Hawai‘i Journal of Health & Social Welfare

A Journal of Pacific Health & Social Welfare

April 2021, Volume 80, No. 4, ISSN 2641-5216

HAWAI‘I JOURNAL WATCH
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Aim:
The aim of the Hawai‘i Journal of Health & Social Welfare is to advance knowledge about health and social welfare, with a focus on the diverse peoples and unique environments of Hawai‘i and the Pacific region.

History:
In 1941, a journal then called The Hawai‘i Medical Journal was founded by the Hawai‘i Medical Association (HMA). The HMA had been incorporated in 1856 under the Hawaiian monarchy. In 2008, a separate journal called the Hawai‘i Journal of Public Health was established by a collaborative effort between the Hawai‘i State Department of Health and the University of Hawai‘i at Mānoa Office of Public Health Studies. In 2012, these two journals merged to form the Hawai‘i Journal of Medicine & Public Health, and this journal continued to be supported by the Hawai‘i State Department of Health and the John A. Burns School of Medicine.

In 2018, the number of partners providing financial backing for the journal expanded, and to reflect this expansion of the name of the journal was changed in 2019 to the Hawai‘i Journal of Health & Social Welfare. The lead academic partners are now the six units of the UH College of Health Sciences and Social Welfare, including the John A. Burns School of Medicine, UH Public Health, the Thompson School of Social Work & Public Health, the School of Nursing and Dental Hygiene, the UH Cancer Center, and the Daniel K. Inouye College of Pharmacy. Other partners are the Hawai‘i State Department of Health and the UH Office of the Vice Chancellor for Research. The journal is fiscally managed by University Health Partners of Hawai‘i.

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HAWA'I JOURNAL WATCH
Karen Rowan MS

Highlights of recent research from the University of Hawai‘i and the Hawai‘i State Department of Health

SOCIAL NETWORKS ARE IMPORTANT TO HAWA‘I HOSPITAL PATIENTS

Interventions for Native Hawaiians and Other Pacific Islanders (NHOPI) with chronic health conditions should include their family members or close friends. Researchers led by Tetine Sentell PhD, of the Office of Public Health Studies, interviewed 22 people, most NHOPI, admitted to The Queen’s Medical Center for a potentially preventable hospitalization, meaning the condition could be managed with access to high-quality primary care. The interview asked about each patient’s health literacy and social network. Results showed many participants had low health literacy and at least 1 person in their social network who helped them with their health. Many, but not all, participants wanted the members of their social networks to be engaged in interventions aimed at improving their chronic condition management. Culturally relevant healthcare should incorporate patient preferences for including network members in interventions.


NEW COMPOUNDS IDENTIFIED FROM FUNGI GROWING IN HAWA‘I ISLAND CORAL

Ten new compounds were isolated from a fungus called Xylaria sp. FM1005, which grows symbiotically in leather coral in the offshore region of Hawai‘i Island. Researchers led by KH Ahammad Uz Zaman, a PhD candidate with the Daniel K. Inouye College of Pharmacy analyzed the fungi using nuclear magnetic resonance spectroscopy and other methods. Results revealed 17 compounds, including 10 that were new to science. In in vitro studies, 2 of the compounds, which were structurally similar to the antiplatelet drug tirofiban, prevented the aggregation of rodent platelets by inhibiting the binding of fibrinogen to other proteins. Tests also showed the compounds were not toxic to human cells. The results suggest these compounds show potential for mediating the blood clotting process. More work is needed to identify biologically active compounds in Hawai‘i’s unique marine ecosystem.


LEADERSHIP CAN PROTECT AGAINST TURNOVER AMONG SOCIAL WORKERS

Turnover is common among frontline social workers, but those who are committed to remaining with their agencies also report strong agency leadership. Researchers including Francie Julien-Chinn PhD, of the Thompson School of Social Work & Public Health, surveyed 119 frontline child welfare staff members and asked about their job satisfaction, intent to stay, coping strategies, peer support, leadership, and other factors. Results showed 39% of respondents said they were committed to staying at the agency. Commitment to stay was associated with reporting that the agency leadership ensures that high-quality programs and services are delivered, and that leaders clearly communicate the links between the agency’s vision and the work goals. The findings suggest that the actions of agency leadership can protect against the high turnover of frontline social workers.


