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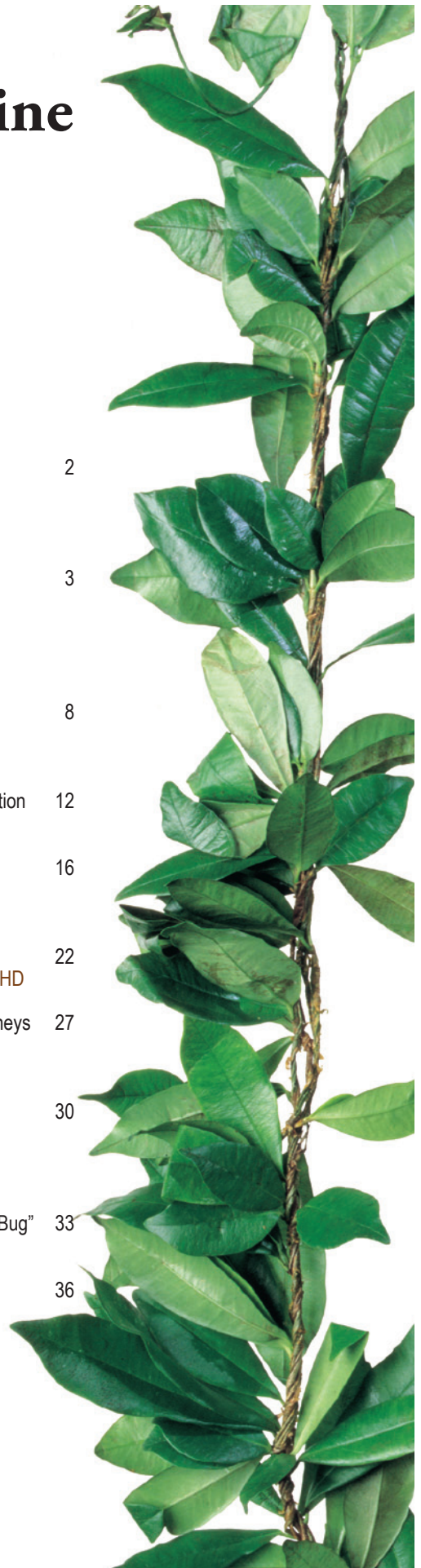
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## Guest Editors' Message: American College of Physicians, Hawai'i Chapter, Annual Meeting 2015

Gurdev Singh MD, FRCS, FACP; Donald Helman MD, FACP; and S. Kalani Brady MD, MACP

We are pleased to present the third supplement to the Hawai'i Journal of Medicine and Public Health based on the Annual Scientific Meeting of the Hawai'i Chapter of the American College of Physicians.

This year, the reviewers had the extremely difficult task of selecting from the 60 abstracts submitted, 10 for oral presentation and from the remaining 50 abstracts, 31 were chosen for poster presentation. The competition was indeed fierce.

Topics are in areas as widely ranging as obstetrics, orthopedics, molecular biology, challenges of healthcare delivery in a state with counties separated by ocean, and end of life issues. Included also are papers on exciting advances such as treatment of hepatitis C and the use of mobile apps in medical education, and intriguing articles on toothpicks and kissing bugs. We believe that the readers will find this supplement both as engaging and informative as we did.

Being a supplement dedicated to medical research, Hawai'i and the American College of Physicians, we would like to take the opportunity to congratulate Marjorie Mau MD, on her being awarded the Mastership of the American College of Physicians at this year's Annual National Meeting in Boston. We are sure our readers are aware of Dr. Mau's many accomplishments in the areas of Medical Research and Training locally, nationally and internationally.

Dr. Mau is the first woman in Hawai'i to be awarded this honor and brings the total number of Masters in this State to five. However, Dr. Mau was unable to attend the awards ceremony in Boston because at around the same time she gave birth to beautiful twins Mia Lauren Makaiwa and Ray Kevin Kaiapo.

We would like to thank Jenny Helman, Executive Director, ACP Hawai'i Chapter, and Drake Chinen, Layout Editor, Production Manager, and Peer Review Coordinator with the "Journal" without whom the work of the co-editors would have been impossible.



*Marjorie Mau MD*



# Real-world Experience with Sofosbuvir-based Regimens for Chronic Hepatitis C, Including Patients with Factors Previously Associated with Inferior Treatment Response

Christina J. Wu BS; Marina M. Roytman MD; Leena K. Hong PA-C; Leslie Huddleston PA-C, RN; Ruby Trujillo APRN; Alvin Cheung; Peter Poerzgen PhD; and Naoky C.S. Tsai MD

## Abstract

The introduction of sofosbuvir, a direct acting antiviral, has revolutionized the treatment of chronic hepatitis C virus (HCV). Phase 3 clinical trials have demonstrated the efficacy, simplicity, and tolerability of sofosbuvir-based regimens and report high rates of sustained virological response (SVR) rates. The purpose of this study was to assess whether clinical trial findings translate into a real-world setting, particularly with treatment of chronic HCV in our diverse, multiethnic population of Hawai'i. Retrospective analysis was performed for 113 patients with genotype 1-6 HCV infection being treated at the Queen's Liver Center between January 2014 and March 2015. SVR rates for our cohort were slightly lower than the rates published by the clinical trials. Data analysis also suggested that most baseline characteristics previously associated with inferior response might not be as significant for sofosbuvir-based regimens; in our cohort, male gender was the only factor significantly related to increased risk of virologic relapse. Pacific Islanders also had higher rate of relapse compared to other ethnic groups, but the small number of patients treated in this subgroup make it difficult to validate this finding. While newer all-oral treatment regimens have been introduced since this study, we highlight the importance of comparing real-world versus clinical trial results for new treatments, and provide data analyses for treatment of chronic HCV in Hawai'i.

## Keywords

HCV, sofosbuvir, Sovaldi, real-world, effectiveness

## Introduction

Hepatitis C virus (HCV) is the most common bloodborne infection, with at least 5.2 million people living with HCV in the United States.<sup>1</sup> If left untreated, chronic HCV leads to hepatic fibrosis, cirrhosis, and hepatocellular carcinoma. Consequently, it is the leading cause of end-stage liver disease and liver transplantation. The introduction of direct acting antiviral agents, in particular sofosbuvir (SOF), has revolutionized the treatment for chronic hepatitis C virus. With SOF-based regimens, we have achieved high cure rates and decreased the duration of treatment. Phase 3 clinical trials (Neutrino, Fission, Valence) have demonstrated the efficacy, simplicity, and tolerability of SOF-based regimens in a clinical trial setting. Patients in large clinical trials are often selected for high adherence and limited comorbidities. Therefore, similar treatment outcomes may be difficult to achieve with patients in a real-world setting. In order to determine whether the results from these Phase 3 trials will translate to a community setting, we report our experience at the Queen's Liver Center with these SOF-based regimens. Our patient population consists of the multiethnic population of Hawai'i, with

patients that have factors previously associated with inferior treatment response that would not have been included in the clinical trials. Through this retrospective review, we analyze the effectiveness, tolerability, adherence, and overall outcomes and compare them to those reported by the Phase 3 trials.

## Methods

### Study Population

We performed a retrospective review of patients  $\geq 18$  years of age with HCV genotype 1-6 infection being treated with SOF-based regimens at the Queen's Liver Center between January 2014 and March 2015. Both treatment-naïve and treatment-experienced patients were included in the review. Patients with any of the following were excluded from review: HIV co-infection, hepatitis B virus co-infection, liver transplant recipient.

### Study Design

Eligible patient charts were reviewed for demographic and relevant clinical data including age, sex, ethnicity, body mass index (BMI), comorbidities, presence of cirrhosis, HCV genotype, and prior treatment history. Patients with prior HCV treatment history were categorized based on their virological response during prior treatment; virologic relapse was defined as undetectable HCV RNA during treatment, but subsequent detectable HCV RNA after end of treatment. Presence of comorbidities was defined as having at least one of the following: chronic obstructive pulmonary disease, diabetes mellitus, coronary artery disease, or anxiety/depression. All patients were treated for chronic HCV according to AASLD guidelines at the time (Table 1), which were based on the results from the sofosbuvir Phase 3 trials.<sup>2,3</sup>

Baseline laboratory values were collected for all patients. Baseline values were defined as the most recent values prior

Population	Regimen	Duration
Genotype 1/4/5/6	Daily sofosbuvir (400 mg) + RBV* + Peg-IFN	12 weeks
Genotype 2	Daily sofosbuvir (400 mg) + RBV*	12 weeks
Genotype 3	Daily sofosbuvir (400 mg) + RBV*	24 weeks

\* RBV Dosage is weight-based: 1000 mg [ $<75$  kg] to 1200 mg [ $>75$ kg]

to starting HCV treatment. These values included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), creatinine, international normalized ratio (INR), hemoglobin (Hb), and platelets. After initiating treatment, these laboratory values were monitored every 4 weeks until end of treatment as well as post-treatment weeks 4 and 12.

This study was approved by the Institutional Review Board at the Queen's Medical Center of University of Hawai'i (RA-2014-048).

### **Efficacy Assessment**

Sustained virological response (SVR) is defined as the absence of detectable HCV RNA in serum after end of treatment, traditionally 24 weeks post-treatment. With the introduction of SOF-based regimens, SVR at 12 weeks post-treatment (SVR12) is now the standard clinical end point of successful antiviral treatment and was used as the primary end point in this study.<sup>4</sup> SVR was evaluated using plasma concentrations of HCV RNA collected throughout and after the course of treatment. Patients provided samples at baseline and treatment weeks 2, 4, 8, 12 (also weeks 16, 20, 24 for genotype 3) as well as post-treatment weeks 4 and 12. The COBRAS TaqMan HCV Test v2.0, which has a lower limit of quantification of 15 IU/mL, was used to quantify HCV RNA. Patients missing HCV RNA results at end of treatment, SVR4, or SVR12 were considered as lost to follow-up. Patients with detectable HCV RNA after receiving SOF-based treatment were categorized accordingly.

Status of IL28B genotype, which has been shown to be an indicator of response to HCV interferon-based therapy, was determined by amplification and sequencing of the rs12979860 single-nucleotide polymorphism. Due to the retrospective nature of this study, IL28B genotype information was not available for all patients.

### **Safety Assessment**

Patient charts were reviewed for adverse events as well as any abnormal findings on physical examination and clinical laboratory tests. Concomitant medications were also recorded.

### **Statistical Analysis**

Data analysis was performed using R v3.0.3 and done by intention-to-treat. Continuous variables were summarized by descriptive statistics (eg, mean, standard deviation, range). Categorical variables were summarized using counts of patients and percentages. Statistical tests were two-sided and levels were set at 0.05. Multivariate logistic regression analyses were performed to compare SVR rates for subgroups.

## **Results**

### **Baseline Characteristics and Demographics**

A total of 113 patients were identified. Baseline characteristics of the patient population are summarized and categorized by regimen in Table 2. Compared to other genotypes, there were fewer genotype 1 patients with cirrhosis included in the cohort as they were being treated with combination of sofosbuvir and

simeprevir, which was more tolerable for these patients and the only interferon-free option at the time. There were no other significant differences in baseline characteristics between each genotype group.

### **Efficacy**

Overall SVR12 rates for our patients were lower than the rates seen during clinical trials (Table 3). Similar to the Phase 3 studies, SVR rates for our cirrhotic patients were lower compared to their non-cirrhotic counterparts (genotype 1/4/5/6: 80% vs 83%; genotype 2: 83% vs 96%; genotype 3: 88% vs 95%). There were no other differences in SVR12 rates for subgroups including ethnicity, age, sex, BMI, and prior treatment history. No patients experienced virologic breakthrough while on SOF-based regimens. All 11 cases of virologic failure were due to relapse; there were 2 genotype 1a, 2 genotype 1b, 1 genotype 6, 3 genotype 2, and 3 genotype 3 patients. Male gender was a statistically significant predictor for relapse, while other baseline characteristics showed no statistical significance (Table 4). Pacific Islander patients also had higher rates of relapse with borderline significance.

There was high concordance (>97%) between SVR4 and SVR12 for all genotypes (Figure 1); 2 out of 104 patients that reached SVR4 had virologic relapse at SVR12.

### **Adherence and Safety**

Adverse effects and resulting treatment interruptions are summarized in Table 5. Most common side effects include fatigue, headache, and anemia. The rate of severe adverse effects was low in all genotype groups, particularly those on interferon-free regimens. Anemia, ribavirin dose reductions, and missed doses were more frequent among genotype 3 patients. Incidence and severity of adverse effects were similar across all subtypes.

Out of the 113 patients treated with SOF-based regimens, 6 were discontinued on treatment: two patients were genotype 1 patients that stopped treatment due to Peg-IFN intolerance; one genotype 2 patient was lost to follow-up; two genotype 3 patients discontinued treatment due to side effects while one was lost to follow-up.

## **Discussion**

In this retrospective review, we compared our real-world experience with SOF-based regimens to the results reported by Phase 3 trials. These comparisons are important since the outcomes from large-scale studies are not necessarily reflected in the real world, where there is less control over patient adherence, comorbidities, and other factors that may affect SVR rates. Additionally, our cohort consisted of a higher percentage of Asian, Pacific Islanders, older age, and cirrhotic patients.

The SVR rates among our patients at the Queen's Liver Center were lower than the rates reported in clinical trials. This can be attributed to the inclusion of patients who may be excluded from clinical trials, such as those with prior treatment history, non-adherence, and comorbidities that make them more likely to discontinue treatment or become lost to

Table 2. Baseline clinical characteristics of patient cohort, by genotype and regimen			
	GT 1, 4, 5, 6 SOF+PEG+RBV for 12 wks (N = 35)	GT2 SOF+RBV for 12 wks (N = 45)	GT3 SOF+RBV for 24 wks (N = 31)
Mean age (range)	56 (29-71)	61 (40-83)	58 (28-72)
Mean BMI (range)	27 (18-44)	28 (15-46)	30 (20-61)
Male sex – n (%)	18 (51)	25 (56)	15 (48)
<b>Ethnicity – n (%)</b>			
Caucasian	18 (51)	18 (40)	14 (45)
Asian	11 (31)	18 (40)	9 (29)
Hispanic/Latin	2 (6)	1 (2)	2 (7)
Pacific Islander	4 (12)	6 (13)	6 (19)
Other	0	2 (5)	0
<b>HCV subtype – n (%)</b>			
1a	19 (54)	--	--
1b	13 (37)	--	--
2	--	45 (100)	--
3	--	--	31 (100)
4	0	--	--
5	0	--	--
6	3 (9)	--	--
<b>Factors Previously Associated with Inferior Response</b>			
Age ≥ 50 – no. (%)	26 (74)	40 (89)	29 (94)
BMI ≥ 30 – no. (%)	9 (26)	20 (44)	10 (32)
HCV RNA ≥ 800,000 IU/ml – no. (%)	26 (74)	29 (64)	21 (68)
Cirrhosis – n (%)	5 (14)	19 (42)	12 (39)
<b>Prior treatment – n (%)</b>			
Null responder†	2 (6)	5 (11)	1 (3)
Partial Responder‡	2 (6)	0	1 (3)
Relapse	7 (20)	4 (9)	2 (6)
<b>IL28B genotype – n (%)*</b>			
CC	3 (9)	--	--
CT	11 (31)	--	--
TT	1 (3)	--	--
Not collected	20 (57)	--	--

\* Non-CC is associated with inferior response

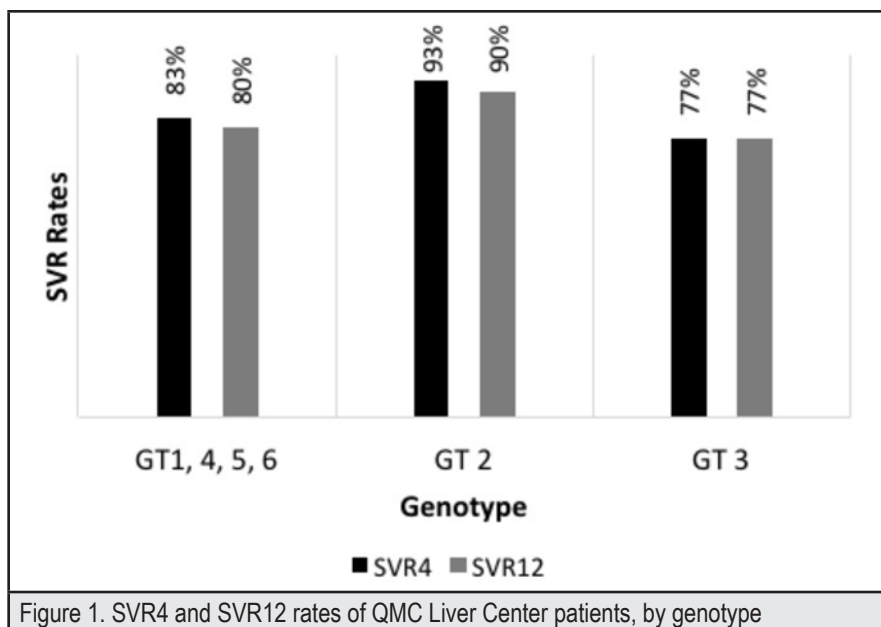
† Null response was defined as HCV RNA that did not decline by at least 2 log IU/mL at treatment week 12.

‡ Partial response was defined as HCV RNA levels that dropped by at least 2 log IU/mL at treatment week 12, but HCV RNA is still detectable at end of treatment.

Table 3. Comparison of SVR12 rates, Phase 3 Trial vs QMC Liver Center			
Study	Population	SVR12 Rates	
		Phase 3 Trial	QMC Liver Center
NEUTRINO	Genotype 1,4,5,6; treatment-naïve	90%	75%
FISSION	Genotype 2; treatment-naïve	97%	93%
VALENCE	Genotype 3; treatment-naïve or experienced	85%	81%

Baseline Characteristic	Odds Ratio (OR)	95% Confidence Intervals	P values
Age: ≥ 50 vs < 50	1.8947	0.2282 to 15.7303	.554
Gender: Male vs female	9.4828	1.1747 to 20.6342	.0348
BMI: ≥ 30 vs < 30	2.2769	0.6533 to 7.9361	.197
Viral load: HCV RNA ≥ 800,000 IU/mL vs < 800,000 IU/mL	0.8867	0.2443 to 3.2178	.855
Cirrhosis vs no cirrhosis	1.7824	0.5101 to 6.2279	.365
Prior treatment: Treatment-experienced vs treatment-naïve	2.1190	0.5726 to 7.8426	.261
Ethnicity: Pacific Islander vs non-Pacific Islander	3.4643	0.9094 to 13.1972	.0686

	GT 1, 4, 5, 6 SOF+PEG+RBV for 12 wks (N = 35)	GT2 SOF+RBV for 12 wks (N = 45)	GT3 SOF+RBV for 24 wks (N = 31)
<b>Discontinuing treatment – n (%)</b>			
Due to adverse effect	2 (6)	0	2 (6)
Lost to follow-up	0	1 (2)	1 (3)
<b>Adverse effects – n (%)</b>			
Any adverse effect during treatment	32 (91)	35 (78)	25 (81)
Serious adverse effect during treatment	4 (11)	1 (2)	1 (3)
<b>Common adverse effects – n (%)</b>			
Fatigue	24 (69)	22 (48)	12 (39)
Headache	7 (20)	10 (22)	4 (13)
Nausea	8 (23)	3 (7)	6 (19)
Anemia	8 (23)	5 (11)	5 (16)
Insomnia	6 (17)	3 (7)	2 (6)
Flu-like symptoms	12 (34)	3 (7)	3 (10)
Pruritus	10 (29)	6 (13)	4 (13)
Myalgia	7 (20)	2 (4)	1 (3)
Neutropenia	4 (11)	0	0
Depression and/or anxiety	4 (11)	2 (4)	0
<b>Anemia-related event – n (%)</b>			
Hemoglobin < 10 g/dL	4 (11)	3 (7)	5 (16)
Ribavirin dose change	4 (11)	6 (13)	4 (13)
Use of erythropoietin	2 (6)	0	0
<b>Missed dose – n (%)</b>	4 (11)	6 (13)	7 (23)



follow-up. Furthermore, our genotype 3 patients had a higher rate of missed doses compared to other genotypes, which was most likely due to longer duration of the regimen (24 weeks vs. 12 weeks). Most factors previously associated with inferior response such as advanced fibrosis, high viral load, or older age may not hold the same importance with SOF-based regimens as they did for interferon-based therapy; based on our analysis, only male gender still remains a statistically significant factor for increased rate of relapse. These findings suggest that most baseline characteristics may no longer be relevant predictive factors when treating patients with SOF-based regimens. While Pacific Islanders also had notably increased rate of relapse, a larger patient pool for this ethnic group is needed to further explore this observation.

Newer all-oral, ribavirin-free treatments for chronic HCV have been approved since this review, along with ongoing efforts to develop a pan-genotypic drug. With the rapid development of more effective and tolerable treatments, the SOF-based regimens discussed here have been replaced with newer options to treat chronic HCV in the United States, although these regimens may remain relevant in developing countries. Yet, this study highlights the importance of evaluating efficacy (ie, will this treatment work under ideal circumstances?) and effectiveness (ie, will this treatment work under real-world circumstances?). We also provide data for future analyses of HCV treatment among our multiethnic populations of Hawai'i.

### Conflict of Interest

None of the authors identify any conflict of interest.

### Acknowledgments

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# Provider Orders for Life-Sustaining Treatment Implementation and Training in Nursing Facilities in Hawai'i

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and Daniel Fischberg MD, PhD

## Abstract

*A Provider Orders for Life-Sustaining Treatment (POLST) document transforms medical wishes for end-of-life care into actionable medical orders. This study was conducted to assess the extent of POLST implementation amongst nursing facilities in Hawai'i. We performed a telephone survey. The survey instrument included questions about advance care planning processes, POLST training procedures, and implementation of the POLST paradigm. Data were collected in July 2014, the month POLST signatory capacity expanded to include Advance Practice Registered Nurses (APRNs). Of the 39 nursing facilities contacted, 23 (59%) responded. All but one facility had a POLST program in place. Social workers and nursing staff usually held the POLST discussions. Of the 23 responding facilities, 13 (57%) had at least one APRN provider, and 8 had APRNs involved in POLST discussions. In all but one instance, APRNs were also already signing the document. The percentage of residents with completed POLST forms per facility was reported to be over 50% for 20 out of 23 (87%) of responding nursing facilities with 10 (43%) reporting achieving 100% implementation rates. Training seminars and online educational materials were the main methods for training staff, with social workers and nurses being the focus for training. The results of this study demonstrate significant penetration of the Hawai'i POLST program into the nursing home community. Most nursing facilities required staff to undergo POLST training. Some facilities reported APRNs were already involved in signing the POLST form, only weeks after their signatory capacity was enacted.*

## Introduction

The Provider Orders for Life-Sustaining Treatment (POLST) form is a standardized, bright green form designed to translate patient preferences for end-of-life care into actionable medical orders and to convey those orders across different settings of care. The portability and range of treatment options make the POLST form particularly useful for nursing home patients.<sup>1</sup> Previous work has demonstrated the effectiveness of the POLST paradigm in ensuring end-of-life preferences are honored.<sup>2,3</sup>

States like Oregon, where the POLST program is more established, have demonstrated high rates of penetration of the POLST paradigm.<sup>4</sup> However no data are yet available regarding the adoption of the POLST paradigm in nursing facilities in Hawai'i. Hawai'i was an early adopter of the POLST paradigm, becoming just the eighth state in the United States to have a nationally endorsed program. As of July 1st 2014, the Hawai'i statute governing POLST expanded signatory authority in Hawai'i beyond physicians to include Advance Practice Registered Nurses (APRNs). This expansion in signatory authority prompted the present study. The objectives of this study were to assess the extent of POLST paradigm implementation among nursing facilities in Hawai'i, as well as to assess the training and involvement of APRNs in particular in the POLST paradigm.

