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MAHALO PEER REVIEWERS! 4

DISPARITIES IN MEDICATION THERAPY IN PATIENTS WITH HEART FAILURE ACROSS THE STATE OF HAWAI‘I 5
Roy Alan Goo PharmD; Carolyn Ma PharmD, BCOP; and Deborah Taira Juarez ScD

HEPATITIS C VIRUS ANTIBODY PREVALENCE, DEMOGRAPHICS AND ASSOCIATED FACTORS AMONG PERSONS SCREENED AT HAWAI‘I COMMUNITY-BASED HEALTH SETTINGS, 2010–2013 9
Lisa C. Takeuchi MPH; Thaddeus K. Pham BS; and Alan R. Katz MD, MPH

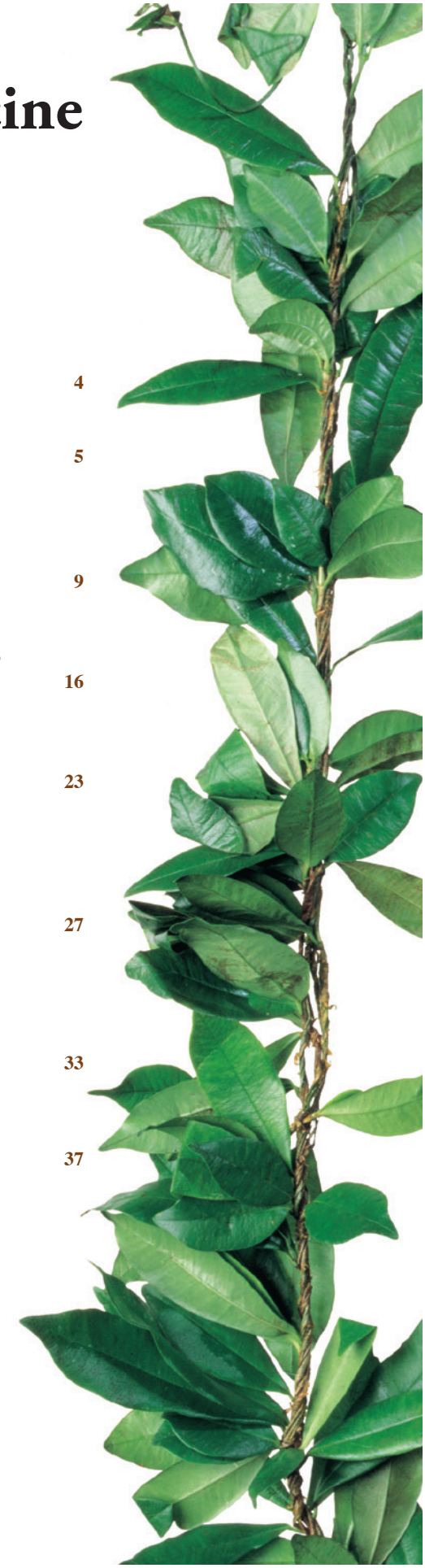
ROUTINE SCREENING FOR CYP2C19 POLYMORPHISMS FOR PATIENTS BEING TREATED WITH CLOPIDOGREL IS NOT RECOMMENDED 16
Adnan M. Bhopalwala MBBS; Robert A. Hong MD; Zia R. Khan MD; Mona R. Valentin PharmD; and Ramy A. Badawi MBBS

MEDICAL SCHOOL HOTLINE 23
Western Group on Educational Affairs (WGEA) 2014 Conference at the John A. Burns School of Medicine
Sheri F.T. Fong MD, PhD; Damon Sakai MD; Jill Omori MD; Kori-Jo Kochi BA; and Yawen Sarah Hsiao MSIS

INSIGHTS IN PUBLIC HEALTH 27
Building Support for an Evidence-Based Teen Pregnancy and Sexually Transmitted Infection Prevention Program Adapted for Foster Youth
Tamara Smith MPH; Judith F. Clark MPH; and Claudio R. Nigg PhD

THE DANIEL K. INOUYE COLLEGE OF PHARMACY SCRIPTS 33
Academic Pharmacy Strikes Hawai‘i (Part 1)
John M. Pezzuto PhD and Mimi F. Pezzuto RPh

THE WEATHERVANE 37
Russell T. Stodd MD



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Hulu Ula (D.Varez)

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Disparities in Medication Therapy in Patients with Heart Failure across the State of Hawai'i

Roy Alan Goo PharmD; Carolyn Ma PharmD, BCOP; and Deborah Taira Juarez ScD

Abstract

The purpose of this study is to evaluate if heart failure patients in Hawai'i are receiving recommended standard therapy of a select beta-blocker in combination with an ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB), and to determine if a gap in quality of care exists between the different regions within the state. A retrospective claims-based analysis of all adult patients (age > 18 years of age) with CHF who were enrolled in a large health plan in Hawai'i was performed (n = 24,149). Data collected included the presence of pharmaceutical claims for ACEI, ARBs and select β-blockers, region of residence, gender, and age. Multivariable logistic regression was used to examine whether there were regional differences in Hawai'i related to medication usage, after adjustment for age and gender. Results showed that only 28.4 % of patients were placed on the recommended therapy of an ACEI or ARB and a select β-blocker with significant differences being found between different regions. Further research is needed to better understand factors affecting regional differences in prescribing patterns.

Keywords

Congestive Heart Failure (CHF), ACEi, ARBs, Hawaii, Hawai'i

Introduction

Despite recent advances in medical care, congestive heart failure (CHF) continues to be a major contributor to patient mortality and cost of health care with nearly $29 billion/year being spent in the United States on heart failure related hospitalizations.[1,2] Multiple studies have shown decreased morbidity and mortality when patients with impaired left ventricular ejection fraction (LVEF), commonly referred to as systolic heart failure, received a combination of a select β- adrenergic receptor blockers (β-blocker)with either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB).[3-7] Current guidelines from both the American College of Cardiology/American Heart Association (ACCF/AHA) and the Heart Failure Society of America (HFSA), recommend that patients with impaired LVEF be prescribed an ACEI or an ARB along with a β-blocker, specifically metoprolol succinate (long-acting).[8-9] In patients with isolated diastolic heart failure (preserved LVEF), which accounts for approximately 1/3 of patients diagnosed with heart failure it is also recommended that patients be placed on an ACEI or an ARB and a β-blocker, although the particular β-blocking agent is not specified.[8] Both ACEI and ARBs exert their effects through modulation of the renin-angiotensin system that has shown to reduce cardiac remodeling.[10] Long term therapy on ACEI and ARBs with β-blockers has also been shown to decrease symptoms, improve clinical status, and enhance the patient's overall feeling of well-being in addition to reducing the risk of hospitalization and/or death.

Several studies have demonstrated the impact of ethnic and socioeconomic factors on the prevalence and mortality associated with CHF.[11] An epidemiological study conducted by the Hawai'i State Department of Health found definite geographic and ethnic disparities in cardiovascular disease mortality in Hawai'i, with Pacific Islanders having a greater overall risk of developing heart failure compared to other ethnic groups.[1,12] Data on native Hawaiians demonstrate a 68% higher incidence of heart disease compared to the national average.[13] Reviews of epidemiological data have also demonstrated that demographic differences such as age, gender, ethnicity, and socioeconomic environment may influence primary medication adherence which may be a major contributing factor to the increased risk of mortality, hospitalizations, and increased health care costs observed in these patient groups. [15-17]

The goal of this study was to examine regional prescribing patterns for CHF patients in Hawai'i. Findings from this study can lay the foundation for targeted interventions to improve the quality of care for patients with heart failure in Hawai'i.

Methods

A retrospective analysis of administrative data from January 1 to December 31, 2010 for adult patients (age > 18 years of age) who were enrolled in a large health plan in Hawai'i was performed and all patients with a medical diagnosis of CHF and enrollment with medical and drug coverage were included in our analysis (N = 24,149). CHF was identified by the health plan based on an ICD-9 code of 428. Pharmaceutical claims data for calendar year 2010 for ACEIs, ARBs, and select β-blockers (metoprolol succinate, bisoprolol, and carvedilol) were obtained from the health plan; the short acting form of metoprolol (metoprolol tartrate) has not shown decreased mortality and is therefore not recommended and was not included in our analysis.

Information on patient age, gender, and region of residence were obtained from the health plan and linked using a unique patient identifier to claims data. Patients were stratified based on billing zip codes into six geographic regions: Hawai'i- East; Hawai'i- West; Kaua'i; Maui County (includes Lana'i and Moloka'i islands); O'ahu- Honolulu Metropolitan Statistical Area (MSA), and O'ahu-Other than Honolulu MSA. Patients with out of state billing zip codes (n = 621) were excluded. Within each demographic region, patients were evaluated based on the presence of pharmaceutical claim(s) for (1) an ACEI or an ARB (regardless of β-blocker fill), (2) one of the selected β-blockers (regardless of ACEI or ARB fill), (3) both a β-blocker and an ACEI or an ARB and (4) pharmaceutical claim(s) for neither ACEI, ARB, nor β-blockers.

Pearson's chi-squared tests were used to examine differences by region, while analysis of variance was used to examine

regional differences in age. Multivariable logistic regression was used to examine whether there were regional differences related to medication usage, after adjustment for age and gender. Age was categorized as: (1) 18-44 years; (2) 45-65 years; (3) 65-84 years; (4) 85+ years. Odds ratios and their 95% CIs for the association of age, gender, and region with recommended medication use were calculated. This research study was deemed exempt by the University of Hawai'i Committee on Human Subjects. All analyses were conducted using Stata 11.0 (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP).

Results

Age and gender differed significantly by region (Table 1). Mean patient age ranged from a low of 68.7 (SD 14.0) years in Maui County compared to a high age of 75.9 (SD 13.8) years in O'ahu-Honolulu MSA. Proportion of patients who were men was highest in Maui County at 62.7 % and lowest in Hawai'i- East (50.5%).

Table 2 describes the unadjusted compliance rates with recommended medication therapy for patients with CHF, of a β-blocker and an ACEI or ARB. Overall results revealed that 28.2% of patients with heart failure were on the appropriate dual drug therapy of both a β-blocker and an ACEI or an ARB. Between the different Hawai'i regions, rates ranged from a low of 21.0% in Hawai'i-West to a high of 35.2% on Kaua'i. Only 41.2% of patients were placed on one of the three recommended β-blockers. West Hawai'i island had the lowest rate of prescription for the three select β-blockers, at 30.6%. Overall 11.0% of patients with CHF were not on either agent, with Kaua'i having the lowest rate of 9.3%.

In adjusted multivariable analyses, patients aged 18 to 44 with CHF were significantly less likely to be filling prescriptions for select β blockers, ACEI, or ARBs, either alone or in combination and more likely to have filled neither prescription, relative to patients aged 45 to 64 (Table 3). Patients over age 85 were also less likely to be on both medications and one of the two recommended medications, relative to patients aged 45 to 64. Prescription fill rates for all medications were similar for patients between ages of 65 and 84 to those aged 45 to 64 years. Women were slightly less likely to be taking select β-blockers than men but did not differ in terms of fill rates for the other medication groups (Table 3).

There were also significant regional differences (Table 3). Compared to patients from O'ahu-Honolulu MSA, those from Kauai'i were significantly more likely to be prescribed one or both recommended medications. In contrast, patients from Hawai'i-West were significantly less likely to be fully compliant with combination ACEI/ARB and β-blocker therapy. Patients from O'ahu-other than Honolulu MSA were more likely to be on ACEI or ARBs (OR = 1.18 95% CI [1.09,1.27]) but less likely to be on select β-blockers (OR = 0.93 95% CI [0.87,0.99]) than patients living in O'ahu-Honolulu MSA. Patients from Hawai'i-West were less likely to be using select β-blockers (OR = 0.57 95% CI [0.50,0.66]), less likely to be using both ACEI or ARBs and select β-blockers (OR = 0.60 95% CI [0.53,0.67]), and more likely to be using neither(OR = 1.18 95% CI [1.00,1.40]). Medication use in Maui County did not differ from O'ahu-Honolulu MSA.

Table 1. Patient Age and Gender by Region of Hawai'i

Region	Age [Years; Mean (SD)]	Female	Male
Overall (N = 24,138)	73.0 (14.3)	44.4%	55.6%
Hawai'i- East (n = 3151)	75.2 (13.6)	49.5%	50.5%
Hawai'i- West (n = 1581)	70.2 (13.2)	44.9%	55.1%
Kaua'i (n = 1339)	72.8 (13.9)	39.5%	60.5%
Maui County (n = 2143)	68.7 (14.0)	37.3%	62.7%
O'ahu- Honolulu (n = 7220)	75.9 (13.8)	45.2%	54.8%
O'ahu- Other (n = 8704)	71.4 (14.7)	44.4%	55.6%
P-value	*P* < .001[a]	*P* < .001[b]	

[a]Analysis of variance was used to examine differences in age across regions.
[b] Pearson's chi-squared test was used to examine differences in gender across regions.

Table 2. Use of ACEI[a], ARBs[b], and select β- Blockers by Region, Unadjusted (N = 24,138)

	Fully Treated as Recommended	Receiving a Recommended Medication		Not Treated as Recommended
Region	ACEI/ARB + select β- Blocker	ACEI[a]/ARB[b]	Select β- Blocker	Neither
Overall (N = 24,138)	6,993 (28.2%)	18,845 (76.1%)	10,202 (41.2%)	2,714 (11.0%)
Hawai'i- East (n = 3151)	926(29.4%)	2,278 (72.3%)	1,427(45.3%)	372(11.8%)
Hawai'i- West (n = 1581)	333(21%)	1,233 (78%)	484 (30.6%)	197(12.5%)
Kaua'i (n = 1339)	472(35.2%)	1,076 (80.3%)	610 (45.6%)	125 (9.3%)
Maui (n = 2143)	619(28.9%)	1,614 (75.3%)	918 (42.8%)	230 (10.7%)
O'ahu- Honolulu (n = 7220)	2,015(27.9%)	5,413 (75%)	3,038 (42%)	684(9.5%)
O'ahu- Other than Honolulu (n = 8704)	2,500(28.7%)	6,805 (78.2%)	3,517 (36.3%)	882(10.1%)
P-value[c]	*P* < .001	*P* < .001	*P* < .001	*P* = .01

[a]ACEI = Angiotensin Converting Enzyme Inhibitors; [b]ARBs= Angiotensin Receptor Blocker; [c]Based on Pearson's chi-squared test.

Table 3. Adjusted Odds Ratio (OR) of Receiving Treatment as Recommended by Age, Gender, and Region (N = 24,138)*								
	Fully Treated as Recommended		**Receiving a Recommended Medication**				**Not Treated as Recommended**	
	ACEI/ARB & β blockers		ACEI or ARB		β blockers		Neither	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age								
45-65	1		1		1		1	
18-44	**0.73**	**[0.62, 0.87]**	**0.58**	**[0.50, 0.68]**	**0.82**	**[0.71, 0.95]**	**2.14**	**[1.76, 2.59]**
65-84	0.97	[0.90, 1.03]	1.03	[0.96, 1.11]	0.96	[0.90, 1.02]	0.97	[0.88, 1.08]
85+	**0.73**	**[0.67, 0.80]**	**0.77**	**[0.71, 0.84]**	**0.91**	**[0.84, 0.98]**	1.12	[0.99, 1.26]
Sex								
Male	1		1		1		1	
Female	0.96	[0.91, 1.02]	1.01	[0.95,1.07]	**0.94**	**[0.89, 0.99]**	1.06	[0.97, 1.15]
Region								
Honolulu	1		1		1		1	
East Hawai'i	1.07	[0.98, 1.17]	**0.86**	**[0.79, 0.95]**	**1.14**	**[1.05, 1.24]**	1.10	[0.97, 1.26]
West Hawai'i	**0.66**	**[0.58, 0.75]**	1.13	[0.99, 1.29]	**0.60**	**[0.53, 0.67]**	**1.18**	**[1.00, 1.40]**
Kaua'i	**1.37**	**[1.21, 1.55]**	**1.33**	**[1.15, 1.54]**	**1.14**	**[1.01, 1.28]**	0.86	[0.70, 1.04]
Maui county	0.99	[0.89, 1.10]	0.98	[0.87, 1.09]	1.01	[0.92, 1.12]	0.99	[0.85, 1.17]
O'ahu – other than Honolulu	1.01	[0.95, 1.09]	**1.18**	**[1.09, 1.27]**	**0.93**	**[0.87, 0.99]**	0.92	[0.83, 1.01]

*Findings significant at $P < .05$ are in bold.