BODY FAT DISTRIBUTION PATTERNS LINKED TO TYPE 2 DIABETES IN JAPANESE INDIVIDUALS

The rate of type 2 diabetes in individuals of Japanese and other Asian ancestry may be partly driven by the pattern of fat accumulation in the body. Researchers led by Gertraud Maskarinec MD, PhD, of the University of Hawai‘i Cancer Center, looked at data from 1746 participants in the Adiposity Phenotype Study, a subset of the Multiethnic Cohort Study. Participants were of Japanese, white, Latino, African American, or Native Hawaiian ancestry. Results showed that the ratio of visceral adipose tissue (VAT) to subcutaneous adipose tissue (SAT) was highest in those with type 2 diabetes (T2D) across all ethnic groups. As the VAT/SAT ratio increased, rates of T2D rose, with each additional standard deviation of the VAT/SAT ratio associated with double the odds of T2D for the entire study population. However, among Native Hawaiians and Japanese Americans, the odds of T2D increased 2.5 times and 4 times, respectively, with each increase of 1 SD of the VAT/SAT ratio. The findings suggest that this body fat distribution pattern may drive the development of T2D in Japanese individuals to a greater degree than in other ethnic groups.


A COMMUNITY-CENTERED INTERVENTION FOR PASIFIKI PEOPLES IN NEW ZEALAND

Community-centered interventions to prevent diabetes should be culturally tailored to meet the needs of the community. Researchers including Joseph Keawe‘aimoku Kaholokula PhD, of the John A. Burns School of Medicine, conducted a program evaluation by interviewing 21 participants in a program aimed at preventing diabetes in adults of Pasifika ethnicity in New Zealand. Results showed that most participants felt the program’s venue was accessible because it was community-based and familiar to them. Participants were motivated to take part in the program for the sake of community fellowship, and they found the physical activity portion of the program enjoyable because it was done as a group. Work-life balance, including the need to find child care, was a common barrier to participating in the program. The findings suggest that culturally relevant intervention programs should consider the values, beliefs, practices, and realities of the communities they serve.

Abstract

Pacific Islanders represent a minority population with a disproportionate amount of risk factors for cholangiocarcinoma, including chronic liver disease, obesity, and diabetes mellitus, compared to other populations in the United States, but are poorly studied independently from Asians. Thus, this study aimed to characterize cholangiocarcinoma in a group of Pacific Islanders compared to Asians. This study retrospectively assessed a population of 40 Pacific Islander and 215 Asian cholangiocarcinoma patients from Hawaiʻi’s primary liver transplant center from 1993 to 2020. Overall, Pacific Islanders were younger at diagnosis and had a higher prevalence of obesity compared to Asians. There were no differences in hepatitis B or C infection, tumor markers, extrahepatic cholangiocarcinoma to intrahepatic cholangiocarcinoma ratio, or surgical resection. When divided into extrahepatic and intrahepatic cholangiocarcinoma, the extrahepatic cholangiocarcinoma cohort reflected the Pacific Islanders’ younger age, higher proportion of obesity, and larger tumor size. The Pacific Islanders in the intrahepatic cholangiocarcinoma cohort had a greater prevalence of obesity and significantly more multifocal tumor presentation compared to Asians. Ultimately, Pacific Islanders presented younger, with higher body mass index, and with more advanced cholangiocarcinoma when divided into extrahepatic and intrahepatic types, but experienced no differences in receipt of surgical resection or 5-year survival compared to Asians. Awareness of cholangiocarcinoma occurrence in younger Pacific Islanders and assessment of premalignant biliary or hepatic pathologies may aid in the earlier identification and intervention of cholangiocarcinoma in Pacific Islanders.

Keywords

cholangiocarcinoma, healthcare disparities, Pacific Islanders, survival

Acronyms and Abbreviations

AFP = alpha fetoprotein
AJCC = American Joint Committee on Cancer
ALT = alanine aminotransferase
API = Asian Pacific Islander
AST = aspartate aminotransferase
BMI = body mass index
CA = Carbohydrate Antigen
CCA = cholangiocarcinoma
CEA = Carcinoembryonic Acid
CI = confidence interval
ECC = extrahepatic cholangiocarcinoma
HBV/HCV = hepatitis B/hepatitis C
HCC = hepatocellular carcinoma
ICC = intrahepatic cholangiocarcinoma
INR = international normalized ratio
PI = Pacific Islander
PT = prothrombin time
SEER = Surveillance, Epidemiology, and End Results
US = United States