## Methods

The research design was a cross-sectional telephone survey conducted in July 2014 using a modified instrument (Appendix 1).<sup>5</sup> The instrument included questions on facility size, advance care planning processes, POLST training procedures and percentage of residents who had a completed POLST form. A list of registered nursing facilities in the State of Hawai'i was obtained from the Department of Health website.<sup>6</sup> The nursing facilities surveyed ranged in size from 10 to 254 licensed beds. The administrator of each nursing home was contacted via telephone to participate in the survey. Up to three attempts were made to contact each administrator. Participation was voluntary and consent was obtained verbally via telephone at the time of the survey interview. Non-respondents and administrators who declined to participate were excluded from analysis. Survey responses were de-identified and no information was attributable to any individual facility. The descriptive results were then tabulated and analyzed.

The study was conducted according to United States and International standards of Good Clinical Practice, applicable government regulation and institutional research policies and procedures. The protocol was approved by the Queen's Medical Center Research and Institutional Review Committee and University of Hawai'i Human Subjects Committee.

## Results

Some 39 registered nursing facilities were called in July 2014 to participate in the study, of which 23 responses were obtained, resulting in a 59% response rate.

### 1. Implementation of POLST

Of the 23 facilities surveyed, all but one (96%) had a POLST paradigm program in place. That single facility cited having insufficient social workers to implement a POLST paradigm program at the present time, but did describe an intention to begin a program in the near future. Over half of the facilities had a POLST program in place for more than 2 years (Table 1). The resident POLST completion rate reported by each facility is shown in Table 2. Of the 23 facilities surveyed, 20 (87%) reported an implementation rate of greater than 50% and 10 facilities (43%) reported 100% implementation rates. All facilities surveyed stated that their goal was to obtain POLST forms for 100% of their residents.



## 2. POLST Training

Facilities reported that social workers and nursing staff were most frequently involved in providing POLST counseling for residents (Table 3). Less often physicians and APRN's provided POLST counseling and only one facility reported case managers had this role.

Social workers and nurses were the focus for staff being trained (Table 4). Only 2 facilities trained all staff. However, most facilities when questioned, did mention that all staff should be trained, rather than focusing on a specific group. Of the 13 facilities that reported having APRN providers, 8 reported APRNs were involved in POLST counseling and 3 reported APRNs were included in POLST training.

The training methods used by nursing facilities varied (Table 5). Most facilities (60%) held training seminars on the POLST paradigm program. Online materials such as those found on the *Kokuama* website<sup>7</sup> were often used, as well as facility-specific material. Videos, specifically the ACP Decisions videos produced by the Nous Foundation were also used by many facilities. Fewer facilities reported making use of POLST conferences produced by Hawai'i Medical Service Association, the largest health insurance provider in Hawai'i.

## Discussion

We found that there is good penetration of the Hawai'i POLST paradigm program into the nursing home community in Hawai'i. Nearly all responding facilities (96%) had a POLST paradigm program in place and nearly half (48%) reported having their program in place for over 2 years. Furthermore, most facilities (87%) had over 50% resident POLST completion rates. This finding is encouraging compared to POLST implementation rates nationally. A cross-sectional sample study conducted in 2004 showed that fewer than 1 in 5 US nursing homes participated in end-of-life programs, with the largest proportion participating in POLST (13.3%).<sup>8</sup> Hawai'i also does well when compared to states where the POLST paradigm is more established. In Oregon 71% of facilities reported using the POLST for at least half of their residents.<sup>4</sup> In California, 54% of nursing home residents were estimated to have a POLST.<sup>9</sup>

The apparent success of the Hawai'i POLST program could be attributed to several factors. We found that most nursing facilities in Hawai'i required staff to undergo POLST training. This could increase awareness and enable discussions of POLST with nursing home residents. Furthermore, Hawai'i Medical Service Association (HMSA), which is the leading health insurance provider in the state has been implementing measures to incentivize advance care planning. In addition, HMSA has been conducting POLST seminars which some facilities claimed they were using for training staff on POLST. Finally, we found that APRN providers were already involved in signing the POLST form, and this was within weeks of their signatory capacity being enacted. Not all nursing facilities had APRN providers (only 13 of the 23 had them); hence the numbers of APRNs involved in POLST discussions were lower than might have been expected.

Duration of POLST program	Number of Facilities
None	1
< 6 months	1
6 months to 1 year	5
1 to 2 years	5
> 2 years	11

Residents with completed POLST (estimates)	Number of Facilities
0-25%	3
56-50%	0
51-75%	5
76-99%	5
100%	10

Provider Type	Number of Facilities
Social service	20
Nursing	16
Physicians	12
APRN provider	8
Case manager	1

Provider Type	Number of Facilities
Social service	19
Nursing	22
Physicians	2
APRN provider	3
Case manager	1
All staff	2

Training Method	Percentage Used
Training seminar	60%
Online material	39%
Facility material	35%
Videos	30%
POLST conference	13%

## Strengths and Limitations

This is the first statewide study on the POLST paradigm to be conducted in Hawai'i. The study included nursing facilities on the islands of Hawai'i, Kaua'i, Maui, and O'ahu. As the first study on POLST in the state of Hawai'i, it provides valuable data on the penetration of the POLST program so far. These findings can serve as a baseline for comparison by future surveys to measure progress of the POLST paradigm in Hawai'i. The limitations of this study include the potential for response bias as nursing homes with POLST programs in place may have been more likely to participate. In addition, the responses obtained were based on estimates from an individual at each facility and could not be verified by chart review.

## Future Directions

The POLST paradigm functions optimally when all settings for care actively participate. Successful expansion to appropriate populations at high risk for critical illness is needed across these settings in Hawai'i including primary care and acute care settings in addition to the long-term care setting studied here. Recent pay for quality initiatives may help advance POLST implementation rates across settings. Future studies will be needed to assess and monitor the progress of the POLST paradigm program across all settings of care.

Promotion of greater knowledge and awareness among the public and healthcare providers about advance care planning in general, and the POLST paradigm in particular, is important in advancing POLST implementation. Education and training on the POLST paradigm should be made widely available. This study highlighted a need to focus on advancing education and training on the POLST paradigm for APRN providers in Hawai'i given their new signatory role.

Finally, the results of this study showing the early successful adoption of the POLST paradigm program in Hawai'i's long-term care community may lend support to the development of a state-wide POLST registry in Hawai'i to promote timely access to POLST forms.

*Disclaimer: The findings of this study do not necessarily represent the views of The Queen's Medical Center or University of Hawai'i.*

## Conflict of Interest

None of the authors identify any conflict of interest.

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## Appendix 1

### POLST NURSING FACILITY QUESTIONNAIRE

Thank you for considering participating in this brief survey on Provider Orders for Life-Sustaining Treatment (POLST). I am gathering information from facilities to evaluate the spread of the POLST program throughout Hawai'i. We expect the information gathered to help in advancing Hawai'i's POLST program statewide. All data will be de-identified for analysis and no information will be attributable to any individual facility. Your participation in this survey is completely voluntary. If you agree to participate, the survey would typically take 5 to 10 minutes for us to complete.

General POLST Information	
Facility Name	
Facility contact/location	
Size of facility	<input type="checkbox"/> <50 beds <input type="checkbox"/> 50 to 150 beds <input type="checkbox"/> > 150 beds
Have you implemented POLST in your facility?	<input type="checkbox"/> No <input type="checkbox"/> <6 months <input type="checkbox"/> 6 mo – 1 year <input type="checkbox"/> 1-2 years <input type="checkbox"/> > 2 years
If you have not implemented, when are you planning to implement POLST to your facility?	<input type="checkbox"/> <3 months <input type="checkbox"/> <6 months <input type="checkbox"/> 6 mo-1 year <input type="checkbox"/> 1-2 years <input type="checkbox"/> Not planning. What are the barriers?
What forms do you use to ensure patient wishes are followed regarding life sustaining treatments (check all that apply)	<input type="checkbox"/> Living Will/ Advance Directive <input type="checkbox"/> Facility Form <input type="checkbox"/> POLST <input type="checkbox"/> None
Who typically does advance care planning with residents? (check all that apply)	<input type="checkbox"/> Physician <input type="checkbox"/> PA <input type="checkbox"/> Social Service <input type="checkbox"/> Nursing <input type="checkbox"/> Case managers <input type="checkbox"/> APRN

POLST Implementation and Training	
How widely is POLST implemented in your facility?	<input type="checkbox"/> 0-25% <input type="checkbox"/> 26-50% <input type="checkbox"/> 51-75% <input type="checkbox"/> 76-99% <input type="checkbox"/> 100%
What is the total percent of the facility that POLST is planned to be implemented	<input type="checkbox"/> 0-25% <input type="checkbox"/> 26-50% <input type="checkbox"/> 51-75% <input type="checkbox"/> 76-99% <input type="checkbox"/> 100%
How have you implemented POLST in your facility? (check all that apply)	<input type="checkbox"/> Training seminar <input type="checkbox"/> Facility communications <input type="checkbox"/> Provide professional education material <input type="checkbox"/> Mandatory Curriculum <input type="checkbox"/> Web/Online training <input type="checkbox"/> Provide patient/resident education material
What training materials are you using? (check all that apply)	<input type="checkbox"/> POLST conference training material <input type="checkbox"/> Facility materials <input type="checkbox"/> Web download material <input type="checkbox"/> Other:
Who is being trained? (check all that apply)	<input type="checkbox"/> All staff <input type="checkbox"/> Physician <input type="checkbox"/> Advanced Practice Nurse <input type="checkbox"/> Social workers <input type="checkbox"/> Case managers <input type="checkbox"/> Clergy <input type="checkbox"/> Admissions <input type="checkbox"/> Other:
Are there APRN providers, if yes: role in POLST	<input type="checkbox"/> None <input type="checkbox"/> Education <input type="checkbox"/> Counseling patient/resident <input type="checkbox"/> Signing the POLST form
Permission to send relevant information via email related to POLST education?	<input type="checkbox"/> Yes <input type="checkbox"/> No If yes, contact information:

# Gender Disparities among Intracerebral Hemorrhage Patients from a Multi-ethnic Population

Alexandra Galati BA; Sage L. King MPH; and Kazuma Nakagawa MD

## Abstract

**Background:** Intracerebral hemorrhage (ICH) is a hemorrhagic stroke with high morbidity and mortality. Recent studies have shown that minorities such as Native Hawaiians and other Pacific Islanders (NHOPI) with ICH are significantly younger compared to whites. However, the interaction of race and gender, and its impact on observed disparities among a multi-ethnic population in Hawai'i, have not been studied.

**Methods:** Consecutive ICH patients (whites, Asians or NHOPI), who were hospitalized at a single tertiary center on O'ahu between 2006 and 2013 were retrospectively studied. Clinical characteristics were compared between men and women among the entire cohort, and within the major racial groups.

**Results:** A total of 791 patients (NHOPI 19%, Asians 65%, whites 16%) were studied. Overall, men were younger than women ( $62 \pm 16$  years vs  $67 \pm 18$  years respectively,  $P < .0001$ ). Among whites, ages of men and women were similar (men:  $67 \pm 14$  years vs women:  $67 \pm 17$  years,  $P = .86$ ). However, among Asians, men were significantly younger than women (men:  $63 \pm 16$  years vs women:  $70 \pm 17$  years,  $P < .0001$ ). Among NHOPI, ages of men and women were similar (men:  $53 \pm 15$  years vs women:  $56 \pm 17$  years,  $P = .34$ ), although NHOPI group overall had significantly younger age compared to whites and Asians (NHOPI:  $54 \pm 16$  years vs whites:  $67 \pm 15$  years,  $P < .0001$ ; vs Asians:  $66 \pm 17$ ,  $P < .0001$ ).

**Conclusions:** Overall, men have younger age of ICH presentation than women. However, this observed gender difference was most significant among Asians, but not among whites or NHOPI.

## Introduction

Spontaneous intracerebral hemorrhage (ICH) is a hemorrhagic stroke with high morbidity and mortality, and accounts for 10-15% of the approximately 700,000 annual strokes in the United States.<sup>1-3</sup> Recent studies have shown that minorities such as African Americans, Native Hawaiian/other Pacific Islanders (NHOPI), and some Asians with ICH are younger and have higher cardiovascular risk factors compared to whites with ICH.<sup>4</sup> Furthermore, younger minorities with ICH have been reported to have worse outcomes compared to whites.<sup>5-7</sup> In addition to racial disparities, studies have shown gender disparities—men having higher incidence of ICH compared to women.<sup>8,9</sup> However, the variation of gender differences for each racial group with ICH have not been adequately studied. This study sought to assess the gender differences in the clinical characteristics for the entire ICH population and for each major racial group that were hospitalized at a tertiary stroke center on O'ahu.

## Methods

The Queen's Medical Center (QMC) Research and Institutional Review Committee approved to conduct this retrospective study of all spontaneous ICH patients hospitalized at QMC between January 1, 2006 and December 31, 2013. QMC is a 505-bed medical center located in Honolulu, O'ahu, and the largest hospital in Hawai'i. During the study period, QMC was the

only Joint Commission-certified Primary Stroke Center, the only American College of Surgeons-verified trauma center with full neurosurgical coverage, and the only dedicated NSICU in the state of Hawai'i.

## Patients

All patients hospitalized at QMC between January 1, 2006 and December 31, 2013 with a diagnosis of spontaneous ICH were retrospectively identified using the institution's stroke database. Case ascertainment of admissions for ICH was conducted by prospective clinical identification and retrospective verification by a review of electronic medical record (Epic). Patients with ICH related to trauma, ruptured cerebral aneurysm or ischemic stroke with hemorrhagic conversion were excluded since these conditions are managed differently from spontaneous ICH.

## Data Collection

Patient demographics and medical history, including history of hypertension, diabetes mellitus, atrial fibrillation/atrial flutter, coronary artery disease (CAD) or prior myocardial infarction (MI), and smoking, were obtained from the database. Initial Glasgow Coma Scale score and coagulopathy were obtained from the electronic medical record. Coagulopathy was defined as the initial international normalized ratio  $> 1.4$ . All initial head computed tomography scans were retrospectively reviewed by a board-certified neurologist/neurointensivist using a standardized protocol, blinded to race, gender and clinical data. Hematoma volume was measured using the ABC/2 method.<sup>10</sup> Presence of intraventricular hemorrhage (IVH) was recorded, and ICH location was coded as basal ganglia, lobar, thalamus, brainstem, cerebellar or primary IVH.

Race and ethnicity information were collected by administrative personnel during the registration process or by the nurses during the intake process on admission. Race was categorized as NHOPI, Asian, or white, black or "other" race. Due to the low number of black patients in Hawai'i, this racial group was combined with the "other" group in subsequent analyses. Since mixed racial background is relatively common in Hawai'i, race was defined as the racial/cultural background that the patient most closely associated with, and was based on patient self-identification or family's identification if the patient was incapacitated.

## Statistical Analysis

Data were analyzed using SPSS (SPSS 22.0, IBM SPSS Inc., New York, USA). Patient characteristics were summarized using descriptive statistics appropriate to variable type. The NHOPI

and Asian racial groups were compared to white subjects (used as the reference group) using chi-squared test for categorical data and 2-tailed t-test for normally distributed, continuous variables. Age of presentation of intracerebral hemorrhage was compared between men and women among the entire cohort, and within each of the major racial groups. Data are presented as means  $\pm$  SD, and levels of  $P < .05$  were considered statistically significant.

## Results

A total of 825 spontaneous ICH patients hospitalized at QMC between 2006 and 2013 were initially identified. Among them, 34 patients with “other” race were excluded for the analysis. As a result, a total of 791 patients (NHOPI 19%, Asians 65%, whites 16%) were included in the final analyses. The clinical characteristics of ICH patients by gender are shown in Table 1. Overall, men were younger compared to women ( $62 \pm 16$  years vs  $67 \pm 18$  years respectively,  $P < .0001$ ). Men had a higher incidence of smoking as compared to women (36% vs 22% respectively,  $P < .0001$ ). There were no other significant differences in risk factors between men and women overall.

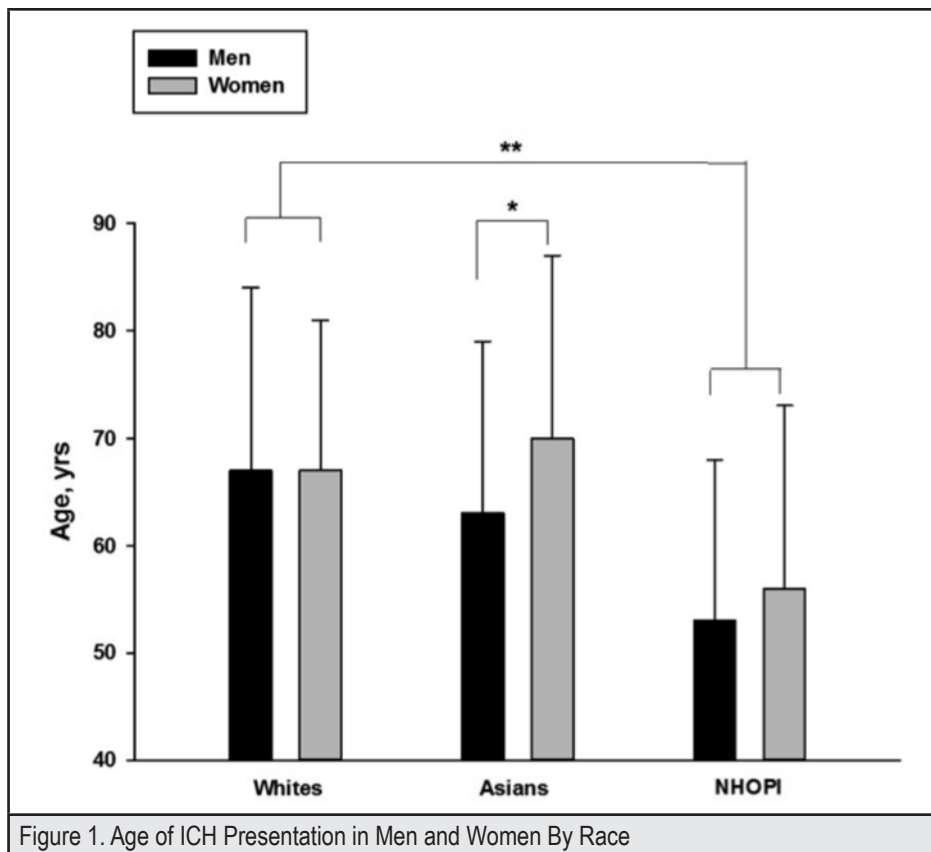
	Men (N = 447)	Women (N = 344)	P
Age, years	62 $\pm$ 16	67 $\pm$ 18	<.0001
Race			.41
Whites	79 (18)	49 (14)	
Asians	282 (63)	229 (67)	
NHOPI	86 (19)	66 (19)	
Risk factors			
Hypertension	360 (81)	258 (75)	.06
Diabetes mellitus	122 (27)	77 (22)	.12
Hypercholesterolemia	171 (38)	123 (36)	.47
Coronary artery disease or prior MI	63 (14)	36 (11)	.13
Atrial fibrillation	63 (14)	44 (13)	.60
Coagulopathy	53 (12)	42 (12)	.88
Smoking	162 (36)	76 (22)	<.0001
Hematoma location			.02
Basal ganglia	148 (33)	107 (31)	
Thalamus	94 (21)	45 (13)	
Lobar	122 (27)	122 (36)	
Brainstem	24 (6)	17 (5)	
Cerebellum	45 (10)	36 (10)	
Primary IVH	14 (3)	17 (5)	
Any IVH	209 (47)	147 (43)	.26
Hematoma volume (cm <sup>3</sup> )	34 $\pm$ 45	36 $\pm$ 47	.57
Hospital length of stay, days	11 $\pm$ 17	9 $\pm$ 11	.008
Mortality	107 (24)	92 (27)	.37

NHOPI, Native Hawaiians and other Pacific Islanders; MI, myocardial infarction; IVH, intraventricular hemorrhage. Data are presented as mean  $\pm$  SD or n (%).

The gender comparison for each racial group is shown in Table 2. Among whites, the mean age of men and women were not significantly different (men:  $67 \pm 14$  years vs women:  $67 \pm 17$  years,  $P = .86$ ). Among Asians, men were significantly younger than women (men:  $63 \pm 16$  years vs women:  $70 \pm 17$  years,  $P < .0001$ ) (Figure 1). Among NHOPI, mean age of men and women was similar (male:  $53 \pm 15$  years vs female:  $56 \pm 17$  years,  $P = .34$ ), although the NHOPI group overall was significantly younger at age of spontaneous ICH as compared to whites and Asians (NHOPI:  $54 \pm 16$  years vs whites:  $67 \pm 15$  years,  $P < .0001$ ; vs Asians:  $66 \pm 17$ ,  $P < .0001$ ) (Figure 1).