Discussion

Our study investigated compliance with the nationally recommended guidelines for pharmacological management of patients with CHF. This analysis uncovered a rather low rate of compliance overall and demonstrated differences between the various regions of Hawai'i. There are three identified limitations to this analysis with the first limitation being that only the use of select β-blockers (carvedilol, bisoprolol, and metoprolol succinate) was evaluated. The analysis was limited to these three β-blockers because these agents are specifically recommended for systolic heart failure due to their proven benefits in reducing morbidity and mortality.[8] Our analysis found that the proportion of patients on β-blockers is significantly lower than those who are on either an ACEI or ARB, and the lack of pharmaceutical claims for the select β-blockers we queried for appears to be the limiting factor for CHF patients in receiving recommended dual therapy. Unlike systolic heart failure, current guidelines do not recommend a specific β-blocker for patients with isolated diastolic heart failure. By only investigating the use of the specific β-blocking agents recommended for systolic heart failure, our analysis may inappropriately label patients with isolated diastolic heart failure as "non-compliant." Patients with isolated diastolic heart failure account for approximately one third of the heart failure population. Another possible explanation for the relatively low rates of compliance with appropriate β-blocker therapy is that there may be some confusion among prescribers in prescribing the appropriate formulation of metoprolol (short versus the long acting). The long acting formulation metoprolol succinate was included in our analysis as it has demonstrated decreased mortality in patients with CHF and is recommended by national guidelines,[6] The short acting form (metoprolol tartrate) has not shown any decreased mortality and is therefore not preferred and was not included in our analysis. The initiation or dose titration of β-blocking agents may also worsen symptoms of CHF such as fatigue and shortness of breath. These adverse experiences may encourage noncompliance in both patients and prescribers.

The second limitation is that pharmaceutical claim data were only present when a patient filled a prescription. This limitation prevents any conclusions from being made regarding physician prescribing patterns, as we are unable to differentiate between prescriber and patient non-compliance. Also, claim data does not ensure medication adherence or even that the ACEI or ARB classes of medications were simultaneously taken with a β-blocker. This limitation introduces the potential for false-positives where patients may have filled claims for medications but were not adherent and/or did not take the medications concurrently. Moreover, patients may have had more than one form of drug coverage and filled prescriptions through a plan for which we do not have information. This would also cause an underestimation of compliance.

Factors such as lower socioeconomic status or ethnicity may influence patient's propensity to fill a prescription. Previous studies have demonstrated that lower socioeconomic status was associated with decreased primary medication compliance.[18]The findings in our analysis however were not entirely consistent with previously published patterns. Hawai'i-West demonstrated the lowest proportion of CHF patients who were on recommended

therapy and the highest proportion of patients on neither an indicated β-blocker or an ACEI or ARB. However all four areas of Hawai'i-West (South Kona, North Kona, South Kohala, and North Kohala) are below the state average in terms of percentage of residents living below the federal poverty level than other Hawai'i regions. In contrast Hawai'i-East demonstrated the second highest rates of patients receiving recommended medication therapy despite demographic data that indicates that the areas of Hilo, Puna, Ka'u, and Hamakua are above the state average for percentage of residents living below the federal poverty level.[14]

Another limitation of this analysis was the inability to detect patient factors such as bradycardia, hypotension, renal instability, or allergies that would preclude the use of the recommended agents. Finally, our findings most likely overstate compliance with the recommended therapy as we require only one fill of a medication to be considered adherent.

Further investigation is needed to determine the key contributing factors that have led to overall low rates of compliance with the recommended medication therapy and the discrepancies between the different regions.

Conclusion

In the population of patients with CHF who were enrolled in a major health plan in Hawai'i, there was a significant difference in compliance rates with ACCF/AHA recommended medication therapy within the state of Hawai'i. Overall it was much more common for patients to be on an ACEI or an ARB compared to the recommended β-blockers. Hawai'i-West demonstrated the lowest rates of compliance with dual therapy (ACEI/ARB + β-blocker), and had the lowest rates of pharmaceutical claims for the recommended β-blockers. Further investigation is needed to determine the causative factors.

Conflict of Interest

None of the authors identify a conflict of interest.

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Hepatitis C Virus Antibody Prevalence, Demographics and Associated Factors among Persons Screened at Hawai'i Community-based Health Settings, 2010–2013

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Abstract

We sought to determine the prevalence of HCV infection and identify factors associated with HCV infection among clients presenting to community-based health settings in Hawai'i from 2010–2013. An earlier report on this study population covered the period from December 2002 through May 2010. Since 2010, the HCV screening inclusion criteria have been relaxed, and the program has greatly expanded. Clients from 26 community-based sites were administered questionnaires, and were screened for HCV antibodies from January 2010 through April 2013 (N = 8,588). Univariate and multivariate logistic regression analyses were performed. HCV antibody prevalence was 5.9% compared with 11.9% from 2002–2010. Persons aged 45–65 years had the highest HCV antibody prevalence (8.4%) compared with all other age groups. Significant independent variables associated with HCV antibody prevalence were injection drug use, blood transfusion before July 1992, and having an HCV-infected sexual partner. While characteristics associated with HCV infection remained essentially unchanged from those identified in the earlier analysis, the expansion of screening sites and less restrictive inclusion criteria led to a much larger study population and a concurrent decrease in overall HCV antibody prevalence. However, while the highest age-specific prevalence remained the same for both screening periods, the prevalence among younger persons (< 30 years old) doubled (from 2.4% to 4.7%). By expanding the HCV screening program and relaxing the inclusion criteria, a greater number of HCV-infected persons and a greater proportion of younger persons with HCV infection were identified while still maintaining a focus on at-risk individuals.

Introduction

As the most common chronic blood borne pathogen in the United States, the hepatitis C virus (HCV) is a leading cause of liver disease and accounts for more than one-third of all liver transplants.[1] Approximately 1.3% of the US population is chronically infected, and without treatment, about half will develop cirrhosis or hepatocellular carcinoma (HCC).[2]

HCV is transmitted primarily via blood-to-blood contact, with the largest risk factor in the United States being injection drug use (IDU).[1] Another established risk factor is having a blood transfusion before July 1992 when blood screening programs were implemented.[1] Recently, sexual contact with an HCV-infected partner has been recognized as a risk factor for specific populations including HIV-infected men who have sex with men (MSM).[4] Unlike hepatitis A and B, there is no vaccine for HCV, though new and effective treatments are being developed. In December 2013, the Food and Drug Administration approved a new drug, sofosbuvir, which showed high rates (up to 90%) of sustained virologic response.[5,6] As chronic infection is often asymptomatic, most infected individuals are unaware and therefore do not seek treatment.

In recent years, there has been a 3–fold increase in HCC incidence, of which about 50% is related to HCV infection decades earlier.[1] Approximately 75% of HCV-infected individuals in the United States were born between1945–1965. The high prevalence in this birth cohort is attributed to high rates of IDU in the 1970s–80s and the risk from blood transfusions before 1992.[1] Most of these individuals no longer engage in risk-related behavior and have not been tested for HCV. As HCV infection can take decades to present symptoms, the burden is now becoming increasingly apparent.[7] The Centers for Disease Control and Prevention (CDC) as well as the US Preventive Services Task Force (USPSTF) recently recognized the importance of screening this age group and amended its recommendations for risk-based HCV testing to include one-time screening for all individuals born between 1945 and 1965.[7,8]

There has been increasing evidence of an epidemic of HCV infection among younger individuals, especially those who inject drugs. In Massachusetts, an increase in newly reported HCV cases among injection drug users aged 15–24 years was observed from 2002–2009.[9] Similar findings have been observed in New York among individuals under 30 years old.[10] Increasing rates of HCV infection in this younger cohort require attention and have implications on screening and intervention priorities. Several studies on HCV prevalence have been done in Hawai'i, but most focused on specific populations—men of Japanese ancestry with HCC,[11] HIV-infected patients,[12] residents of a homeless shelter,[13] and Pacific Islander patients with HCC.[14] A population-based case-control study was also conducted to investigate HCV risk factors.[15]

Since 2002, the Hawai'i State Department of Health (HDOH) Adult Viral Hepatitis Prevention Program has offered risk-based HCV antibody testing based on CDC recommendations,[1,16] and has concurrently collected demographic and behavioral/blood exposure data on all persons screened through the program. In 2010, Porter, et al, conducted a study to determine the prevalence of HCV antibody in Hawai'i and identify characteristics associated with HCV infection among screening program clients. The study analyzed data from December 2002–May 2010, when the program included 23 test sites, and employed strict screening criteria for the majority of that time period. They found an HCV antibody prevalence of 11.8%.[17]

Since January 2010, the program expanded to include the HIV/AIDS Early Intervention Services (HEIS) program, which offers HCV antibody testing at substance abuse treatment centers statewide. Clients at HEIS sites account for over 40% of all testing. The purpose of this study was to assess the impact of test site expansion on HCV prevalence estimates as well as demographic and behavioral/blood exposure associations with HCV infection from January 2010–April 2013 using Porter, et al,'s findings as a reference.

Methods

This study analyzed data from three years of HCV data collection efforts conducted at community-based health settings across the state. The total number of participating sites from January 2010 to April 2013 was 26. HEIS represented four of these sites, and all clients from HEIS sites were offered screening for HCV antibody. Clients presenting to the remaining 22 sites were screened individually and considered at risk for HCV infection if they reported at least one of five risk factors previously identified by the CDC:[16] an unsterile tattoo or piercing, blood transfusion before July 1992, exposure to blood, sexual contact with an HCV-infected partner, or IDU.

Clients undergoing HCV testing completed a questionnaire prior to testing. Questionnaires collected information on self-reported age, gender, race/ethnicity, and HCV risk factor history. A unique identifier was assigned to each client to link HCV antibody test results. From January 2010 until April 2011, a paper questionnaire was administered, but starting in May 2011, the questionnaire changed to an electronic form that was used for HCV, as well as HIV and HBV, screening. The electronic questionnaire included more items on HIV risks and sexual history; for demographic items, the new questionnaire grouped Native Hawaiian and Pacific Islander ethnicities together, while the previous questionnaire separated them. The items addressing HCV risk factors were unchanged. Prior to May 2011, questionnaires were completed either by a counselor or client; since May 2011, questionnaires were completed by the counselor conducting the interview. Clients with a negative test but positive history of risk factor exposure were encouraged to return for a repeat test. In our analysis the denominator is the number of tests performed since clients may have had multiple tests within our study period.

HCV antibody testing was performed via whole blood laboratory testing with Home Access® finger-stick blood collection kit or Oraquick® HCV Rapid Antibody Test point-of-care kit. Blood specimens from Home Access® test kits were tested for anti-HCV antibody using an enzyme immunoassay (EIA) (Abbott HCV EIA 2.0 or Ortho HCV EIA 3.0). A positive result was determined by either a positive EIA signal-to-cut-off ratio of 3.8 or greater, or a positive EIA signal-to-cut-off ratio of less than 3.8 and a confirmatory positive Recombinant Immunoblot Assay (RIBA).[18] The Oraquick® HCV Rapid Antibody Test provides results within twenty minutes utilizing whole blood specimens via finger-stick. For each test performed, the sensitivity is ≥95% and the specificity is ≥99%.[18,19]

Demographic characteristics and behavioral/blood exposure factors were analyzed using chi-square tests. Odds ratios and 95% confidence intervals were calculated for each factor. Univariate and multivariate logistic regression analyses were performed, and analyses were stratified by gender. Univariate analyses were performed using EpiInfo, versions 3.5.1 and 7 (CDC, Atlanta, GA); logistic regression analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). *P*-values less than or equal to .05 were considered statistically significant. All tests were 2-tailed. The study was approved by the HDOH institutional review board.

Results

From January 2010 through April 2013, 9,107 tests were conducted; only 7.8% of individuals who were offered testing declined. Of the 9,107 tested, 519 (5.7%) had indeterminate or no reported HCV antibody result and thus were excluded. Of the 8,588 records included in the analysis, 508 (5.9%) had positive HCV antibody results. In regards to data collection, 1,623 results came from the old questionnaire before May 2011, while 6,965 came from the new questionnaire. Along with a unique identifier, 13 HDOH sites used a client identification number (ID) to link clients to their medical records. By comparing these records with client IDs (n = 2,006), we estimate that 2.7% of our population consisted of repeat clients. Among the repeat clients, an estimated 3.7% had a positive test result.

Table 1 shows demographic associations with HCV antibody positivity among the study population. Gender and age group differences were statistically significant while ethnicity was not. Men had a significantly higher prevalence compared to women and transgender individuals (OR = 1.45, 95% CI: 1.18–1.77, *P*-value < .001). HCV antibody prevalence was significantly higher for persons aged 45-64 years [8.4%, *P*-value < .001]. Individuals under 30 years old had an HCV antibody prevalence of 4.7%. While not statistically significant, Native Americans had the highest and Asians the lowest HCV antibody prevalence.

Figure 1 shows HCV antibody prevalence and total number of tests by site. HEIS sites conducted a large percent of tests (42.6%), and HCV antibody prevalence at HEIS sites (6.5%) was not significantly different than all other sites.

Table 2 shows unadjusted univariate analysis of behavioral/blood exposure factors for HCV infection. IDU was the behavioral/blood factor most strongly associated with HCV antibody prevalence (OR = 2.40, 95% CI: 1.96–2.94, *P*-value < .001). Exposure to blood showed a significantly inverse association with HCV antibody prevalence (OR = 0.68, 95% CI: 0.54–0.85, *P*-value = .001). Getting an unsterile tattoo or piercing was not significantly associated with HCV antibody prevalence (OR = 1.02, 95% CI: 0.83–1.26, *P*-value = .823).

Table 3 shows multivariate logistic regression results when adjusted for all behavioral/blood exposure factors—having an unsterile tattoo or piercing, blood transfusion before July 1992, exposure to blood, sexual contact with an HCV-infected partner, or IDU. All factors except having an unsterile tattoo or piercing were significantly associated with HCV antibody positivity. Having a blood transfusion and IDU demonstrated the strongest association. Gender stratified behavioral/blood exposure factors were also examined (Table 4). For men, IDU, receiving a blood transfusion prior to July 1992, and having an HCV-infected sexual partner were significantly associated with HCV antibody positivity. For women, IDU was significantly associated with HCV antibody positivity (OR = 2.84, 95% CI: 1.61–5.00, *P*-value < .001), and exposure to blood or needlestick injury had a significant inverse association with HCV antibody positivity (OR = 0.45, 95% CI: 0.24-0.85, *P*-value = .013). Having an HCV-infected sexual partner (OR = 1.51, 95% CI: 1.10–2.07, *P*-value = .012) and receiving a blood transfusion prior to July

Table 1. Demographic characteristics and HCV antibody status of participants screened at community-based health settings, Hawai'i, 2010–2013

Variables	HCV Antibody Positive (n=508) Number (%)	HCV Antibody Negative (n=8080) Number (%)	Total Tested	*P*-value
Gender				
Men	364 (6.6%)	5149 (93.4%)	**5513**	.0023
Women	139 (4.7%)	2795 (95.3%)	**2934**	
Transgender	1 (1.4%)	69 (98.6%)	**70**	
Not Reported	4 (5.6%)	67 (94.4%)	**71**	
Total	508 (5.9%)	8080 (94.1%)	**8588**	
Age Group (in years)				
0-13	0 (0.0%)	0 (0.0%)	**0**	< .001
13-14	1 (25.0%)	3 (75.0%)	**4**	
15-19	14 (4.9%)	273 (95.1%)	**287**	
20-24	68 (5.1%)	1275 (94.9%)	**1343**	
25-29	68 (4.4%)	1485 (95.6%)	**1553**	
30-34	65 (5.0%)	1233 (95.0%)	**1298**	
35-39	48 (5.0%)	904 (95%)	**952**	
40-44	54 (6.5%)	774 (93.5%)	**828**	
45-49	67 (8.7%)	700 (91.3%)	**767**	
50-54	47 (7.4%)	584 (92.6%)	**631**	
55-59	40 (9.2%)	397 (90.8%)	**437**	
60-64	19 (8.1%)	217 (91.9%)	**236**	
65 or older	16 (8.6%)	169 (91.4%)	**185**	
Not Reported	1 (1.5%)	66 (98.5%)	**67**	
Total	508 (5.9%)	8080 (94.1%)	**8588**	
Ethnicity*				
White	312 (6.4%)	4540 (93.6%)	**4852**	.200
Asian	164 (5.4%)	2883 (94.6%)	**3047**	
Black	19 (5.5%)	324 (94.5%)	**343**	
Hispanic	49 (5.8%)	790 (94.2%)	**839**	
Native American	38 (7.7%)	453 (92.3%)	**491**	
Hawaiian[a]	204 (5.6%)	3412 (94.4%)	**3616**	
Total	786 (6.0%)	12,402 (94.0%)	**13,188**	

*Ethnicity totals exceed 8,588 as categories were not mutually exclusive. [a]The new questionnaire combined Hawaiian and Pacific Islander together.

