “good death” included gathering of family to absolve conflicts, and proper and timely cultural practices such as *Ilomej* (wake) and *Eorak* (post-burial memorial service). Dying at home is the norm among people living in the Marshall Islands. After migrating to Hawai‘i, having family present at the time of death was more important than the actual locale of death. Factors associated with “bad deaths” included young age, active suffering, accidents, suicides, or “black magic/curses,” lack of timely burial or proper burial site. Barriers included mortuary fees, cost of transporting bodies, US government policies, and wait times for death certificates.

Conclusions: There are many underlying cultural factors contributing to “good or bad” death. Overcoming identified barriers may facilitate cultural practices necessary for a good death.

Conflict of Interest

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A Rare Disease: The Carney Complex Revisited

Mazie Tsang MSIII; Diane Elegino-Steffens MD; and Arthur Guerrero MD

Abstract

Introduction: The Carney complex (CNC) is a rare syndrome with autosomal dominant inheritance pattern characterized by spotty skin pigmentation, myxomas and endocrine hyperactivity. The incidence of this disease is not well established, but there were approximately 160 index cases known in 2006 after review of cumulative reports from Mayo Clinic, Cochin center in France and Cornell Center in New York. Here we present a case of CNC in a young woman that was diagnosed as a child and later developed ACTH-independent Cushing's Disease.

Case Report: Patient is a 29-year-old woman dependent of an active duty sailor who was diagnosed with CNC in Mayo clinic at the age of 5. Diagnosis was confirmed by a skin biopsy obtained from a blue nevus. Genetic testing was positive for a heterozygous mutation in the PRKAR1A Gene. Her childhood medical history was complicated by multiple cutaneous myxomas, most of which have been resected from her head, forearm and vaginal area. Annual surveillance screening with transthoracic echocardiograms and lab work were all normal until 15 years later when she re-presented with gradual development of cushingoid features. Baseline ACTH was suppressed and a dexamethasone suppression text was consistent with an ACTH-independent Cushing's Disease. Cross sectional imaging of adrenal glands via a Computed Tomography scan was normal in appearance and without evidence of nodularity or abnormal enhancement. She underwent bilateral adrenalectomy in 2009 and both adrenal glands were noted to have diffuse spotty hyperpigmentation on gross examination intra-operatively. Pathology reports revealed normal sized adrenal glands with brown micro- and macro-nodules in the area of the cortex that was consistent with Primary Pigmented Nodular Adrenocortical Disease (PPNAD). She subsequently developed iatrogenic adrenal insufficiency and also has a multi-nodular goiter that was negative for evidence of papillary thyroid carcinoma on fine needle aspiration. The patient,s youngest child was diagnosed with CNC at 6 months of age and her 7-year-old son has not been tested.

Discussion: Systematic CNC was first described in 1985 after review of Mayo Clinic Tissue registry that identified individuals with at least two of the following features: Cushing's syndrome, cardiac or cutaneous myxoma, myxoid mammary fibroadenoma or spotty pigmentation of the skin. Although this complex has only recently been described, there has been major genetic advancement in the diagnosis of this complex. Clinical diagnosis is made by establishing at least two if its main manifestations or a single manifestation is sufficient with confirmed germline PRKAR1A mutation and/or a first degree relative is affected. PPNAD is a rare cause of Cushing's syndrome, but it is the most common endocrine finding in CNC with a frequency of 25-60%. Other endocrine anomalies observed in CNC patients include growth hormone secreting pituitary adenomas (however, prolactinomas have also been described in one family), thyroid tumors (most often benign, although some patients present with carcinoma), testicular tumors (specifically Large-Cell Calcifying Sertoli Cell Tumor) or ovarian cysts. There are no current evidence-based recommendations on surveillance screening for CNC patients, but general consensus has been to work-up all manifestations of CNC annually. The importance of this case is to highlight the complexity of this disease and to review its clinical manifestations, genetics and management.

Conflict of Interest

The authors report no conflict of interest.

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The Prevalence and Comorbidities of Shoulder and Neck Symptoms in an Older Population: The Johnston County Osteoarthritis Project

Anne Wright MS; Amanda E. Nelson MD, MSCR; Xiaoyan A. Shi PhD;
Jan Busby-Whitehead MD; and Joanne Jordan MD, MPH

Abstract

Background: The increasing prevalence of neck and shoulder symptoms is particularly concerning for the geriatric population; however, little is known about associated determinants, comorbidities, level of disability, and functional status limitations. The objective of this study was to examine associations between specific comorbidities, functional outcomes, and neck and shoulder symptoms.

Methods: This is a retrospective, cross-sectional analysis of neck and shoulder symptoms in white and black, men and women with an average age of 68 years, participating in the 2nd follow up visit of the Johnston County Osteoarthritis Project (N=1672, 68.7 % white, 67.5 % women). Data on self-reported musculoskeletal symptoms, comorbidities, depressive symptoms, and disability were from interviewer-administered questionnaires; functional assessments (DASH: Disability of the Arm, Shoulder, and Hand; HAQ: Health Assessment Questionnaire; grip/pinch strength, functional reach) were performed by trained staff. Descriptive statistics and frequencies for neck and shoulder symptoms were assessed and compared among severity groups. Logistic regression models for medical comorbidities and other joint symptoms, and linear regression models for functional outcomes, were adjusted for age, sex, race, and body mass index, and additionally for other joint symptoms and comorbidities.

Results: Neck symptoms were reported by 12.8% of participants, shoulder symptoms were reported by 8.2%, and both neck and shoulder symptoms were reported by 12.6%. White women had the highest prevalence of neck symptoms ($P \leq .001$), while shoulder symptoms were evenly distributed across all groups. The presence and severity of neck and shoulder symptoms were associated with lung problems, cardiovascular problems, musculoskeletal problems, cancer, diabetes mellitus, and depression in adjusted models. Most notably, lung problems (bronchitis, emphysema) and musculoskeletal problems (fibrositis, gout, tendonitis) were associated with greater than 2 times the odds of moderate/severe neck and shoulder symptoms (aOR 2.1 to 2.5 compared with no neck or shoulder symptoms), and depressive symptoms were associated with 3.3 times the odds (aOR 3.3 [95% CI 2.2, 4.9]) of moderate/severe neck and shoulder symptoms. Neck symptoms were significantly associated with pain, aching or stiffness at other sites, with a particularly strong association with shoulder symptoms (aOR 12.1). Similar findings were demonstrated for shoulder symptoms and pain, aching, or stiffness at other sites. Finally, among joint symptoms, shoulder and neck symptoms were independently associated ($P<.05$) with poorer functional outcome scores (DASH, HAQ, pinch, and functional reach).