	Men	Women	P
<b>Whites (N = 128)</b>			
N	79	49	
Age, years	67 $\pm$ 17	67 $\pm$ 14	.86
Hypertension	57 (72)	30 (61)	.20
Diabetes mellitus	15 (19)	8 (16)	.70
Hypercholesterolemia	34 (43)	17 (35)	.35
Coronary artery disease or prior MI	22 (28)	3 (6)	.003
Atrial fibrillation	17 (22)	11 (22)	.90
Coagulopathy	13 (17)	7 (14)	.74
Smoking	30 (38)	9 (18)	.02
<b>Asians (N = 511)</b>			
N	282	229	
Age, years	63 $\pm$ 16	70 $\pm$ 17	<.0001
Hypertension	234 (83)	177 (77)	.11
Diabetes mellitus	75 (27)	45 (20)	.07
Hypercholesterolemia	110 (39)	87 (38)	.81
Coronary artery disease or prior MI	31 (11)	23 (10)	.73
Atrial fibrillation	35 (12)	25 (11)	.60
Coagulopathy	29 (10)	24 (11)	.94
Smoking	98 (35)	43 (19)	<.0001
<b>NHOPI (N = 152)</b>			
N	86	66	
Age, years	53 $\pm$ 15	56 $\pm$ 17	.34
Hypertension	69 (80)	51 (77)	.66
Diabetes mellitus	32 (37)	24 (36)	.92
Hypercholesterolemia	27 (31)	19 (29)	.73
Coronary artery disease or prior MI	10 (12)	10 (15)	.52
Atrial fibrillation	11 (13)	8 (12)	.90
Coagulopathy	11 (13)	11 (17)	.50
Smoking	34 (40)	24 (36)	.69

NHOPI, Native Hawaiians and other Pacific Islanders; MI, myocardial infarction. Data are presented as mean  $\pm$  SD or n (%).



## Discussion

This multi-ethnic ICH study demonstrated that men with ICH are younger than women with ICH, which is consistent with prior studies.<sup>8,9</sup> However, this gender difference in age was mainly driven by the Asian group and not by whites or NHOPI.

Gender differences in age of presentation have been reported in other cardiovascular diseases. For example, women have been shown to develop coronary heart disease 10-15 years later than men.<sup>11</sup> Similarly, women have been shown to develop atrial fibrillation at an older age compared to men who develop atrial fibrillation.<sup>12</sup>

Reasons for gender disparities in cardiovascular diseases are complex, and likely involve both biological and social determinants of the disease. Hormonal differences in men and women have been shown to account for some of the gender disparities. Estrogen is known to be cardioprotective in a number of ways.<sup>13</sup> In animal studies, estrogen inhibits formation of atherosclerotic plaque via suppressing proliferation of smooth muscle cells, decreasing lipoprotein(a) sequestration and oxidation as well as preventing platelet thrombi formation.<sup>14,15</sup> Androgens, on the other hand, increase proliferation of smooth muscle cells,<sup>16</sup> which may hasten the progression of atherosclerosis. Sex hormones affect cerebrovascular pathways as well. Estrogen influences cerebral vascular reactivity by increasing the production of and the sensitivity to vasodilatory factors,<sup>17-19</sup> thus decreasing vascular tone. In comparison, androgens increase vascular tone.<sup>20-22</sup> Estrogen shifts the balance

of prostanoid production toward vasodilatory factors such as prostacyclin (PGI<sub>2</sub>); testosterone, on the other hand, shifts the balance toward vasoconstrictors such as thromboxane.<sup>12</sup> Estrogen has also been shown to be neuroprotective by improving blood flow during and after ischemic cerebrovascular events.<sup>23-25</sup>

Although these biological differences may have contributed to the disparities seen in this study, differences in social and behavioral factors such as diet, lifestyle, and medication compliance may have also affected the gender differences. Since the gender difference was more significant among one ethnic group compared to other groups, more non-biological factors such as cultural factors may have accounted for our observation. Longitudinal studies demonstrate that gender is an important predictor of healthcare utilization; women utilize health services more frequently than men do.<sup>26</sup> For example, women in the United Kingdom are twice as likely to have visited their primary care physician within the last year compared to men.<sup>27</sup> Similarly, men may be more reluctant than women to consult a physician,<sup>28,29</sup> putting them at risk of delayed diagnosis and treatment. Men tend to use emergency services more often than women, whereas women make use of preventive services more often than men.<sup>30</sup> Along with utilizing more primary care services as compared to men, it has been shown that women implement lifestyle changes according to dietary recommendations more so than their male counterparts.<sup>31</sup> Research demonstrates that women with heart failure were more adherent to a salt-restricted diet compared to men.<sup>32</sup>

Unfortunately, there is paucity of data on gender disparities in healthcare access and outcome among Asian Americans. One study showed that Chinese immigrant men were less likely to be adherent to their hypertensive medications compared to Chinese immigrant women.<sup>33</sup> Further research is needed to thoroughly assess the underlying causes of the gender disparities found within the Asian American population.

This study has several limitations. First, the data is derived from a single-center study and thus may lack generalizability. Second, because our institution is a tertiary referral center, there may have been a referral bias toward more severe ICH patients as ICH patients with small hematomas and minor neurologic symptoms may not be transferred to our facility. It is also possible that some of the older ICH patients with preexisting do-not-resuscitate orders or those with terminal illness may not have been transferred to our facility, creating a possible selection bias toward younger ICH patients. Lastly, Asian race was not further specified (ie, Japanese, Filipino, Chinese, Korean) and thus it is unclear if similar age and gender disparities exist within each specific Asian race.

This study demonstrates not only racial disparities in stroke risk factors, but also gender disparities in stroke risk factors in the state of Hawai'i, which have not been previously studied. Further studies are needed to determine factors contributing to the gender disparity in this multi-ethnic population.

### Conflict of Interest

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# Presentation of Anatomical Variations Using the Aurasma Mobile App

Trudy Hong BA; Georg Bézard MD; Beth K. Lozanoff BS; Steven Labrash CFSP; and Scott Lozanoff PhD

## Abstract

*Knowledge of anatomical variations is critical to avoid clinical complications and it enables an understanding of morphogenetic mechanisms. Depictions are comprised of photographs or illustrations often limiting appreciation of three-dimensional (3D) spatial relationships. The purpose of this study is to describe an approach for presenting anatomical variations utilizing video clips emphasizing 3D anatomical relationships delivered on personal electronic devices. An aberrant right subclavian artery (ARSA) was an incidental finding in a routine dissection of an 89-year-old man cadaver during a medical student instructional laboratory. The specimen was photographed and physical measurements were recorded. Three-dimensional models were lofted and rendered with Maya software and converted as Quicktime animations. Photographs of the first frame of the animations were recorded and registered with Aurasma Mobile App software ([www.aurasma.com](http://www.aurasma.com)). Resulting animations were viewed on mobile devices. The ARSA model can be manipulated on the mobile device enabling the student to view and appreciate spatial relationships. Model elements can be de-constructed to provide even greater spatial resolution of anatomical relationships. Animations provide a useful approach for visualizing anatomical variations. Future work will be directed at creating a library of variants and underlying mechanism of formation for presentation through the Aurasma application.*

## Keywords

*Aberrant right subclavian artery, bicarotid trunk, Aurasma app, anatomical animation*

## Introduction

Anatomical variations are frequently described in the literature and encountered in the medical setting. The ability to recognize structural variants is crucial since it can help to reduce confusion and possibly prevent serious injuries in patients during surgical procedures. Although the literature is replete with reports of anatomical variations, most descriptions are confined to two-dimensional (2D) portrayals due to the hardcopy, page-based communication medium<sup>1</sup> and hence, do not demonstrate important three-dimensional (3D) spatial relationships. The use of electronic media and animations to present variations and underlying basic morphogenetic mechanisms thus represents a major technological advantage.

Current medical education paradigms include a wide variety of biomedical communications media. In fact, many programs require the use of personal electronic devices and use them heavily as a means to instruct. The devices are useful in anatomy instruction given the large number of applications currently available and their ease of use. Anatomy applications are especially popular with students since they can be conveniently accessed with smartphones, and allow for clear visualization, learning, practice, and eventually easier recall of complex structures and spatial relationships described in detail in text-

books and encountered in the dissection lab. Regarding unique anatomical variations, custom 3D models of specific structures can be created easily and presented effectively with augmented reality applications. This is particularly useful when combined with a gross anatomical dissection course because the atypical structures can be communicated to students even when they may not be encountered directly in the anatomy laboratory.

One augmented reality tool, called Aurasma, seems particularly well suited for communicating anatomical variations. Aurasma is a popular application that recognizes physical images and real-life objects, and instantly activates realistic 3D digital models and animations. This free mobile app can be downloaded on virtually any smartphone or tablet and is currently used in a variety of settings including advertisements, apparel, locations, and catalogues ([www.aurasma.com](http://www.aurasma.com)). In anatomy education, 2D trigger images of anatomical structures can be overlaid with custom 3D model animations to create an Aura, or augmented reality experience. Images can then be quickly scanned and activated during poster presentations at conferences or while reading textbooks and journal articles to display 3D animations without interrupting the flow of the presentation or text (Figure 1).

The aim of this study was to implement Aurasma for the purpose of communicating common anatomical variations. As an example, animations of an anatomical variant, an aberrant right subclavian artery (ARSA) was created and implemented. The models can be generated easily and are valuable for demonstrating 3D relationships even within the confines of a 2D communication medium.

## Methods

Anatomical specimens utilized for this study were drawn from permanent donations and all activities conformed to standard operating procedures of the Willed Body Program at the John A. Burns School of Medicine, University of Hawai'i, Manoa and available for public review.<sup>2</sup>

A case of ARSA was identified as an incidental finding in an 89-year-old man during a routine gross anatomy dissection in the medical student instructional laboratory. The individual had a history of cardiopulmonary disease and cardiopulmonary arrest was the cause of death. Photographs were taken of the relevant features and measurements were recorded using calipers (Helios).

To model the ARSA, a previously obtained formalin fixed heart and great vessels (non ARSA variant) was dissected free of surrounding tissue, removed and washed. The specimen was



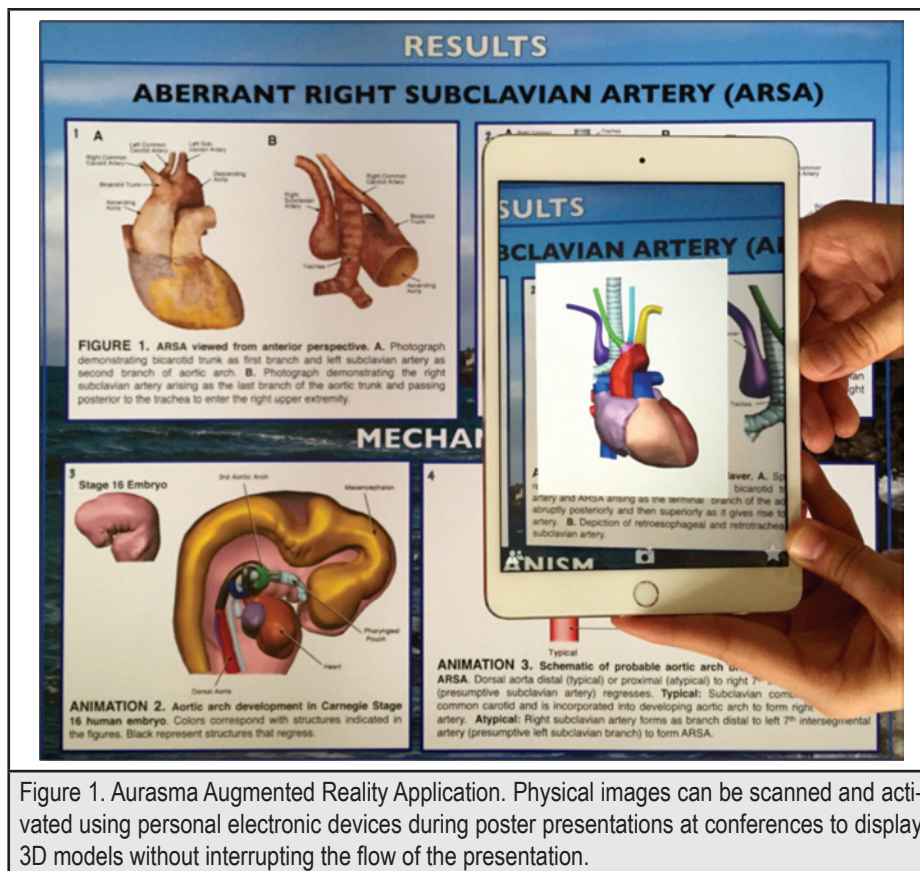
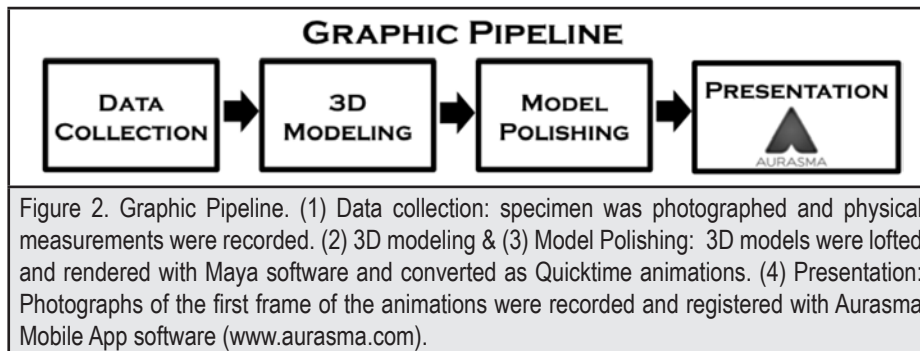


Figure 1. Aurasma Augmented Reality Application. Physical images can be scanned and activated using personal electronic devices during poster presentations at conferences to display 3D models without interrupting the flow of the presentation.



rinsed for 12 hours in running tap water and subsequently excess moisture was removed. The heart chambers and great vessels were injected with *inr-seel* (Dodge Company, NY) to retain patency utilizing a Heavy Compound Injector with an injection nozzle. The specimen was subjected to room temperature plastination utilizing the routine steps of dehydration, defatting, forced impregnation and curing.<sup>3</sup>

The plastinated heart was subjected to a graphics pipeline following Tunali, et al, (Figure 2).<sup>4</sup> The plastinated normal (typical) specimen of the aortic arch outflow was digitized using a hand-held scanner (Polhemus, MA). A wire mesh was generated and exported as an .obj file into Maya ([www.autodesk.com](http://www.autodesk.com))

where it was lofted based on the measurements recorded from the ARSA specimen and polished. Surface models were color-coded exported to QuickTime ([gufile.com](http://gufile.com)) for animation and depiction of spatial relationships.

The animation was then prepared for viewing through Aurasma ([www.aurasma.com](http://www.aurasma.com)). Two-dimensional trigger images were overlaid with custom QuickTime 3D animations to create an Aura (augmented reality experience). To activate the Aura: (1) Download free Aurasma app from the App Store, (2) Follow “JABSOMAnatomy” channel, (3) Scan Figure 6 and 7 to launch 3D model digital overlay.

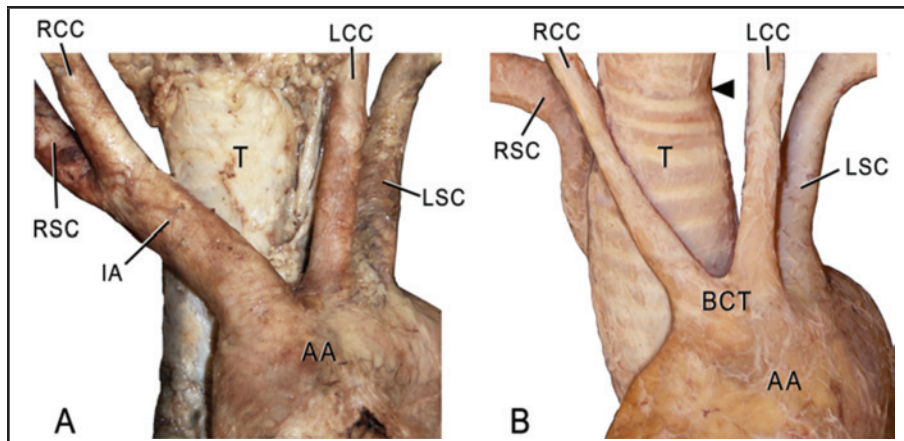


Figure 3. A) Typical and B) atypical morphological features of the cardinal branches of the aortic arch. A) The aortic arch (AA) typically gives rise to three cardinal branches including the innominate artery (IA, aka Brachiocephalic artery) with right subclavian (RSC) and common carotid branches (RCC), the left common carotid (LCC) and the left subclavian arteries (LSC). B) In the ARSA patient, however, the first branch is a bicarotid trunk (BCT), followed by the left subclavian artery while the right subclavian artery forms the third tributary. T= trachea.

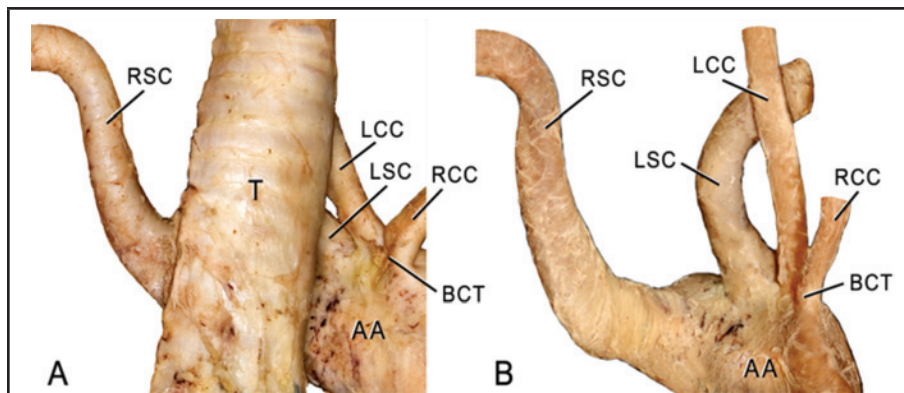


Figure 4. Morphological features of ARSA. A). Right subclavian artery (RSC) formed as the third branch distal to the left subclavian artery (LSC) coursing horizontally and posteriorly around the trachea (T) and esophagus. B). Right subclavian artery turned abruptly and at a right angle to ascend, and then curved sharply again to enter right upper extremity (trachea removed to show path RSC took to enter right upper extremity). LCC = Left common carotid, RCC= Right common carotid, BCT = Bicarotid trunk, AA= Aortic arch.

## Results

### ARSA Identification

The overall cardiac morphology and spatial relationships appeared normal; however, the aortic outflow displayed atypical morphology (Figure 3). The right subclavian was not present as the first branch of the aortic arch. Rather, right and left common carotid arteries arose from a common bicarotid (Figure 3). The left subclavian artery branched next and it continued superiorly curving laterally into the upper extremity. The right subclavian formed as the third branch distal to the left subclavian artery coursing horizontally and posteriorly around the trachea

and esophagus (Figure 4). It continued for 34.2 mm and then turned abruptly and at a right angle to ascend for 54.8 mm and curving sharply again to enter the right upper extremity (Figure 4). A Kommerrell diverticulum was not evident. The trachea also displayed unique features including a constriction near the horizontal portion of the right subclavian (Figure 5). The contour of the trachea was also novel displaying a sharp, flat right border while the left border showed a more typical curved, rounded edge and the posterior tracheal membrane was atypically wide (Figure 5).

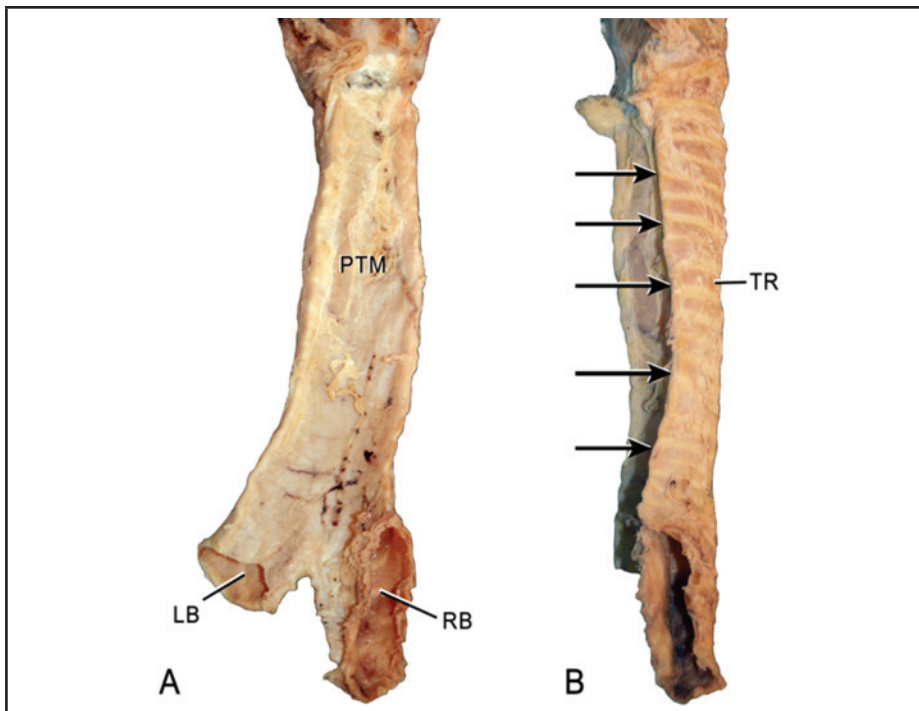


Figure 5. Atypical constriction of trachea by ARSA. A) Posterior tracheal membrane (PTM) was atypically wide. B) Arrows point to the posterior edge of the tracheal rings that ended abruptly and appeared shorter than typical suggesting that tracheal development was affected by the ARSA. Contour of trachea displayed typical curved rounded edge on left but sharp flat right border on right. LB= Left bronchus, RB= Right bronchus.