1992 (OR = 1.92, 95% CI: 1.28–2.89, *P*-value = .002) were only significant in men.

Discussion

HCV antibody prevalence among our tested clients was 5.9%. This is lower than the 11.8% prevalence found by Porter, et al, but still much higher than the 1.6% prevalence estimated for the general US population.[1,2] This higher prevalence is expected because, excluding testing at HEIS sites, all clients were identified as having at least one risk factor for HCV infection. Within HEIS sites, 33.2% tested for HCV antibody did not have any risk factors. Thus, HEIS sites captured more clients with no history of risk factors and with a negative HCV antibody result, leading to a lower HCV prevalence compared to the findings of Porter, et al. Even though the previous study was conducted over an eight year period, the study population (3,306) was smaller.[17] Inclusion of HEIS sites increased the number of clients receiving HCV antibody testing more than 2-fold in just over three years. While HCV prevalence has been lower in recent years, the increase in testing has effectively identified more HCV antibody positive clients (508) in three years than were identified previously (390) over eight years.[17] Increased testing has also been supported by the introduction of the rapid test and electronic questionnaire. However, there are

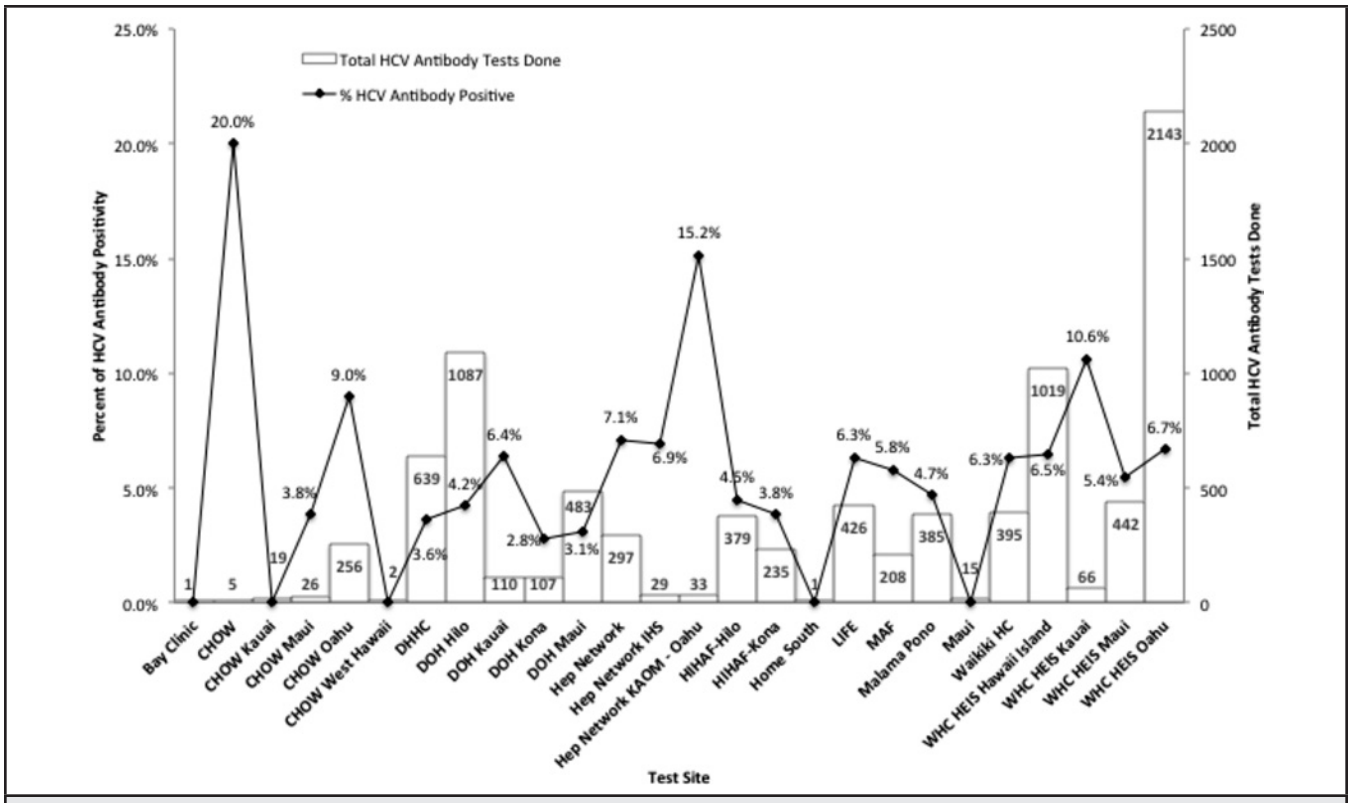

Figure 1. HCV Antibody Prevalence and Total Tests Done by Site, January 2010–April 2013

Table 2. Univariate analysis of behavioral/blood exposure factors for HCV antibody positivity, among participants screened at community-based health settings, Hawai'i, 2010–2013

Variables	HCV Antibody Positive (n=508) Number (%)	HCV Antibody Negative (n=8080) Number (%)	OR (95% CI)	*P*-value
Tattoo or Piercing (Unsterile)				
Yes	136 (5.6%)	2305 (94.4%)	1.02 (0.83–1.26)	.823
No	305 (5.4%)	5293 (94.6%)	1.00	—
No Data Reported or Unknown	67 (12.2%)	482 (87.8%)	—	—
Blood Transfusion before July 1992*				
Yes	56 (8.2%)	631 (91.8%)	1.67 (1.24–2.24)	.001
No	379 (5.2%)	6958 (94.8%)	1.00	—
No Data Reported or Unknown	56 (17.1%)	272 (82.9%)	—	—
Exposure to Blood (eg, needlestick)				
Yes	105 (4.0%)	2520 (96.0%)	0.68 (0.54–0.85)	.001
No	305 (5.8%)	4938 (94.2%)	1.00	—
No Data Reported or Unknown	98 (13.6%)	622 (86.4%)	—	—
HCV-infected Sexual Partner				
Yes	98 (6.6%)	1388 (93.4%)	1.50 (1.17–1.94)	.002
No	176 (4.5%)	3745 (95.5%)	1.00	—
No Data Reported or Unknown	234 (7.4%)	2947 (92.6%)	—	—
Injection Drug Use				
Yes	144 (11.3%)	1133 (88.7%)	2.40 (1.96–2.94)	< .001
No	363 (5.0%)	6863 (95.0%)	1.00	—
No Data Reported or Unknown	1 (1.2%)	84 (98.8%)	—	—

*Includes only persons born prior to July 1992

Table 3. Multivariate analysis[a] of behavioral/blood exposure factors for HCV antibody positivity, among participants screened at community-based health settings, Hawai'i, 2010–2013

Variables	OR (95% CI)	*P*-value
Tattoo or Piercing (Unsterile)	1.06 (0.80–1.39)	.700
Blood Transfusion before July 1992	1.91 (1.35–2.70)	< .001
Exposure to Blood (eg, needlestick)	0.66 (0.49–0.89)	.006
HCV-infected Sexual Partner	1.49 (1.14–1.95)	.004
Injection Drug Use	1.93 (1.40–2.67)	< .001

[a]Each variable in the multivariate analysis is adjusted for all other behavioral/blood exposure variables.

Table 4. Gender-stratified, multivariate analysis[a] of behavioral/blood exposure factors for HCV antibody positivity, among participants screened at community-based health settings, Hawai'i, 2010–2013

Variables	Men		Women	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Tattoo or Piercing (Unsterile)	0.94(0.68–1.31)	.722	1.41(0.84–2.37)	.197
Blood Transfusion before July 1992	1.92(1.28–2.89)	.002	1.85(0.94–3.65)	.074
Exposure to Blood (eg, needlestick)	0.74(0.52–1.04)	.084	0.45(0.24–0.85)	.013
HCV-infected Sexual Partner	1.51(1.10–2.07)	.012	1.52(0.91–2.56)	.110
Injection Drug Use	1.70(1.14–2.54)	.009	2.84(1.61–5.00)	< .001

[a]Each variable in the multivariate analysis is adjusted for all other behavioral/blood exposure variables.

cost challenges in providing treatment for HCV-infected individuals as drug therapy ranges from $70,000 to $170,000,[20] and insurance payers may begin to prioritize coverage for treatment based on new recommendations by the American Association for the Study of Liver Disease.[21]

Persons aged 45–65 years, which includes participants born between 1945-1965, had significantly higher HCV antibody prevalence (8.4%) compared to all other age groups (5.1%), similar to the findings from Porter, et al.[17] This is consistent with national findings.[8] Recommendations from the USPSTF for one-time screening for individuals born between 1945 and 1965 should ensure that screening tests are covered by most insurance payers under provisions of the Affordable Care Act.[8]

Changes in the screening protocol and test sites since the study of Porter, et al, led to an increase in the percentage of clients tested who were under 30 years old (from 28% to 37%). These clients had twice the HCV antibody prevalence (4.7%) as those identified in the earlier study period (2.4%).[17] While a true increase in HCV prevalence among this younger cohort may have occurred, changes in the screening protocol disallow our ability to make this conclusion. However, an increase may indeed be occurring among younger injection drug users in Hawai'i, as the statewide syringe exchange program reported an increase of HCV antibody prevalence in its clients under 30 years old, from 18.4% in 2011 to 28.6% in 2012.[22] An increase in drug use and sharing of equipment has been observed in other states, and law enforcement data showed the number of heroin initiates annually in the United States increased 1.8 times in 2009 compared to 2002.[9]

Overall, men had the highest HCV antibody prevalence, followed by women and then transgender individuals. Porter, et al, found the highest prevalence among transgender individuals followed by men and then women.[17] The observed difference may be due in part to the small population (0.8%) who identified as transgender in this study. Previous studies observed that men have a higher prevalence of HCV infection than women especially among injection drug users, noting higher lifetime rates of IDU and substance use disorders in men.[23] Native Americans had the highest HCV antibody prevalence among ethnic groups, whereas Asians had the lowest. While not significant, this finding is consistent with the most recent CDC surveillance data.[24]

While all HCV behavioral/blood exposure factors—except for having an unsterile tattoo or piercing—were significantly associated with HCV antibody positivity, the magnitude of the odds ratios were lower than what was found in the previous study. IDU still had the strongest association and was significant for both men and women; however, our OR was much lower than that found by Porter, et al, (1.9 and 13.6, respectively).[17] Having a blood transfusion before July 1992 was also significantly associated with HCV antibody positivity, but after gender stratification remained significant for men only.

Having an HCV-infected sexual partner was significantly associated with HCV antibody positivity but after gender stratification, remained significant only among men; similar to findings from the earlier Hawai'i study. While the risk of HCV transmission through sexual contact is believed to be low, this could represent an important risk for MSM.[25] Recent evidence has shown increasing incidence of HCV infection for MSM who are also HIV infected.[25]

Having an unsterile tattoo or piercing was not significantly associated with HCV antibody positivity. Of note, the CDC classifies individuals with a history of tattooing or piercing as "persons for whom routine testing is of uncertain need."[26] Needlestick injury was found to have a significant inverse association with HCV antibody positivity, and it remained significant for women only after gender stratification. Porter, et al, showed similar magnitudes of association. It is possible that being a healthcare worker may have confounded the results. A previous study looking at blood exposures and HCV infection among emergency responders found that these workers had a high rate of blood exposures, but HCV infection was not significantly

associated with blood exposure.[27] Another study found a protective effect among healthcare workers when socioeconomic and environmental factors were not taken into account and these may also have confounded our results.[28]

While iatrogenic transmission is the leading cause of HCV infection globally and accounts for the majority of cases in Egypt, the country with the highest HCV infection prevalence,[29,30] iatrogenic transmission is not considered a major population-based risk factor for HCV infection in the United States, where injection drug use has consistently been identified as the leading risk factor for past and current HCV infection.[7,29,31]

This study has several limitations. The population was not randomly selected, hence selection bias may have occurred. Our results therefore may be considered anecdotal and are not generalizable to the population at-large. Secondly, this study only detected the presence of HCV antibodies, which indicates previous exposure to HCV, not necessarily active infection. Still, 50%–80% of antibody positive individuals are chronically infected.[2] Also, some repeat clients were considered separate participants for analytic purposes. However, the estimated percentage of repeat clients was low at 2.7%, with only 3.7% of those clients having a positive test result. This is similar to the study of Porter, et al, that estimated 4.0% repeat clients with 1.5% of repeat clients having positive test results.[17] Finally, 5.7% of the questionnaires collected were excluded due to missing or inconclusive HCV antibody test results.

Missing information could have lowered the power of the analysis. However, demographic questions had over 95% completion, and the completion of behavioral/blood exposure factor questions ranged from 86.3% (HCV-infected sexual partner) to 98.6% (IDU). An analysis was done for the study population who answered all five behavioral/blood exposure factor questions. The findings were similar to the total study population's results; therefore missing information seems not to have significantly impacted the results. Also, our behavioral/blood exposure multivariate analysis was not adjusted for age or ethnicity, which may have confounded our results.

Changes to the questionnaire after April 2011 may also have affected the results. Having the counselor complete the new questionnaire resulted in greater completion rates and less missing information. However, this change in survey instrument and interview style presents potential for information and mode biases since clients may be less inclined to reveal their behavioral history to a counselor. Also, changes to the ethnic categories between questionnaires could make ethnic comparisons problematic.

Conclusion

Our study shows that a relaxed screening protocol, leading to expanded screening for HCV, has effectively increased the number of clients tested while still remaining concentrated on a relatively high prevalence population. While the behavioral/blood exposure factor associations found were lower in magnitude than those identified by Porter, et al, they are consistent with national findings. Use of the rapid test and electronic questionnaire has supported expanded testing by improving the ease, costs, and completeness of HDOH's screening efforts. Questions on referral and linkage to care were added to the HDOH questionnaire after our study was completed. Hopefully they will provide more insight on HCV treatment in Hawai'i. Meanwhile, clinicians should continue to identify patients at risk for HCV, such as IDU, and offer screening to individuals born between 1945 and 1965 to ensure appropriate testing and treatment.

Conflict of Interest

None of the authors identify a conflict of interest.

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Routine Screening for CYP2C19 Polymorphisms for Patients being Treated with Clopidogrel is not Recommended

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Abstract

Recent efforts directed at potential litigation in Hawai'i have resulted in a renewed interest for genetic screening for cytochrome P450 2C19 (CYP2C19) polymorphisms in patients treated with clopidogrel. Clopidogrel is an antiplatelet agent, frequently used in combination with aspirin, for the prevention of thrombotic complications with acute coronary syndrome and in patients undergoing percutaneous coronary interventions.

Cytochrome P-450 (CYP) 2C19 is an enzyme involved in the bioactivation of clopidogrel from a pro-drug to an active inhibitor of platelet action. Patients of Asian and Pacific Island background have been reported to have an increase in CYP2C19 polymorphisms associated with loss-of-function of this enzyme when compared to other ethnicities. This has created an interest in genetic testing for CYP2C19 polymorphisms in Hawai'i.

Based upon our review of the current literature, we do not feel that there is support for the routine screening for CYP2C19 polymorphisms in patients being treated with clopidogrel; furthermore, the results of genetic testing may not be helpful in guiding therapeutic decisions. We recommend that decisions on the type of antiplatelet treatment be made based upon clinical evidence of potential differential outcomes associated with the use of these agents rather than on the basis of genetic testing.