Conclusions: Neck and shoulder symptoms were associated with several comorbidities, increased disability, and decreased functional status in this older cohort. Approach to treatment of chronic diseases, such as lung problems, may be improved by understanding the strong associations with neck and shoulder symptoms.

Conflict of Interest

The authors report no conflict of interest.

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Splenectomy: A Treatment for Bleeding Gastric Varices with Underlying Essential Thrombocythemia

Lior Yacobbe MD; Jeffrey Berenberg MD; and John Garvie MD

Abstract

Introduction: Gastric varices are less common than esophagogastric varices in patients with portal hypertension, occurring in up to 33% of patients. Gastric varices are more common in patients with noncirrhotic portal hypertension and extrahepatic portal vein thrombosis, are associated with a lower incidence of bleeding, and have a higher mortality rate than esophageal varices. Optimal management of gastric variceal bleeding is debatable. We present a case of gastric variceal bleeding caused by pre-hepatic venous thrombosis from essential thrombocythemia which was successfully treated by therapeutic splenectomy.

Case Description: A 59-year-old woman with history of thrombocytosis presented with progressive abdominal pain, decreased appetite, and vomiting. Initial laboratory results showed a white blood cell count of 10.6 (x10^9/L), hemoglobin of 14.6 (g/dL), platelet count of 279 (x10^9/L) and normal PT/ PTT. Triphasic liver computed tomography (CT) revealed splenomegaly and extensive portal, superior mesenteric, and splenic vein thrombosis with no collateral vascularity. Transabdominal catheter directed thrombolysis with continuous tissue plasminogen activator (tPA) infusion was unsuccessful. She was anticoagluated with heparin and then warfarin. A hypercoagulation workup showed positive heterozygous prothrombin gene mutation and JAK2 V617F gene mutation. Bone marrow biopsy was diagnostic of essential thrombocythemia. Two months later at an outside facility she had an evaluation for gastric cancer with esophagogastroduodenoscopy (EGD) and biopsy. She subsequently complained of epigastric pain, melenic stools, and fatigue. Hemoblobin was 10.4 (x10^9/L) and INR was 3.2. Abdominal CT showed reduced clot burden but new periportal collateral veins and gastric varices. EGD showed an erosion over a gastric varix with stigmata of a recent bleeding. Anticoagulation was reversed and octreotide and propranolol were started. The patient continued to bleed with a drop in hemoglobin to 7.1(x10^9/L) and splenectomy was performed. Post-operative EGD demonstrated complete resolution of gastric varices. Three months after discharge on warfarin, there has been no recurrence of hemorrhage.

Conclusion: Gastric variceal bleeding is usually caused by left-sided portal hypertension, most commonly from extrahepatic venous thrombosis. Optimal management of gastric varices remains controversial. In this case, traditional treatment of multivessel thrombosis (portal, mesenteric, and splenic veins) failed. Splenectomy is often reserved for patients with isolated splenic vein thrombosis, however, splenectomy was a successful treatment for this patient with gastric varices from multivessel extrahepatic thrombosis and essential thrombocythemia.

Conflict of Interest

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The PMAG-UH JABSOM Medical Professionalism Essay Contest was established to promote professionalism among physicians and physicians in training at the University of Hawai'i John A. Burns School of Medicine. The contest was generously funded by PMAG (Pacific Medical Administrative Group, Inc.), one of Hawai'i's leading IPAs (Independent Physician Associations), which is made up of more than 700 physicians on O'ahu providing high quality care to more than 86,000 people in Hawai'i.

The essay contest was open to all current UH JABSOM medical students, residents, fellows and faculty. The essays were required to identify and demonstrate understanding of one or more of the following seven attributes/domains of medical professionalism:

1. Honesty/Integrity (truthfulness, adherence to ethical principles)
2. Responsibility/Reliability/Accountability (punctuality, compliance, accountability, feedback)
3. Respect for colleagues, faculty and staff (appearance, interactions, teamwork)
4. Altruism (concern for others)
5. Empathy (compassion)
6. Commitment to Excellence (goal setting, motivation)
7. Respect for patients (relationships, autonomy, confidentiality)

Here are the winners:

Medical Student 1st Place — **Jacques Ambrose MSIII**; "Are You Okay?"
Medical Student Runner-Up — **Mazie Tsang MSIII**; "The Importance of Empathy - As I Have Studied and Experienced It"

Resident/Fellow 1st Place — **Mark Joven MD**, PGY3 Resident, Department of Medicine; "Watermelon Smoothie"
Resident/Fellow Runner-Up — **Nikki Higa MD**, Chief Resident, Department of Medicine; "The Other Pain"

Faculty 1st Place — **William Fong MD**, Department of Obstetrics, Gynecology and Women's Health, "Medical Professionalism: Is It On Your Mind?
Faculty Runner-Up — **Linda Wong MD**, Department of Surgery; "Youngest Member of the Old School"

Are You Okay?

Jacques Ambrose MSIII – Medical Student, 1st Place

As the clouds of brilliant white languidly were traversing the cerulean Hawaiian sky, flashes of blue scrubs darted swiftly around the gathering crowds of pale faces. As bystanders were watching with amusement, I, notably crimson from a mixture of panic and fatigue, briskly maneuvered around the hospital furniture to keep up with the cardiac code team. My mind ran over my intern's earlier morning presentation, "This is a 58-year-old man with a history of atherosclerosis and hypertension who was admitted yesterday for a complaint of chest pain and EKG changes." With my white coat fluttering on my back, perhaps sharing in my anxiety, I raced to the room to meet the tumult of a code. As my attending supervised attentively, my resident bellowed commands at frantic staffs scurrying to find the appropriate medications. Stricken with nervousness, I stood by the door, unsure if I should enter the threshold of responsibility or presume my current idle role. As I was taking in the flurries of IVs, chest compressions, and mechanical beeps, a somber sob tore through the commotion. Tightly clutching an older Asian woman's hands, a young girl was vacillating between watching the medical interventions and turning away in anguish.