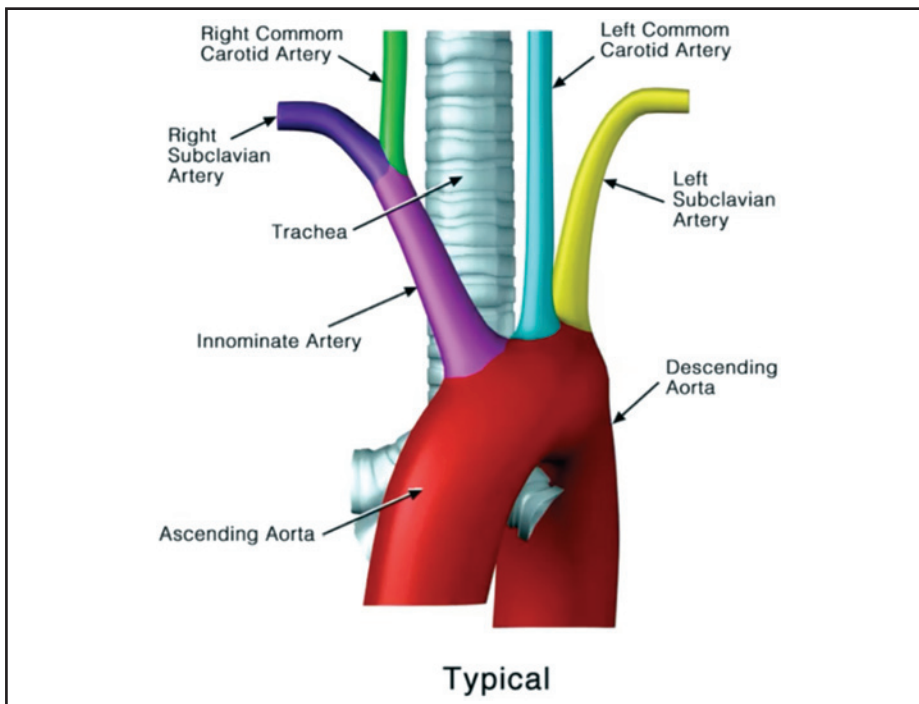
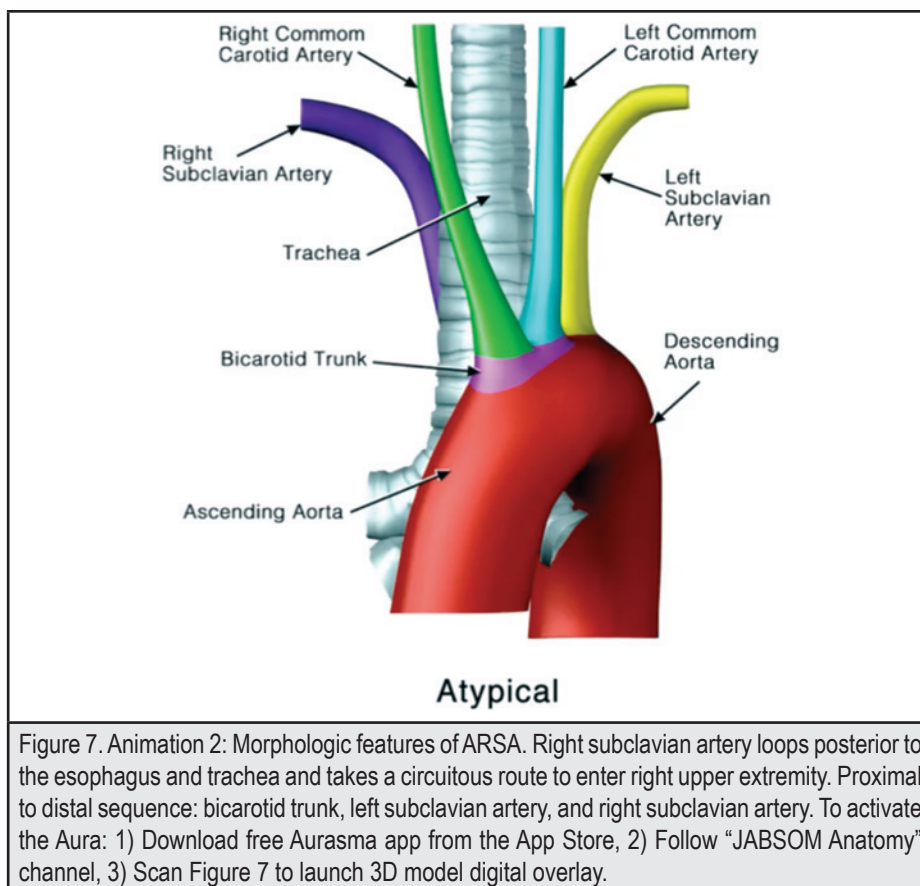


Figure 6. Animation 1: Typical aortic arch morphology. Three cardinal branches arise from arch in proximal to distal sequence: innominate artery, left common carotid artery and left subclavian artery. To activate the Aura: 1) Download free Aurasma app from the App Store, 2) Follow "JABSOM Anatomy" channel, 3) Scan Figure 6 to launch 3D model digital overlay.



Animations demonstrate the important spatial relationships of the relevant aortic structures. The typical condition shows the three cardinal branches arising from the arch of the aorta in proximal to distal sequence: innominate artery, left common carotid artery and left subclavian artery (Figure 6). The ARSA condition showed a right subclavian looping posterior to the esophagus and trachea while the innominate artery did not form (Figure 7). In ARSA, the third aortic arch only becomes partially absorbed into the dorsal aorta and the typical spatial arrangement of the common carotid arteries is lacking, instead giving rise to a bicarotid trunk (Figure 7). The left subclavian arises in its typical location ascending into the neck and then to the upper extremity. Interestingly the right subclavian takes a circuitous route to the right upper extremity, but nonetheless achieves its normal position approaching and then running deep to the clavicle (Figure 7). The animation also demonstrates that ARSA can cause respiratory and digestive complications since it forms a potential stenosis.

### Discussion

The ARSA has been imaged within the clinical setting through various advance methodologies providing important clinical information and insight.<sup>5-8</sup> However, voxel-based representations have limitations within an educational setting due to large memory requirements necessary for rendering. Addi-

tionally, contiguous anatomical structures such as the trachea and esophagus are not depicted. Contiguous structures can be instantaneously removed from the scene enabling the student to investigate spatial relationships of the region such as retroesophageal position of the horizontal branch of the ARSA. The approach used here combining photographic recordings with 3D computer modeling facilitates ease-of-presentation.<sup>9</sup> The model can be viewed on virtually any personal electronic device.

The ARSA atypical variant forms during development of the aortic arches between approximately embryonic days 22-49 (Carnegie stages 11-20), as the cardiac outflow transforms into the ascending aorta and its cardinal branches.<sup>10-11</sup> The derivation of adult structures from aortic arch components is well known and summarized by Sadler (2012).<sup>12</sup> The truncus arteriosus separates into aortic and pulmonary outflow systems. The right and left common carotids arise from the third aortic arch providing blood supply to the head and neck. The right and left subclavian arteries form from their corresponding 7th intersegmental artery that contributes to vascularization of the upper extremity. On the right side, typically the dorsal aorta regresses distal to the intersegmental artery and the intersegmental artery merges with the right third aortic arch to form the innominate (brachiocephalic) artery. Thus, the subclavian and right common carotid artery join. In ARSA, the portion of the dorsal aorta proximal to the 7th intersegmental artery

regresses atypically. As a result, the right 7th intersegmental does not join the right third arch (presumptive right carotid common carotid artery), but instead joins the arch of the aorta directly and distal to the left subclavian artery. The course of the right subclavian is posterior to the trachea and esophagus, but other configurations have been reported.

As demonstrated here in the example above, 3D models and animations displaying complex spatial relationships can be created and presented effectively with augmented reality applications. Anatomical variations alone are valuable since they provide unique opportunities for learning and teaching typical embryological mechanisms. Understanding embryological development exclusively from textbooks however is challenging since it requires individuals to correctly interpret and visualize complex transformations of unfamiliar structures over time. Descriptions of mechanisms, eg, aortic arch development, are often difficult to follow and frequently require students to read detailed texts multiple times with still a high chance for misinterpretation. Color-coded structures of adult variants associated with text descriptions in this case then, can aid in the display and appreciation of typical developmental transformations, are easy to remember, and are useful in clearly demonstrating how disruptions can produce the atypical adult variants. This 3D technology may eventually eliminate the need by instructors to create actual models to teach embryology in the future.

Beyond anatomical variants, realistic 3D models and Aurasma can augment anatomy textbook images, lab manuals, and posters with supplementary models of complex adult structures (pelvis, cranial nerves, etc) and animations of structural functions or actions, eg, extra-ocular eye movements. As a whole, augmented reality tools enrich the anatomy learning experience by allowing students to use their personal iPhones and iPads to interact with 3D virtual structures as if they were real objects in front of them. Ultimately, these tools alongside dissection lab experiences, will play a significant role not only in communicating interesting variations but also in helping students to better visualize and in turn, grasp and remember fundamental anatomy concepts that will be crucial to them now and in the future.

### Conflict of Interest

None of the authors identify any conflict of interest.

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# IgG4-Related Disease: Imitating A Great Imitator

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## Abstract

*Immunoglobulin G4-related disease (IgG4-RD) is a rare, but increasingly recognized, multi-organ fibro-inflammatory condition characterized by distinct pathologic and histologic features. The clinical variability and relative novelty of IgG4-RD make accurate diagnosis of the condition quite challenging. We report a case of a 71-year-old man presenting with hypertrophy of the facial glands and generalized lymphadenopathy who was previously diagnosed with sarcoidosis. We recognized that he had atypical epidemiologic characteristic for sarcoidosis and his prior work-up documented elevated serum IgG4 to > 300 mg/dL. Immunostaining of an axillary lymph node biopsy showed an IgG4+/IgG+ plasma cell ratio of > 40% and a plasma cell concentration of > 100 IgG4+ plasma cells per high powered field, findings consistent with the diagnosis of IgG4-RD. This case report is an example of how analysis of collective clinicopathologic data led to a diagnosis of IgG4-RD. The pathologic complexities which contribute to the elusive nature of IgG4-RD are also illustrated.*

## Introduction

The association of IgG4 antibodies with autoimmune pancreatitis is well established, but patients with primarily extra-pancreatic manifestations of IgG4-related disease present a much greater diagnostic challenge. IgG4-RD is a recently described entity characterized by tissue infiltration of IgG4-positive plasma cells. This systemic condition was only recognized in 2003 and over the next decade IgG4 antibodies were identified in association with diseases of nearly every organ system.<sup>1</sup> A number of conditions that were previously thought to be unique clinical syndromes are now recognized as clinical manifestations of IgG4-RD. The condition formerly known as “Mikulicz disease,” for example, is now recognized as IgG4-related dacryoadenitis and sialadenitis.<sup>2</sup>

The full clinical scope of IgG4-RD, its pathogenesis, and epidemiology continue to be poorly understood. Expert consensus on recommended diagnostic criteria and terminology were established quite recently, in 2012.<sup>3</sup> Not surprisingly, many primary care providers and other clinicians know very little about the clinical features of IgG4-RD, and some are unaware of the existence of the condition at all. The clinical variability and relative novelty of IgG4-RD present a difficult diagnostic challenge. Misdiagnosis and diagnostic delays prevent timely treatment of affected individuals, putting them at increased risk for disease progression and permanent organ dysfunction.<sup>1,4</sup> Additionally, there may be an association between untreated or undertreated cases IgG4-RD and the development of certain malignancies.<sup>4</sup>

## Case Report

A 71-year-old Filipino man, with history of psoriasis, asthma, and type-2 diabetes, presented for evaluation of persistent bilateral swelling of the lacrimal, submandibular, and parotid glands. He also reported non-tender enlargement of the cervi-

cal, axillary, and inguinal lymph nodes. These symptoms began 2-years ago and, after an extensive evaluation for infectious, malignant, and other inflammatory etiologies, he was diagnosed with sarcoidosis with glandular involvement (Heerfordt’s syndrome). This diagnosis was established based on positron emission tomography–computed tomography (PET-CT) findings of multi-focal hypermetabolic lymphadenopathy of the cervical, axillary, mediastinal, hilar, and iliac chains and hypertrophy of the bilateral parotid, submandibular, and lacrimal glands (Figure 1). This led to an axillary lymph node biopsy which reported follicular hyperplasia, lymphoplasmacytic infiltrate, and rare granulomata. No glucocorticoids or other therapies were prescribed for this condition.

On our evaluation, we observed that the patient’s Filipino ethnicity, male sex, and onset of symptoms at nearly 70 years of age are epidemiologic characteristics that are rare in sarcoidosis. This led us to review his prior work-up. Review of laboratory data documented a serum IgG of 2264 mg/dL with marked elevations in IgG3 and IgG4 subclasses to 400 mg/dL and >300 mg/dL, respectively. He had mild peripheral eosinophilia, proteinuria (624mg/ 24 hrs) with preserved renal function, and SPEP showed a polyclonal gammopathy. In addition to the hypermetabolic lymphadenopathy and glandular hypertrophy, his PET-CT showed an area of hypertrophy and hypermetabolism in the pancreatic head without a distinctive mass; though his pancreatic and liver enzymes were normal. His prior axillary lymph node specimen was retrieved and reviewed with our pathologist. There were, in fact, very few non-caseating granulomas (1-2 per slide) present in the specimen. This is a non-specific finding that is not consistent with overt granulomatous disease. We suggested an alternate diagnosis of IgG4-RD and his axillary lymph node specimen was submitted for total IgG and IgG4 subclass immunohistochemical staining. These stains revealed >100 IgG4-positive plasma cells per high-powered field (IgG4+/hpf) and the ratio of IgG4 staining plasma cells to IgG staining plasma cells (IgG4+/IgG+) was greater than fifty-percent (Figure 2).

When the patient was seen for follow-up, he had been incidentally treated for asthma with a 12-day prednisone taper. He reported complete resolution of his lymph node and glandular hypertrophy. Though his symptoms were improved, the duration of therapy was much shorter than recommended for IgG4-RD. He refused a prolonged glucocorticoid course due to reported fatigue and malaise with previous use. We contacted Dr. John Stone of The Massachusetts General Hospital IgG4-Related Systemic Disease Program to discuss this case and the patient has been referred for expert evaluation.

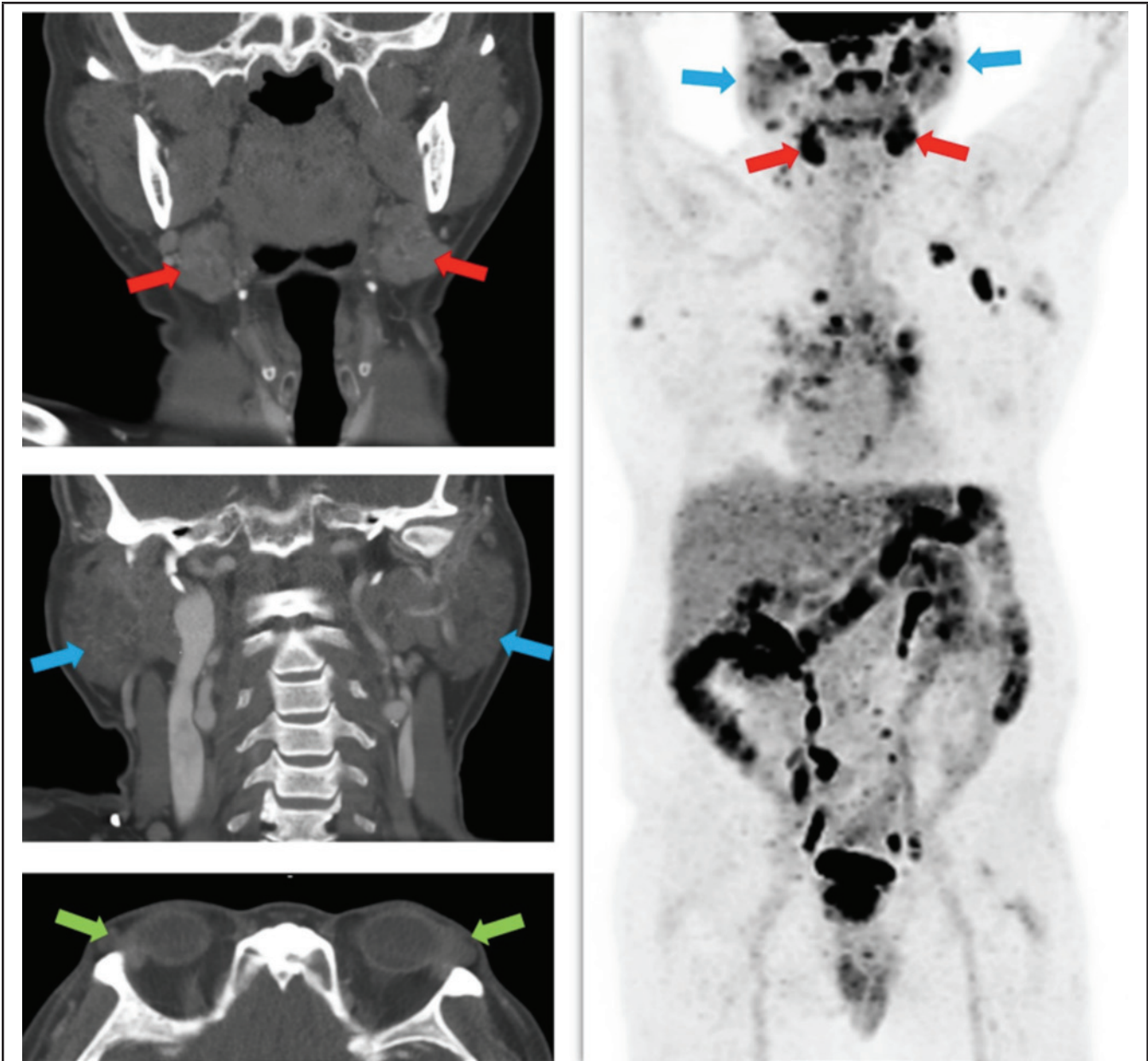


Figure 1. CT and PET/CT images in a patient with IgG4-Related Disease. CT and 3D PET/CT images showing bilateral enlargement of the submandibular (red arrows), parotid (blue arrows), and lacrimal glands (green arrows). The 3D PET/CT image also illustrates the systemic nature of IgG4-RD with abnormal metabolic activity in the facial glands, pancreas, and lymph node chains of the neck, axilla, mediastinum, abdomen, and pelvis.

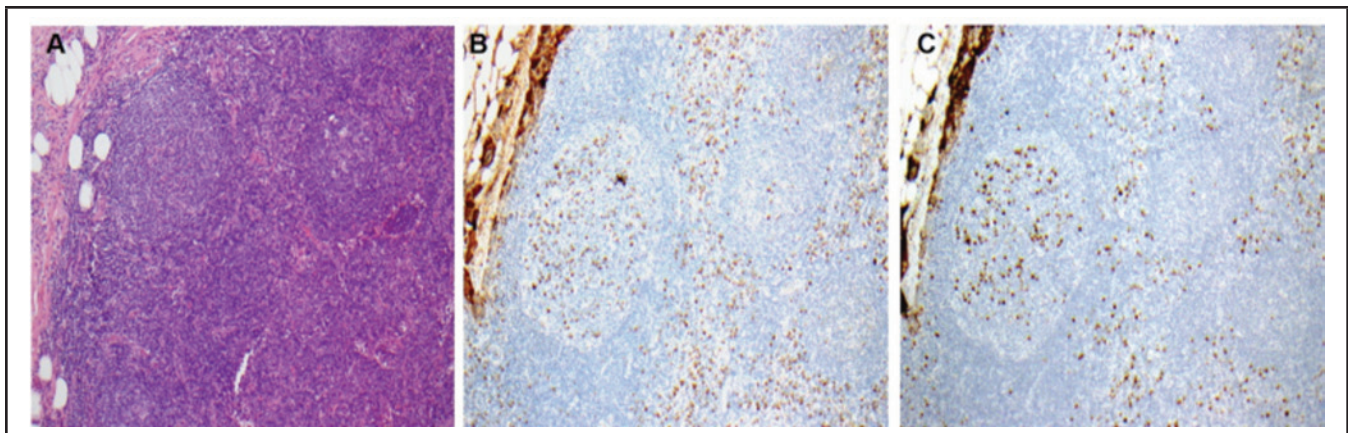


Figure 2. Axillary lymph node biopsy in a patient with IgG4-RD. Axillary lymph node specimen revealing dense lymphoplasmacytic infiltration (Panel A, hematoxylin and eosin). Storiform fibrosis and obliterative phlebitis are notably absent; which is typical of IgG4-RD affected lymph nodes. Immuno-peroxidase staining for total IgG (Panel B) and IgG4 (Panel C) show markedly elevated IgG secreting plasma cells, a majority of which are strongly positive for IgG4.

## Discussion

IgG4-related disease can have a wide variety of presentations with clinical and pathological features that are very similar to other systemic inflammatory and malignant processes.<sup>1,5</sup> The development of tumefactive lesions in 1 or more organs is the classic clinical feature of IgG4-RD. The disease can affect nearly every organ system, however, and often affects multiple organs simultaneously.<sup>5</sup> Many patients present with generalized symptoms of malaise, weakness, and weight loss. Organ specific symptoms may be equally vague.<sup>1,4,5</sup> For example, a patient with IgG4-related sclerosing cholangitis or pancreatitis may present with mild abdominal pain, jaundice, and pruritus; a patient with IgG4-related pulmonary disease may have symptoms of dyspnea and wheezing.

The diagnosis of IgG4-RD is often missed or delayed due to failure to recognize the seemingly unrelated symptoms as a systemic condition. Further, the differential diagnosis differs from case to case and is often directed by the presenting symptoms and distribution of organ involvement.<sup>4,5</sup> As an example, cases in which multi-focal lymphadenopathy and glandular enlargement are the predominate features, lymphoma, sarcoidosis, Sjogren's syndrome, and Castleman's disease may be considered in the differential diagnosis or incorrectly diagnosed.<sup>4,6</sup> Careful analysis of the history, laboratory results and imaging studies can aid in narrowing the differential diagnosis, but definitive diagnosis hinges on histologic evaluation of affected tissues.