Introduction

Clopidogrel is used in the treatment of patients with atherosclerotic vascular disease and percutaneous coronary interventions (PCI) to prevent thrombotic complications associated with enhanced platelet activation. Patients undergoing PCI or with acute coronary syndromes (ACS) are usually placed on dual antiplatelet therapy. The treatment of these patients with aspirin and clopidogrel has been well documented to be related to improved clinical outcomes.[1,2]

Clopidogrel is a pro-drug that is activated in a two-step process in the liver by several cytochrome pathways. Clopidogrel is converted to 2-oxyclopidogrel by hepatic enzymes: cytochrome P-450 (CYP) 2C19, CYP1A2 and CYP2B6; 2-oxyclopidogrel is converted into an active metabolite by CYP3A4/5, CYP2B6, CYP2C19 and CYP2C9. This active metabolite irreversibly inhibits activation of the platelet GIIb/IIIa complex by binding to the P2Y12 receptor.[3-5]

CYP2C19 polymorphisms associated with decreased rates of clopidogrel activation have been identified in approximately 12-13% of the Caucasian population.[6,7] Polymorphisms in the CYP2C19*2 and CYP2C19*3 alleles have been ascribed to decreased antiplatelet response to clopidogrel and potentially increased rates of thrombotic events. The reduced-function alleles have been found in frequency ranges of 25-50% among patients from East Asian and South Asian backgrounds.[6,7] It has been proposed that genetic testing for CYP2C19 polymorphisms might be useful in identifying patients with reduced-function alleles.[3-5] It has been further suggested that patients with reduced-function genetic profiles may benefit from the routine conversion from clopidogrel to agents such as ticagrelor or prasugrel, which may not require bioactivation by CYP2C19 enzymes.

In 2010, an expert panel published recommendations addressing potential genetic testing for CYP2C19 polymorphisms in patients treated with clopidogrel. This panel was convened by the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) to address a "boxed warning" that had been issued by the US Food and Drug Administration concerning the possible need for pharmacogenomics testing to identify patients with potentially altered clopidogrel metabolism, who may be at increased risk for adverse clinical outcomes.[8] It was the conclusion of this panel that while clinicians should be aware that genetic variability in CYP enzymes may alter clopidogrel metabolism and in turn affect the drug's inhibition of platelet function, the evidence, at that time, was insufficient to recommend that either routine genetic testing for CYP polymorphisms or routine platelet function testing be performed. Furthermore, the panel recommended against basing clinical decisions upon the results of genetic testing.[8]

Nevertheless, on March 20, 2014, David Louie, the Attorney General of the state of Hawai'i, charged Bristol-Meyer Squibb and Sanofi with failing to disclose that a significant portion of patients in Hawai'i had genetic polymorphisms in the cytochrome P450 2C19 (CYP2C19) gene.[9] This finding was proposed to be associated with the potential loss of function of clopidogrel in a significant portion in Asians and Pacific Islander ethnicities. It was asserted that patients of Asian and Pacific Island ethnicity may be both less responsive to the actions of clopidogrel and at persistent risks for adverse reactions to this medication including gastrointestinal bleeding. This announcement created a renewed interest in the role of genetic testing for CYP2C19 polymorphisms in Hawai'i.

Since the publication of the ACCF/AHA expert panel consensus in 2010,[8] there have been several additional studies that have looked at the testing of platelet reactivity and clinical outcomes in patients with different CYP2C19 polymorphisms. This paper reports on the state of the literature on CYP2C19 screening and targeted treatment with clopidogrel, to determine if recent studies continue to support the panel's recommendations.

Methods

A systemic search of the literature between January 2009 and June 2014 was conducted using PubMed. PubMed is a publication search engine supported by the U.S. National Library of Medicine and the National Institutes of Health. An additional review was performed using the Google search engine. The search terms used were "coronary artery disease," "CYP," "myocardial infarction," "cytochrome P450," and "clopidogrel."

A retrospective review of references provided by the 2010 ACCF-AHA expert consensus was also performed to provide a selective review of historical references. Finally, the National Institutes of Health Clinical Research Trial database was queried to identify potential trials that may have addressed the use of genetic testing for CYP polymorphisms in assessing clinical outcomes but may have not been published.

Studies specifically outlining clinical outcomes and genetic testing were reviewed by the first two authors.

Results

Studies and Clinical Trials Conducted Preceding the 2010 Consensus Statement

The internet-based literature search generated several articles published before the 2010 consensus statement; 53 articles were reviewed and 18 are included in this review. Another 16 articles published after the 2010 consensus statement were separately reviewed, out of which 8 have been included in this review

It has been long recognized that there may be variation in platelet function inhibition, as assessed by platelet aggregometry, while on PGY12 inhibitors. In 2002, Järemo and colleagues reported individual variations in platelet inhibition after loading doses of clopidogrel in a group of 18 patients with stable angina undergoing PCI.[10] This finding was reproduced in a group of 96 patients in 2003 by Gurbel, et al.[11]

To explain these findings, a linkage between the intensity of clopidogrel-induced inhibition of platelet reactivity and clinical outcomes was also suggested.

In 2004, Matetzky described 60 patients with clopidogrel resistance who were at an increased risk of recurrent atherothrombotic events while being treated with antiplatelet therapy after acute myocardial infarctions.[12] Schuldiner, et al, and Mega, et al,[4,5] in separate publications, linked nonresponsiveness to clopidogrel to CYP2C19 polymorphisms associated with a potential loss-of-function (LoF) of this enzyme required for the bioactivation of clopidogrel.[4,5] Between 2009 and 2011, several reviews of CYP2C19 polymorphisms and outcomes were performed.[13-16] They contended that clopidogrel non-responsiveness may result in an increased risk for major cardiac events while on antiplatelet treatment. The described studies were performed using retrospective analyses.

This opinion was confirmed by some clinical trials conducted during the time period. In the results of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON TIMI 38), published in 2007,[17] 13,608 patients undergoing treatment for ACS or ST segment elevation myocardial infarction were randomized to treatment with clopidogrel versus prasugrel. A genetic study was performed assessing CYP2C19 allele status. Carriers of the LoF allele treated with clopidogrel had higher rates of the primary outcomes, including death from cardiovascular causes, non fatal MI, or non fatal stroke (12.1% versus 8.0%; hazard ratio = 1.53; $P = .01$) and definite/ probable stent thrombosis (2.6% versus 0.8%; hazard ratio = 3.09; 95% confidence interval = 1.19-8.00; $P = .02$) compared with non-carriers. However among prasugrel treated patients, LoF carrier status was unrelated to outcomes. Higher rate of events occurred predominantly in the group of patients treated with PCI.[17] This study suggested that genetic testing for CYP2C19 polymorphisms might be used to predict clinical outcome while on antiplatelet therapy.

The Platelet Inhibition and Patient Outcomes (PLATO) study, published in 2010, was a double-blinded randomized clinical trial involving 10,285 subjects, comparing the effects of clopidogrel and ticagrelor in patients presenting with ACS.[18] In this study, 60% of patients underwent PCI. Routine genetic testing for CYP2C19 polymorphisms was performed, which identified a subgroup of 27% of the study population with the LoF of at least one CYP2C19 allele. In this subgroup, patients treated with clopidogrel had a higher risk of adverse cardiovascular events, with a hazard ratio of 1.37 (CI 1.04-1.82; $P = .028$). In patients treated with ticagrelor, an antiplatelet agent that does not require bioactivation by CYP2C19, no clear relationship between genotype and clinical outcome was established. Based upon these findings, the authors suggested that the routine use of ticagrelor obviated the need for genetic testing and that the presence of at least one CYP2C19 allele associated with potential LoF resulted in decreased cardioprotection in patients treated with clopidogrel. The validity of this interpretation was limited by the fact that these results were based upon a retrospective analysis and changes in the definitions of the intention to compare groups, with the original intention to compare six phenotype groups which was later changed to compare just two genotype groups.

Nevertheless, conflicting information regarding the utility of identifying LoF CYP2C19 polymorphisms in the prediction of associated cardiovascular events while on antiplatelet therapy was obtained from other prospective clinical studies. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, published in 2010, 5,059 patients were treated for ACS with either placebo or clopidogrel and underwent genetic testing.[19] CYP2C19 polymorphisms associated with a potential LoF were noted in 19.8% of patients. These investigators found that the clinical outcomes of patients on clopidogrel were not significantly different based upon metabolizer status. Of note, in this study, only 18% of the patients underwent PCI. The authors concluded that CYP2C19 LoF allele status did not preclude the use of clopidogrel in patients with ACS who were being managed conservatively.[19]

Studies and Clinical Trials Conducted Following the 2010 Consensus Statement

Table 1 summarizes the results of the 6 clinical trials initiated between 2010-2014 addressing genetic testing and treatment strategies. Since the publication of the ACCF AHA expert consensus in 2010,[8] there have been no randomized trials that have demonstrated that treatment strategies based upon genetic testing for CYP2C19 polymorphisms have affected clinical outcomes.

In a substudy of the Gauging Responsiveness with A VerifyNow assay- Impact on Thrombosis and Safety (GRAVITAS) study, called the Genotype Information and Functional Testing (GIFT) study, the influence of single nucleotide polymorphisms (SNPs) on the pharmacodynamic (PD) effect of high- or standard-dose clopidogrel after PCI was evaluated.[20] DNA samples obtained from 1,028 patients were genotyped for 41 SNPs in 17 genes related to platelet reactivity. The presence of CYP2C19*2 allele was found to be significantly associated with increased on-treatment platelet reactivity (OTR) at 12 to 24 h ($R^2=0.07$, $P=<.001$), 30 days ($R^2=0.10$, $P=<.001$), and 6 months after PCI ($R^2=0.07$, $P=<.001$), but not with significant differences in clinical outcome (HR 1.07; CI: 0.91 -1.25; $P=.42$).

In the recently published findings from the Assessment by a double Randomization of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and of Treatment Interruption versus Continuation one year after stenting (ARTIC) trial, 2440 patients were placed on different antiplatelet treatment strategies based upon the results of platelet function testing. The authors reported that tailored therapy based upon genetic testing did not result in improved outcomes when compared to standard treatments that were not based on genotyping.[21]

Several other trials were terminated prior to completion because of concerns that the study population would be inadequate to provide significant statistical analysis. As a representative example, it was hoped that the Thrombocyte Activity Reassessment and Genotyping for PCI (TARGET-PCI) trial would bring

Table 1. Summarizing Six Clinical Trials Initiated between 2010-2014 Addressing Genetic Testing and Treatment Strategies

Study	Outcomes
TARGET-PCI (NCT01177592) Sponsor: LifeBridge Health 2010. Prospective, single-center, randomized trial including 1500 patients with stable coronary artery disease (CAD) and elective PCI. Patients within 24 hrs of PCI were randomized to either Control (remain on clopidogrel) or Guided therapy (CYP2C19*2 carriers and/or if Platelet reactivity unit (PRU)>230, reload with prasugrel). Major Adverse Cardiac Events (MACE) including death, myocardial infarction (MI) and target vessel revascularization were recorded in a follow up (FU) period of 6 months.	The study was suspended in October 2010 after it was concluded that the sample size was underpowered to address the initial hypothesis
TRIGGER-PCI (NCT00910299) Sponsor: Eli Lilly 2009-2012. A randomized, active-control, double blind, phase II, multicenter trial enrolled 2150 patients with stable CAD and elective PCI. Selection criteria of patients 24 hour post-drug eluting stent (DES) and 2 to 7 hour post clopidogrel and HRPA randomized to either Prasugrel 60 mg load/10 mg daily; or Clopidogrel 75 mg daily. Cardiovascular (CV) death or nonfatal MI was recorded for a FU period of 6 months.	In 212 patients assigned to prasugrel, PRU decreased from 245 to 80 at 3 months, whereas in 211 patients assigned to clopidogrel, PRU decreased from 249 to 241 ($P<.001$ vs prasugrel). The primary efficacy endpoint at 6 months occurred in no patient on prasugrel versus 1 on clopidogrel.[25] Thus Switching from clopidogrel to prasugrel in patients with high on treatment platelet reactivity (HTPR) did not demonstrate clinical utility given low rate of adverse ischemic events after PCI with contemporary drug eluting stents (DES) in stable CAD
CLOVIS-2 (NCT00822666) PI: J.-P. Collet PI: G. Montalescot 2012. A randomized, open-label, phase III, crossover Pharmacodynamic, PD/ Pharmacokinetic, PK study) trial including 120 patients who were Post-MI, 45-years-old and enrolled in AFIJI registry. Comparison of 2 loading strategies of clopidogrel (300 mg vs 900 mg) in 2 genetic profiles: wild-type 2C19*1 and carriers of 2C19*2 was performed. Inhibition of Residual platelet activity (IRPA) by optical aggregometry; measurement of active metabolites, was studied at 6 hour post loading dose.	Carriers of CYP2C19*2 display significantly lower responses to clopidogrel with a gene-dose effect. Clopidogrel resistance can be overcome by increasing the dose in heterozygous carriers but not in homozygous carriers[26] Clinical outcomes were not studied.
ACCEL-2C19, (NCT01012193) PI: Y.-H. Jeong 2011. A randomized, active control, single-blind (PD study) of 80 patients with Stable CAD with type 2 DM and elective PCI. Patients genotyped for CYP2C19 variants randomized to high dose clopidogrel (150 mg) and ASA 200 mg vs cilostazol 100 mg bid, 75 mg clopidogrel and ASA 200 mg (triple therapy) and Inhibition of maximum platelet aggregation (MPA) by optical aggregometry; VerifyNow, was studied at 30day FU.	Among T2DM patients, adding cilostazol achieves greater platelet inhibition compared with clopidogrel (150 mg/d), which is not influenced by genetic polymorphisms. Clinical outcomes were not studied with genetic polymorphisms
ACCELAMI2C19 (NCT00915733) PI: I.-S. Kim 2009. Randomized, active control, open-label (PD study) of 60 patients with acute MI, post PCI. Patients genotyped for CYP2C19 variants randomized to high dose clopidogrel (150 mg) and ASA 100 mg vs. cilostazol, 100 mg bid, 75 mg clopidogrel and ASA 100 mg. Inhibition of MPA studied at 30 day follow up.	Adjunctive cilostazol reduces the rate of high post treatment platelet reactivity (HPPR) and intensifies platelet inhibition as compared with a high-maintenance dose (MD) clopidogrel of 150 mg/day. Clinical outcomes were not studied with genetic polymorphisms
ACCEL-2C19 (NCT00891670) PI: Y.-H. Jeong 2009. Randomized, active control, open-label (PD study) of 126 patients with stable CAD and elective PCI. Patients genotyped for CYP2C19 variants randomized to high dose clopidogrel (150 mg) ASA 100 mg vs. cilostazol, 100 mg bid, 75 mg, clopidogrel ASA 100 mg (triple therapy). Maximum platelet aggregation was studied at 30 day follow up.	Among PCI-treated patients receiving high-MD clopidogrel, carriage of CYP2C19 variant relates to increased PR and predicts risk of HPPR. Clinical outcomes based on prespecified genetic testing were not studied

TARGET PCI, Thrombocyte Activity Reassessment and Genotyping for PCI; TRIGGER PCI, Testing Platelet Reactivity in Patients Undergoing Elective stent placement on Clopidogrel to Guide Alternative Therapy with Prasugrel; ACCEL-2C19, Adjunctive Cilostazol Versus High Maintenance-dose Clopidogrel According to Cytochrome 2C19 Polymorphism; ACCELAMI2C19, Adjunctive Cilostazol Versus High Maintenance-dose ClopidogreL in Acute Myocardial Infarction Patients According to CYP2C19 Polymorphism; AFIJI, Appraisal of Risk Factors in Young Ischemic Patients Justifying Aggressive Intervention; CLOVIS-2, Clopidogrel and Response Variability Investigation Study 2

definitive information demonstrating whether guided antiplatelet therapy using genotyping and platelet function testing would have advantages over standard antiplatelet therapy. Approximately 1,500 patients were randomized in this trial. The trial was suspended in October 2010 after it was concluded that the sample size was underpowered to address the initial hypothesis. It was recognized that the event rates such as stent thrombosis would be so low that effective analysis of significance would be difficult. Similarly, a large scale clinical trial addressing Genotype Guided Comparison of Clopidogrel and Prasugrel treatment outcomes (NCT00995514) had been planned but was terminated prior to analyses due to administrative reasons.