The older woman, visibly weathered by a lifetime of tribulations, held the young girl closer and uttered some words in a foreign language, as if trying to reassure her, and then the pair watched on. Snapped out of my bewilderment, I approached the pair to offer my assistance, albeit uncertain of how. The older woman watched me apprehensively, and stuttered in broken English, "I am wife. That her dad." I quickly tried to assuage their distress with a quick overview of the pathophysiology of myocardial infarction and the current ACLS protocols being applied to their loved one. However, I found my explanation, albeit in appropriate "patient-friendly" vernacular, eliciting only their vacant faces and monotone choruses of "Okay, doctor." As I was ransacking my brain to provide more information to them, my train of thoughts was derailed by the daughter's heart wrenching wail. A jolt from the defibrillator had coursed through her father's body and sent his limbs flailing eerily. Her repetition of "Okay, doctor" was interspersed with the renewed sobbing. The mother embraced her daughter and again muttered words of encouragement in their native language. Suddenly realizing that I understood their conversation, I offered a simple "Are you okay?" in Vietnamese.

My greeting startled the grieving pair, and their sullen eyes opened widely in astonishment. In Vietnamese, the mother sheepishly replied, "Can you understand us?" When I nodded, the pair ran to me and dissolved on my shoulders. Feeling the tight embrace of the mother, who had desperately tried to remain strong for her daughter, I squeezed back at the now weeping figure. As I held the two in my arms, a solemn calm fell over us. The thundering noises of the code team faded into the background, and I could only hear the silent anguish of their tears. I heard the endless cascade of medical words and foreign explanations. I heard the deafening silence of their husband and father lying insensate on the hospital bed. Then I looked down and heard the muffled bawling of two lonely people without any family or financial support. Suddenly, I felt the dampness of their confusion, fear, and heartache seeping through my white coat, and the coldness of its melancholy stunned me.

Wiping the cathartic tears from her eyes, the young girl stepped back and finally spoke in her native tongue, "This is my mom. My dad came here yesterday because of a heart attack." Still clutching her daughter's hands, her mother looked forlornly at her daughter and then at her motionless husband. "He was just complaining about his chest pain this morning, and he still wanted some fried food." Her woeful chuckle trailed off as she continued, "We went to get him some food, and when we came back, there were so many people in here doing all sorts of things on him." The mother reticently nodded and squeezed her daughter's hand. The daughter went on dejectedly, "A doctor came by and told us that there's something wrong with his heart, and he could die if they don't fix it." Shaking her head, her tears began anew, "He was just asking for food this morning. How could he leave us like this?"

Her question was so simple, yet immensely complex. My explanation of post-myocardial infarction ventricular arrhythmias was not able to explain why her father would not be eating dinner with them, nor was it able to provide her family with the income of her father's taxicab. As I was struggling to find the right words, I was interrupted again, this time by an eerie absence of noise. The code team had stopped; the patient had been completely asystolic for the past twenty minutes. Suddenly, noticing the dead silence, the mother started repeating louder and louder "No, no, no!" Her screaming shredded the tense air in the room until she finally collapsed in her daughter's arms. Holding her mother tightly, the daughter wept desolately, as our medical team stood tacitly around them.

In the aftermath, our attending explained meticulously, as I tried to interpret as much as possible, the events leading up to his cardiac arrest and the course of interventions and treatments during his code. Although their crying had somewhat subsided, the mother and daughter only nodded. As our team was leaving, I lingered by the door and asked again, "Are you okay?" The pair finally looked up and shook their head. I was utterly floored, trying to swallowing the uncomfortable lump in my throat, and trying desperately to restrain the insurgent tears in my eyes. I told myself that I was the healthcare provider, and I needed to maintain my professional image. Perhaps, perceiving my internal turmoil, the daughter came over and asked me, "Are you okay?" Those three simple words evaporated all my burdens, and suddenly, I felt a familiar dampness rolling down my cheeks.

I ended up staying behind for several hours, just simply speaking to them about their lives: their home in Vietnam, their immigration journey to America, and even their favorite foods. They were no longer the patient's family, nor I the healthcare provider. We were just talking and sharing our lives. As we continued our musing, I realized that medicine permitted me the incredible opportunity to connect with them. Yet, this medicine was not the archetypal pill, or injection, nor was it involving the familiar stethoscopes or CT scans. The lack of familiar scaffolding, upon which I frequently relied in medicine, made me feel vulnerable. As my train of thoughts stopped at the word "vulnerable," I found myself entrenched in the sensation. As healthcare providers, we incessantly ask our patients to lay bare their lives; yet, I wondered how emotionally and mentally unclad are we in receiving their life stories. In this story, I could not cure the ventricular arrhythmia of the husband/father, nor could I heal the heartaches of the daughter and mother; however, I comforted them in their moment of need.

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The Importance of Empathy—As I Have Studied and Experienced It

Mazie Tsang MSIII – Medical Student, Runner-Up

Empathy is a crucial component of the patient-physician relationship and has been associated with improved patient outcomes in multiple studies. The importance of empathy has been of major interest to me as a student of the John A. Burns School of Medicine (JABSOM). At the medical school I have learned that Kim, et al,[1] for example, analyzed the role of patient-perceived empathy and demonstrated that affective empathy led to a greater exchange of information, increased partnership, and interpersonal trust. Both partnership and perceived empathy had the largest effect on patient compliance and satisfaction.[1] Empathy has been shown to me to be the crux of a good therapeutic relationship. In order to emphasize its importance, the American Association of Medical Colleges (AAMC) has made it an essential learning-objective for medical professionalism so that schools will teach the meaning of and instill empathy. Meeting this challenging task requires an understanding of the meaning of empathy, the use of diverse educational techniques, and incorporation of students' personal experiences.

Acknowledging the role of empathy is easy, but teaching empathy is difficult because empathy is an elusive idea. The word is derived from the Greek *empatheia*, which means emotions and feelings.[2] Hojat, who developed the Jefferson Scale of Physician Empathy (JSPE), further clarified the meaning of empathy, differentiating it from sympathy in the following definition: "predominantly a cognitive (as opposed to affective) attribute that involves an understanding (as opposed to a feeling) of a patient's concerns and experiences with a capacity to communicate this understanding, and an intention to help."[3] Patients, however, perceive empathy as both cognitive and affective. They define it as their "feelings being understood and accepted by the physician" because empathetic physicians recognize and convey the patients' mental state (cognitive) and tend to the patients' emotional state (affective).[4] Based on these definitions, teaching empathy must address two important aspects: the physicians' understanding of patient concerns and their ability to convey to the patient this understanding and compassion.