There is no laboratory test that, in isolation, establishes or rules-out the diagnosis of IgG4-RD.<sup>3,7</sup> Common lab abnormalities include elevations in inflammatory markers and IgE, mild to moderate peripheral eosinophilia, and polyclonal hypergammaglobulinemia.<sup>1,8</sup> Non-specific organ related lab findings such as abnormal liver function tests in IgG4-related pancreatic and biliary disease or proteinuria in IgG4-related renal disease may also be found. An elevated serum IgG4 level (>135 mg/dL) is found in the majority of biopsy proven cases of IgG4-

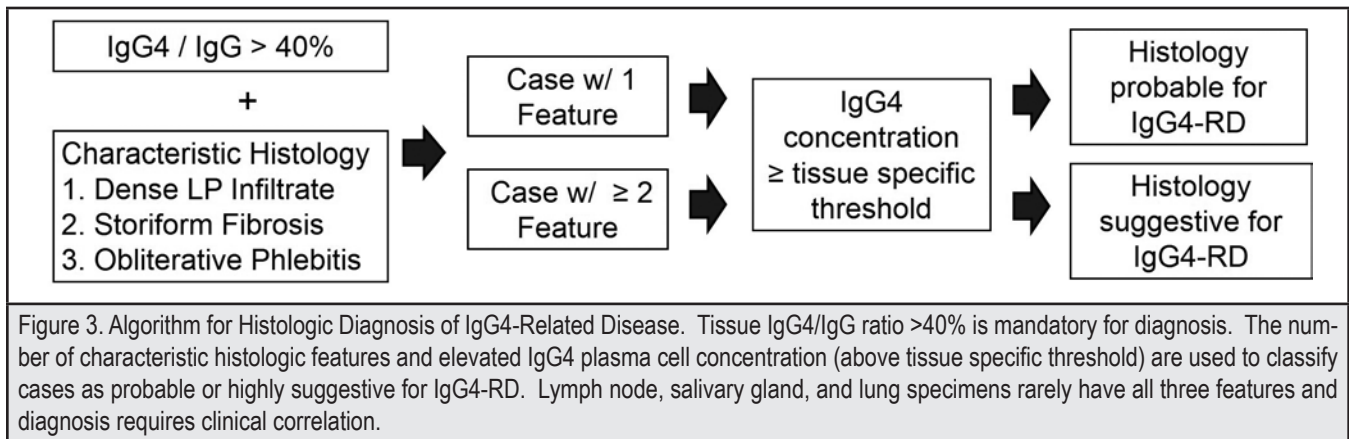
RD; however, it has been proven to have poor specificity and positive predictive value for the diagnosis. A large proportion of patients with histologically proven cases of IgG4-RD have normal serum levels of IgG4.<sup>5</sup> Measurement of serum IgG4 is still recommended by current diagnostic criteria; however, reliance on this value to establish or refute the diagnosis of IgG4-RD would lead to a substantial number diagnostic errors.<sup>3,7</sup>

Imaging studies are not absolutely necessary to establish the diagnosis of IgG4-RD, but most patients will have been evaluated by one or more imaging modalities during their evaluation. Ultrasound guidance is often used to guide biopsy or evaluate affected organs, but findings are not specific to IgG4-RD. CT and MRI studies often identify more extensive disease and involvement of additional organs incidentally.<sup>1,9</sup> Some studies have suggested a role for PET/CT in the evaluation of IgG4-RD due to increased sensitivity in detecting lymph node, salivary gland, and vascular involvement but its utility as a diagnostic tool is limited.<sup>10,11</sup>

Confident pathologic diagnosis of IgG4-RD relies on characteristic quantitative and qualitative histopathologic findings in biopsy specimens obtained from affected tissues (Figure 3). The major histologic features of IgG4-RD are a dense lymphoplasmacytic infiltrate, storiform pattern fibrosis, and obliterative phlebitis. Additionally, non-obliterative phlebitis and elevated tissue eosinophils are often seen, but are not specific to IgG4-RD. A conclusive histologic diagnosis requires the presence of two out of three major histologic features.<sup>3,5,7</sup> An exception is stipulated, however, when evaluating lymph node, lung, minor salivary gland, and lacrimal gland specimens. In these organs, storiform fibrosis and obliterative phlebitis is often inconspicuous or absent.<sup>3</sup>

Immunostaining for IgG4 and total IgG is an essential element in the evaluation for IgG4-RD as well. The IgG4+/IgG+ plasma cell ratio and the number of IgG4+ plasma cells/hpf is determined from immunostained tissue samples. An IgG4+/IgG ratio greater than 40% is mandatory for the diagnosis





of IgG4-RD. Additionally, the number of IgG4+/hpf should be above the tissue specific threshold established by expert consensus.<sup>3,7</sup> The aim of these criteria is to prevent over-diagnosis in cases where there are very few plasma cells or under-diagnosis in tissues with abundant fibrosis at diagnosis.

Cases meeting the criteria for IgG4+/IgG+ ratio and IgG4+/hpf are categorized as highly suggestive of IgG4-RD if they have two or more major histopathologic features. If just one major histopathologic feature is present they are categorized as having probable features of IgG4-RD.<sup>2,3</sup> In the latter circumstance, correlation with additional clinical, serological, or radiological data is necessary to support the diagnosis. Elevated serum IgG4 and/or imaging studies showing characteristic organ involvement, for example, would confirm the diagnosis of IgG4-RD in a histologically probable case.<sup>3,7</sup> It should be noted that these criteria are based on expert consensus and no studies have evaluated the sensitivity and specificity of this diagnostic approach.<sup>5</sup>

In the case reported above, careful attention to the patient's history and epidemiologic characteristics compelled us to question his existing diagnosis of sarcoidosis. Further, a review of prior laboratory, pathology, and imaging studies gave rise to an alternative diagnosis of IgG4-RD. Immunostaining of the lymph node specimen showed an IgG4+/IgG+ ratio of > 50%, meeting the mandatory criteria of >40%. Additionally, the concentration of IgG4+ plasma cells was > 100/hpf, which is above the established concentration threshold for a lymph node specimen. Histologically, a dense lymphoplasmacytic infiltrate was present, but no storiform fibrosis or obliterative phlebitis was identified. These findings are typical of IgG4 related lymphadenopathy, however, and the case was histopathologically classified as 'probable for IgG4-RD.' Definitive diagnosis of IgG4-RD was supported by a significantly elevated serum IgG4 and PET/CT findings consistent with recognized IgG4-related disorders: IgG4-related lymphadenopathy, IgG4-related sialadenitis and dacryoadenitis, IgG4-related lung disease, and IgG4-related pancreatitis.

This case report serves as an example of the clinically and diagnostically complex features of IgG4-related disease. Further, it illustrates the necessity of collectively analyzing clinical, serological, radiological, and histopathological data to arrive at a definitive diagnosis of IgG4-RD.

### Conclusion

IgG4-related disease is an increasingly recognized systemic fibroinflammatory disease characterized by tissue infiltration of IgG4+ plasmocytes. Failure to accurately diagnose and treat this condition can allow for disease progression and, ultimately, permanent organ dysfunction. The greatest barriers to diagnosis include lack of awareness of IgG4-RD its ability to clinically imitate many better recognized systemic conditions. The diagnosis of IgG4-RD should be considered in all patients with unexplained bilateral salivary or lacrimal gland enlargement, pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, orbital pseudotumor, or other tumefactive tissue lesions. An elevated serum IgG4 is not diagnostic but increases the likelihood of this disease in patients with unexplained pseudotumor or a pattern of multi-organ pathology characteristic of IgG4-RD. Establishing a definitive diagnosis of IgG4-RD requires correlation of multiple clinicopathologic data and exclusion of conditions with closely shared characteristics.

### Conflict of Interest

None of the authors identify any conflict of interest.

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# Granulomatosis with Polyangiitis: A Case of Nasal Mass, Necrotic Lung, and Normal Kidneys

Ittikorn Spanuchart MD; Nath Zungsonitporn MD; Pichaya O-charoen MD; Bhisit Changcharoen MD; and Dennis T. Bolger Jr. MD

## Abstract

*A diagnosis of granulomatosis with polyangiitis (GPA) can be challenging given various clinical manifestations. We report an incident case of GPA presenting with chronic sinusitis and mimicking an early lung abscess without renal involvement. A 51 year-old woman with chronic obstructive sinusitis presented with subacute dyspnea, pleuritic chest pain and fever. Physical examination revealed a right nasal mass without discharge or bleeding. Decreased to absent breath sounds and dullness to percussion were noted at the left lung base. Laboratory findings were significant for leukocytosis but normal renal function. The chest CT demonstrated dense consolidation with hypo-enhancement of the lingula. The sinus CT revealed an enhancing mass in the right nasal cavity and anterior ethmoid sinuses with associated bony destruction. Patient did not improve with empiric antibiotics for lung abscess. Aspiration of the lingular fluid showed purulent material, however, microbes did not grow in culture. A positive C-ANCA screen was confirmed. A right nasal biopsy was performed which revealed granulomatous inflammation with focal necrosis and vasculitis. The final diagnosis was GPA. Given various clinical manifestations, the diagnosis of GPA can be difficult to distinguish from infectious etiologies. This can delay the treatment, which may be life-saving and organ sparing. We emphasize that an initial screening ANCA serology test is recommended in patients with suggestive clinical findings of GPA. Biopsy of an affected organ is paramount for the definitive diagnosis.*

## Keywords

*granulomatosis polyangiitis, lung abscess and nasal mass*

## Introduction

Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis, is one of the ANCA-associated vasculitides (AAV). The prevalence and incidence is approximately 30,000 and 2,600 per 300 million people respectively.<sup>[1]</sup> Clinical manifestations commonly involve multiple organ systems including ear-nose-throat (upper respiratory), pulmonary (lower respiratory system,) and renal systems. Given various manifestations, a diagnosis can be challenging. Antineutrophil cytoplasmic antibody (ANCA) serologies including proteinase-3 (PR-3) and myeloperoxidase (MPO) antibodies and histologic examination of the affected organs are generally required to make the diagnosis of GPA. We report an incident case of GPA presenting with chronic sinusitis and mimicking an early lung abscess without renal involvement.

## Case Report

The patient is a 51 year-old Chinese-American woman with history of chronic obstructive sinusitis with right nasal mass who presented with progressive pleuritic chest pain, exertional dyspnea, non-productive cough and fever for two weeks. Upon admission, vital signs include body temperature 38.0 C, blood

pressure 130/80 mmHg, pulse rate 105 per minute, respiratory rate 18 per minute and oxygen saturation was 97% on room air. Physical examination revealed a right nasal mass without discharge or bleeding. Decreased to absent breath sounds and dullness to percussion were noted at the left lung base. Bilateral fine crackles were also present in the right lung and left upper lung zone. The exam was otherwise unremarkable. Initial laboratory findings were significant for leukocytosis, WBC 13,000/mm<sup>3</sup> with 75% neutrophils, no bands, BUN 12 mg/dL and creatinine 0.5 mg/dl. Urinalysis was unremarkable and without active sediment or proteinuria. The computer tomography (CT) of thorax demonstrated dense consolidation with hypo-enhancement of the lingula which suggested an early lung abscess. A small left pleural effusion was noted (Figure 1). The right lung was without infiltrative lesion. CT of the sinuses revealed a 2.5 x 1.5 cm heterogeneously enhancing mass-like lesion in the upper right nasal cavity and anterior ethmoid sinuses with associated destruction of the anterior body septum and nasal bone. Patient was empirically treated for lung abscess with vancomycin, piperacillin-tazobactam, and azithromycin (Figure 2). The CT-guided needle aspiration of the potential lingular abscess drained purulent material. However, the culture showed no growth. Left pleural fluid was also sterile. Given no response to the empiric treatment for potential lung abscess, non-infectious causes including GPA were suspected. Erythrocyte sedimentation rate and anti-neutrophilic antigen were later obtained which showed 77 mm/hr and <40 respectively. A positive C-ANCA screen was confirmed by positive PR-3 antibody but negative MPO antibody. A right nasal biopsy was performed which revealed granulomatous inflammation with focal necrosis and vasculitis. The patient was diagnosed with GPA (Figure 3).

## Discussion

In regard to various clinical manifestation of GPA due to multiple organ involvement, the upper and lower respiratory and genitourinary systems are commonly affected. Although renal involvement is common in the disease course, only 18 percent of patients have glomerulonephritis at presentation. Glomerulonephritis does subsequently develop in 77 to 85 percent of patients, usually within the first two years of disease onset.<sup>[2,3,4,5]</sup> Accordingly, normal renal function at presentation cannot rule out GPA as in our patient with chronic sinusitis and pulmonary symptoms without renal involvement. Given various clinical presentations, the diagnosis of GPA can be challenging and



Figure 1. CT of thoracic abdominal aorta showed dense consolidation with hypo-enhancement present in the lingula.



Figure 2. CT of facial and soft tissue showed heterogeneously enhancing mass like lesion in the upper right nasal cavity and anterior ethmoid sinuses with associated destruction of the anterior body septum and nasal bone.

difficult to distinguish from infectious etiologies. Most of the time, work up for GPA is started after failure of improvement with empirical antibiotic therapy as in our patient who presented with the early abscess-like lesion, but did not respond to the empiric antibiotics and drainage of the potential lung abscess. This can delay the diagnosis and further delay treatment.

In patients with clinical manifestations suspicious for GPA, ANCA serologies should be tested. Cytoplasmic localization of ANCA (c-ANCA) is 90-95% sensitive in acute generalized GPA and 60% sensitive in early or localized disease.<sup>[6]</sup> A positive ANCA serologies should be confirmed with PR-3 and MPO antibodies which are more specific. A tissue biopsy of an affected organ is required to cinch the diagnosis of GPA<sup>[7]</sup> which may show specific abnormalities, such as vasculitis, granulomas,

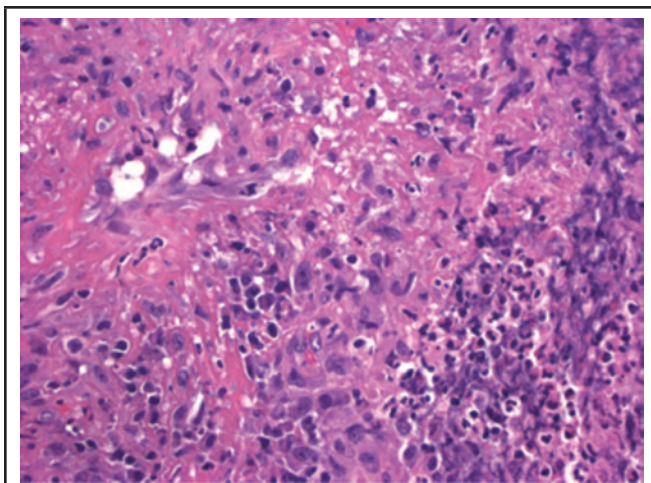


Figure 3. pathology of right nasal showed diffuse chronic inflammation and coagulative necrosis with multinucleated giant cells forming granulomas which are surrounded by plasma cells, lymphocytes and neutrophils. A number of large vessels showed infiltration by lymphocytes.

giant cells and necrosis. The sensitivity and specificity of tissue biopsy varies depending on a site of active disease. Even though nasal biopsy has higher rate of false negativity when compares to biopsy at other affected sites, it is less invasive and should be considered early in the evaluation. Prompt diagnosis is important to initiate therapy which may be life –saving and organ sparing.

Therapy of GPA is comprised of two components which are induction of complete remission and maintenance therapy. Induction phase treatment includes combination of glucocorticoids plus cyclophosphamide for three to six months to achieve remission. Plasma exchange therapy is suggested in the presence of diffuse pulmonary hemorrhage, rapidly worsening kidney function or overlap syndrome of AAV and anti-glomerular basement membrane antibody glomerulonephritis as in Goodpasture syndrome. Remission is defined as a clearing of active lesions or resolution of organ dysfunction. For the maintenance therapy, azathioprine or methotrexate is recommended for greater than 18 months.

Prompt initiation of treatment for AAV can achieve remission at 6 months in >90% of patients, however, relapse rates approach 50%. Severe vital organ-threatening damage and treatment related adverse events may develop in approximately 25% of patients. Without treatment, the average survival rate is 5 months with one and two year mortality rates of 82% and 90% respectively.

### Conclusion

We emphasize that the initial screening ANCA serology test is recommended in patients with suggestive clinical findings of GPA. Biopsy of an affected organ is paramount for the definitive diagnosis. Early initiation of treatment is crucial once the diagnosis is established.

## Conflict of Interest

None of the authors identify a conflict of interest.

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# Mouth in Foot Disease

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## Abstract

Toothpicks are commonly used household items that rarely cause serious injury or infection. Toothpick-related injuries often occur due to ingestion with subsequent trauma/infection at distal sites within the gastrointestinal tract; however, cardiovascular, pleural, and soft tissue infections have been reported. *Eikenella corrodens* is a gram-negative, facultative anaerobic bacillus found in oral flora associated with bite wound infections. A few case reports describe *E. corrodens* osteomyelitis from toothpick puncture wounds. We report a case of foot cellulitis and abscess in an elderly diabetic after toothpick puncture injury that was unresponsive to empiric antibiotics. Wound cultures grew *E. corrodens* and rare *Peptostreptococcus* species. *E. corrodens* is resistant to first-generation cephalosporins, macrolides, aminoglycosides, clindamycin, and metronidazole. This case highlights the insidious nature of *E. corrodens* infections and the need to tailor empiric antibiotics for skin and soft tissue infections based on the mechanism of injury. In addition, this case stresses the importance of protective footwear in diabetics and serves as a cautionary tale regarding the use of seemingly innocuous toothpicks.

## Introduction

Toothpicks are frequently used household items that can be a potential source of trauma leading to serious infection. Although injuries from toothpicks are relatively common, serious injuries are thought to be rare. Often, toothpick-related injuries result from ingestion leading to subsequent trauma/infection at distal sites within the gastrointestinal tract; however, cardiovascular, pleural, and soft tissue infections have been reported in rare instances in the medical literature. We report a case of *Eikenella corrodens* foot cellulitis and abscess in an elderly diabetic patient after a toothpick puncture injury.

## Background

Between 1979 to 1982, an estimated 8,176 toothpick-related injuries occurred annually.<sup>1,2</sup> According to the US Consumer Product Safety Commission's National Electronic Injury Surveillance System (NEISS), which tracks emergency room visits related to consumer products, the annual incidence of toothpick-related injuries remains relatively unchanged since the early 1980s.<sup>2</sup> The estimated number of persons hospitalized annually due to toothpick-related injuries ranged from 105 to 184, with the highest incidence among the pediatric population (less than 15 years of age). Additionally, the most common site of injury involved the extremities and/or trunk within all age groups except for those less than 5 years of age.<sup>1</sup>

Few case reports describe extra-oral *E. corrodens* infections, such as skin and soft tissue infections/abscesses, intra-abdominal abscesses, and osteomyelitis.<sup>3</sup> It is most commonly recovered as part of a polymicrobial infection involving human bite wounds and less commonly as part of the HACEK organisms

causing endocarditis.<sup>4,5</sup> Even fewer report *E. corrodens* infections from toothpick-related injuries.<sup>5,6</sup> *Eikenella corrodens* is a gram-negative, facultative anaerobic bacillus found within the normal flora of the human mouth, upper respiratory tract, gastrointestinal tract, and genitourinary tracts. *E. corrodens* grows slowly on blood and chocolate agar. The colonies are small, emit a bleach-like odor, and yield a characteristic pitting of the agar for which the organism was given its name.<sup>4</sup>

Bite wounds are typically treated with broad spectrum beta-lactam antibiotics (eg, ampicillin-sulbactam, piperacillin-tazobactam, meropenem, etc.) and coverage for *E. corrodens* should be considered in injuries involving contamination with oral flora. *E. corrodens* is resistant to first-generation cephalosporins, macrolides, aminoglycosides, and antimicrobials traditionally used against anaerobes, such as clindamycin and metronidazole.<sup>7</sup> For penicillin-allergic patients, clindamycin plus a fluoroquinolone is often substituted as empiric therapy in bite wounds. In penicillin-allergic patients, therapy for *E. corrodens* proves more difficult. One case report showed successful treatment of penicillin-allergic patients with doxycycline and *in vitro* data report susceptibility to newer fluoroquinolones.<sup>7,8</sup>

## Case Report

A 79-year-old Japanese-American woman with a history of type 2 diabetes mellitus, hypertension, hyperlipidemia, and left eye prosthesis was evaluated in the Acute Care Clinic for left foot pain. She endorsed walking in her home barefoot and sustaining a toothpick impalement injury to the bottom of her left foot approximately 1 week prior. The toothpick was removed intact. The patient was uncertain if the toothpick had been used as she denied personal use however, her vision-impaired husband used toothpicks frequently. The patient first noticed warmth, erythema, and tenderness at the site of injury several days following the incident. She attempted home management with bacitracin ointment and over-the-counter analgesics, but sought medical attention once the pain affected her ability to ambulate. At her initial appointment, the patient denied symptoms of systemic infection or drainage from the injury site. The patient had no prior history of peripheral vascular disease or peripheral neuropathy and her most recent hemoglobin A1C was 7%. Her outpatient medication regimen included metformin, atorvastatin, lisinopril, and alendronate. On physical examination the patient was afebrile with normal vital signs. Her left mid-foot revealed a small puncture wound to the medial plantar aspect with circumferential erythema and warmth. The affected area was tender to palpation however, no fluctuance was appreci-

ated. Bedside superficial wound exploration did not identify a retained foreign body. A small amount of exudate was expressed after incision but no cultures were obtained. The patient was treated with clindamycin to cover potential methicillin-resistant *Staphylococcus aureus* and a tetanus booster was given.

Two days following her initial appointment, the wound looked improved with decreased erythema and edema but a wound check three days later revealed a new area of fluctuance with increased edema, erythema, and tenderness. The patient remained well-appearing and afebrile. Laboratory analysis showed no leukocytosis and normal inflammatory markers. Plain films of the affected foot did not show retained foreign material or bony involvement.

Approximately 2 weeks after the initial injury, the patient reported increasing pain and difficulty ambulating. Bedside sonography revealed a small fluid collection to the plantar aspect of her left foot. She was admitted to the hospital to start empiric intravenous antibiotics with vancomycin and piperacillin/tazobactam. Surgical debridement showed no involvement of bone or tendon. Inflammatory markers and white blood cell counts remained normal and blood cultures were negative. She was transitioned to amoxicillin/clavulanate for empiric coverage of skin and oral flora given her recent history of toothpick injury. Six days after hospital admission, wound cultures grew *Eikenella corrodens* and rare *Peptostreptococcus* species. The patient experienced a full recovery from the injury/infection.

On a subsequent follow up home visit, it was noted the patient observed the custom of removing footwear before entering the home. Shag carpeting was present in all rooms except the kitchen and bathroom. Several round, pointy toothpicks were spotted within the carpet of the living room and on the kitchen floor. The couple lived alone and the patient was the primary caretaker for her ailing husband. She stated that her husband frequently chewed on toothpicks as a means to curb his desire to smoke. The patient was counseled on the importance of wearing protective footwear even while in the house to prevent foot trauma. It was recommended the household switch from round to flat toothpicks if possible, given the latter has more blunted ends that are less likely to cause serious injury. In addition to education on diabetic foot care and injury prevention, homecare and cleaning services were requested for the elderly couple.

## Discussion

Toothpicks are found in 96% of American homes.<sup>9</sup> A major toothpick manufacturer in the United States estimates annual sales at \$60 million, producing between 4-20 billion toothpicks a year.<sup>10</sup> Toothpicks are ubiquitous in today's society as their

use expands far beyond the initial intention of dental cleaning. They are often seen garnishing fancy cocktails, assisting with finger-food consumption, and securing food items. Toothpicks used by bartenders and in the food industry should be clearly labeled to help prevent accidental ingestion by patrons. The common utilization of toothpicks precludes them from being seen as potentially injurious household items. Budnick, et al's, article highlights the danger of toothpick use in specific populations including the intellectually disabled, denture-wearers, alcohol consumers, and those with dulled palatal sensoria due to increased risk of toothpick ingestion.<sup>1</sup> Cautious use of toothpicks should be expanded to elderly persons, the visually impaired, and diabetics as evidenced in this case. In the United States, data on the incidence of toothpick-related injuries/deaths, such as those reported by the NEISS, are likely underestimated as they only track patients cared for in an emergency room setting.

Susceptibility testing is not routinely performed in standard clinical microbiology laboratories for anaerobic organisms and treatment is often based on those reported in the literature. This patient's isolate was consistent with susceptibilities previously reported.<sup>11</sup> We reviewed microbiological data at Tripler Army Medical Center (TAMC) from 2009 to 2014 and found *Eikenella* species were isolated from 56 patients (data not published). These isolates were often polymicrobial in nature and took several days for adequate growth (2-16 days). The vast majority of TAMC's *Eikenella* species were isolated from extra-oral sites of infection.