Discussion

Genetic testing for CYP2C19 polymorphisms is now readily available and costs $300-$400 which is covered by most insurance companies with varying co-payments.[22] At issue, however, is whether all patients on antiplatelet therapy should undergo routine genetic testing for CYP2C19 polymorphisms.

As mentioned previously, in 2010, the U.S. Food and Drug Administration (FDA) published a "Boxed Warning" for clopidogrel noting that patients who were CYP2C19 poor metabolizers exhibited higher cardiovascular event rates than patients with normal CYP2C19 function. This warning also noted that there were tests available to assess CYP2C19 genotypes and that these tests could potentially be used as an aid in determining therapeutic strategies. While the FDA clearly informed physicians and patients about the availability of genetic testing, it did not recommend or mandate testing.[23]

The ACCF and AHA responded to this "Boxed Warning" and convened a panel to create a clinical expert consensus document.[8] The consensus document was published in 2010 and concluded that "the role of genotyping in everyday practice remains unknown at this present time." This group also noted that at the time of publication, there were "no prospective studies demonstrating a clinical benefit to personalizing antiplatelet therapy based on genotype analysis." Advocates of genetic testing were present on the panel and argued that "given the magnitude of the potential clinical consequences of suboptimal platelet inhibition based on genetic variation, assessment of genotypes would be justifiable."

However, an opposing opinion was also noted by panel members who stated there was no definitive proof that intervening on the basis of genotype would improve outcome. Opponents to recommending routine genetic testing also raised the question of whether genotyping should be confined to LoF mutations involving only the CYP2C19*2 and CYP2C19*3 alleles or be extended to other variants, including potential hypermetabolizers of clopidogrel. Opponents of testing also noted that the predictive performance of the presence of CYP2C19*2 and CYP2C19*3 allele variants was low, ranging only from 12-20% in predicting adverse clinical events. It was suggested that the state of knowledge was incomplete and that further studies would be useful to address these issues.[8]

In an editorial in 2011, Nissen described genetic testing for clopidogrel as a case of "irrational exuberance," a phrase popularized by former chairman of the Federal Reserve Alan Greenspan when describing the exponential increase in stock prices a few years before the "dot-com bubble" burst in March 2000. The enthusiasm for dot-com stocks led to unrealistic expectations for rapid success of companies without documented financial performance. Similarly the success of pharmacogenomics in some fields of medicine has led to unrealistic expectations for many other specialties, including cardiovascular medicine.[24]

A review of the literature reveals that the findings of recent studies do not support the routine screening for CYP2C19 polymorphisms or targeted antiplatelet therapy based upon the results of genetic testing. Based upon our review we feel that decisions regarding conversion to newer antiplatelet agents such as ticagrelor or prasugrel should not be based upon genetic testing but on evidence of potentially improved clinical outcomes for patients treated with these newer agents but balanced against bleeding risks. With the end of the patent on clopidogrel and its current availability as a generic formulation, it is unlikely that a trial with a sample size of 20,000-30,000 patients, necessary to definitively study potential effects of genetic variation in CYP2C19 correlated with clinical outcomes would be funded or undertaken.

Summary

In 2010, an expert panel convened by the ACCF and AHA concluded that the routine testing for CYP2C19 polymorphisms in patients treated with clopidogrel was not warranted.[8] In our review of the published data since this recommendation and our overview of clinical trials on this subject registered by the NIH, we have not found any additional supporting evidence for tailored therapy based upon genetic testing. As clopidogrel is now available in a generic formulation, it is unlikely that further studies clarifying the role of genetic testing will occur and we suspect that there will be limited additional information clarifying a potential role of genetic testing targeted-therapy. While we do not recommend the routine testing for CYP polymorphisms as a basis for changing antiplatelet therapies, clear differences in clinical outcomes have been noted with the use of newer antiplatelet agents such as ticagrelor and prasugrel. The choice of antiplatelet agent should not be based upon the results of genetic testing but rather on clinical indications.

Conflict of Interest

None of the authors identify any conflict of interest.

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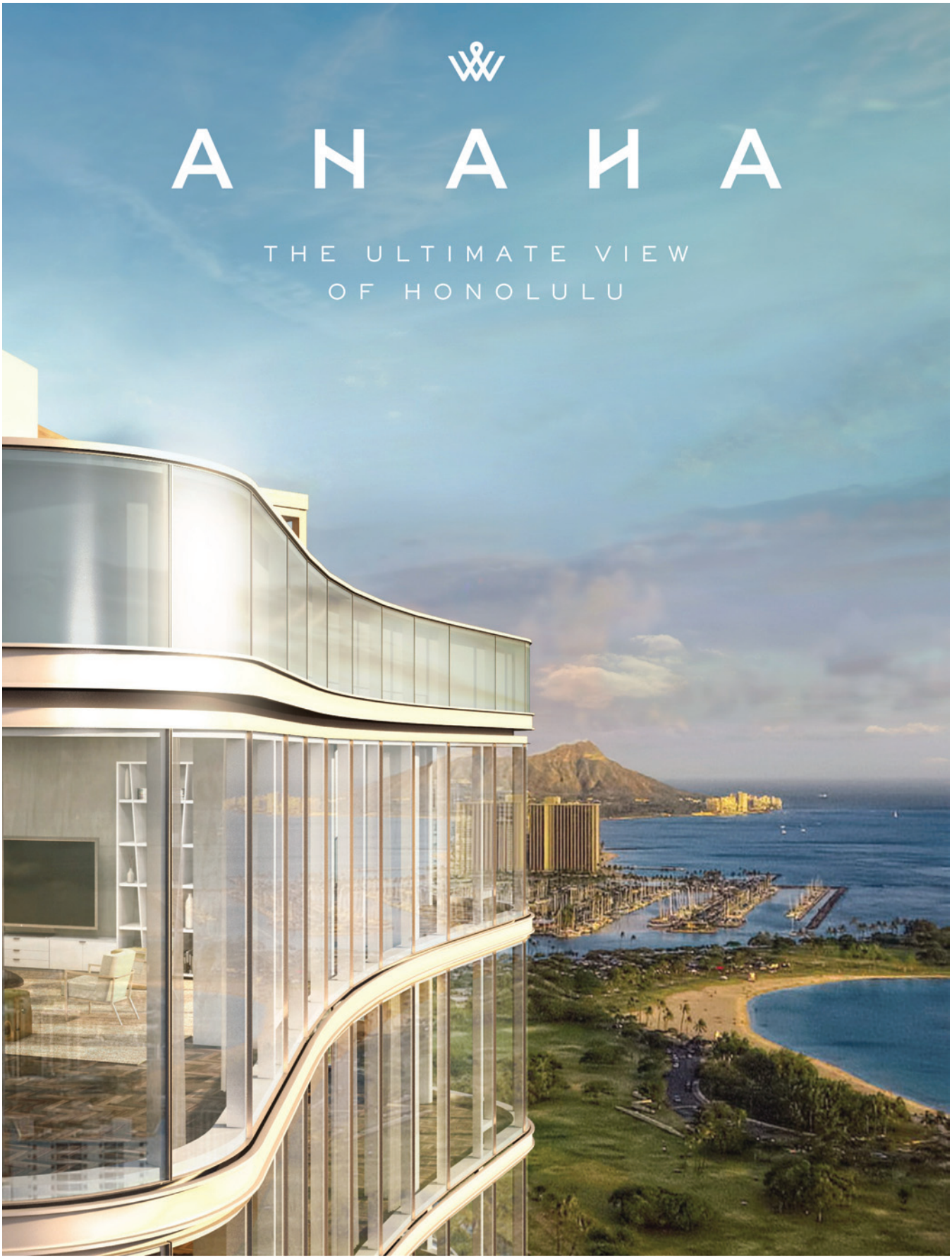
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Western Group on Educational Affairs (WGEA) 2014 Conference at the John A. Burns School of Medicine

Sheri F.T. Fong MD, PhD; Damon Sakai MD; Jill Omori MD; Kori-Jo Kochi BA; and Yawen Sarah Hsiao MSIS

The Medical School Hotline is a monthly column from the John A. Burns School of Medicine and is edited by Satoru Izutsu PhD; HJMPH Contributing Editor. Dr. Izutsu is the vice-dean of the University of Hawai'i John A. Burns School of Medicine and has been the Medical School Hotline editor since 1993.

Background

The Western Group on Educational Affairs (WGEA) is one of four regional groups of the Association of American Medical Colleges (AAMC) Group on Educational Affairs. The WGEA institutional members are:

- Alberta Faculty of Medicine
- University of Arizona College of Medicine
- University of British Columbia Faculty of Medicine
- University of Calgary Faculty of Medicine
- University of California, Davis School of Medicine
- University of California, Irvine School of Medicine
- University of California, Riverside School of Medicine
- University of California, San Diego School of Medicine
- University of California, San Francisco School of Medicine
- Charles R. Drew University of Medicine and Science
- University of Colorado School of Medicine
- David Geffen School of Medicine at UCLA
- John A. Burns School of Medicine, University of Hawai'i at Manoa
- Keck School of Medicine of University of Southern California
- Loma Linda University School of Medicine
- University of Nevada School of Medicine
- University of New Mexico School of Medicine
- Oregon Health and Science University School of Medicine
- Stanford University School of Medicine
- University of Utah School of Medicine
- University of Washington School of Medicine

The WGEA strives to promote excellence in the continuum of medical education, from undergraduate and graduate medical education to continuing medical education, by fostering professional development of medical educators and advancing research in medical education.[1] Its annual spring regional meeting provides conference attendees to share ideas, resources and research, and is hosted by one of the WGEA institutional members on a rotating basis.

JABSOM last hosted in 2007, and had a record attendance of 234 people. JABSOM maintained this record until Stanford hosted a combined spring meeting with WGEA, WGSA (Western Group on Student Affairs), WOSR (Western Organization of Student Representatives) and WAAHP (Western Association of Advisors for the Health Professions), in 2011 and had 510 attendees.

Although JABSOM was not scheduled to host the spring regional meeting until later in the 2020 decade, JABSOM requested to host in 2014 for a number of reasons, including promotion of faculty development, providing an opportunity for faculty, staff, and students to present at a regional conference in a local venue, enhancing JABSOM's profile regionally, and allowing the school (JABSOM) to prepare for LCME accreditation, which is scheduled for the academic year 2016-2017.

Conference

The WGEA 2014 Spring Meeting was held on March 23-25 at the Ala Moana Hotel (March 23) and JABSOM (March 24 and 25). The theme was, "A SLICE of Paradise: Accreditation Standards Leading Innovation and Creativity in Education." The WGEA Planning Committee invited Dr. Dan Hunt, Co-Secretary of the Liaison Committee on Medical Education (LCME) and Senior Director of Accreditation Services at AAMC, to be the plenary speaker. In his plenary speech, titled "Medical Education Accreditation: THE Leverage for Quality and Creativity," Dr. Hunt shared innovative programs across the country that were helping those institutions address accreditation standards. Some of the feedback received was:

> "Awesome. Very practical for all…"

> "It was engaging and provided a perspective on LCME that was different than I had expected, a helpful way to look at LCME."

> "Very useful and practical!"

The WGEA Planning Committee also invited Dr. Richard Kasuya, Associate Dean of Medical Education and Dr. Damon Sakai, Director of Medical Student Education, to give a Host Institution Presentation. In their talk, "Medical Student Education in the Aloha State: The John A. Burns School of

Medicine," they shared unique aspects of the JABSOM curriculum along with cultural aspects of Hawai'i that have influenced the curriculum and impacted the learning environment, including Hawai'i's geographic isolation, value of storytelling, and the importance of personal relationships in the design of JABSOM's PBL program, longitudinal integrated clerkships, and community outreach. The session was the most cited by the attendees for exceptional presentations at the conference, and feedback included:

> "Great way to introduce us to the culture not only of Hawai'i but of the school. We will all be challenged to create such a welcoming and exciting feeling for our own schools when it is our turn to host. I think this approach should be a WGEA tradition!"

> "The presentation…about the school and its cultural fabric really provided a great example for how we can explore and describe diversity and address the issue of cultural competence at our own institution, and think of ways to improve on that."

> "A fantastic and moving presentation. It made me want to take your students into our residency. It made me want to work there!"

The majority of the program was selected from submissions in response to an open call for proposals. WGEA 2014 received 226 proposal submissions, compared to 147 submissions in 2007, the last time JABSOM hosted. The number of submissions was also higher than the three previous WGEA conferences. All submissions were peer-reviewed by faculty outside of the submitters' home institution. From these submissions, the final WGEA 2014 program contained 8 sessions, each with 6-9 concurrent presentations, composed of a total of 15 panels, 27 workshops, 20 small discussion groups, and 51 oral abstract presentations. There was also a separate poster session with 97 presentations.

The program also included 8 AAMC-sponsored sessions, 2 Medical Education Research Certificate (MERC) workshops, a Medical Education Scholarship Research and Evaluation (MESRE) workshop, and meetings of various groups including the WGEA Steering Committee, MESRE, Computer Resources in Medical Education (CRIME), and Libraries in Medical Education (LIME). In addition, there was the inaugural offering of the Leadership Education and Development (LEAD) Certificate program for the WGEA region, a two-year leadership development program that provides the knowledge, skills, values, and practical experience needed to be successful leaders in academic medicine.[2] Finally, there was a Clerkship Administrator Certificate Program aimed at optimizing one's career and contributions through leadership development. Attendees were able to claim CME credit, which was offered through the Hawai'i Consortium for Continuing Medical Education.

WGEA 2014 had 320 attendees. Of this number, there were 71 attendees from JABSOM, including 4 department chairs, 42 faculty, 6 staff, 9 residents and fellows, 5 medical students, 1 post-doctoral student, and 3 graduate students. When comparing to just the WGEA attendees from previous WGEA/WGSA/WOSR/WAAHP combined conferences, the attendance exceeded WGEA attendance at the three previous conferences.

The attendees at WGEA 2014 represented 25 medical schools in US and Canada, as well as nine schools in Japan, Taiwan and Thailand. Non-WGEA schools that participated were:

- University of Missouri School of Medicine
- University of Saskatchewan
- Texas Tech University at El Paso
- Wake Forest School of Medicine
- Washington University School of Medicine
- Fu-Jen Catholic University, Taiwan
- Kobe University, Japan
- Kochi Medical School, Japan
- Okayama University, Japan
- Juntendo University, Japan
- University of the Ryukyus, Japan
- Thammasat University, Thailand
- Jikei School of Medicine, Japan
- Tohoku University, Japan

Besides the educational aspects of the conference, there was also sharing of our Hawaiian culture. This took the form of an opening *oli* (chant; prayer) performed by Drs. Dee-Ann Carpenter, Martina Kamaka, Vanessa Wong, and others from the Native Hawaiian Center of Excellence, and a *luau* (feast) hosted on the grounds of JABSOM with hula performances from first and second year medical students, as well as JABSOM faculty and staff. As hosts, JABSOM conveyed the sense of aloha, and many attendees commented on the welcoming and friendly atmosphere of the conference. Some of the feedback received was:

> "...the atmosphere was warm, relaxed and collegial, so thank you for your and your team's superb planning!"

> "The conference was warm-hearted and fruitful." Thank you for your hard work and hospitality."

> "The conference was stimulating, but also was heart-warming with full hospitality."

Presentations by JABSOM

JABSOM faculty and staff; fellows and residents; post-doctoral, graduate, and medical students participated in 4 panels, 4 workshops, 5 small group presentations, 3 oral abstracts and 20 posters.