In order to meet this AAMC learning objective, medical schools have employed various techniques to train students to be more compassionate and empathetic toward their patients. I am grateful that JABSOM has utilized nearly all of the primary teaching modalities that have been studied.[5] First, JABSOM emphasizes proper communication techniques through lectures, problem-based learning, and clinical skills workshops. Our Hawaiian custom of "talking story" is initially encouraged at the beginning of an interview in order to establish rapport. Studies have demonstrated a significant increase in empathy from pre- to post-intervention when researchers employ communication techniques as a learning modality.[5] Second, the JABSOM Family Medicine clerkship asks students to write a narrative on personal illness as a strategy to foster empathy. The focus of this assignment is to place the medical student in the role of a patient or her family member. In addition to this particular session, the JABSOM Department of Family Medicine also addresses patient care and empathy from other angles such as cultural consideration and understanding the needs of the marginalized in society. Participants in studies that employed narrative as a learning modality have reported increased empathy and understanding of illness.[5] Third, several preceptors instill empathy by having students experience medical care from the patient's perspective, such as when several of my classmates had to wear a cast for weeks as though they had broken their arm. In a study by Wilkes, et al,[6] students who were taught empathy by being admitted to a teaching hospital with fake diagnoses had reported that that experience would help them be more empathetic. Fourth and last, JABSOM stresses self-care ("taking care of your goose") from the first day of medical school. As stress is inevitable in medicine, my professors promote wellness and balance so that students can attend to their own health and happiness via time with loved ones, exercise, healthy diet, hobbies, and spiritual activities. Because personal stress can be a barrier to compassion and patience,[7] this lifestyle does foster empathy. Since I have studied at JABSOM, I feel well-trained and equipped with the necessary skills that will be useful in my patient interactions.

The first time I really experienced the gift of my JABSOM training in empathy and communication was on my Internal Medicine rotation. As I spoke with my middle-age male patient, an alcoholic of 40 years, I did my best to utilize all the techniques that my professors had taught me in order to show this patient that I empathized with his suffering. Initially, my heart was filled with compassion when I heard him relate his childhood trauma that eventually led him to self-loathing and despair; I saw in him a reflection of all those I know who yearn for love and understanding in their darkest hours. Because of my JABSOM training, I was able to be empathetic with my patient by giving him my full attention, responding with comforting words or body language, nodding appropriately, and asking reflective questions. At the end of my history taking, the patient said that I was the first person he had told about his past trauma and that he did so because he felt I really cared about his welfare and had made him comfortable. As honored as I was by his comment, I also recognized that there were additional tests and physician consults that my team would have to order; these tests, which I would not have ordered otherwise, would be based on what he shared with me. Through this experience, I finally understood the supreme importance of the patient-physician relationship and the role of empathy in fostering that relationship.

My interactions with this former alcoholic led to one of my most profound lessons in compassion and empathy to date. When I spoke of my experience with a JABSOM faculty member who is also a psychiatrist, he defined compassion to me as acknowledging that we all are interconnected and interdependent. He taught me that all people suffer; all people have a desire to be heard, to be loved. He insisted that practicing compassion is thus to identify and respond to my patient's innate desire to be heard and loved, which separates curing from healing. My patient had been cured of his alcoholism in the past, but he relapsed multiple times because he was not healed of his compounding suffering which had begun in his childhood; he continued to long for compassion and empathy. Our ability as health care providers to make him feel heard and understood makes us so different from a computer or person who follows algorithms.

In conclusion, I realize that physicians fulfill a dual role, for which empathy is indispensable. One of my JABSOM professors told me, "We cure with modern medicine, and we heal with our presence and compassion." Because we are both mind and body, as is evident in fields such as psychiatry, primary care, and oncology, this idea of healing and curing is rooted in the nature of humanity. Never have I learned so much about human nature as I have from my patients who are willingly open with me as I am open with them. Their emotions are raw—comprised of anger and despair as they face their impending death or happiness as they rejoice over the birth of their child, welcoming a new life. I am honored to share in my patients' emotions and experiences, and I will do my best to be a good, responsible steward of their trust. Working with patients during medical school has brought together all the lessons I learned about empathy and has taught me the privilege of being a physician: my journey to becoming a good doctor necessitates empathy, which is to understand my patients' multi-dimensional suffering and to convey my compassion to them because we are all interconnected. All of this reinforces my decision to continue studying medicine.

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Watermelon Smoothie

Mark Joven MD – Resident/Fellow, PGY3, Department of Medicine, 1st Place

After a particularly grueling ICU call, I was walking through the streets of Chinatown in downtown Honolulu looking for a decent lunch. I ordered roasted duck and char siu pork, foods which reminded me of home. Afterwards, I wanted something refreshing, so I went to this store that sells fruit smoothies. I couldn't decide at first if I wanted the avocado or the mango, but when I saw watermelon, I knew that was the drink I wanted. The drink reminded me of Ms. X, a writer in her late 40's, who had chemotherapy-resistant myeloma. She came in for neutropenic fevers and severe pancytopenia, requiring numerous blood transfusions as well as antibiotics. I still remember the first time I saw her. Eyes wide, anxiously breathing through a breathing mask, looking very much like a frightened bird would as she sat atop the hospital bed. She needed both blood transfusions given her waning blood counts, and diuretics as she was clearly volume overloaded because of prior transfusions. I kept a professional demeanor as I explained all these to her. I used a firm authoritative voice, I faced her squarely, and I looked straight into her eyes. I needed to give her strength I told myself. Yet looking unto her eyes, I saw something I did not expect to see, not in someone close to dying, I saw hope. Somehow that heartened me more than I could ever express in words. And even as she grew sicker each day, I kept up my optimism. I counseled her to eat more to feel stronger and healthier. Her condition worsened however, and we soon had to talk about goals of care if things didn't go the way we wanted them to. She said she just wanted to be in a happy and peaceful place. She wanted to be home. With the end getting close, we tried to make her as comfortable as possible. The staff were able to make her room feel as close to a home as possible. It had all the things she wanted—her books, her family, her friends. Amidst the busy hallways of the Oncology floor was a calm room, her sanctuary amidst the storm. When I asked her if there was anything else she wanted. She said she wanted a watermelon smoothie, a drink that makes her refreshed. Ms. X soon passed away with her family at her bedside. It was quiet and peaceful, just the way she wanted.