*E. corrodens* infections are insidious in nature with a predilection for deep tissue infection. It may take more than one week from the time of injury to manifest clinical disease with few systemic symptoms or signs of inflammation on laboratory testing. This case underscores the importance of tailoring empiric antibiotics for skin and soft tissue infections based on the mechanism of injury in combination with surgical debridement. Cultures should be performed to aid in diagnosis and implementation of appropriate antibiotic therapy, especially in those failing to respond. If oral flora is suspected as a causative agent, the laboratory should be notified to optimize isolation of key organisms.

*The views expressed in this manuscript are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.*

## Conflict of Interest

None of the authors identify a conflict of interest.

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# The Kiss of Death: A Rare Case of Anaphylaxis to the Bite of the “Red Margined Kissing Bug”

Caleb Anderson MD and Conrad Belnap MD

## Abstract

*Triatoma* (kissing bugs), a predatory genus of blood-sucking insects which belongs to the family Reduviidae, subfamily Triatominae, is a well-known vector in the transmission of *Trypanosoma cruzi*, the causative agent in Chagas disease. However, it is less well appreciated that bites from these insects can cause a range of symptoms varying from localized cutaneous symptoms to a generalized anaphylactic reaction. While anaphylactic reactions following bites have been reported with five of the eleven species endemic to the United States, the majority are associated with *Triatoma protracta*, and *Triatoma rubida*. There have been very few reported cases of anaphylactic reaction to the bite *Triatoma rubrofasciata*, which is endemic to Florida and Hawai'i. We report a case of a 50 year old previously healthy female from a rural area in Honolulu County who suffered three separate bites from *Triatoma rubrofasciata* and experienced a generalized anaphylactic reaction on each occasion. There is currently no commercially available skin test to determine allergy to *Triatoma* bites, and there is likewise no immunotherapy. Avoidance is the best strategy and allergic patients should always have an epinephrine auto injector readily available.

## Introduction

*Triatoma* “kissing bugs” are a predatory genus of blood-sucking insects that belong to the family Reduviidae, subfamily Triatominae. There are 141 species worldwide, of which 11 species are found in the United States.<sup>1,2</sup> *Triatoma rubrofasciata* is the only triatomine species found in the state of Hawai'i and is characterized by a triangular scutellum and an orange-red margin along the outer edge of the abdomen and the sides of

the pronotum, as shown in Figure 1.<sup>1,5</sup> These insects are usually found in rural areas and feed on warm blooded mammals to include chickens, rodents, dogs, and humans. They are able to consume two to four times their body weight in blood a day, and typically feed at night. The term “kissing bug” is a consequence of the insect’s predilection of biting the victim’s face because it is often the most accessible body part.<sup>2</sup>

*Triatoma* bites are associated with a variety of other adverse reactions, which can range from mild localized inflammation to a severe, systemic, anaphylactic reaction. Allergic reactions following bites from five different *Triatoma* species have been reported. The majority of allergic reactions have been attributed to *Triatoma protracta*, which is found in California; and *Triatoma rubida*, which is found predominately in Arizona. The other three species associated with reported adverse reactions are *Triatoma gerstaeckeri*, *Triatoma sanguisuga*, and *Triatoma rubrofasciata*.<sup>2,4</sup> One death following an anaphylactic reaction secondary to a *Triatoma* bite was reported in Arizona in 2004, though that case report did not delineate the species.<sup>5</sup>

While most *Triatoma* bites leave a barely noticeable punctum without surrounding swelling or erythema, other reported bite manifestations include bullae, vesicles, papules, and cellulitis. Lymphedema following a bite has also been reported. Reports of anaphylactic reactions frequently involve patients awoken from sleep with generalized cutaneous symptoms including urticaria,

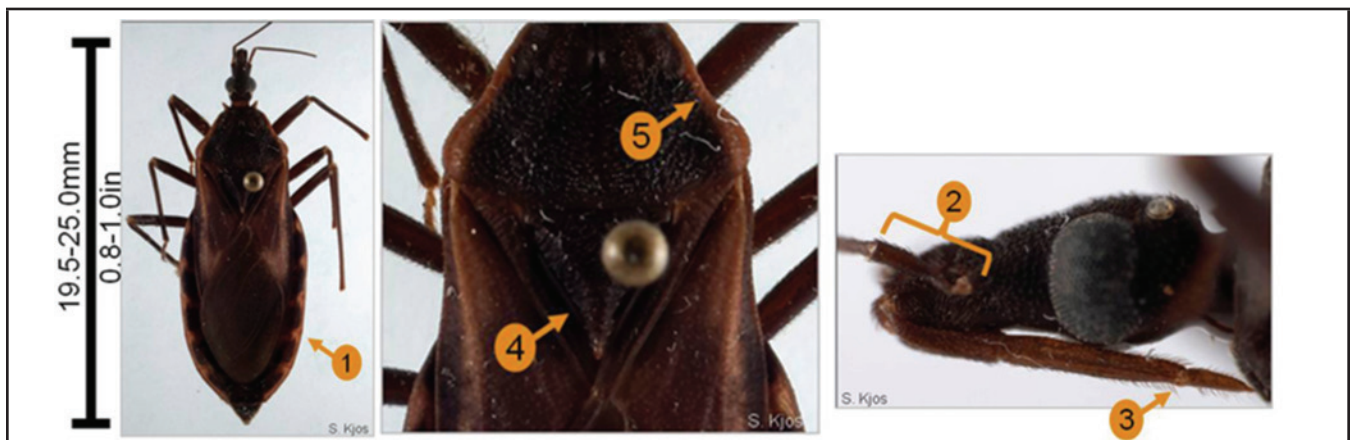


Figure 1. Key identification characteristics of *Triatoma rubrofasciata*, images obtained with permission from CDC website<sup>3</sup>

- 1, 5. Orange-red margin along the outer edge of the abdomen as well as the side of the pronotum
2. 1st segment of antenna surpasses the head
3. Hairs of mouthpart become longer towards the tip
4. Scutellum is triangular to the tip

flushing, pruritus, and angioedema. Gastrointestinal symptoms of nausea, vomiting, abdominal cramps, and diarrhea have also been reported. Respiratory symptoms may include dyspnea, wheezing, and laryngeal edema. Cardiovascular involvement is generally manifested by hypotension and syncope.<sup>2</sup>

Unlike other triatomine species such as *T. protracta*, and *T. rubida*, there are few cases of reactions to *T. rubrofasciata* reported in the literature. Two cases were reported from the Kaimuki district of O‘ahu in 1944. In the first case one patient suffered localized swelling around the bite followed by lymphangitis and axillary adenitis while the second patient suffered localized pain and swelling.<sup>6</sup> A case of an anaphylactic reaction to *T. rubrofasciata* was reported in Singapore in 1973. This case involved a 19 year old Chinese male who suffered a bite to the back of his chest while sleeping. On arrival to the Emergency Department, he was in a state of shock with an unrecordable blood pressure. The patient was treated with hydrocortisone, adrenaline, and promethazine for anaphylaxis. He became anuric and was kept on mannitol for 24 hours. He was discharged in stable condition 48 hours after admission.<sup>7</sup>

This paper presents a rare case of an anaphylactic reaction to the bite of *T. rubrofasciata* which occurred on the island of O‘ahu. The purpose of this paper is to further review available epidemiological data on the insect specific to the Hawaiian Islands, as well as to discuss the diagnosis and management of patients with hypersensitivity to its bite. The importance of avoidance strategies and potential avenues for further research are also discussed.

### Case Presentation

We present a case of a healthy 50-year-old woman with no previous history of allergies or known hypersensitivity from Waianae, a rural farming area on the west side of the Hawaiian Island of O‘ahu. Over the course of two years she suffered two shock events with a third shock event following a witnessed insect bite. The insect was subsequently captured and identified as *Triatoma rubrofasciata*. On her first reported event, she felt a sudden onset of dizziness, systemic pruritus, and a feeling of “tightness” in her throat. This progressed to whole body urticaria, dyspnea and lightheadedness. The patient was taken promptly to the Emergency Department (ED). On arrival she was hemodynamically stable. She was given IV diphenhydramine, methylprednisolone, and ranitidine with gradual amelioration of her symptoms. Two days after this event she noted a large, erythematous, warm welt on her left medial upper arm. She hypothesized that she had suffered an insect bite, though at that time she was unsure of the culprit organism. Approximately one year later while lying in her bed, she felt pain on her right lateral forearm and visualized two raised welts in the area of discomfort. She then developed dyspnea, urticaria, and lightheadedness. She suffered a witnessed loss of consciousness from which she recovered and was not taken for medical care. A search of the bed revealed an insect with characteristics suggestive of *Triatoma rubrofasciata*, though it was not captured for identification at this time.

The third reaction occurred approximately nine months after the second event. On this occasion she experienced urticaria, shortness of breath, and lightheadedness without loss of consciousness following an insect bite. An immediate search of the bed revealed the culprit insect which was captured by the patient’s husband and later identified as *T. rubrofasciata* by a medical entomologist (Figure 2). The patient’s husband had also experienced bites from a similar insect in the past, though he had not suffered a systemic allergic reaction. The patient was provided with avoidance measures and prevention education, and was instructed to obtain an epinephrine auto-injector from her primary care physician.



Figure 2. *Triatoma rubrofasciata* insect captured and identified by entomologist.

### Discussion

Overall, *Triatoma rubrofasciata* bites are rare, and systemic, anaphylactic reactions are even rarer. The insect has been found on the Hawaiian Islands of Kaua‘i and O‘ahu.<sup>8</sup> There is no recent epidemiological data detailing the occurrence and distribution of the insect in Hawai‘i, though older literature describes finding them in great numbers in the Kaimuki district of Honolulu.<sup>9</sup> The two previously reported bites also occurred in Kaimuki.<sup>6</sup> Review of the Hawai‘i Entomology Society Proceedings has shown that the insect has been noted near the Ewa Plantation mill on O‘ahu and at the Honolulu Zoo.<sup>10,11</sup> On Kaua‘i, *T. rubrofasciata* has been found near Barking Sands Beach.<sup>12</sup> Another closely related Reduviidae insect, *Onococephalus pacificus* (Pacific kissing bug), has been found in Wahiawa and at the Kaimana Beach Hotel in Waikiki, as well as a documented human bite at Radford Terrace, O‘ahu in 1970.<sup>13,14</sup>

The diagnosis of *T. rubrofasciata* hypersensitivity is based on clinical presentation and identification of the insect. Currently, serum specific IgE testing for *T. rubrofasciata* is not performed by any commercial labs and serum extracts are likewise unavailable, thus precluding skin testing. As specific serum is not available for *Triatoma*, desensitization using immunotherapy is not performed outside of a research setting. Although there have been no reports of using immunotherapy on *T. Rubrofasciata* bites, there have been two successful studies using *T. protracta* extracts. The first reported use of immunotherapy to

prevent an anaphylactic reaction in a known allergic patient was by Marshall and Street in 1982. In this instance, a patient who had previously experienced a generalized reaction to *T. protracta* bite was given progressively increasing doses of a salivary gland extract. Observed bite challenges elicited mild cutaneous reactions without evidence of anaphylaxis.<sup>15</sup> In a 1984 study by Rohr et al, five patients who had life-threatening anaphylactic reactions from the bite of *T. protracta* were treated with immunotherapy using extract-antigen preparations from the insect's salivary glands. The anti-Triatoma IgG and IgE responses were found to rise after four weeks of treatment, plateau by 12 weeks, and remain steady after 30 weeks of treatment. The patients were subsequently challenged by *T. protracta* bites. One patient exhibited a local wheal with scattered urticarial lesions while four other patients developed limited wheals at the site of bites.<sup>16</sup> Although the antigenic cross reactivity between *T. rubrofasciata* and *T. protracta* is unknown, *T. rubrofasciata* desensitization is theoretically possible. However, because of the complexity of obtaining the serum from Triatoma glands, it is not a viable treatment option outside of a research setting.

In susceptible individuals known to have an anaphylactic reaction to *T. Rubrofasciata*, avoidance of exposure is the only effective preventive measure. The greatest risk factor is living in a rural area in close proximity to animals which can serve as vectors, as did the patient in the above case who lived on land adjoining both a pig and chicken farm. According to the 1982 Hawai'i Vector Control Manual, a number of avoidance and insect proofing strategies can be instituted. All wild animal harborages within 100 yards of a home, to include mongoose and rodent shelters, should be destroyed. The fur of domesticated animals should be regularly checked for the presence of these insects and pet entryways should be bug-proofed. The flooring, moldings and foundations of the home should be checked for cracks, and discovered imperfections should be filled with caulking. Also, beds should be moved at least a foot away walls and adhesive tape should be applied to the legs of beds with the sticky side out.<sup>13</sup>

As the kissing bug is a nocturnal insect capable of flight, outside lights should be turned off or away from the home so as not to attract them to the area. Other avoidance strategies include use of approved indoor pesticides as well as use of bed nets. The floor of the bedroom should be kept free of clutter and bed linens should not touch the floor. In high incidence areas, examination of bed sheets prior to getting into bed may be helpful. As the insect rarely bites covered skin, wearing pajamas with long sleeves and long pants is reasonable, as is spraying insect repellent on uncovered skin prior to bed.<sup>2</sup>

Epinephrine is the only effective treatment for anaphylaxis. Sensitized patients should always have an epinephrine auto injector readily available. The patient and close contacts should be taught how and when to use this medication.<sup>2</sup> Altogether, true hypersensitivity to this insect is a rare occurrence, but when it does occur, avoidance is the best strategy and clinicians should be aware of this sequela to the *T. rubrofasciata* bite. There is no current skin testing or immunotherapy, though this presents a potential area for future research.

## Conflict of Interest

None of the authors identify any conflicts of interest.

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# Atypical Presentation of Eosinophilic Fasciitis with Pitting Edema

Chih-Wei Chang MSIV and Matthew S. Lau MD FACAAI

## Abstract

*Eosinophilic fasciitis (EF) is a rare condition involving inflammation of the fascia and peripheral eosinophilia of unknown etiology leading to tissue fibrosis. Clinical presentation includes peripheral eosinophilia, symmetrical skin thickening with subcutaneous tissue induration of the extremities and rashes developing acutely over a period of days to weeks. An unusual feature of EF is the presence of symmetric pitting edema presumed to be secondary to vascular leakage. This is a case of eosinophilic fasciitis presenting in atypical fashion with pitting peripheral edema in addition to the classic symptoms.*

## Keywords

*Eosinophilic fasciitis; Pitting edema; Biopsy*

## Introduction

Eosinophilic fasciitis (EF) is a rare condition involving inflammation of the fascia and peripheral eosinophilia of unknown etiology leading to tissue fibrosis.<sup>1-3</sup> As of 2007, there are approximately 250 cases reported in the medical literature.<sup>4</sup> Clinical presentation includes peripheral eosinophilia, symmetrical skin thickening with subcutaneous tissue induration of the extremities and rashes developing acutely over a period of days to weeks.<sup>5-7</sup> The absence of Raynaud's phenomenon and internal organ involvement distinguishes this condition from collagen vascular disease such as scleroderma.<sup>1,8-11</sup> An unusual feature of EF is the presence of symmetric pitting edema presumed to be secondary to vascular leakage.<sup>3,6,8</sup> Full-thickness skin biopsy showing perivascular inflammation composed of lymphocytes, plasma cells, and eosinophils in the subcutis and fascia or characteristic MRI findings are required to confirm the diagnosis.<sup>8,12,13</sup> This is a case of an atypical presentation of eosinophilic fasciitis with symmetric pitting edema.

## Case Report

DM is a 64-year-old man with a chief complaint of generalized arthralgia and stiffness, and numbness, with symmetric pitting edema of all of his extremities. He denied fever, GI symptoms, unexplained weight loss, rash, hives, angioedema, adenopathy, and had had no history of atopic disease. PMHx included Hx of skin cancer and paroxysmal atrial fibrillation controlled on Diltiazem. He was not taking any herbal medicine. The general physical examination was remarkable for 2+ pitting edema of bilateral lower extremities (Figure 1), and mild edema of the bilateral forearms. There was no jugular venous congestion, hepatomegaly, or pre-sacral edema. Musculoskeletal and cardiopulmonary examinations were normal.

Initial laboratory values included a complete blood count remarkable for 69% eosinophilia (9,900 Eosinophil count), normal serum levels of electrolytes, creatinine, alkaline phosphatase, and aminotransferases. The serum albumin level was

decreased at 3.6 gm/dl without proteinuria on UA. ESR, RF, ANA, ANCA, and IgE were unremarkable. Parasitic infection studies were negative. Bone marrow biopsy showed no evidence of malignancy. Analysis of a full-thickness skin biopsy while on systemic steroids revealed chronic inflammation of the fascia with scattered eosinophils consistent with partially treated Eosinophilic fasciitis (Figure 2, Figure 3).

After initiating therapy with oral prednisone, the patient reported marked decrease in peripheral edema, joint stiffness and labs indicated normalization of peripheral eosinophil counts. He remained clinically improved with complete remission of pitting edema and joint stiffness on tapering daily doses of prednisone to 15 mg, below which symptoms returned. The patient remains clinically stable and is currently on titrating dose of cyclosporine and prednisone of 3.5 mg/day.

## Discussion

The etiology of EF is unknown. Most cases are idiopathic. Some cases are associated with strenuous exercise, trauma, initiation of hemodialysis, infection with *Borrelia burgdorferi*, radiation therapy, hematologic disorders, and Graft-versus-host disease.<sup>1,3,8,9,14-17</sup> Some drugs including simvastatin, atorvastatin, and phenytoin have been implicated.<sup>18-20</sup>

The pathophysiology of EF is unclear but it is postulated to involve a proinflammatory and fibrogenic cytokine response including IL-5, IFN-gamma, and TGF-beta resulting in an inflammatory cell infiltration that dysregulates production of extracellular matrix proteins and increases collagen production by fibroblasts, which ultimately leads to progressive fibrosis of affected tissues.<sup>21-25</sup>

The differential diagnosis of symmetric pitting edema includes conditions associated with low oncotic pressure or venous insufficiency and congestive heart failure.<sup>8</sup> Other differential diagnoses to consider with similar presentation accompanied by peripheral eosinophilia include eosinophilia-myalgia syndrome, localized fibrosing disorders, scleroderma, and systemic sclerosis.

Full-thickness biopsy including skin, subcutaneous fat, fascia and muscle of the affected area is the essential study for diagnosing eosinophilic fasciitis especially in an atypical presentation.<sup>26</sup> In EF, perivascular eosinophilic inflammation is predominantly in the subcutis and deep fascia.<sup>8</sup> In contrast, scleroderma shows signs of inflammation, collagen deposition, and fibrosis more in the superficial dermis.<sup>8</sup>

In our patient, bone marrow biopsy results indicated no leukemic etiology and further workup showed no evidence of nephrotic syndrome, parasitic infection, or collagen vascular



Figure 1. Patient's right lower extremity demonstrates 2+ pitting edema.

disease. Skin biopsy confirmed the presence of chronic fascial inflammation with scattered eosinophils consistent with the patient being partially treated on systemic corticosteroids. Therapy using corticosteroids at 1mg/kg/day is considered first line therapy based on consensus.<sup>3,9,27</sup> Since relapses can occur, and many patients do not respond to corticosteroids, other immunosuppressive or immunomodulatory agents are required for some patients to obtain a therapeutic response and/or used as steroid-sparing agents.<sup>3,10</sup> Alternative agents including cyclosporine, dapsone, hydroxychloroquine, azathioprine, and methotrexate have been used as steroid sparing or disease modifying therapy.<sup>8,10,28,29,30</sup>

### Conclusion

This is a case of Eosinophilic fasciitis presenting in atypical fashion with pitting peripheral edema in addition to the classic symptoms of joint stiffness and peripheral eosinophilia on CBC. Bone marrow biopsy results indicated no leukemic etiology and further workup showed no evidence of nephrotic syndrome, parasitic infection, or collagen vascular disease. Skin biopsy confirmed the presence of chronic fascial inflammation with scattered eosinophils consistent with the patient being partially

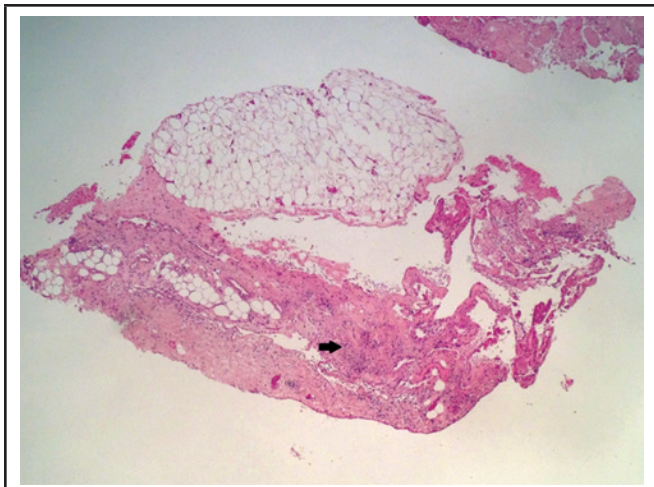


Figure 2. A full thickness biopsy specimen from the patient in low power of magnification revealed chronic inflammation of the fascia with marked cellular inflammation.

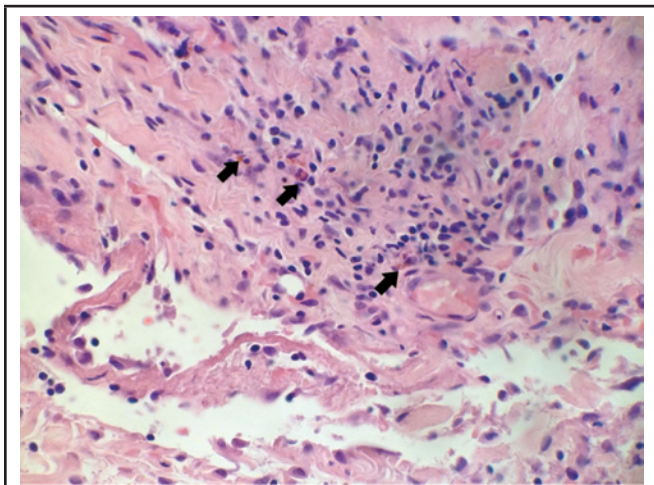


Figure 3. A full thickness biopsy specimen from the patient in high power of magnification revealed chronic inflammation of the fascia involving lymphocytic infiltration and scattered eosinophils consistent with partially treated Eosinophilic fasciitis.

treated on systemic corticosteroids. Therapy using corticosteroids at 1mg/kg per day is considered first line therapy based on consensus.<sup>3,9,27</sup> Alternative agents including cyclosporine, dapsone, hydroxychloroquine, azathioprine, and methotrexate have been used as steroid sparing or disease modifying therapy though EF often regresses spontaneously.<sup>8,10,28,29,30</sup> To date the patient remains on oral prednisone and cyclosporine with improved symptom control and normalized peripheral eosinophil counts.