Panels

- International Experiences with Problem-Based Learning
- IS-16 Diversity Policy: Perspectives and Experiences
- Optimizing the Workforce Pipeline into a Critically Understaffed Specialty: Perspectives from Three Faculty Psychiatrists
- What's Genealogy Got to Do with It? Exploring Innovative Cultural Competency Training at JABSOM

Workshops
- Best Practices and Lessons Learned for Developing Dynamic Web-Based Resources for Healthcare Education and Research
- Culturally Cognizant Communication
- Google Sites and Forms: Enhancing Your Courses with Limited Resources
- New Life-Saving Devices: The Tablet Computer Revolution

Small Group Presentations
- Are you Ready to See Patients on Your Own? Determining Resident Competency to Practice with "Direct Supervision Available"
- Creating Invested Learners – a Community-Based, Participatory Approach to Residency Curricular Improvements
- Developing Future Nursing Home Medical Directors: A Curriculum for Geriatric Medicine Fellows
- Honoring the Past, Preparing Physicians for the Future: The Kalaupapa Service Learning Project
- Understanding Pacific Islander Cultural Nuances and Norms Affecting Success in US Medical Education Systems

Oral Abstract Presentations
- Enhancing Nutrition Education through Diet Experiences
- Melding Western Medicine and Traditional Native Hawaiian Health in a Senior Medical Student Elective
- The Standardized Patient and Standardized Interdisciplinary Team Meeting: Validation of a New Performance-Based Assessment Tool

Poster Presentations
- Can a Standardized Interdisciplinary Team Meeting Measure Facilitative Communication Skills?
- Combining Quality Improvement and Geriatrics Training: The Nursing Home Polypharmacy Outcomes Project
- Curriculum Development in Skin and Wound Care
- Curriculum Mapping of Geriatric Medicine Core Competencies in the Preclinical Problem-Based Learning Curriculum at the John A. Burns School of Medicine, University of Hawai'i
- Developing a 3 Year Geriatric and Palliative Care Curriculum for Internal Medicine Residents
- Doctors as Teachers: Implementation of an iPad-Based Resident Curriculum
- Education on Depression for Frontline Nursing Home Staff: The Practice Improvement in Education (PIE) Project
- Efficient Integration of Anatomy and Physiology in ECG Training
- Enhancing Clinical Skills Education Through the Use of Programmable Computerized Stethoscopes during the Processing of PBL Cases
- Enhancing Ethnogeriatrics Education for Geriatric Medicine Fellows
- Integration of Indigenous Hawaiian Cultural Values into a Clinical Training Experience
- Medical Student Outcomes: Longitudinal Clerkships vs Traditional Block Rotations
- Peer Coaching: Harnessing and Controlling the Hidden Curriculum
- A Quality Improvement Program to Enhance Resident Understanding of Appropriate Methods for Indwelling Port Access
- Removing the Clutter to Help Patients: Teaching Residents a New Format for the Progress Note in the Electronic Medical Record
- Self-Directed Learning Readiness of Undergraduate Students in a Medical School with PBL Curricula: A Cross-Sectional Study
- Teaching the Affordable Care Act to First-Year Medical Students Using Problem-Based Learning
- Teaching Japanese Emergency Medicine Residents About Delirium
- Use of Visual Displays to Teach Medical Microbiology in the Preclerkship Years
- You're Being Paged! Outcomes of a Nursing Home On-Call Role-Playing and Longitudinal Curriculum

Dr. Dee-Ann Carpenter received an award from the MESRE Section for her outstanding oral abstract presentation titled, "Melding Western Medicine and Traditional Native Hawaiian Health in a Senior Medical Student Elective."

Evaluation

An online survey was sent to all the participants. Approximately 117 responses were received. The majority of participants agreed or strongly agreed that they were able to achieve the following overall objectives of the conference:

- Describe the continuous improvement process associated with undergoing the accreditation process (70%, n=82)
- Describe and apply the knowledge, tools, and skills associated with providing quality teaching in critical evaluation of medical education (91%, n=108)
- Describe and apply ways to demonstrate, teach, and promote non-cognitive attributes such as professionalism, cultural competency, and interdisciplinary teamwork (85%, n=100)
- Discuss and apply examples of educational research relevant to one's responsibilities in medical education (88%, n=105)

When asked to rate the projected impact of the conference on their competence, performance, and student outcomes, the majority of participants agreed or strongly agreed that:

- The conference increased my competence (91%, n=109)
- The conference improved my performance (87%, n=101)
- The conference will improve my students outcomes (85%, n=100)

As a result of attending the conference, 41% (n=62) stated they planed to create/revise their curriculum, 38% (n=57) stated they would change the methodology in teaching, and 9% (n=14) said they would change their practice in another way. The largest barrier to implementing changes was cost (23%, n=47).

Benefit to JABSOM

Hosting the WGEA 2014 Conference benefited JABSOM in several ways. Based on evaluations, the conference was a success and allowed the JABSOM faculty and staff to present a favorable impression of JABSOM to the WGEA region and beyond. Faculty members shared what makes JABSOM special, and showed the strengths in their curriculum. The conference allowed for networking with colleagues interested in medical education from different JABSOM departments and other schools, nationally and internationally. JABSOM faculty demonstrated the breadth and depth of their scholarly work in medical education. Finally, the WGEA 2014 Conference provided an opportunity for faculty development in education of medical students, residents and fellows. The latter two, scholarly activity and faculty development in medical education, are particularly beneficial to JABSOM as they are both important for LCME accreditation.

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Building Support for an Evidence-Based Teen Pregnancy and Sexually Transmitted Infection Prevention Program Adapted for Foster Youth

Tamara Smith MPH; Judith F. Clark MPH; and Claudio R. Nigg PhD

Insights in Public Health is a monthly solicited column from the public health community and is coordinated by HJMPH Associate Editors Jay Maddock PhD from the Office of Public Health Studies at John A Burns School of Medicine and Donald Hayes MD, MPH from the Hawai'i Department of Health in collaboration with HJMPH Manuscript Editors Tonya Lowery St. John MPH and Ranjani Starr MPH from the Hawai'i Department of Health.

Abstract

Hawai'i Youth Services Network (HYSN) was founded in 1980 and is incorporated as a 501(c) (3) organization. HYSN plays a key role in the planning, creation, and funding of local youth services. One of HYSN's focuses is teen pregnancy and sexually transmitted infections (STI) prevention among foster youth. Foster youth are at a greater risk for teen pregnancy and STI due to a variety of complex factors including instability, trauma, and emancipation from the foster care system. This article highlights how HYSN is leveraging both federal and local funding, as well as other resources, in order to implement an evidence-based teen pregnancy and STI prevention program adapted for foster youth.

Keywords

Teen Pregnancy Prevention, Teen Sexually Transmitted Infection Prevention, Foster Youth, Adapting Evidence-Based Programs

Background

Hawai'i Youth Services Network

Hawai'i Youth Services Network (HYSN) was founded in 1980 and is incorporated as a 501(c) (3) organization. HYSN plays a key role in the planning, creation, and funding of local youth services through partnerships with 50 membership agencies. While HYSN programs are based on community needs and funding availability, all of HYSN's work is rooted in their Positive Youth Development Philosophy:[1]

> The children and youth of Hawai'i are our future. The way we treat them today, the opportunities we provide them, and the investments we make in their development will influence the kind of adults they will become.
>
> Children and youth live and participate in our communities. We must recognize and value them as community assets. We need to include young people in decisions that affect their lives in communities, school systems, churches, and in our public policy decision-making.
>
> We must meaningfully engage youth in all aspects of community life.

HYSN is a training and technical assistance provider for Hawai'i and other Pacific Island nations and territories for grant writing, sustainability, collaboration, evaluation, and teen pregnancy prevention. Executive Director, Judith F. Clark, MPH (HYSN ED), is well known locally and nationally for her ability to successfully build partnerships and collaborations and develop culturally relevant and sustainable programs. In 2005 and 2010, HYSN ED received the Hawai'i State Legislature's Award for Hawai'i's Outstanding Advocate for Children and Youth.

Teen pregnancy and sexually transmitted infection (STI) prevention are among HYSN's primary foci. In 2010, HYSN received a 5-year, Tier 1: Teen Pregnancy Prevention – Replication of Evidence-Based Programs grant from the Federal Office of Adolescent Health (OAH).[2] HYSN was awarded $999,999 annually to manage the Teen Pregnancy Prevention Partnership of the Pacific (TPPPP), which includes ten organizations throughout the Hawaiian Islands (see Figure 1).[2]

Additionally, HYSN recognizes that foster youth have unique needs when it comes to pregnancy and STI prevention. Hawai'i was one of five teams that participated in The Prevention of Pregnancy and Sexually Transmitted Infections Among Foster Youth Institute (The Institute). The Institute was a partnership between The National Campaign and the American Public Human Services Association and funded by the Annie E. Casey Foundation.[3] Hawai'i's core team included HYSN ED, HYSN Teen Pregnancy Prevention Director, DHS – Child Welfare Service Assistant Administrator, Hale Kipa Deputy CEO, and Hale 'Opio Kaua'i Executive Director (HYSN ED, personal communication, October 2014).

Making Proud Choices and the Importance of Teen Pregnancy and STI Prevention

Making Proud Choices (MPC) is one of two evidence-based curricula used by the TPPPP.[2] MPC can be implemented in community-based or school settings as it consist of eight modules that can be conducted in two, four-hour sessions or eight, one-hour sessions.[4,5] Using a randomized control trial with a

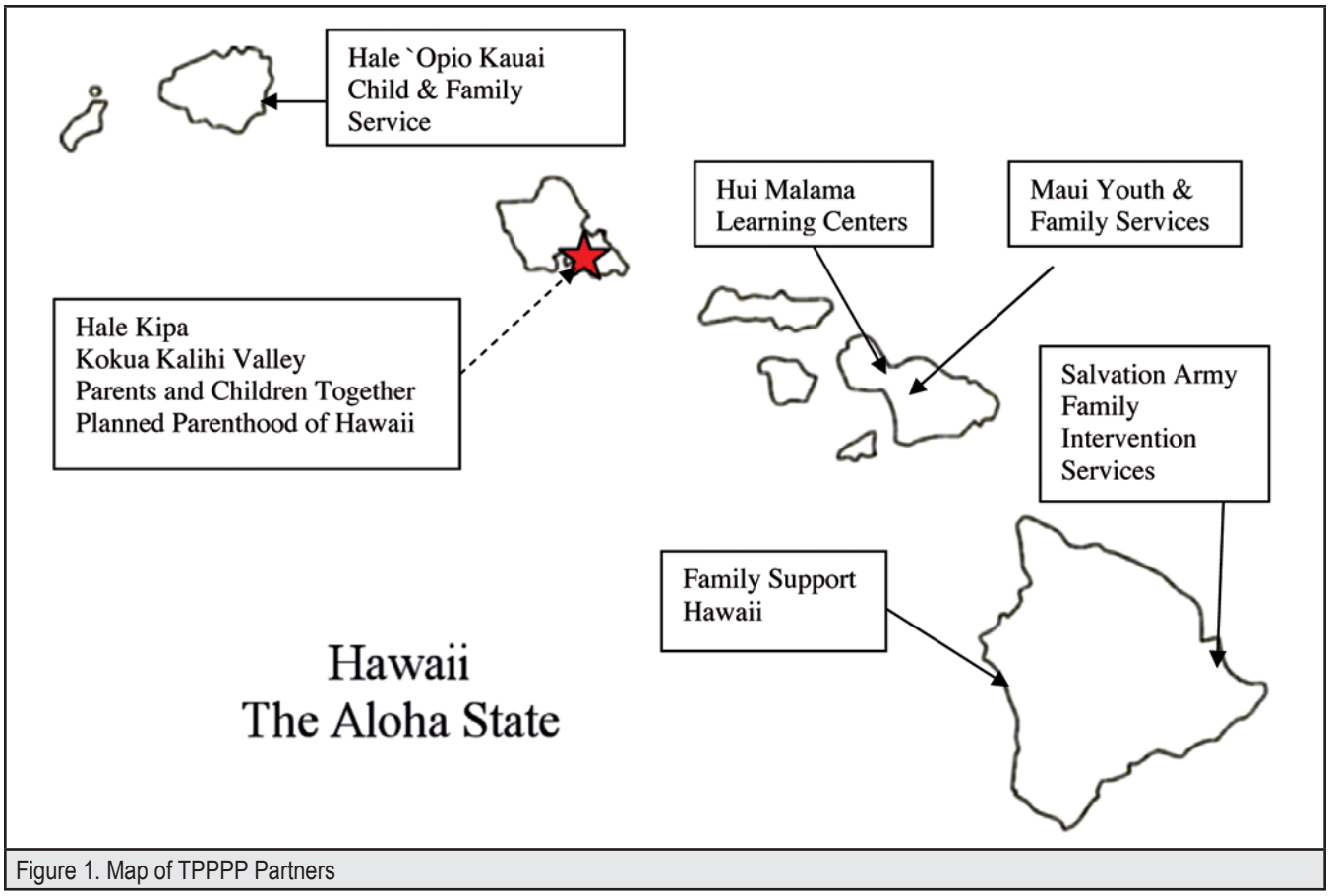

Figure 1. Map of TPPPP Partners

pre-test and post-tests at 3, 6, and 12 months, evaluation of MPC found sexually active participants had decreased frequency of intercourse and were more likely to use condoms.[5]

HYSN has also had previous success with MPC, and in 2008 received the CDC's Horizon Award for Excellence in Health Education for adapting MPC to be culturally appropriate for Asian and Pacific Islander youth. HYSN post-tests at end of MPC instruction show significant increases in knowledge, attitudes, and skills that decrease the risk of unplanned pregnancy and STIs. HYSN began implementing MPC in 2007 with previous CDC funding and more than 5,417 students have participated in the program during CDC and OAH grant years. The following indicators, derived from post-test surveys administered to students who completed the program, lend support to MPC's effectiveness:

- 94% got the correct answers to questions on behaviors that will help prevent HIV, STDs, and pregnancy
- 92% report that they can say "no" to sex and unsafe sex
- 91% report positive attitudes/beliefs about condom use
- 88% report the ability to get or buy condoms and to put them on correctly
- 98% report that it is a good idea to use a condom every time a couple has sex
- 90% report intention to use condoms if they have sex

Reducing teen pregnancy rates is an important public health issues because three out of ten women in America experience pregnancy before age 20.[6] In 2010, there were 57 pregnancies per 1,000 teen girls (aged 15 to 19 years) nationally and 64 pregnancies per 1,000 teen girls in Hawai'i.[7] There are also ethnic disparities among Hawai'i teen pregnancy rates. In 2010 there were 31 pregnancies per 1,000 White teen girls, 40 pregnancies per 1,000 Asian teen girls, and 181 per 1,000 Native Hawaiian and Other Pacific Islander teen girls.[8] Additionally compared to sexually active youth nationwide, sexually active youth in Hawai'i are less likely to use condoms.[9]

While not all teen pregnancies result in birth, teen childbearing is costly. In 2010, taxpayers spent $9.4 billion on teen childbearing nationwide and $32 million in Hawai'i.[6,10] Another consequence of teen childbearing is that teen mothers are less likely to receive prenatal care, which can result in low-birth weight babies, birth defects, and infant mortality.[11] Moreover, teen mothers are less likely to graduate from high school or earn a GED. Research on teen fathers is limited, but according to one research brief, half of teen fathers have additional children by their early twenties, which can negatively affect education and financial stability.[12]

STIs (including chlamydia, gonorrhea, syphilis, herpes, and the Human Papilloma virus) are another costly public health issue.[13] The United States spends $16 billion annually on new STI cases.[14] Unfortunately, teens and young adults (ages 15-24) account for half of 20 million new STI cases nationally each year.[14] The Hawai'i State Department of Health (DOH) reports rising STI since 2000.[15] For example, Hawai'i has seen increased gonorrhea rates, from 47 per 100,000 in 2008 to 50 per 100,000 in 2011.[16] Similar to trends seen nationally, young people in Hawai'i bear a disparately higher burden of STI.[17] For example, 15-19 year olds account for 30% of local chlamydia cases.[18]

Arguably the most serious type of STI is the Human Immunodeficiency Virus (HIV), which causes Acquired Immune Deficiency Syndrome (AIDS). Although HIV rates have decreased since the 1980s,[19] it is important to remain vigilant about prevention because HIV can be asymptomatic for up to 10 years.[13] Moreover in 2010, youth (ages 13 – 24) accounted for 26% of new HIV cases in the United States and almost 60% of youth infected with HIV were unaware of their status.[19] Over the past decade, Hawai'i has been below the national average for HIV and AIDS incidence.[20] According to a 2013 DOH HIV/AIDS Surveillance Annual Report, from 1983 – 2012, 13 – 24 year olds account for 13% of all HIV and 4% of AIDS cases respectively.[21]

Youth in Foster Care

Foster care can be defined as "24-hour substitute care for children outside their own homes" and placements include locations such as non-relative foster care home, relative foster care home, group homes, and emergency shelters.[22] On September 30, 2013, there were 402,378 children in foster care nationwide, with over 50% being at least 11 years old.[23] According to the National KIDS COUNT, in 2012, Hawai'i had 1,079 children and youth (ages 0 -17) in foster care.[24]

Foster youth are more likely to be sexually active by age 13, have more sexual partners, experience sexual assault or rape, not use contraception, and experience teen pregnancy.[25] The Midwest Study, a longitudinal study conducted in Illinois, Iowa, and Wisconsin (n=536), found that compared to the overall population, by age 26, former foster youth are more likely to have an STI, with chlamydia being the most common STI for both women and men.[26] According to State of Hawai'i Department of Human Services (DHS), 266 girls gave birth to 269 babies while in foster care from 2005-2010 (Lee Dean, Assistant Administrator, email, January 2011).