Introduction

Cholangiocarcinoma (CCA) is a heterogeneous group of biliary cancers categorized into intrahepatic (ICC) and extrahepatic (ECC) types. Most patients with CCA face a poor prognosis, presenting at advanced stages and with a median survival that is less than 2 years after diagnosis.1 The incidence of CCA is highest in Asian countries such as South Korea, Thailand, and Japan, but is increasing in the United States (US).2,3 Within the US, Asian/Pacific Islanders (APIs) had the highest incidence for ICC, ECC, and hepatocellular carcinoma (HCC) from 2000 to 2009.4 Pacific Islanders (PIs) comprise 1.5 million or 0.4% of the US population and are represented in majority by Native Hawaiians, Samoans, and Guamanians.5 PIs, especially Samoans, have as much as an 8-fold increase in incidence and more than twice the mortality of liver and intrahepatic bile duct cancer compared to Non-Hispanic whites.5

Risk factors for CCA include male sex, older age, cirrhosis, viral hepatitis, diabetes mellitus, obesity, smoking, cholelithiasis cysts, hepatolithiasis, primary sclerosing cholangitis, and other chronic liver diseases, but there may be geographic variations in these risk factors.6-9 The higher incidence in Asia is attributed to widespread liver fluke infections, while in western countries, metabolic conditions including obesity and diabetes mellitus have been associated with a 50% increase in risk for ICC.10,11

With higher reported rates of smoking, alcohol consumption, diabetes mellitus, liver disease, and obesity compared to other racial groups, PIs bear many of the described risk factors for CCA development.5 While PIs have been previously identified as a high-risk group for developing HCC, receiving less cancer screening and having the lowest 5-year survival rates, little is known about CCA in PIs as a separate population from Asians.12,13 The high risk for CCA in PIs, in the context of APIs being the racial group with the highest incidence for CCA and HCC in the US, suggests the significance of identifying disparities within this typically aggregated population. Analyzing PIs and Asians as separate populations may advance our understanding of CCA presentations in PIs to inform physicians how to approach diagnosis and treatment in this understudied group. This study aims to characterize the presentation, treatment, and outcome of CCA in PIs compared to Asians in Hawaiʻi.
Methods

This study is a retrospective review of a prospectively collected database of 255 cases of CCA between August 1993 and February 2020. This study was approved by the Institutional Review Board at the University of Hawai‘i.

All patients were referred to a group of surgeons who are associated with Hawai‘i’s only liver transplant program and a dedicated liver center. From 1993–2011, these were located at St. Francis Medical Center, but from 2012 to present, these have been relocated to Queen’s Medical Center; each was the only tertiary referral centers (during the specific time frame) for liver and biliary disease for the State of Hawai‘i as well as for the US territories, including American Samoa, Guam, the Federated States of Micronesia, and the Northern Mariana Islands. Patients may include foreign nationals from Japan, Korea, China, and the Philippines who may have traveled to Hawai‘i to receive medical care.

The data collected included demographic information of age, sex, ethnicity, and birthplace. Ethnicity was determined by patient self-report at the initial consultation. Patients were classified as “PI” if they were Hawaiian, Chamorro Samoan, Tongan, Micronesian, or Marshallese. Patients of mixed race (more than 1 ethnicity) were deemed “PI” if they were at least 50% of one of these PII ethnicities. Patients who were Filipino were considered to be “Asian” along with those who were Japanese, Chinese, Korean, or Southeast Asian.

Medical history data obtained included the presence of diabetes mellitus, hypertension, hyperlipidemia, inflammatory bowel disease, primary sclerosing cholangitis, and pancreatitis. Patients’ histories of smoking or significant alcohol use (defined as 2 or more alcoholic beverages for 10 years) were noted. At the initial visit, height and weight were determined to calculate body mass index (BMI). Patients with BMI of 30 kg/m² or higher were categorized as “obese.”