I was once told that I should avoid any sort of emotional attachment with patients, that I should steel myself, if I wanted to be the objective physician I needed to be. Being devoted to any one patient is emotionally draining, and I could not survive medical school wearing my heart on my sleeves. I should just take each day as if I'm part of a giant corporation: focus on results, goals, and outcomes.

Medical school was an excellent training ground for this. There, we learned a lot about the intricacies and peculiarities of the human body, different disease entities, and the corresponding cures for each of them. We are constantly bombarded with examinations and deadlines, all in the hopes of equipping us for the hurdles of medical practice. Yet none of these are guarantees. All the years of training will not equip us with the basic elements of patient care—compassion, empathy, and genuine concern. Our first encounters with the realities of suffering and death were more than just baptisms of fire that leave us reeling in shock. It's but a glimpse to the all-too-real caveat of our profession. The realization that we hold so much sway on another person's life is a scary responsibility. And there's the hard lesson of having to deal with the consequences of the suffering we might inflict on a patient, unintentionally or not.

It was at the beginning of clerkship, still in the process of developing my clinical acumen when I was tasked to manually check the hourly vital signs of this boy who suffered dengue shock syndrome at a referral facility for infectious and communicable diseases in the Philippines. This child, about 10 years old, stayed in a room with three other sick children. Except for mild tachycardia, the rest of his vitals were normal for the preceding 5 hours. On the sixth hour of monitoring, something felt wrong. The child was unresponsive, without a pulse or a heartbeat. "Call the Attending! We have a code blue," I shouted to the nurse while I began chest compressions. The attending physician came in two minutes later. He appeared worn out. He intubated the patient while epinephrine was running through the child's bloodstream. The code team consisted of two frantic nurses, a worn-out attending physician, and me—an inexperienced medical subintern. The code lasted for 30 minutes without a return of spontaneous circulation. I then saw the attending physician telling the child's father who was in tears, "The patient is gone," then hurriedly left. I have long since forgotten the attending physician's name, or even the child's name. What I could never forget though was this scene: the father, still unable to accept his loss, perhaps feeling that our efforts were inadequate, continuing chest compressions as he cried out in anguish.

After having had the privilege of being Ms. X's physician, I realized that I've matured and grown as a person and as a physician. I know for sure what type of doctor I want to become—an emphatic, compassionate doctor who empowers and motivates, instead of one who projects an air of superiority, and intellectual arrogance. A marked contrast from my first encounter with a patient's death.

Each time I see a patient where death is imminent, I know now the value of reconnecting my experiences with previous patients that I've treated, even loved ones that I've lost. I've been on the other side of the scenario as well, having a loved one be at death's door, knowing the uncertainties of the diagnosis and prognosis of the disease, the fear of being harmed by medications or the physician, the very real possibility of their death, or worse, their suffering. I understand that all these uncertainties cause undue distress and emotional suffering not only to the anxious patients but also to those who hold them

dear. And while skill is of the utmost importance, the challenge is much greater. A doctor in this case needs to exercise compassion and empathy, assuring the patient that everything will be done for them, comforting them by your personal guarantee, that whatever the outcome might be, you will stand by them. Ultimately, such is not a mere professional relationship, but an emotional contract.

Residency has further honed my clinical judgment and medical insight. More than that though, I've learned to see each patient as part of my ohana, my extended family. I'm emotionally invested in their personal well-being. And I have my patients, mentors, and experiences to thank for this metamorphosis. To me, Medicine will never be more science than art. Whatever breakthrough the science of healing will discover now or in the future, a patient will always be a living, breathing, feeling being, whose life experiences, personal triumphs, and human dignity deserve professional respect, and careful consideration. Reimbursements might be less, and medical liabilities might be unavoidable; but at the end of it all, a compassionate physician is all it takes to heal if not cure a patient, no more no less.

I'm almost done with my watermelon smoothie. Not surprisingly, I'm refreshed and ready for my next call. I really shouldn't have worried about choosing my drink. I always knew which one I wanted.

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The Other Pain

Nikki Higa MD – Chief Resident, Department of Medicine, Runner-Up

Each day a little more of my memory returned to me. I slowly began to piece together the seconds that lead up to the car accident that had landed me in the hospital. Between the around-the-clock pain medications, the physical therapy sessions, the flurry of surgical residents on rounds and visiting family members, there were also moments of quiet in my hospital room. I had put up a strong front for my family out of concern that they would worry too much for my recovery. It sometimes seemed exhausting to repetitively reassure them that I would be just fine. After visiting hours were done and the last members of my family had gone home, the hospital room became a venue of quiet reflection for me. It gave me time to be honest with myself in how I really felt about my situation and how much I was actually hurting from the accident. In and out of sleep and sedation I found myself recounting the details of the accident and I started to question the "why" of the entire situation. "Why did this happen? Why me? Why would God put me through this test?" This reflective time was always the hardest part of the day for me.

Despite the numerous staff, therapists, and providers that would sweep in and out of my room during the day, it was the nurses that would still be around during my 'reflective time'. There is one nurse in particular that I will never forget and for purposes of anonymity, I will refer to him as Sam. Sam, like the other nurses would come in and ask the usual, "How is the pain - on a scale of 1 to 10, 10 being the worst pain, what would you rate it?" While some nurses might be busily occupied fixing my IV or taking my blood pressure as they asked me this question, Sam would deliberately pause from his tasks, and look straight at me when he asked me this. Even though I gave him the same answer every time, "7", he could always tell by looking at me that the 'other' pain - the emotional pain in trying to grasp the events that had suddenly flipped my life in a different direction, was actually a "10". I didn't have to say anything else as he would let out a small sigh and then find a chair in the room to pull up next to my bed. "Ok, talk to me - what's wrong?" he would say.