Many complex factors contribute to increased risk of teen pregnancy and STI among foster youth. Three examples—instability, trauma, and emancipation—are described below.

Instability. In a recent article, Friedman questioned if foster youth receive adequate medical care and education regarding sexual health due to unstable living situations.[27] One study found from elementary through high school, 65% of former foster youth changed schools seven or more times.[28] Likewise, the average number of foster care placements is three.[27] Consequences of instability include gaps in medical care, missing out on school-based teen pregnancy and STI prevention programs, and unstable relationships with adults.[27,29] The absence of relationships with trusted adults can be especially detrimental as 80% of teens cite parents as a major influence in decisions about sex.[30] Moreover, changes in caregivers, social workers, and physicians, coupled with lack of sound policies, result in confusion about who is responsible for educating foster youth about sexual health.[27,29]

Trauma. There are many different definitions of trauma. One, provided by the Jim Casey Youth Opportunities Initiative, notes that "three common elements characterize all forms of trauma: the event was unexpected, the individual was unprepared, and there was nothing that the person could do to prevent the event from happening."[31] Foster youth experience high rates of trauma and events can occur both before and during foster care.[32] Examples of trauma foster youth may experience include direct forms of abuse and neglect, separation from family and friends, instability, and being exposed to domestic and community violence.[33]

Trauma has been linked to a variety of health conditions including depression, anxiety, substance abuse/dependence, self-harm, personality disorders, and Post-Traumatic Stress Disorder (PTSD).[31] Some types of trauma have also been linked to an increase in sexual risk behaviors. For example, men who have sex with men with a history of childhood sexual abuse are more likely to participate in sexual risk behavior and report being HIV positive.[34]

Emancipation. Around 11% of foster youth are aging out of foster care nationally and locally each year, which means 18 year olds are often left to navigate the complexities of adulthood alone.[35] Lack of family or state support during this crucial transition puts former foster youth at high risk for academic struggles, financial instability, homelessness, poor mental and physical health, involvement with the criminal justice system, and pregnancy.[35] In hopes of creating smoother transitions for foster youth, some states have extended care to age 21.[35] Hawai'i is one of these states and launched the Imua Kakou (http://www.imua21.org) program on July 1, 2014. While it is too early to ascertain if this change will impact teen pregnancy and STI locally, another study using the Midwest cohort found that 19 year olds who stayed in care past 18 were more likely to attend college, be financially stable, and for women, report fewer pregnancies.[36]

Presently no studies or reviews have been identified addressing foster youth specific teen pregnancy or STI prevention programs. Thus, the strategy needs to be informed by related evidence and best practices. Important examples include:

Trauma-Informed Practice. Due to high rates of trauma among foster youth, it is key for service providers to be educated about trauma. The Jim Casey Youth Opportunities Initiative states

"trauma-informed practice involves understanding the impact of trauma on young people's current functioning and recognizing the ways systems are capable of adding to young people's trauma. Trauma-informed practice provides supports and opportunities to promote healthy recovery and optimal brain development throughout adolescence and emerging adulthood."[31]

Inclusive Language. When working with foster youth, it is also important to use inclusive language to ensure youth do not feel stigmatized or overlooked. For example, research has found many LGBTQ youth are forced to leave home due to rejection and/or lack of safety, thus it is believed there is high prevalence of foster youth who identify as LGBTQ.[37] Examples of inclusive language include using partner instead of boyfriend or girlfriend and trusted adult instead of parent.[38]

Adapting MPC for Foster Youth

Starting in 2011, The Institute teams worked with an advisory committee, Dr. Loretta Sweet Jemmott (lead MPC developer), and directly with foster youth to adapt and pilot test the MPC program for foster youth.[3] The adapted curriculum is titled Making Proud Choices! – For Youth In Out-Of-Home Care (MPC+), consists of ten, 75-minute modules, and includes the following modifications to address the needs of foster youth:[3]
Facilitator Guide: Education about the foster care system and trauma
Module Content: Increased opportunities to discuss healthy vs. unhealthy relationships, acknowledging experiences of trauma and abuse, inclusive language (eg, LGBTQ, pregnant or teen parents, talk with a trusted adult about sexual health questions)

Implementing MPC+ in Hawai'i

While participation in The Institute did not include funding for MPC+ implementation, other valuable resources were provided. HYSN received five copies of the MPC+ curriculum, a two-day facilitator training on adaptations, and dedicated time and tools for core team members to solidify plans to implement and sustain the program (HYSN ED, personal communication, October 2014).

Additionally HYSN received approval from OAH to utilize TPPPP funds to implement MPC+ (eg, facilitator time and training). In order to obtain approval for use with OAH funds, HYSN submitted the curriculum for an extensive medical accuracy and adaptation review process conducted by OAH. The review generated multiple small changes that were incorporated into the final published version of MPC+. HYSN also worked with a University of Hawai'i at Manoa Master of Public Health practicum student to submit applications to two local foundations and was awarded $15,000 from the Atherton Family Foundation to further support MPC+.

MPC+ is currently being implemented at four, Independent Learning Programs (ILP); one on O'ahu, one on Kaua'i, one on Maui, and one on the Big Island. ILP are offered through community-based organizations and focus on providing foster youth (ages 12 – 18) and former foster youth (ages 18 – 21) with support and skills to transition into adulthood.[39] ILP services can be extended to age 26 if former foster youth are attending college or a full-time vocational program (HYSN ED, personal communication, October 2014).

ILP have reported that participant recruitment is a challenge due to the voluntary nature of the MPC+ program and some youth do not see the need for ILP services. Additionally, in rural areas such as Kaua'i, physical distance between foster youth and transportation challenges have been noted (HYSN stakeholder meeting, personal communication, April 2013). HYSN has been able to utilize funding from the Atherton Family Foundation to mitigate these barriers. For example, ILP staff can offer incentives (eg, gift cards) for participation and/or successfully recruiting participants. Likewise, session refreshments are provided, which serve as a secondary incentive and ensure participants are not hungry and better able to focus. Additionally, former foster youth who are currently stable in their life situation can be hired as recruiters/co-facilitators to help increase program creditability. Kaua'i recently hired the first group of former foster youth who are called "peer-mentors."

To enable access to foster youth on Kaua'i, staff decided to hold day camps during school breaks. MPC+ sessions are conducted between other activities such as arts and crafts and geocaching (using GPS coordinates to locate hidden objects).[40] An added benefit of the camp format is foster youth have been able to expand their network by meeting peers from the other parts of the island (HYSN stakeholder meeting, personal communication, April 2013). Finally, to help with transportation barriers, some Atherton Family Foundation funds can be used to fuel ILP vehicles or provide mileage reimbursement to caregivers to ensure foster youth attend MPC+ sessions.

As of December 2013, 43 foster youth in Hawai'i have participated in MPC+ (HYSN ED, personal communication, October 2014). Evaluation of MPC+ includes pre-and post-tests at 3, 6, and 12 months, facilitator fidelity logs, and monitoring of sessions by HYSN's Teen Pregnancy Prevention Director. Additionally, HYSN regularly convenes stakeholders, including MPC+ facilitators, to discuss quality improvement issues (HYSN stakeholders meeting, personal communication, April 2013). Based on post-tests collected so far, foster youth demonstrate gains that are comparable to other students who have received MPC training.

HYSN is aware that implementing MPC+ is not a stand-alone solution to the complexities of teen pregnancy and STI among foster youth.[41] Therefore HYSN is also dedicated to increasing community capacity to address pregnancy and STI prevention as well. For example, if MPC+ is encouraging foster youth to talk to trusted adults, then adults who work with foster youth need to be equipped to talk about sexual health. To address this need HYSN partnered with another program, It Takes an Ohana, to offer five trainings titled Helping Our Providers Educate (H.O.P.E.), which teaches adults how to be more approachable and comfortable when talking to foster youth about sexual health. Similar trainings have also been provided to caregivers and other stakeholders (HYSN ED, personal communication,

October 2014). Trainings like H.O.P.E. are important as one California study found many service providers do not speak with foster youth about relationships and sexual health and 64% of social workers feel they have not received adequate training in comprehensive sex education.[29]

One lesson HYSN learned after completing the 2-day MPC+ facilitator training is the importance of cross-training public health and social service professionals before moving forward with MPC+ curriculum training. In other words, social service providers need to be trained in Sex Ed 101 (eg, anatomy, puberty, contraception, and STI) and on the flip side, health educators need to have a basic understanding of Hawai'i's foster care system. The need for cross-training was recognized through participant feedback (HYSN ED, personal communication, October 2014). Constantine, et al, received similar feedback in their study as one social worker shared "it would be better support to our foster youth by first starting off with providing staff with the proper education and not just assuming that staff are aware of the issues."[29]

Conclusion

While some progress has been made in reducing the overall teen pregnancy and STI rates, there is more to be done, especially among high-risk groups such as foster youth.[7,42] Offering MPC+ through ILP is one way to help ensure foster youth in Hawai'i have greater access to education about their sexual health. HYSN's ability to strategically leverage resources in order to implement MPC+, as well as attention to building community capacity through relevant trainings, are also important steps in ensuring Hawai'i's foster youth are supported in an appropriate and healing manner by both public health and social service professionals.

Conflict of Interest

None of the authors identify a conflict of interest.

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Academic Pharmacy Strikes Hawai'i (Part 1)

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Abstract

The Daniel K. Inouye College of Pharmacy is the newest professional school to be established in the State of Hawai'i. The College is based at the University of Hawai'i at Hilo, but faculty and students are located and practice on every major island. The mission of the College is to serve the entire Pacific Region. Having reached a respectable level of maturity over the past few years, we are now pleased to announce a partnership that has been established with the Hawai'i Journal of Medicine & Public Health*. With Dr. Carolyn Ma serving as column editor and coordinator, our main objective is for faculty and affiliates of the College to provide communications of contemporary interest in the field of professional pharmacy. Since academic pharmacy is new to the State, this inaugural article (Part 1) describes a brief history of the profession leading up to the founding of the Daniel K. Inouye College of Pharmacy. An article describing the mission, vision, and infrastructure of the College, as well as some objectives and accomplishments will follow this inaugural column. The pharmacist is an integral member of the health care team with unique expertise in pharmaceutical care. The topics we present should be of broad interest to the readership of this journal but, additionally, any suggestions for specialized topics in our realm of expertise are welcome.*

Introduction

The *Hawai'i Journal of Medicine & Public Health* and the Daniel K. Inouye College of Pharmacy (DKICP), University of Hawai'i at Hilo, have established a partnership that will enable faculty and affiliates of the College to submit articles describing contemporary issues of pharmacy education and practice. We hope these articles will be of broad interest to the readership of the Journal. We welcome any suggestions for topics falling within the realm of our expertise.

The first class of student pharmacists at the DKICP was accepted in 2007; full professional accreditation was earned in 2011. Realizing that academic pharmacy is relatively new for the State of Hawai'i, this inaugural article will focus on the practice of pharmacy from a historical perspective. Part 1 leads us to the point of creating the DKICP, which is the only pharmacy program in the entire Pacific Region. In Part 2 of the inaugural article, various aspects of the College itself will be described, and we will provide a glimpse of articles to be submitted for ensuing issues.

The Discipline of Pharmacy: A Historical Perspective

Some of the first signs of pharmacy as a profession can be traced to Baghdad *ca*. 750 AD. The collective Arab civilization is credited with educating students of pharmacy, establishing hospital pharmacies, and creating accountability though governmental inspections. In Palermo, *ca*. 1240 AD, under the rule of King Frederick II, the disciplines of medicine and pharmacy were separated. Pharmacy became an independent branch of public welfare service with the implementation of various regulations: The number of pharmacies was limited; fixed prices of remedies were set; pharmaceutical practice required official supervision; bribes were prohibited; use of a prescribed formulary (fixed formula for a certain drug) was made compulsory. Over time, similar standards and responsibilities were implemented in other urban centers throughout Italy, Spain, and France.

Another important milestone was the establishment of the first pharmacopeia (Florence, 1498). In effect, standards were set for the identification and preparation of drugs. The public was provided with greater protection from adulterated drugs, and prescribers as well as consumers could have greater assurance of uniformity and quality of products. Over 100 years later, in 1607, the first English Apothecaries Guild was established in London. Under the rule of King James I, the special skill and knowledge of the apothecary was recognized. Apprenticeships, examinations, and inspections were established; the special skill of preparing drugs was entrusted to the apothecary, rather than the grocer, spicer, doctor, etc.

The profession continued to grow throughout Europe over the next century. Official pharmacopoeias were produced in major European cities, organized activities and a periodical literature were implemented, prolonged apprenticeships were required, as well as examinations to assess competency. The Guilds were eventually replaced by professional societies. Even today, the practice of pharmacy in Europe is more tightly regulated than in the United States. For example, on the European continent, the number of pharmacies is limited, there are no 24-hour stores, ownership is limited, and there are no large chains of community pharmacies.

Pharmacy in the United States

During the colonial period of the United States, pharmacy was basically practiced by anyone who wanted to set up a shop. The success of the business was strictly determined by the market. Patent medicines were a major source of profit. Although a few well-trained genuine European apothecaries set up professional shops in cities, in general, the field was characterized by pandemonium. There was no regulation of the "profession." No formal educational requirements were in place. The number of drugstores was growing, wholesalers were dispensing to the public, and physician dispensaries were gradually phasing out. As a result, there was even greater dependence on ill-trained druggists and self-declared apothecaries for medication compounding.

One of the first signs of progress was documented in 1816. In the State of Louisiana, one apothecary and four physicians and surgeons were entrusted with the examination of other health professionals. L.J. Dufilho became the first licensed pharmacy professional in the state. The sale of poisons was restricted and the sale of deteriorated drugs was banned. Shortly thereafter, in 1818, an examination for licensure was instituted in South Carolina. Candidates were tested on the definition of chemistry and pharmacy, and preparations involving substances such as mercurous chloride, tartar emetic, ipecac preparations, laudanum, arsenic, and plasters.

In essence, no controls were in place for the practice of pharmacy and early attempts at legislation failed due to the general attitude of laissez faire. Both educated and self-declared uneducated pharmacists were opposed to regulation. Merchants, wholesalers, and apothecaries drifted in and out of professions at will. Some drugs were adulterated, deteriorated, and dangerous. Outcomes were unreliable, differed from store-to-store, and it was generally not clear what was being dispensed. With pharmacies cutting corners, providing unreliable drugs with unreliable outcomes, the public was not being well-served.

As a result, in 1820, the dean of medicine at the University of Pennsylvania published a report in a local newspaper describing the poor quality of drugs. Physicians had just organized (nationally) the first pharmacopeia (USP), without any input from pharmacy. Following a university board action, the medical school gained authority to award a Master of Pharmacy degree to any student who completed the required number of lectures. It was further agreed they would award the degree to pharmacists if they determined the pharmacist met the standard. As might be expected, this led to some acrimony, and four days later, pharmacists created a committee and it was decided to start a college to regulate, educate, and control some of the problems in the profession.

Philadelphia College of Pharmacy

In 1821 the first college of pharmacy was established in the United States, the Philadelphia College of Pharmacy (PCP). Although this was a major step in the history of pharmacy education, PCP was not really an educational institution by modern day standards. It was still believed that pharmacy was an art that could be learned through the apprenticeship system. However, some important steps were taken for regulating the practice of pharmacy. A formulary was published, sale of adulterated drugs led to being expelled, a dispute resolution committee was created, and guidance was provided, especially for producing patent medicines, a very large business at the time.

Largely driven by pressure from the medical profession, other early colleges were founded such as the Massachusetts College of Pharmacy (1823), the College of Pharmacy of the City of New York (1829), and the Maryland College of Pharmacy (1840). In addition, the New York Pharmaceutical Literary Society (1851) was founded by extremely well-qualified German pharmacists to train and examine apprentices.