## Conflict of Interest

None of the authors identify any conflict of interest.

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# The Practice Improvement in Education (PIE) Project: Patient Outcome Related to Education on Depression in Nursing Homes

Sung Eun Jang MD; Aida Wen MD; Christina Bell MD, PhD; Sebrina Parkins BSN; Jan Shishido MPH; and Kamal Masaki MD

## Abstract

**Background:** Depression is an important factor related to agitation and other behaviors in nursing home residents. As the next step in our Geriatric Education Center (GEC) Practice Improvement in Education (PIE) project on depression in nursing homes, we focused on non-pharmacologic behavioral management and psychoactive medication reduction.

**Methods:** This quality improvement (QI) pilot included training on effective interdisciplinary management approaches for depressive symptoms and challenging behaviors, and implementing an adapted ABC (antecedents, behaviors, consequences) log and behavioral activation. We targeted two nursing home floors and included data on residents present both before and after the QI, in June 2013 and July 2014. We examined changes in depressive symptom scores (Patient Health Questionnaire, or PHQ-9, scale 0-27, higher=worse) and antipsychotic/antidepressant medication use with paired T-tests and Fisher's exact tests.

**Results:** Of the 66 nursing home residents in this QI pilot, 70% were female, 60.6% were >89 years old (range = 48-108, mean = 88.8), 83% were Asian and 51% had severe cognitive impairment. Mean PHQ-9 scores decreased significantly from 3.74 to 2.38 ( $P = .017$ ). Of the 13/66 (19.7%) residents on an-

tippsychotic medications, 10/13 (76.9%) had dose reductions and 4/13 (30.8%) had medications completely discontinued ( $P < .0001$  for change pre/post). Of the 34 (51.5%) residents on antidepressant medication, 15/34 (42.9%) had dose reductions and 3/34 (8.8%) had medications completely discontinued ( $P < .0001$  for change pre/post).

**Conclusion:** Mean depression scores and antipsychotic and antidepressant medication use decreased significantly in this GEC PIE QI project to manage depression and behaviors non-pharmacologically in nursing home residents.

## Conflict of Interest

The authors report no conflict of interest.

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# Cationic Liposomes Promote in Vivo Transfection, Innate Immunity Activation and Antigen-Specific CD8+ T-Cell Activation Following Vaccination with Piggybac DNA Plasmids

Jared Hara; Pietro Bertino PhD; FuKun W. Hoffmann PhD; Aaron H. Rose PhD; Stefan Moisyadi PhD; and Peter R. Hoffmann PhD, MPH

## Abstract

**Introduction:** DNA vaccination with plasmid has conventionally involved vectors designed for transient expression of antigen in injected tissues. Next generation plasmids are being developed for site-directed integration of transgenes into safe sites in host genomes and may provide an innovative approach for stable and sustained expression of antigens for vaccination. In our previous study, we have demonstrated the improved efficacy of site-directed integration using hyperactive piggyBac transposase-based integrating vectors (pmhyGENIE-3) over non-integrating plasmids. Adjuvant technologies such as Adjuplex™ may further improve vaccine efficacy by producing a strong immunostimulatory effect to elicit more potent immune responses via both cell-mediated and antibody-mediated mechanisms.

**Study Design:** The goal of this study was to evaluate in vivo antigen expression and the generation of cell mediated immunity in mice injected with plasmids and various adjuvants. The efficacy of Adjuplex™ to promote antigen expression and CD8+ T cell activation after vaccination with pmhyGENIE-3 was compared with the efficacy of two other adjuvants: liposomes, jetPEI $\bar{U}$ . Groups of mice injected with pmhyGENIE-3 expressing luciferase (pmhyGENIE-GL3) and adjuvants were used to compare antigen expression. In another experiment, mice injected with pmhyGENIE-3 plasmids expressing eGFP (pmhyGENIE-3-eGFP) with different adjuvants were used to compare eGFP-specific T cell activation.

**Results:** When luciferase activity was measured using IVIS imaging, mice vaccinated with pmhyGENIE-3-GL3 and Adjuplex™ showed the strongest antigen expression at 28 days after subcutaneous injection. Flow cytometry analysis of blood cells, using antigen-specific pentamers, demonstrated that vaccination with pmhyGENIE-3-eGFP and Adjuplex™ generate higher numbers of CD8+ T cells when compared with liposomes and jetPEI $\bar{U}$ . Analyses of eGFP peptide-pulsed spleen cells from vaccinated mice using ELISPOT and intracellular cytokine staining confirmed higher antigen-specific, interferon- $\gamma$ -producing CD8+ T-cell responses after vaccination using Adjuplex™.

**Conclusions:** Overall, these findings suggest that plasmids designed to direct integration of transgenes into the host genome used in conjunction with Adjuplex™ provide a promising approach for DNA vaccines. Robust cell mediated CD8+ T cell responses generated using this vaccine/adjuvant combination may provide effective, sustained immune responses against intracellular pathogen or tumor antigens.

## Conflict of Interest

The authors report no conflict of interest.

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# A Real Life Experience with the Comsos Regimen in Genotype 1 Chronic Hepatitis C Treatment: Including Patients with East Asian Ancestry and Decompensated Cirrhosis

Marina Roytman MD; Resham Ramkissoon BSc; Leena Hong PA-C; Ruby Trujillo APRN; Leslie Huddleston PhD; Peter Poerzgen PhD; Todd Seto MD; and Naoky Tsai MD

## Abstract

**Background/Aims:** The COMSOS phase 2 trial showed high cure rates and a favorable side effect profile of a 12-week regimen of Sofosbuvir (SOF) and Simeprevir (SIM) in patients with a genotype 1 Hepatitis C infection. However, given the small number of patients in the COSMOS trial, there is uncertainty regarding the efficacy and safety of this combination therapy. We now report our experience with the COSMOS regimen in the multiethnic population of Hawai'i, including patients of East Asian ancestry and decompensated cirrhosis.

**Methods:** Retrospective review of 99 patients treated with a fixed dose regimen of SIM 150 mg and SOF 400 mg daily, beginning January 2014 at a single referral center. We collected data on demographics, side effects, laboratory studies and SVR (sustained virological response). Statistical analysis was performed with Stata v8.2 software.

**Results:** 99 patients began treatment prior to December 2014. Baseline characteristics: 63.3% cirrhotic (18.2% of those Child-Pugh Class B/C), 38% Asian, 12% Pacific Islander, 64% male, mean age 61.5  $\pm$  8.4, mean BMI 27  $\pm$  5.9, 62% diabetic, 62% genotype 1a, 22/42 IL28B non-CC genotype, 7/32 positive for Q80K mutation.

At interim analysis, 72 patients have reached week 4 and 45 have reached week 12 post-treatment. Overall, the SVR12 rate is 86.5%. 100% decompensated cirrhotic patients achieved SVR12, compared to 85.2% of cirrhotic patients and 82.1% of non-cirrhotic patients. 90% of Asian patients reached SVR12

compared to 84% of non-Asians. Treatment naive patients had higher SVR12 rates than treatment experienced patients (96% vs 82%). Main side effects: headache 16.2%, fatigue 24.2%, pruritis 14.1%; none were >grade 2 in severity. There were no differences in side effect profiles of patients with decompensated cirrhosis. Pruritis was the only statistically significant difference between Asians and non-Asians (24% vs 8%).

**Conclusions:** The 12 week fixed dose course of SIM+SOF was well tolerated in a multiethnic population of primarily cirrhotic patients, including those with decompensated disease, with the SVR12 rates at interim analysis comparable to COSMOS data. There was a trend toward better SVR12 rates in patients with decompensated cirrhosis and of Asian ancestry possibly due to higher Simeprevir exposures. Higher incidence of adverse side effects was not observed with an exception of higher rate of pruritis in Asians. Complete data on SVR4 and SVR12 will be available on all patients by February 2015.

## Conflict of Interest

The authors report no conflict of interest.

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# Provider Documentation of Geriatric Issues among Older Adults Receiving Care in Safety Net

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## Abstract

**Background:** In a safety net setting, we evaluated primary care provider (PCP) documentation of geriatric issues and whether geriatric consultation influences subsequent documentation.

**Methods:** We performed a retrospective chart review of patients referred to an outpatient geriatric consult service at San Francisco General Hospital. The geriatrics service serves two primary care clinics and provides advice through an e-consult, an e-consult with care coordination services, or a comprehensive geriatrics assessment. We queried charts for patients  $\geq 60$  years of age, referred from October 2012 to November 2013, and received care for  $\geq 6$  months after the consult. For two primary care visits pre- and post-consult, we recorded documentation of geriatric issues, such as cognitive impairment, falls, and symptoms prevalent in older adults. Comparisons were analyzed using descriptive statistics and paired sample t-tests.

**Results:** Among 90 patients referred, mean age was 77.9 years (7.3) and 62.2% were female. Most patients (66.7%) were non-English speaking. Patients' race included 40% Hispanic, 32.2% Asian, 15.6% African-American, and 12.2% White. Many, 78.9%, were dual-eligible. The most common conditions included diabetes (43.3%), dementia (37.8%), and mental health disorders (31.1%). Pre-consult, PCPs documented screening for falls in 54.4%, cognitive impairment in 38.9%, mental health conditions in 35.6%, and activities of daily living in 28.9%. An advance directive or goals of care were documented in 45.6% of

charts. Symptoms (pain, shortness of breath, insomnia, fatigue or anorexia) were often documented pre-consult (91.1%). The only difference in a pre-post comparison was that providers documented fewer screens post-consult for cognitive impairment (38.9 vs 21.1%).

**Conclusion:** Among PCPs in safety net clinics, less than half had documentation of common geriatrics issues, other than symptoms, prior to consulting a geriatrician. The consult did not affect post-consult documentation. More studies are needed to determine how to improve documentation of important geriatric issues.

## Conflict of Interest

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# Can a Dietary Supplement Induce Autoimmune Hepatitis?

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## Abstract

**Purpose:** The etiology of autoimmune hepatitis (AIH) is largely unknown, but xenobiotics, rare viruses and drugs like minocycline and nitrofurantoin have been implicated. With this report we want to bring attention to dietary supplements as a possible trigger for AIH. OxyElite Pro New Formulation (USPlabs, Dallas, Texas), a popular weight-loss herbal dietary supplement was linked to severe hepatotoxicity in 56 patients across the United States. Our center has encountered 35 of these cases and seen most of them recover after discontinuation of OxyElite Pro. We now report a subgroup of patients that went on to developed AIH.

**Methods:** Clinical data on demographics, drug use, laboratory studies, biopsies and outcomes were collected. We assessed causality and severity of liver injury according to Roussel Uclaf Causality Assessment Method/ Council for International Organizations of Medical Sciences (RUCAM/CIOMS) scale and Drug-Induced Liver Injury Network (DILIN) method respectively. We assessed likelihood of AIH diagnosis using the Revised Original Scoring System of the International Autoimmune Hepatitis Group.

**Results:** 35 patients with acute liver injury were identified at our medical center between May 2013 and January 2014. Two patients were transplanted, two died, 25 recovered. Six patients continued to have progressive worsening of liver function despite discontinuation of OxyElite Pro. Four out of six patients were hospitalized at initial presentation, all had liver biopsies. Histol-

ogy was consistent with AIH and distinctly different from other patients with OxyElite Pro DILI. All six patients were treated with corticosteroids and entered remission thus strengthening the diagnosis of AIH. Use of the Revised Original Scoring System revealed 2 cases as definite and 3 cases as probable.

**Conclusions:** We report six cases of AIH in the setting of DILI due to OxyElite Pro in a five month period (August 2013-January 2014) observed in a single center. We postulate that DILI due to OxyElite Pro has induced de novo AIH or unmasked preexisting, quiescent disease.

*(This poster has previously been presented at the American Association for the Study of Liver Diseases 2014 conference in Boston, MA.)*

## Conflict of Interest

The authors report no conflict of interest.

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# Management of In-vitro Fertilization Twin Pregnancy with Pulmonary Hypertension Secondary to Systemic Lupus Erythematosus

Thomas Aldan MD; Brent Matsuda MD; Howard Yang MD; and Gehan Devendra MD

## Abstract

Systemic lupus erythematosus (SLE)-associated severe pulmonary hypertension developing in pregnancy is a rare and clinically serious phenomenon. Mortality in this patient population is as high as 56%. We present a case of new onset SLE-associated pulmonary hypertension with in-vitro fertilization (IVF) twin pregnancy.

This is a 44-year-old Chinese woman with past medical history significant for SLE who initially presented to outpatient pulmonology clinic with progressive shortness of breath during the 21st week of her IVF pregnancy. Initial work up included a transthoracic echocardiogram that estimated pulmonary artery systolic pressure to be 55 mm Hg. Further evaluation including right heart catheterization revealed mean pulmonary artery systolic pressure of 48 mm Hg. At 25 weeks into pregnancy, she was admitted to the medical intensive unit for epoprostenol infusion under the care of a multidisciplinary team including pulmonology, obstetrics-gynecology, neonatology, and cardiology. Additional management included oral furosemide, fluid restriction and sildenafil. Enoxaparin for thrombosis prophylaxis was discontinued due to significant thrombocytopenia that developed during hospitalization. She did not develop a lupus flare during her hospitalization while on hydroxychloroquine and prednisone. Patient delivered at 30 weeks via cesarean section under slow epidural infusion. A viable male infant and female infant were delivered without complications. She continued

epoprostenol infusion until worsening thrombocytopenia led to transition to treprostinil therapy. She was discharged from the hospital in stable condition and is doing well on continued treprostinil infusion with sildenafil.

Combination of immunosuppressive and intravenous-vasodilator therapy have been implemented and subsequently reported in available case studies of this rare phenomenon. A similar regimen aimed at management of profound hemodynamic changes and lupus control was successfully utilized in the care of this patient with twin pregnancy, which may suggest a potential standard of care in these rare cases. Patients in the postpartum are at particular risk for mortality due to the loss of pulmonary vasodilation that normally occurs, leading to right ventricular failure. Long term prognosis and complications of SLE-associated pulmonary hypertension are still under investigation.

## Conflict of Interest

The authors report no conflict of interest.

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# Efficacy of Tocilizumab in a Patient with Adult-onset Still's Disease and Elevated Cocksackie B Viral Titers

Caleb Anderson MD (Associate) and Jefferson Roberts MD (Associate)

## Abstract

**Introduction:** Adult-onset Still's disease (AOSD) is a rare, inflammatory disorder characterized by arthralgia, evanescent, salmon-colored rash, daily fevers, lymphadenopathy, pharyngitis, and hepatosplenomegaly. Frequently seen laboratory abnormalities include leukocytosis, transaminitis, elevated ferritin and acute phase reactant levels, and aberrant production of pro-inflammatory cytokines. The inciting etiology of this syndrome is unknown, and both viruses and bacteria have been isolated in patients with AOSD leading to the hypothesis that infection triggers an autoimmune response. Treatment is empirical and includes symptom control with non-steroidal anti-inflammatory drugs and corticosteroids, as well as disease modifying anti-rheumatic drugs (DMARDs) and biologic agents. While biologic agents such as TNF $\alpha$ -blockers and IL-1 inhibitors have established efficacy in treating AOSD, emerging literature suggests that IL-6 inhibitors, which are generally used for rheumatoid arthritis, can be used in cases refractory to first-line treatment. We present the case of a 32 year old male with elevated coxsackie viral titers and AOSD refractory to numerous immunomodulating agents who experienced disease remission with Tocilizumab, thus suggesting a possible subset of patients in whom this less established regimen may have efficacy.

**Case:** A 32 year old previously healthy male presented with febrile illness, lymphadenopathy, pharyngitis, macular rash, red eye syndrome, and myalgias. Labs were notable for elevated CRP to 32, ESR greater than 100, negative ANA/RF, leukocytosis, transaminitis, ferritin of 1300, and a elevated Cocksackie B viral titers. The concern initially was for a viral illness versus AOSD, and the patient's symptoms initially responded to high dose prednisone. However, the patient's fever and myalgia returned, and his course was complicated by recurrent fevers

and arthralgias refractory to various combinations of plaquenil, colchicine, methotrexate, etanercept, adalimumab, and repeated doses of steroids, with disease relapse seen upon steroid taper. Anakinra, an IL-1 inhibitor was tried with marginal success, though the patient continued to have elevated inflammatory markers and large joint arthritis. The patient was finally tried on Tocilizumab in combination with methotrexate, and has experienced an extended disease remission which has persisted for eight months despite complete steroid taper.

**Discussion:** Adult Onset Still's Disease is an inflammatory disease of unknown etiology often thought to be secondary to interaction between infectious antigens and host genetic factors and autoimmune mechanisms which ultimately lead to the disease state. We present a case of a patient with four major and four minor criteria of AOSD with elevated coxsackie viral titers who was refractory to conventional treatment yet experienced complete disease remission upon treatment with Tocilizumab, thus suggesting a possible subset of patients in whom this emerging second line treatment may prove beneficial.

*Disclaimer: The views expressed in this abstract/manuscript are those of the author(s) and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.*

## Conflict of Interest

The authors report no conflict of interest.

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# Sleep Quality in HIV Patients: Efavirenz Use, CD4 Status, Cytokine and Monocyte Profiles

Ariel Dunn; Louie Mar A. Gangcuangco MD, Dominic C. Chow MD, PhD;  
and Cecilia M. Shikuma MD

## Abstract

**Background:** Efavirenz is an antiretroviral drug known to cause CNS side effects, which often cause sleep disturbances. These are more pronounced during early treatment, but it is unclear whether these persist on chronic use. Low CD4 levels, indicative of substantial immune dysfunction, as well as alterations in cytokine and monocyte parameters have been implicated in sleep disturbances. We therefore investigated the effects of efavirenz use, CD4 status, and cytokine and monocyte levels on self-reported sleep quality in HIV-infected patients.

**Methodology:** Retrospective analysis of data collected among HIV-infected subjects  $\geq 40$  years old stable on antiretroviral therapy enrolled in the Hawai'i Aging with HIV Cohort Study. Pittsburgh Sleep Quality Index (PSQI) was administered once during the 5 yr study to assess sleep quality: duration (DURAT), disturbance (DISTB), latency (LATEN), daytime dysfunction (DAYDYS), efficiency (HSE), self-perceived overall sleep quality (Q6), and use of sleeping medication (Q7). PSQI scoring algorithm from the University of Pittsburgh Sleep Medicine Institute was used to calculate these parameters. A global PSQI score (PSQITOT) was determined with scores  $>5$  indicating clinical sleep impairment. Efavirenz and non-efavirenz users' PSQITOT (and its 7 components) were compared using the Mann-Whitney two-sample T-test and PSQITOT by chi-square after dichotomizing values. We assessed the significance of current CD4 levels (obtained within 3 or less months of the study administration) and CD4 nadir levels to PSQITOT and its seven components using linear regression. The correlation

between PSQITOT and its 7 components to subjects baseline cytokine and monocyte profiles (measured  $<3$  years prior to the study) were assessed using Spearman's rho.

**Results:** 80 subjects were available for analysis (median age 51, 91% males and 56% Caucasians) 36% were on efavirenz, all for a duration of  $\geq 1.5$  years. No statistical significances were seen in the PSQITOT, its 7 components, or the PSQIDICH between efavirenz users and those on other ARV therapy or by CD4. Serum Amyloid A (SAA) levels were positively correlated with PSQITOT, DAYDYS, and Q6. IL-10 levels were positively correlated with PSQITOT, DURAT, DISTB, and Q6. IL-6 levels were also positively correlated with Q6. Classical monocytes (CD14+ and CD16-) were positively correlated with PSQITOT and Q6.

**Conclusions:** No differences in sleep quality were seen between chronic efavirenz use or by CD4 counts. High levels of pro-inflammatory cytokines SAA, IL-10 and IL6 and classical monocytes were associated with sleep disturbances, suggesting an inflammatory component in its pathogenesis.

## Conflict of Interest

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# The Excess Cost of Inter-island Transfer of Intracerebral Hemorrhage Patients

Kazuma Nakagawa MD; Alexandra Galati BA; and Deborah Taira Juarez ScD

## Abstract

**Background:** Spontaneous intracerebral hemorrhage (ICH) is a hemorrhagic stroke with high morbidity and mortality, and accounts for 10-15% of the approximately 700,000 annual strokes in the United States. Current guidelines recommend all ICH patients be managed initially in a facility with the capacity to perform subspecialized neurosurgical procedures (SNP). In Hawai'i, many ICH patients from neighbor islands are air transported to a higher-level facility on O'ahu with neuroscience expertise. However, the majority of them do not receive SNP upon transfer. Hence, their transfer may potentially be considered excess cost.

**Methods:** Consecutive ICH patients hospitalized at a tertiary center on Oahu between 2006 and 2013 were studied. SNP was defined as any neurosurgical procedure or conventional cerebral angiogram. Minimum cost of inter-island transfer for ICH patients was conservatively estimated as \$15,000 per transfer. Total excess cost was estimated as the cost of inter-island transfer multiplied by the number of inter-island transfer patients who did not receive SNP. In sensitivity analyses, we varied the cost of inter-island transport from \$5,000 to \$25,000 (baseline = \$15,000). Multivariable analyses were performed to identify independent factors associated with receiving SNP.

**Results:** Among 825 patients, 100 patients (12%) were transferred from neighbor islands. Among the neighbor island patients, 69 patients (69%) did not receive SNP, which translates to \$1,035,000 of excess cost over an 8-year period (approximately \$129,375/year). The sensitivity analysis resulted in annual excess cost estimates ranging from \$43,125/

year to \$215,625/year. Multivariable analyses showed age (OR 0.95, 95% CI: 0.94, 0.96), lack of hypertension (OR 1.62, 95% CI: 1.002, 2.61), initial Glasgow Coma Scale (OR 0.94, 95% CI: 0.89, 0.98), lobar hemorrhage (OR 2.74, 95% CI: 1.59, 4.71), cerebellar hemorrhage (OR 5.47, 95% CI: 2.78, 10.76), primary intraventricular hemorrhage (IVH) (OR 4.40, 95% CI: 1.77, 10.94), and any IVH (OR 2.47, 95% CI: 1.53, 3.97) to be independent predictors of receiving SNP.

**Conclusion:** Approximately two-thirds of air-transferred ICH patients did not receive SNP. Many ICH patients from neighbor islands are being transferred to a tertiary center with neurosurgical coverage even though higher-level neurosurgical procedures may not be indicated. Our cost analysis demonstrates that approximately \$129,375/year is spent in unnecessary medical air transport. It can be argued that ICH patients who do not require SNP should be immediately admitted to the general ICU of their local hospital to receive optimal medical management rather than delaying management by arranging inter-island transfer. Further study is needed to assess the cost-effectiveness of creating a triage algorithm to optimally select ICH patients who would benefit from air transport to a higher-level facility.