Every shift he would somehow find time, even just a few minutes, to sit with me to allow me to reflect on the situation—mostly being a kind ear for me to talk to. He was always motivating and would share his own experiences caring for other patients in my situation as a testament that he strongly believed I would make a full recovery. He seemed like a veteran at counseling distraught patients and it was not hard for me to find trust in him as my advocate. He was consistently positive, empathized with me and most importantly, gave me hope. He knew I feared the unknown. Not knowing where I would be going as the transporters rolled me to radiology on the gurney or not knowing why I was suddenly getting woken up to have extra labs drawn in the middle of the night would be frightening. He always kept me updated, even if it meant repeating it to me since I was exhausted most of the time. It was as if he knew that during this time when it seemed I had lost so much independence and control of my life (I could not get out of bed on my own, I could not sit up to eat on my own), he gave me the little bit of control that he could. He let me know exactly what the plan was for the day. He would give me choices, ask me if it was 'ok' to do something and explain what 'the docs' had ordered. No matter how many times he would need to check on me or how many times my family would ask him questions he always remained patient and compassionate. Although I was grateful for the medical care of the physicians on the team, I feel that Sam provided me not only with excellent medical care but in being my primary nurse for most of the day, he really became my closest ally and advocate on the medical team. In his years of experience, I am sure he has had hundreds of patients with similar injuries, dealing with similar mental struggles and yet, he listened to me speak as if it was the first time he was hearing a good friend tell him an important story.

Luckily I was able to make a full and speedy recovery. It is amazing to think that this person, Sam, who was initially a stranger to me, was then suddenly forced to get to know me during one of my toughest life challenges and yet within a few days had immediately become an important bearer of inspiration and encouragement. It is a privilege in medicine to have the ability to get to know patients and Sam is one of those people that truly understands this. In my weakest moments he had shown me the compassion and altruism that inspire me even today as I myself take care of patients. Today Sam and I work in the same hospital and every so often I will see him working his usual shift on the same floor on which I at one time used to be a patient almost 7 years ago. I can't help but smile when I see him, because I know that even today he is helping patients, just as he helped me, regain their strength through his compassion and empathy.

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Medical Professionalism: Is It On Your Mind?

William Fong MD – Faculty, Department of Obstetrics, Gynecology and Women's Health, 1st Place

When the television series, House, M.D. debuted in 2004, the title character was described this way:

> Dr. House, a brilliant doctor with no bedside manner, brings a whole new meaning to the words "obnoxious" and "abrasive". House trusts no one, doesn't know what proper grooming is, and is addicted to Vicodin…a classic example of a sociopathic jerk who under normal circumstances wouldn't be worth the time it took to mention his name. Except for one thing: Dr. House happens to be a genius in his field…[1]

If television has a way of creating a mindset and influencing culture, those of us who grew up admiring and emulating Marcus Welby, M.D. would cringe to think that Dr. House has established the new norm for professional demeanor by a physician.

The American Board of Internal Medicine Foundation had just earlier, in 2002, published the monumental document, "Medical Professionalism in the New Millennium: a Physician Charter". This set off a surge of consciousness (and probably conscience as well) among academics and practitioners to incorporate principles of professionalism into medical curricula and organizational by-laws. Every prominent medical society in the United States and many from all over the world, over 130 of them, has now endorsed the Charter. It has been translated into 12 different languages. The number of journal articles on the subject has tripled to over 300 per year since the Charter was published.[2] It is safe to say that the Charter would not look kindly upon the unconventional behavior of the fictionalized Dr. House, no matter how brilliant he is.

Not that medical professionalism is a novel concept. Parts of the Hippocratic Oath (circa late 5th century B.C.) have been rewritten by the current generation of progressive post-modern physicians. But when the Oath stated, "in whatever houses I may visit, I will come for the benefit of the sick, remaining free of all intentional injustice, of all mischief…what I may see or hear in the course of the treatment or even outside of the treatment, I will keep to myself," it was a pledge to uphold certain tenets of what we now call medical professionalism—namely altruism, accountability, and confidentiality. When Scribonius, court physician to the Roman Emperor Claudius (circa 47 A.D.), said, "all men should despise any physician whose heart is not full of humanity and mercy according to the purpose of the profession…medicine does not measure men's worth by their fortune or good qualities, but offers help to all who seek it," he too was insisting on medical professionalism long before the term was conceived. And of course, Sir William Osler, set the tone of 20th century medical professionalism with maxims such as, "The practice of medicine is an art, not a trade; a calling, not a business; a calling in which your heart will be exercised equally with your head (1904)."

What exactly is professionalism: what does it look like, what does it involve? It is "good bedside manner", to be sure, but it is much broader and more profound than just that. In academic medicine, the questions go even further: how do you teach it, how do you evaluate it? Wherever professionalism is an expectation—whether in a medical school, residency program or professional society—a set of character traits felt to embody professionalism is usually listed alongside. For example, the JABSOM Objectives for Graduation says this of Professionalism:

> Graduates will be professional and ethical, demonstrate an enthusiasm for medicine, and value honor, integrity, altruism, respect, accountability, excellence, scholarship, and leadership while delivering compassionate care to their patients.[3]

What is important to note is that professionalism is not just an assortment of expected or desirable behaviors on the part of a practitioner or a trainee. It is not merely a checklist of do's and don'ts, although phone-slamming, dishonest research and lazy record-keeping are clearly unacceptable behaviors. Instead it is the possession of a set of core values, based on a commitment to the high calling of physicians, which in turn motivates commensurate behavior. Dr. Jordan Cohen, professor emeritus of the Association of American Medical Colleges, qualified the meaning of professionalism thusly,

> Professionalism is a way of acting. Physicians could, in theory, act in such a way as to fulfill all the expectations of professionalism without actually believing in the virtues or principles that underpin them—going through the motions, so to speak…Humanism, by contrast, is a way of being. It manifests itself by such personal attributes as altruism, duty, integrity, respect for others, and compassion. Humanism provides the passion that animates authentic professionalism. Professionalism denotes a way of behaving; humanism denotes an intrinsic set of deep-seated convictions.[4]

I was on the Labor and Delivery floor one night with one of our residents. It was a typical crazy-busy night and one of the patients who had been somewhat uncooperative and difficult to work with was about to deliver. In the frenzy of the delivery, intensified by way too many hyper-excited visitors in the room,

the patient inexplicably reached down and grabbed the arm of the resident just as she was about to assist with the rather chaotic birth. Completely startled, the resident jerked her arm away and in a not-too-soft voice scolded, "Don't you ever do that again!" This quieted things down in a hurry and re-set the mood of the room from excitement to subdued. The delivery itself concluded uneventfully and we left the room to finish our paperwork. I noticed however that the resident looked a bit somber and after a few moments decided to ask about the events that had just taken place. Before I could finish my question, the floodgate of tears opened up and the resident moaned, "I don't know what got into me. I never do things like that with a patient." And in my mind, I concurred because it was completely out of character for this resident that I had known for several years. So we went off to the side and in consoling her I reminded her that the work we do certainly has its stressful moments. I told her I was not overly worried about the brief outburst of hers that had just happened. I would have been more concerned if the outburst did not bother her as much as it clearly did, if she chose to merely shrug it off. To me, her real character was revealed not by her impulsive reaction but by the remorse that she showed afterwards. We ended our conversation by my encouraging her that when the time was right, when the emotions had settled down, to go back to check on the patient and in the process make sure that everything between her and the patient was right again. And that's exactly what she did.