Laboratory data were recorded at initial diagnosis, which included bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, albumin, prothrombin time (PT) with international normalized ratio (INR), creatinine, and platelet count. Hepatitis B (HBV) and C (HCV) serologies and tumor markers of alpha fetoprotein (AFP), Carcinoembryonic Acid (CEA), and Carbohydrate Antigen (CA) 19-9 were collected. “Elevated AFP” was defined as greater than or equal to 10 ng/mL. “Elevated CEA” was defined as greater than or equal to 5 units/mL. “Elevated CA 19-9” was included as greater than 37 units/mL and also defined a category as “CA 19-9 above 1000 units/mL”. Tumor characteristics included tumor type: ICC vs ECC and tumor location; proximal, middle, or distal for those patients with ECC. Tumor size, number, and American Joint Committee on Cancer (AJCC) stage were noted when available. Finally, whether or not the patient underwent surgical intervention was noted. Surgical resections were defined as a liver resection with or without bile duct resection and portal node dissection for patients with ICC. For ECC patients, surgical resections included bile duct resections and liver resections for proximal and middle lesions and pancreaticoduodenectomy for distal lesions.

Additional clinical and pathologic data, as well as vital status and survival information were obtained through linkage with the Hawai‘i Tumor Registry, the state cancer registry of the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program. Survival duration was based on the period from the date of cancer diagnosis to the date of death (all causes) or date of last follow-up.

Statistics

Patients were divided into 2 groups: PIs vs Asians. Categorical variables including sex, birthplace, BMI, smoking and alcohol history, hypertension, diabetes mellitus, hyperlipidemia, HBV and HCV infection, inflammatory bowel disease, and other comorbidities in this cohort included obesity (22.5%), smoking (54.8%), alcohol use (31.0%), HBV (14.8%), HCV (6.7%), diabetes mellitus (25.6%), hypertension (55.2%), and hyperlipidemia (49.0%). In terms of CCA type, 46.3% of the patients had ICC, and 53.7% had ECC.

Survival analysis was performed with R version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria) as well as EZR version 1.36 (Division of Hematology, Saitama Medical Center, Jichi Medical University, Japan). The Kaplan-Meier survival curve was used to compare median survival between PIs and Asians for the entire cohort. A subgroup analysis was performed for ICC and ECC.

Results

In the entire cohort of 255 patients with CCA, 40 patients were PI, and 215 were Asian. The mean age of the cohort was 66.8 years, 73.7% were older than 60 years, and 58.0% were men. Overall, the comorbidities in this cohort included obesity (22.5%), smoking (54.8%), alcohol use (31.0%), HBV (14.8%), HCV (6.7%), diabetes mellitus (25.6%), hypertension (55.2%), and hyperlipidemia (49.0%). In terms of CCA type, 46.3% of the patients had ICC, and 53.7% had ECC.

PIs vs Asians

The characteristics of PIs compared to Asians are detailed in Table 1. PIs presented at a younger mean age (61.3 vs 67.8
years; \( P<.001 \) and were more likely to be obese (55% vs 16%; \( P<.001 \)). There was no difference in smoking history, alcohol history, diabetes, hypertension, hyperlipidemia, other malignancies, HBV or HCV infection, or the presence of inflammatory bowel disease. No difference was observed in laboratory values, including tumor markers: elevated AFP, CEA, and CA 19-9, or liver function and serum tests: bilirubin, AST, ALT, alkaline phosphatase, albumin, creatinine, or platelets. There was no difference in the distribution between ECC and ICC in PIs when compared to Asians.

ECC

The ECC cohort consisted of 137 patients, which included 25 PIs and 112 Asians. 58% were men and 80% were older than 60 years, with a mean age of 69.3 years. The comorbidities in this population included obesity (22%), smoking (56%), alcohol use (34%), diabetes mellitus (26%), hypertension (45%), HBV (9%), and HCV (3%). Of the total population with ECC, 55%, 11%, and 45% of tumor locations were proximal, middle, and distal, respectively, and 33% underwent surgical resection.

Table 2 compares the comorbidities, laboratory values, and tumor characteristics between PIs and Asians with ECC and ICC. Of the ECC patients, PIs had a significantly lower proportion of patients over age 60 years (60% vs 85%; \( P=.005 \)) and higher rates of obesity (53% of PIs vs 14% of Asians, \( P<.001 \)). No significant differences were observed in other risk factors, including smoking or alcohol history, diabetes mellitus, hypertension, hyperlipidemia, other malignancies, sclerosing cholangitis, HBV, HCV, or inflammatory bowel disease. There was no difference in laboratory values, including elevated AFP, CEA, CA 19-9, bilirubin, AST, ALT, alkaline phosphatase, albumin, creatinine, or platelets. Regarding tumor characteristics, 64%,