## Conflict of Interest

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# Early Outcomes of Simultaneous Bilateral Direct Anterior Approach Total Hiparthroplasty: A Retrospective Review

Trudy M. Hong and Cass K. Nakasone MD

## Abstract

**Introduction:** Total hip arthroplasty (THA) is one of the most common orthopedic surgeries performed. Simultaneous bilateral THA, however, a procedure where both hip joints are replaced during a single anesthetic event, is relatively uncommon. The primary objective of this study is to describe the short-term outcomes and early complications encountered in a relatively large cohort of patients who underwent simultaneous bilateral THA utilizing a direct anterior approach by a single fellowship trained surgeon.

**Methods:** A retrospective chart review was performed on a group of 94 patients who had undergone simultaneous bilateral THAs thru a direct anterior approach at Straub Clinic & Hospital, Honolulu, HI, from January 2006 to March 2014. Minimum follow up was 3 months. There were 44 males and 50 females. The average age was 62.4 years (24.9-79.4) and BMI was 26.3 (17.9-40.3). Preoperative diagnoses included osteoarthritis (89 patients [94.7%]), avascular necrosis (4 patients [4.3%]), and rheumatoid arthritis (1 patient [1.1%]). Data collected from electronic medical records included outcomes such as average days to ambulation, distanced walked on each postoperative day until discharge, hospital length of stay, disposition (home or short-term rehab facility), and early complications.

**Results:** Following surgery, the average number of days to ambulation was one day (0-2). The average distance walked on the first postoperative was 76 ft and this increased to 193 ft on the second postoperative day. The average hospital length of stay was three days (1-7). Seventy nine percent of patients (average age: 60 years) were discharged home and 21% (average age: 72 years) were discharged to a short-term rehab facility prior to returning home.

There were no dislocations, two superficial infections, one deep infection (requiring irrigation and debridement with head and liner exchange and six weeks of IV antibiotics), two peri-prosthetic fractures (one due to fall requiring revision of the stem and reduction of the fracture and the other not requiring surgical intervention), one postoperative hematoma (requiring irrigation and debridement), and one greater trochanter fracture (not requiring surgical intervention). There were no deep vein thrombosis, pulmonary emboli, myocardial infarctions or other serious systemic complications. Forty-nine patients required transfusion of at least one unit of packed red cells. For those requiring transfusions, the average number of units transfused was 2.6.

**Conclusion:** Overall the simultaneous bilateral direct anterior approach THA has been a safe and successful surgery for patients with severe bilateral hip pain who failed conservative medical treatment. It has resulted in short hospital stays, rapid return to early ambulation with assistive devices, decreased need for short-term rehabilitation facilities, and few early postoperative complications.

## Conflict of Interest

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# End-of-Life Preference Discussions between Elderly Japanese American Men and Their Families: The Honolulu-Asia Aging Study

Shinji Ito MD; Lauren Okamoto MD; Christina Bell MD, PhD; Kaon Fong BS;  
and Kamal Masaki MD

## Abstract

**Background:** Challenging cases in geriatrics often involve lack of communication regarding end-of-life preferences and cultural issues. There have been no previous population-based studies on acculturation and end-of-life preference discussions among older Japanese-Americans.

**Methods:** The Honolulu-Asia Aging Study is a continuation of the Honolulu Heart Program, a longitudinal cohort study in Japanese-American men in Hawai'i that began in 1965. In the 2009-10 exam, participants identified a proxy informant who answered questions about their knowledge of the men's end-of-life preferences. We studied the relationship between end-of-life preference discussions and completion of a written advance directive and actual preferences for end-of-life care, as well as associations between discussions and demographic and cultural factors. The Cultural Assimilation Scale (CAS) consisted of 8 questions assessing degree of Japanese identity and lifestyle. Results: Among 350 participants aged 89-108 years, proxy informants were wives (29.4%), daughters (29.4%), sons (22.0%), other relatives (8.0%) and others (mostly paid caregivers, 11.1%). On proxy interview, 70.7% reported end-of-life preference discussions and 29.3% did not. Those who had end-of-life preference discussions were more likely to have completed a written advance directive compared to those without discussions (93.6% vs 61.5%,  $P < .0001$ ). Even among those with discussions, many proxies were unsure about certain preferences, including tube feeding (27.4%), nursing home care (23.8%) and dementia care (20.2%). Factors associated with

having end-of-life preference discussions included Christian religion (vs Buddhist/Shinto, OR = 1.85, 95% CI = 1.00-3.41,  $P < .05$ ) and daughter as proxy informant (vs wife, OR = 2.34, 95% CI = 1.20-4.54,  $P = .01$ ), but no associations with age, education, marital status or acculturation scores.

**Conclusion:** Among this oldest-old population, there were almost 30% who did not have end-of-life preference discussions. Among those who did have these discussions, almost a quarter did not know about preferences regarding tube feeding, nursing home care or dementia care. Religion was the only acculturation factor associated with end-of-life preference discussions. Participants with daughters as proxy informants had higher odds of end-of-life preference discussions.

## Conflict of Interest

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# Sjögren's, Steroids, and Subcutaneous Emphysema

Jamie M. Kagihara MD; Christian Y. Kitamura MD; and Samuel J. Evans MD, FACP

## Abstract

A 62-year-old woman presented with 4 months of non-productive cough. She reported progressive dyspnea, anorexia, fatigue, and weight loss over 3 months. She had no prior history of autoimmune disease or occupational exposures. She denied fever, sweats, chills, or recent travel. Review of systems was positive for dry eyes and mouth. Exam was notable only for bilateral basilar crackles, left greater than right. Serology revealed positive ANA, SSA, and SSB antibodies. PFTs showed a moderately severe restrictive pattern with severely impaired diffusion. Chest CT showed diffuse, ground glass like interstitial infiltrates.

Bronchoscopy with bronchoalveolar lavage and biopsies was negative for infection or malignancy. She was subsequently started on Prednisone, 1 mg/kg daily, for presumed Sjögren's associated interstitial lung disease (ILD). On 4 week follow up, she noted improvement on steroid therapy with decreased dyspnea, fatigue, and increased appetite.

However, the patient then complained of new symptoms of bubbles under her neck. Chest X-ray confirmed subcutaneous emphysema without pneumothorax. She presented to the ER and CT chest showed extensive mediastinal air without pneumothorax. The patient was discharged and her pneumomediastinum resolved without intervention.

Sjögren's syndrome presents with pulmonary disease in 10%-20% of affected individuals, most often in females (9:1) aged 40-60.<sup>1</sup> ILD is the most common respiratory presentation, followed by small airways disease, xerotrachea, and bronchial obstruction.<sup>2</sup> ILD is typically diagnosed 5 years after THE onset

symptoms. Pneumomediastinum is a reportedly rare complication of ILD with an unclear etiology at this time.<sup>3,4</sup> Spontaneous pneumomediastinum has been well documented, primarily with dermatomyositis and other mixed connective tissue disorders; but not seen in primary Sjögren's syndrome.<sup>4,5</sup> Current theories of dermatomyositis-associated pneumomediastinum suggest that it could be related to a ruptured pulmonary bleb,<sup>4,5</sup> vasculitis-induced,<sup>4</sup> versus alveolar wall weakening due to steroid treatment.<sup>3</sup> Our case demonstrates the rare complication of pneumomediastinum with another autoimmune process that has yet to be extensively documented in the literature.

## Conflict of Interest

The authors report no conflict of interest.

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# Parkinsonism Motor Findings in the University of California San Francisco Over Sixty Cohort

Eric K. Lau; Pardis Esmaeili-Firidouni; Lauren Wendelken-Riegelhaupt; and Victor Valcour MD, PhD

## Abstract

**Background:** Due to widespread availability of effective antiretroviral regimens, the HIV population over 60 years old is growing, but this population suffers from more morbidity. This morbidity includes HIV Associated Neurocognitive Disorders (HAND) and it affects > 50% of HIV patients of all ages. The high frequency and effects of cognitive impairment may be more burdensome in HIV patients over 60 years old. Motor findings are a common consequence of neuroAIDS and can even be the presenting symptom of HIV infection. There have been few studies investigating HIV motor dysfunction in the aging HIV population.

**Methods:** HIV-infected subjects were enrolled into the UCSF HIV over 60 cohort and subjects with normal cognition and Alzheimer's disease (AD) were evaluated from matching studies at the UCSF Memory and Aging Center. Trained physicians completed the Unified Parkinson's Disease Rating Scale motor exam (UPDRS). Nonparametric ANOVA was used to compare UPDRS scores across groups. All UPDRS comparisons were adjusted for age and Clinical Dementia Rating score. Spearman linear regressions were used to investigate correlation between UPDRS scores and brain volumes measured by FreeSurfer® from 3T Siemens images.

**Results:** The UPDRS scores were significantly higher in HIV compared to controls (median [IQR]: 4 [1-5] and 2 [0-2], respectively,  $P=.003$ ). HIV infected subjects with cognitive impairment had higher UPDRS scores than those without ( $P=.018$ ). Although both were higher than controls, HIV and

AD groups did not differ from each other on UPDRS scores ( $P=.48$ ). The amygdala and thalamus volumes both correlated with UPDRS score in the HIV group in models adjusted for intracranial volume (amygdala  $r^2=0.131$ ,  $P=.006$ , thalamus  $r^2=0.053$ ,  $P=.085$ ); but significance was lost in thalamus volume when adjusted for age.

**Conclusions:** These findings provide evidence that motor findings are more frequent in HIV and AD compared to controls; but we did not find evidence that they were higher in HIV compared to AD. The volumes of the thalamus and the amygdala showed a weak but significant correlation with UPDRS scores supporting their involvement in motor dysfunction.

## Conflict of Interest

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# Multigene Molecular Profiling in Nasopharyngeal Carcinoma: A Case of Monozygotic Twins

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## Abstract

**Introduction:** Nasopharyngeal carcinoma (NPC) is an epithelial tumor with high incidence in southern China and Southeast Asia. Oncogene mutation patterns in NPC have yet to be fully elucidated. It is also unclear if the inheritance of oncogene mutations contribute to the development of NPC. Using a multigene cancer exome sequencing panel, we sought to investigate oncogenes that were shared between both NPCs that developed in a pair of monozygotic female twins. We also examined these patterns, in the context of germline variants found in their unaffected brother.

**Case Summary:** Twin A was first diagnosed with Stage I poorly differentiated NPC in 1988 and underwent radiation therapy with complete remission. Her cancer relapsed in 1991 as lung metastasis. She underwent left thoracotomy followed by systemic chemotherapy with cisplatin/5FU. In 2000, she had recurrence of cancer to her cervical lymph nodes again for which she received chemoradiation that resulted in complete remission. Her sister, Twin B was diagnosed with Stage I poorly differentiated NPC twenty years later (2008) and received radiation with complete remission. Both monozygotic twins were of southern Chinese ethnicity and had an unaffected brother.

**Methods:** Archival formalin fixed paraffin embedded tumor tissue was retrieved from excision specimens of the two twins. A blood specimen was obtained from the unaffected brother. DNA was extracted and amplified using primer pairs targeted to 50 oncogenes selected by the Wellcome Trust Sanger Genomic Institute. Samples were barcoded and sequenced on a PGM™ semiconductor sequencer (Life Technologies, Foster City, CA).

**Results:** Sequence of the twin NPCs identified similar mutations on KIT (1708A>C; M541L; rs3822214) and HRAS (269T>C; H27H; rs249860) with a closely related novel TP53 variants of 587G>A; R196Q and 567C>T; A189A between twin A and twin B, respectively. Both TP53 variants were located near the Zinc binding regions of the TP53 protein (P04637). The unaffected brother showed a similar HRAS mutation (269T>C; H27H; rs249860). All siblings possessed a complex inframe deletion on Exon 12 of PDGFRA (AGCCCAGATGGACATG; S566\_E571delinsR; rs121913271).

**Conclusions:** An intriguing relationship between these two twins affected by nasopharyngeal carcinoma was identified by multigene targeted exome sequencing. A possible inheritance pattern was also elucidated in their unaffected brother. This cluster of genes suggests a possible role for tyrosine kinase inhibitors as molecularly targeted therapies in NPC. Further analysis by tumor-normal comparisons may work toward confirming an effector pathway that could broaden our understanding of this aggressive tumor.

## Conflict of Interest

The authors report no conflict of interest.

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# Polycystic Liver Disease Presenting as Expanding Mass Following Cholecystectomy

Cory G. Madigan MD (Associate) and James Y. Wang MD

## Abstract

A 45-year-old man with no significant past medical history was referred to gastroenterology for evaluation of a large hepatic mass and abnormal liver tests following laparoscopic cholecystectomy. Postoperative abdominal computed tomography (CT) scan was remarkable for a subcapsular mass in the left hepatic lobe, which was not present on preoperative CT. Over the course of three months, the patient had a total of five abdominal CT scans which revealed a gradual expansion of the mass to peak dimensions of 7.1 x 3.9 x 11.3 cm, followed by complete resolution approximately ten weeks after the mass was first noted. Portal vein thrombosis and massive splenomegaly were also discovered during these imaging studies.

Upon further questioning, the patient endorsed years of painful breast enlargement and leg swelling. His family history was remarkable for a distant cousin with hemochromatosis, but negative for any other hepatic or renal disease. He denied excessive alcohol use. His physical exam was remarkable for painful gynecomastia, 1+ pedal edema, and splenomegaly, but lacked other typical stigmata of cirrhosis. The patient's laboratory values were remarkable for an elevated international normalized ratio 1.3, albumin 3.1 g/dL, alanine aminotransferase 68 U/L, aspartate aminotransferase 57 U/L, alkaline phosphatase 171 U/L, total bilirubin 2.5 mg/dL, direct bilirubin 0.9 mg/dL, and platelets 109,000/mm<sup>3</sup>. Of note, neither radiographic nor laboratory studies revealed evidence of cystic kidney disease. The patient was evaluated for common causes of cirrhosis including hemochromatosis, viral hepatitis, autoimmune hepatitis,

and Wilson's disease. This workup returned negative except for H63D homozygosity. Liver biopsy was performed and revealed fibrosis, hepatocellular extinction, mild iron deposition, and numerous von Meyenburg complexes, consistent with PCLD.

This case illustrates a previously undescribed presentation of PCLD. Typically asymptomatic, PCLD is most commonly discovered incidentally or due to compressive hepatomegaly, cyst infection, rupture, or hemorrhage. In our patient, PCLD presented as what was initially thought to be an evolving abscess or inflammatory fluid collection related to his cholecystectomy. Another unique aspect of this case is that it is very unusual for PCLD to present with decompensated cirrhosis. When significant liver disease does develop, it typically occurs in the setting of massive hepatomegaly due to cyst enlargement. This case highlights PCLD's ability to cause advanced liver dysfunction in the absence of these complications. PCLD should be considered in the differential when considering causes of unexplained cirrhosis and when there are hepatic fluid collections of unclear etiology.

## Conflict of Interest

The authors report no conflict of interest.

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# Improving Confidence in Teaching Geriatric Medicine to Internal Medicine Residents

Masayuki Nogi MD; Thomas DeLeon MD; Cody Takenaka MD; and Kamal Masaki MD

## Abstract

**Introduction:** The Chief Resident Immersion Training (CRIT) is a national program to train chief residents of different specialties in principles of geriatric medicine, so they can provide this training to their residents who manage elderly patients on a daily basis. The chief residents at the University of Hawai'i Internal Medicine Residency program created an education action project using principles learned in the CRIT.

**Methods:** We created an educational curriculum for PGY-2 and PGY-3 internal medicine residents on their 4-week ward rotations. They were assigned to lead a team with interns and a 3rd year medical student. Each senior resident was required to provide teaching on common geriatric problems in the inpatient setting. To help them achieve this goal, the chief residents posted teaching materials on 5 core geriatrics topics (dementia, delirium, polypharmacy, functional decline/falls and end of life discussions) on the chief resident blog site. Before and after the rotation, each senior resident completed a survey about comfort levels in teaching and managing common geriatric syndromes, using a 5-point Likert scale (higher is better). Senior residents were also asked about barriers to teaching these topics. We compared mean scores before and after this educational intervention using paired t-tests.

**Results:** Between August 2014 and October 2014, we collected data from 28 senior residents, with 19 having complete data. Improvement in comfort teaching geriatric topics was reported by 42% of residents (mean change 0.44  $\pm$  0.60;  $P = .004$ ). Im-

provement in comfort managing common geriatric problems was reported by 58% of residents (mean change 0.66  $\pm$  0.67;  $P = .0004$ ). Improvement in effectively identifying resources was reported by 53% of residents (mean change 0.63  $\pm$  0.68;  $P = .0008$ ). We created a composite mean score for each resident, and found an overall improvement (mean change 0.58  $\pm$  0.49;  $P < .0001$ ). There were no significant differences in improvements in scores by hospital or PGY group. Most residents felt that this intervention was helpful (mean 4.0  $\pm$  0.59). The most common barrier before the intervention was lack of resources (62%), which improved after the intervention (21%).

**Conclusions:** This innovative educational program utilized chief residents to encourage senior residents to teach geriatric topics to peers, and demonstrated effectiveness in improving confidence in teaching and managing geriatric problems and identifying resources. The majority of residents found this to be a helpful experience.

## Conflict of Interest

The authors report no conflict of interest.

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# Two Human Cases of *Wohlfahrtiimonas chitiniclastica* Infection: Case Reports

Masayuki Nogi MD; Matthew J. Bankowski PhD; Francis D. Pien MD, FACP

## Abstract

*W. chitiniclastica* is a recently described  $\gamma$ -proteobacterium isolated from larvae of the parasitic fly, *Wohlfahrtia magnifica*. It has been reported in Europe, Egypt and Asian countries, but is rarely reported in low altitude or suburban areas. *W. chitiniclastica* bacteremia has only been reported in three clinically relevant human cases worldwide. The two cases of this report will be the first reported in Hawai'i.

The first case was a 69-year-old homeless woman with a history of right hemiparesis secondary to a ruptured cerebral aneurysm. She complained of sacral pain and painful urination for one week and blood test showed leukocytosis associated with pyuria on urinalysis. Physical examination revealed stable vital signs, disheveled appearance and multiple decubitus ulcers in her sacral area with stage III appearance and profuse pus. She was started on IV ceftriaxone and IV vancomycin to cover both the urinary tract and decubitus ulcer infections. She underwent surgical debridement of her decubitus ulcers where a deep tissue wound culture was obtained during the procedure. The wound culture grew polymicrobial flora, which included *W. chitiniclastica*, *Staphylococcus aureus*, *Aeromonas spp.*, *Staphylococcus simulans* and *Bacteroides fragilis*. A blood culture grew *Anaerobiospirillum succinicproducens* and *Proteus mirabilis* was cultured from the urine. She was successfully treated and discharged.

The second case was a 72-year-old man with history of stroke and communication disability secondary to deafness. After being unattended for three days, he was found unconscious on his home floor. He appeared hypothermic, hypotensive and bradycardic. Multiple lacerations were seen mainly on his right leg and umbilicus. Notably there were maggots continuously crawling out of his wounds. Blood cultures grew *Escherichia coli* and *W. chitiniclastica*. The patient was started on piperacillin/tazobactam, clindamycin and vancomycin, but unfortunately expired as a result of septic shock.

Distribution of the vector fly *Wohlfahrtia magnifica* is expanding, and it is possible that it currently exists in Hawai'i. This case report is intended to increase the awareness of this specific type of infection related to myiasis in the homeless and hygiene-deficient patient population. Furthermore, this report should also offer treatment options for the infection.

## Conflict of Interest

The authors report no conflict of interest.

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# Septic Arthritis and Osteomyelitis Due to *Bordetella petrii*

Masayuki Nogi MD; Matthew J. Bankowski PhD; Francis D. Pien MD, FACP

## Abstract

We report a case of *Bordetella petrii* elbow septic arthritis and osteomyelitis that resulted from a dirt bike accident in Hawai'i. Initial incision and drainage followed by one month of oral doxycycline were given. Because of persistent infection of the elbow, additional 10 weeks of intravenous piperacillin/tazobactam and repeated surgeries were required to cure this infection. *B. petrii* was isolated from the synovial fluid and identification was obtained using 16S rRNA sequencing showing the highest match of 99.3% with *B. petrii* type strain DSM 12804. This was also confirmed with matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Inc., Billerica, MA).

The *Bordetella* genus includes nine species. The most noteworthy is *B. pertussis*, and *B. parapertussis*, but in the past 15 years, five additional species were reported in human infection, including *B. hinzii*, *B. holmesii*, *B. trematum*, *B. petrii*, and *B. ansorpii*. This is only the third human clinical case report regarding bone or joint infection caused by *B. petrii*, and the first case reported in Hawai'i.

Our case, and literature review, suggests that carbapenems, piperacillin/tazobactam, tetracycline, and trimethoprim/sulfamethoxazole are good treatment options. Our case demonstrated resistance to cefepime, which suggest the high probability of resistance to cephalosporin in general. The notable discrepancies with previous reports were that our strain was susceptible to tetracycline and levofloxacin.

The susceptibility information from our case and others found in the literature will assist in the empiric choice of antibiotics.

## Conflict of Interest

The authors report no conflict of interest.

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# Takotsubo Cardiomyopathy in the Setting of Immersion Pulmonary Edema: Case Series

Tara Reed BS; Dante Sorrentino MD; and Steven Azuma MD

## Abstract

Immersion Pulmonary Edema is a unique medical condition being increasingly described in the medical literature as sudden-onset pulmonary edema in the setting of scuba diving and or swimming. Case reports have associated immersion pulmonary edema with cardiac dysfunction, but there are no known case reports describing submersion pulmonary edema resulting in Takotsubo cardiomyopathy. We report on three patients with unique presentations of immersion pulmonary edema with associated Takotsubo cardiomyopathy. All three cases occurred in O'ahu, Hawai'i and were seen by the same cardiologist within a span of seven years. Each patient was scuba diving with sudden dyspnea with pulmonary edema on chest X-ray. Cardiac catheterization revealed no significant epicardial stenosis. Wall motion abnormalities resolved. EKG's showed typical evolution of symmetric T wave inversion. Immersion pulmonary edema

and Takotsubo cardiomyopathy may occur together and may be more common than initially thought. Dyspnea has been long known to be stressful as in "waterboarding." Stressful events are known to trigger Takotsubo cardiomyopathy. Takotsubo cardiomyopathy should be considered as a possible complication of immersion pulmonary edema and EKG's, troponins, echocardiogram and in the appropriate situation cardiac catheterization should be considered.

## Conflict of Interest

The authors report no conflict of interest.

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