One of the challenges in working with residents and medical students is to draw out the character that we hope is intrinsic to them. Character is a difficult thing to teach and evaluate. It doesn't fit the same template that's used for assessing medical knowledge or surgical dexterity. Interestingly, character is often revealed in the Personal Statements that 4th year students compose in preparation for applying to residency programs. No doubt, some of the Personal Statements read as though they could have been lifted from the memoirs of Dr. Osler himself. But in my experience with interviewing residency applicants that is a good place to uncover the depth and sincerity of the character and core values that we desire in our residents. Delving into Personal Statements with applicants can highlight these intangibles in a way that transcripts and research authorships won't. Responses that reflect genuine passion, humility and balance in life produce good vibes. Glibness, narcissism, and rigidity do not.

Personal Statements are then taken one step further. I will annually sit down with those who become our residents to review their Personal Statements and reflect on the traits they mentioned that indicate a commitment to professionalism. Their conscience is roused when reminded about their previous claims, when asked, "Do you remember what you said about being a team-player; being compassionate; communicating well; earning a patient's trust; and having a strong work ethic or a love of teaching? Are these still your convictions? Is this still who you are?" This provides a wonderful opportunity to celebrate when these self-declared expectations are being met, or to get back on track if for whatever reason they aren't. Hopefully setting time aside each year to ponder these things is appreciated, especially on those days when a resident feels their entire measure of success is dependent only on board scores and surgical logs. And hopefully this effort represents an important part of the process of developing and maintaining professionalism among our doctors-in-training.

Who among us, no matter how long we have been around, would not benefit from timely reminders of the idealism we had and the oaths we took at the beginning of our careers? Perhaps we all need to dust off our own Personal Statements every now and then so that we not only stay on track ourselves but also effectively model professionalism to those trainees who have been entrusted to us. There is sobering evidence that professionalism may be somewhat lacking these days and as a result the public's trust in physicians is diminishing.[5,6] On the other hand, there is respected opinion that the process of instilling professionalism in medical students and residents is highly dependent on and can successfully come about with effective mentoring and role modeling.[7-9] So an important responsibility for everyone in the medical community is to nurture and develop not only knowledgeable and skillful physicians but also well-balanced, conscientious, and ethical ones. In this way as we personally make the effort to demonstrate professionalism at the highest level, we also help to maintain the profession of medicine in its purest form.

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The Youngest Member of the Old School

Linda Wong MD – Faculty, Department of Surgery, Runner-Up

It's 2013. It's an age of information technology, immediate results, instant gratification and a continuous rush to get things done better and faster. In medicine, there are electronic medical records, robots, minimally invasive surgery, acute care surgeons, hospitalists, locums tenens, physician extenders, shift work and limited duty hours for residents. Physicians want to specialize, do things quicker and better and just get out of the hospital. I am the youngest member of the old school.

It's 1993. The liver transplant program has been open for a few months and I am its fledgling surgeon. I am sitting in my un-busy office when my associate says, "See this patient. He could use a liver." I will never forget that day I met Mr. X. He was late-40s, a little nerdy looking, but zoned out, bloated like a blimp and with funny-looking scaly skin. His older brother wheeled him in and pleaded to me. "He has cirrhosis. Please save my little brother from dying"

Yikes. He looked really sick and my experience in this new program was a bit limited (N=1), but I gave it my best shot. We put him thru the evaluation process, we placed him on the transplant list and a few months later, we did his transplant. The liver worked well, but I watched him have some peculiar drug reactions. On the second day after surgery, I found him wandering around his room, looking under the bed and he told me, "I'm looking for my other liver." Then he stopped talking for a week for some mysterious reason and then woke up on the tenth day, looked me in the eye and said in a robotic voice "You are not the real doctor. You are from the dark side. Please find the real one". According to his brother, he was a big Star Trek fan.

I was able to discharge him after he recovered and a few months later he had severe headaches. I waited for him in the emergency department as he underwent a CT scan of the head and someone did a lumbar puncture. He had cryptococcal meningitis, likely from feeding the birds that were flying into his attic. He recovered from this and I instructed him "no more feeding the birds" and he needed to clean out that attic from bird droppings.

I watched him go back to his normal life. He had a high-tech job, drove a little sporty Toyota, and almost ran me over in the parking lot one day as he came to clinic. I learned about how he took care of his mom and drove her around to medical appointments. He had a niece and nephew who were born shortly after the transplant and I watched him be a fun yet reliable uncle. Then his caring brother that I met the first day died suddenly from a heart attack. Mr. X then worked harder and became almost a second dad to his niece and nephew.

He showed up religiously to my clinic every 3 month. He was completely compliant with all of his medications and fastidious about his blood pressure, attending all of his appointments, and correcting all of the errors on his medical bills. I made sure he saw his primary care physician, got his screening colonoscopy, went to the dentist, and was screened for prostate cancer. I learned about his work, his hobbies, and his idiosyncrasies. I also learned that the funny scaly skin was ichthyosis and his brother had the same thing. I learned all about his niece and nephew – from what they did in pre-school all the way until college.

This went on for 17 years, and then he developed esophageal cancer. A thoracic surgeon wanted to do an esophagogastrectomy but Mr. X would not let the surgeon get near him until I promised to be there at surgery. So, I stood in surgery, hung onto that liver that I put in 17 years ago and protected it from any harm. He did fine for a year but eventually had a recurrence. He had multiple readmissions for chemotherapy in the next year and he made sure to call me every time he went to the emergency department. He also made sure the nurse on the floor called me whenever he got admitted and he never went thru any procedure or test unless I gave him my approval.