The Father of Pharmacy and the American Pharmacists Association

As is often the case, adversity is required for the implementation of change. In the mid-1800s, a pharmacist discovered a container labeled calcium carbonate was actually calcium sulfate (pharmacists were trained to test chemicals and drugs). This was reported to the NY College of Pharmacy (later to become part of Columbia University), and it was discovered other contaminated drugs were being imported from England and passing port inspection. Port Inspectors were political appointees who were not educated to detect contaminated drugs. Since physicians owned stores and practices of pharmacy, the NY College of Medicine got involved with the issue. The American Medical Association (AMA) proposed standards for the ports, but since pharmacists were trained to test drugs, the problem was referred to the NY College of Pharmacy. In turn, other colleges of pharmacy were invited to participate in resolving the problem. As a result, a letter was received from William Procter, a professor at PCP, who wanted to broaden the scope of the meeting and form a national pharmacy organization.

Procter, later dubbed as the Father of Pharmacy, owned a pharmacy in Philadelphia. Moreover, he was an administrator and teacher at PCP, published over 550 research papers, wrote the first pharmacy textbook, and served as editor of the first pharmacy journal in the United States, the *American Journal of Pharmacy*. He felt strongly that only graduates of a pharmacy school should practice in the profession. Receiving a diploma involved three evening lectures per week, with no laboratories, for two 6-month sessions. Botany was emphasized. But unlike European practice, he supported a free-market system, where competition would regulate the number of practicing pharmacists, not the government. With a growing population, he did not support limiting the number of pharmacies. He believed European immigrants had and would continue to elevate the standards of the profession, and competition and reputation would be self-limiting. Importantly, however, according to Procter, everyone involved in the practice of pharmacy would be accountable to the law and regulation.

As a result of Procter's vision, 20 pharmacists founded the American Pharmaceutical Association (now named the American Pharmacists Association, APhA) in 1852, and he

became the corresponding secretary (now called CEO). Today the organization represents more than 62,000 practicing pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in advancing the profession. In the beginning, the elected officers wrote a constitution mandating members to abide by a code of ethics. This eliminated the promulgation of sham medicines, promoted pharmacy education in science and practice, provided regulations to prevent adulteration and contaminated products, regulated apprenticeships, limited drug sales to qualified pharmacists, and provided punishment for improper conduct.

The Evolution of Pharmacy Education and Regulation

During the period of 1870-1900, many more colleges of pharmacy were created, several associated with universities, in part due to the Morrill Land-Grant Act of 1862. In addition to the tenets established by the APhA, states began to introduce legislation to protect community pharmacists and the health of the public. Nonetheless, training in the profession was still integrally linked to the apprenticeship. But again, change was inspired by one individual, Albert Prescott, a physician-chemist, who was Dean of Pharmacy at the University of Michigan (1876). The Michigan program ignored the apprenticeship requirement of all other schools, and opened admission to fulltime day students, rather than as an add-on to employment. The approach was shunned by APhA and opposed by the leading program of the time, PCP. In due course, however, the approach pioneered by Prescott was adopted by other programs, and he became president of the APhA in 1900.

Concurrently, starting in 1870, John Maisch, APhA committee chairman, was charged with creating a model state law to provide some guidance. The goal was to define practice, examinations, and established a Board of Pharmacy in every state. With opposition from various factions such as "saddlebag" doctors and "prescribing" pharmacists, Maisch mailed the "model" law to various state governors, but without APhA endorsement. The situation changed by 1900, when the proposal was revised and sent openly to each state. Finally, about 25 years after the start, approximately 35 states adopted laws specifically related to pharmacy and the sale of adulterated drugs and poisons. If adulterated drugs were knowingly dispensed, fines and imprisonment could result.

The National Association of Boards of Pharmacy (NABP), an organization that currently manages standardized tests that are part of the professional licensing process (such as the Multistate Pharmacy Jurisprudence Examination and NAPLEX), was formed by 16 states at an APhA meeting in 1904. Creation of the NABP was critical for promoting cooperation and uniformity between various states, enhancing reciprocity, resolving conflicts between state standards, and promoting uniformity of licensing requirements. NABP member boards now include all states. The Hawai'i State Board of Pharmacy, serves mainly to protect consumers against unfair practices. The three main areas of responsibility include legislative, adjudicatory, and executive decisions. The Board reviews statutes and amendments on upcoming senate and house bills, holds public hearings, and serves as resource for legislators. Duties related to adjudicatory review involve review and approval of settlement agreements negotiated by the Regulated Industries Complaints Office (RICO) to discipline licensed pharmacists who fail to follow the legal and professional standards of practice. Lastly, executive decisions assure that appropriate licensing of persons who seek to enter the profession meet the legal competency standards as well as permitting of pharmacies within state and out-of-state.[1]

Thus, as described above, there has been a continuous progression in the profession over the millennia. Over the last century educational programs have evolved from the two-year PhG (Graduate in Pharmacy) (1907), to the three-year PhC (Pharmaceutical Chemist) (1925), to the four-year BS in Pharmacy (1932), to the five-year BS in Pharmacy (1960), and finally, to the six-year PharmD (Doctor of Pharmacy). As mandated by current accreditation standards, the only degree leading to professional licensure is the PharmD.

According to the Accreditation Council for Pharmacy Education (ACPE),[2] there are currently 133 pharmacy programs with accreditation status. However, prior to 2004, no program had ever been launched in the State of Hawai'i.

The Fiasco of Private Pharmacy Education in Hawai'i[3-5]

As evidenced by the rapid proliferation of pharmacy programs throughout the United States,[6] over the past 20 years or so, the number of students interested in pursuing the profession of pharmacy has exceeded the number of places available in established programs. With no pharmacy education whatsoever in the State of Hawai'i, this led to the creation of a bogus program in Kapolei given the name Hawai'i College of Pharmacy. In the fall of 2004, the program opened with an inaugural class of 240 students. Approval had not been obtained from the ACPE. Although an application was retrospectively submitted, it was denied, presumably due to poor planning and infrastructure, as well as excessive class size. Nonetheless, the founders of the program, Denise Criswell and David Monroe, wrongfully collected nearly $7 million in student tuition. In the spring of 2005, the dean of the program (H.A. Hasan) resigned and some faculty members were fired. By summer, it was clear a successful application could not be submitted to the ACPE, and the dean of the pharmacy program at the University of South Nevada disavowed being associated with the program in Hawai'i, which was run through Nevada-based Pacific Educational Services. In addition to pharmacy, this organization had also boasted plans for opening dental and nursing programs in Hawai'i.

The end of the fiasco became clear in July 2005 when the enrolled students were informed that only the top 100 could go onto the second year of the program while the others would need to repeat the first year and, of course, continue paying tuition. By this time, the Hawai'i Department of Commerce & Consumer Affairs, Office of Consumer Protection had assigned

workers to investigate the program, leading to freezing assets for unfair and deceptive business practices. Within a month, the Hawai'i College of Pharmacy used this as a reason for closing the program with roughly $6 million from student tuition having supposedly "disappeared."

A Time for Excellence in Hawai'i's Pharmacy Education

Surprisingly, the defunct Hawai'i College of Pharmacy had little or no bearing on the building of the University of Hawai'i College of Pharmacy. Discussions and planning with the profession's state leaders were ongoing since the late 1990s. Receiving pre-candidate status from the ACPE is absolutely essential prior to enrolling a class of student pharmacists, but one of the first obligatory steps is the appointment of a qualified dean. A search commenced in 2005. In essence, the Hawai'i College of Pharmacy did everything wrong. For anyone with experience in academic pharmacy, it was perfectly clear the program had absolutely no chance for success.

When the Founding Dean of the UH College of Pharmacy was appointed in 2006, over 25 years of experience gained at Top-10 pharmacy programs came to the table. Ambitious goals were set to create a college that not only would meet all of the standards for full professional accreditation, but to strive to achieve a position among the Top-25 programs in the country. Although the program has yet to reach its tenth anniversary, progress has been strong, many milestones have been crossed, and the unit has become an integral part of the community and University as a whole.[7]

Conflict of Interest

None of the authors identify a conflict of interest.

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THE WEATHERVANE

RUSSELL T. STODD MD; CONTRIBUTING EDITOR

INSPECT TWICE. CLOSE ONCE.

Obstetrics continues to be the most vulnerable medical specialty. A jury awarded damages of $4.5 million for malpractice in the case of a botched caesarian section on a healthy 31-year-old woman. During the procedure the surgeon unknowingly lacerated the small bowel, and closed the primary incision without checking the upper abdomen. The patient continued to have severe pain and nausea during the three-day post-op period. No additional tests or blood work were done. The patient was discharged without being seen again. Because her symptoms persisted, her husband brought her back to the hospital the following day. She was immediately placed in the intensive care unit with a diagnosis of abdominal sepsis and renal failure. Her condition rapidly deteriorated and she was transferred to Wake Forest Baptist Medical Center where she died the same evening. The hospital settled their portion of the malpractice complaint, but the doctor proceeded to trial. The jury recognized medical negligence and awarded $4.5 million to the woman's estate.

GASTRO-INTESTINAL INDULGENCE QUANTIFIED AT THE TABLE.

Provisions in the 2010 Affordable Care Act will require chain restaurants of 20 or more US locations to display calorie information on their menus, including drive-thru menu boards. The Food and Drug Administration (FDA) has delayed final regulations, but they are expected before the end of 2014. Several states have already enacted calorie menu labeling laws, with New York City leading the way in 2008. Research shows labeling can help encourage people to consume fewer calories. Results of NYC studies were inconsistent, but consumers did report greater recognition and self-reported use of calorie information. Across the country a representative survey found that 81% of respondents supported menu labeling in chain restaurants. Look at all the calories I am enjoying in my grease-burger and pecan pie a la mode. Next week I shall cut down.

DOES OBAMACARE COVER FOOT-IN-MOUTH DISEASE?

Jonathan Gruber, an economics professor from Massachusetts Institute of Technology, made a dozen or more trips to the White House in 2010 as the Democratic Party fashioned the Affordable Care Act. At least one of the Professor's visits included President Obama, and others were with senior advisors who composed the legislation. For his contributions he received about $400,000 from the Department of Health and Human Services. The White House is trying to distance itself from the professor following the recent release of a video that surfaced. The professor said the law passed because of the "huge political advantage" of the legislation's lack of transparency. Moreover he referred to the "stupidity of the American voter." Now he says, "I was speaking off the cuff and basically spoke inappropriately and I regret having made those comments." At a news conference the president called the professor merely an adviser who never worked on the staff. He disavowed the description of voters and the remarks about the actual process. Are medical people in the Boston area born arrogant, or is it taught?

ANTI GMO (OMG) – A TRAVELING CIRCUS OF ACTIVISTS.

Voters on Maui fell victim to the anti-GMO referendum that scored 51% to 49% in favor of a ban. This will prove to be an ongoing legal struggle with nobody better off save some attorneys and consultants. In the 20 years GMOs have been commercialized not a single person has become sick from eating food produced by genetic engineering. By 2013, 169 million acres of U.S. farmland were planted with genetically engineered corn, soybeans and cotton. Voters in Colorado and Oregon rejected anti-GMO efforts. The impressionable citizens of Portlandia couldn't carry the measure because other counties all voted no. Colorado was even deeper in opposition voting 66% to 34% against. Busybodies with the same mentality as opposing immunization and pasteurization will take their organic roadshow elsewhere. One can hope they will meet with voters who know better.

EBOLA FAITH HEALERS ARE ALWAYS SELF LIMITED.

When Surbeh Alpha, a 25-year-old Red Cross volunteer tried to advise people in Kailahun, Sierra Leone, to avoid the Ebola sick and the dead, he was approached by the village healer. She confronted him, "You are just telling lies." She had been treating patients from Guinea by applying mud packs to feverish bodies. She soon was dead, as is the American surgeon who contracted Ebola in Sierra Leone. The episode became a microcosm of what can go wrong in controlling the virus. Healers in parts of Africa are often more highly regarded than those who come to promote unfamiliar forms of medical care. Locals blame the rising death toll on witchcraft and organ harvesting, then spread the risk by secretly cleaning and burying the bodies at night. Deaths in Kailahun are decreasing now as a result of education, but Ebola is spreading elsewhere in Sierra Leone.

ARE BODIES FLOTSAM OR JETSAM?

Sailing events for the summer Olympics 2016 will be held in Rio De Janeiro's Guanabara Bay. Several red flags have gone up pointing out that the squalid bay is grossly contaminated with car tires, dog carcasses, floating mattresses, and free flowing raw sewage. A competitive Brazilian sailor said he has personally seen four human bodies in the bay. Cleaning up is underway with three boats working and several dozen planned. By comparison, Beijing dispatched 1,000 boats just to clean up the algae for the sailing competition in 2008.

YES, SHE IS BOOTIFUL!

In keeping with the constant desire to look more appealing (?) women are turning to booty modification. Feel Foxy, maker of padded panties, says 2014 has been its best year since launching 10 years ago. Booty Pop which hawks $22 foam padded panties on its website, said sales are up 47% in the past 6 months. The Brazilian butt lift, a procedure where fat is sucked from love handles and the belly wall then inserted in the buttocks, is increasing in popularity in the United States. Businesses that specialize in butts say pop culture has had a direct impact on their bottom line. Apparently the Kardashian effect prevails. Shake your booty, Kim.

A REVEALING STORY.

Police in Ottawa, Ontario, arrested a 62-year-old man who had been indecently exposing himself in Mooney's Bay Park. Sergeant Iain Pidcock detained the offender, Donald Popadick. Reporters could find only three Canadian households with that name which is believed to be derived from Serbian Popadic. Whatever. It all redounds to a crotchety story.

ADDENDA

- First president to hold a news conference was Woodrow Wilson on March 15, 1913.
- Presidents Lincoln, Wilson, Coolidge and Reagan all played the harmonica.
- In 1339 B.C. Florence, Italy was the first city to pave all its streets.
- After age 40, people should be banned from using the words, girlfriend or boyfriend in reference to someone they're sleeping with. It sounds sort of creepy.
- There are now robots that simulate dance movements. They are called white people.
- A man in Vienna received the first tongue transplant. If it is not successful he is going to become a Bob Dylan impersonator.

ALOHA AND KEEP THE FAITH rts

(Editorial comment is strictly that of the writer.)

Biostatistical Guideline for HJM&PH

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Guidelines for Publication of HJM&PH Supplements

The following are general guidelines for publication of supplements:

1. Organizations, university divisions, and other research units considering publication of a sponsored supplement should consult with the editorial staff of HJMPH to make certain the educational objectives and value of the supplement are optimized during the planning process. It is important that the sponsoring editor is aware of all steps to its publication. Please contact Drs. Kalani Brady or Michael Meagher for further information.

2. Supplements must have educational value, be useful to HJMPH readership, and contain data not previously published to be considered for publication.

3. Supplements must have a sponsoring editor who will be involved in every step of the development, editing, and marketing of the publication since HJMPH staff will only be reviewing final proofs.

4. Supplements should treat broad topics in an impartial, unbiased manner. Please prefer specific classes of drugs, rather than products, unless there are compelling reasons or unique properties of the drug (product) that justifies its treatment.

5. The authors are solely responsible for the content of their manuscripts and the opinions expressed. They are also responsible for the replicability, precision, and integrity of the data and may be asked to sign a statement to that effect prior to publication. All authors are required to disclose any primary financial relationship with a company that has a direct fiscal or financial interest in the subject matter of products discussed in submitted manuscripts, or with a company that produces a competing product. The sponsoring editor must ensure that each article submitted incorporates a disclosure statement from the authors within the body of the text. For more information, please refer to the Disclosure Statement within "Instructions to Authors" on the journal website.

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8. The sponsoring editor may decide to include advertisements in the supplement in order to defray costs. Please consult with the HJMPH advertising representative Michael Roth at 808-595-4124 or email rothcomm@lava.net for assistance.

9. Supplement issues are posted online for full-text (PDF) retrieval on the HJMPH website at www.hjmph.org. An announcement of its availability will be made through our normal email distribution list. Full-text will also be available on PubMed Central.

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11. Timing of a supplement issue publication will be formalized once all required materials have been submitted to the production manager and payment made.

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