The chemotherapy did not help him much and he developed metastases, but he kept on trying. He said to me one day in the hospital, "do you really think this chemotherapy stuff works? I'm a little skeptical and I'm wondering if they should try something different." That was Mr. X—forever intellectualizing and analyzing the situation. He gave every ounce of effort to enduring this. I then watched the palliative care team eventually convince him to go to hospice and after a long talk with me, he agreed.

I didn't hear from him for about a week when he called me from his cell phone in hospice. The nurse had dialed the phone for him and told me "we thought he was going to die today but he apparently woke up again." Mr. X then got on the line and said, "I just wanted to thank you—for 19 years that I wouldn't have had without you. It's been a good life". His voice was a little quiet and scratchy and I was pretty stunned. Before I could say anything more, he then said, "You know, these nurses in hospice don't give me the anti-rejection medicine. How long can I go on without these pills?" I reassured him and he felt better. He said, "Thank you again" and hung up.

I kept thinking about this and a few days later I left on a trip to the East Coast. As the plane was taking off and I left the islands, Mr. X. died in hospice.

Sometimes in this high-tech world that we live in and an environment where everyone wants to hurry to get work done faster and better, we lose sight of why we really do all of this. Patients become procedures, hospital admissions, and pay for performance measures. I may be the youngest member of the old school or maybe I am just an old dinosaur, but making a difference in one patient's life for 19 years is the best part of my job.

General Recommendations on Data Presentation and Statistical Reporting (Biostatistical Guideline for Hawai'i Journal of Medicine & Public Health)

The following guidelines are developed based on many common errors we see in manuscripts submitted to HJMPH. They are not meant to be all encompassing, or be restrictive to authors who feel that their data must be presented differently for legitimate reasons. We hope they are helpful to you; in turn, following these guidelines will reduce or eliminate the common errors we address with authors later in the publication process.

Percentages: Report percentages to one decimal place (eg, 26.7%) when sample size is >=200. For smaller samples (<200), do not use decimal places (eg, 26%, not 26.7%), to avoid the appearance of a level of precision that is not present.

Standard deviations (SD)/standard errors (SE): Please specify the measures used: using "mean (SD)" for data summary and description; to show sampling variability, consider reporting confidence intervals, rather than standard errors, when possible to avoid confusion.

Population parameters versus sample statistics: Using Greek letters to represent population parameters and Roman letters to represent estimates of those parameters in tables and text. For example, when reporting regression analysis results, Greek symbol (β), or Beta (b) should only be used in the text when describing the equations or parameters being estimated, never in reference to the results based on sample data. Instead, one can use "b" or β for unstandardized regression parameter estimates, and "B" or β for standardized regression parameter estimates.

***P* values:** Using *P* values to present statistical significance, the actual observed *P* value should be presented. For *P* values between .001 and .20, please report the value to the nearest thousandth (eg, *P* = .123). For *P* values greater than .20, please report the value to the nearest hundredth (eg, *P* = .34). If the observed *P* value is greater than *.999*, it should be expressed as "*P* > *.99*". For a *P* value less than .001, report as "*P* < .001". Under no circumstance should the symbol "NS" or "ns" (for not significant) be used in place of actual *P* values.

"Trend": Use the word trend when describing a test for trend or dose-response. Avoid using it to refer to *P* values near but not below .05. In such instances, simply report a difference and the confidence interval of the difference (if appropriate), with or without the *P* value.

One-sided tests: There are very rare circumstances where a "one-sided" significance test is appropriate, eg, non-inferiority trials. Therefore, "two-sided" significance tests are the rule, not the exception. Do not report one-sided significance test unless it can be justified and presented in the experimental design section.

Statistical software: Specify in the statistical analysis section the statistical software used for analysis (version, manufacturer, and manufacturer's location), eg, SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

Comparisons of interventions: Focus on between-group differences, with 95% confidence intervals of the differences, and not on within-group differences.

***Post-hoc* pairwise comparisons**: It is important to first test the overall hypothesis. One should conduct *post-hoc* analysis if and only if the overall hypothesis is rejected.

Clinically meaningful estimates: Report results using meaningful metrics rather than reporting raw results. For example, instead of the log odds ratio from a logistic regression, authors should transform coefficients into the appropriate measure of effect size, eg, odds ratio. Avoid using an estimate, such as an odds ratio or relative risk, for a one unit change in the factor of interest when a 1-unit change lacks clinical meaning (age, mm Hg of blood pressure, or any other continuous or interval measurement with small units). Instead, reporting effort for a clinically meaningful change (eg, for every 10 years of increase of age, for an increase of one standard deviation (or interquartile range) of blood pressure), along with 95% confidence intervals.

Risk ratios: Describe the risk ratio accurately. For instance, an odds ratio of 3.94 indicates that the outcome is almost 4 times as likely to occur, compared with the reference group, and indicates a nearly 3-fold increase in risk, not a nearly 4-fold increase in risk.

Longitudinal data: Consider appropriate longitudinal data analyses if the outcome variables were measured at multiple time points, such as mixed-effects models or generalized estimating equation approaches, which can address the within-subject variability.

Sample size, response rate, attrition rate: Please clearly indicate in the methods section: the total number of participants, the time period of the study, response rate (if any), and attrition rate (if any).

Tables (general): Avoid the presentation of raw parameter estimates, if such parameters have no clear interpretation. For instance, the results from Cox proportional hazard models should be presented as the exponentiated parameter estimates, (ie, the hazard ratios) and their corresponding 95% confidence intervals, rather than the raw estimates. The inclusion of *P*-values in tables is unnecessary in the presence of 95% confidence intervals.

Descriptive tables: In tables that simply describe characteristics of 2 or more groups (eg, Table 1 of a clinical trial), report averages with standard deviations, not standard errors, when data are normally distributed. Report median (minimum, maximum) or median (25th, 75th percentile [interquartile range, or IQR]) when data are not normally distributed.

Figures (general): Avoid using pie charts; avoid using simple bar plots or histograms without measures of variability; provide raw data (numerators and denominators) in the margins of meta-analysis forest plots; provide numbers of subjects at risk at different times in survival plots.

Missing values: Always report the frequency of missing variables and how missing data was handled in the analysis. Consider adding a column to tables or a footnote that makes clear the amount of missing data.

Removal of data points: Unless fully justifiable, all subjects included in the study should be analyzed. Any exclusion of values or subjects should be reported and justified. When influential observations exist, it is suggested that the data is analyzed both with and without such influential observations, and the difference in results discussed.

Maika‘i (D. Varez)