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pacific Islander (n=40) n (%)</th>
<th>Asian (n=215) n (%)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 60 years or older</td>
<td>25 (62)</td>
<td>163 (75.8)</td>
<td>.079</td>
</tr>
<tr>
<td>Male</td>
<td>26 (65)</td>
<td>122 (56.7)</td>
<td>.33</td>
</tr>
<tr>
<td>BMI above 30</td>
<td>17/31 (54)</td>
<td>25/156 (16)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>18/39 (46)</td>
<td>120/213 (56.3)</td>
<td>.24</td>
</tr>
<tr>
<td>Alcohol history</td>
<td>14 (35)</td>
<td>65/212 (30.7)</td>
<td>.59</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11/39 (28)</td>
<td>52/207 (25.1)</td>
<td>.69</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20/39 (51)</td>
<td>116/207 (56.0)</td>
<td>.58</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>14/27 (51)</td>
<td>64/132 (49)</td>
<td>.98</td>
</tr>
<tr>
<td>Presence of a second cancer</td>
<td>6 (15)</td>
<td>36/211 (17.1)</td>
<td>.75</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>0</td>
<td>1/208 (0)</td>
<td>.66</td>
</tr>
<tr>
<td>Elevated AFP</td>
<td>3/16 (18)</td>
<td>16/110 (15)</td>
<td>.66</td>
</tr>
<tr>
<td>Elevated CEA</td>
<td>6/26 (23)</td>
<td>56/143 (39)</td>
<td>.118</td>
</tr>
<tr>
<td>Elevated CA 19-9</td>
<td>24/33 (72)</td>
<td>131/177 (74)</td>
<td>.88</td>
</tr>
<tr>
<td>CA 19-9 &gt;1000 units/mL</td>
<td>5/32 (15)</td>
<td>47/177 (27)</td>
<td>.188</td>
</tr>
<tr>
<td>Elevated CEA or CA 19-9</td>
<td>28/34 (82)</td>
<td>148/192 (77)</td>
<td>.50</td>
</tr>
<tr>
<td>Hepatitis B surface Ag positive</td>
<td>5/32 (15)</td>
<td>22/150 (15)</td>
<td>.89</td>
</tr>
<tr>
<td>Hepatitis B core Ab positive</td>
<td>11/30 (36)</td>
<td>32/126 (25)</td>
<td>.79</td>
</tr>
<tr>
<td>Hepatitis C positive</td>
<td>2/32 (6)</td>
<td>10/147 (7)</td>
<td>.91</td>
</tr>
<tr>
<td>Tumor size &gt;5 cm</td>
<td>10/26 (38)</td>
<td>67/144 (47)</td>
<td>.45</td>
</tr>
<tr>
<td>Surgical resection</td>
<td>11 (27)</td>
<td>62 (28.8)</td>
<td>.86</td>
</tr>
<tr>
<td>ECC:ICC</td>
<td>25:15</td>
<td>112:103</td>
<td>.23</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>61.3</td>
<td>67.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>31.5</td>
<td>25.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean tumor size (cm)</td>
<td>4.88</td>
<td>5.60</td>
<td>.27</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, alpha fetoprotein; BMI, body mass index; CA, Carbohydrate Antigen; CEA, Carcinoembryonic Acid; ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma.

\(^{a}\) Total sample size (N=255).

\(^{b}\) For some characteristics, percentage represents the numerator divided by total number in subgroup.
8%, and 28% of the total ECC PI population and 53%, 12%, and 35% of the total Asian population had proximal, middle, and distal tumors, respectively. PIs had a larger mean tumor size (3.9 vs 2.2 cm; \( P = .040 \)) and a higher proportion of tumors larger than 5 cm (15% vs 2%; \( P = .042 \)). No significant differences in tumor location and surgical resection were observed between these 2 populations.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pacific Islander</th>
<th>Asian</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 25 )</td>
<td>( n = 112 )</td>
<td></td>
</tr>
<tr>
<td><strong>Extrahepatic cholangiocarcinoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 60 years or older</td>
<td>15 (60)</td>
<td>95 (85)</td>
<td>.005</td>
</tr>
<tr>
<td>Male</td>
<td>17 (68)</td>
<td>63 (56)</td>
<td>.28</td>
</tr>
<tr>
<td>BMI above 30</td>
<td>10/19 (53)</td>
<td>10/74 (14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>11/24 (46)</td>
<td>64/110 (58)</td>
<td>.27</td>
</tr>
<tr>
<td>Alcohol history</td>
<td>8 (32)</td>
<td>38/110 (35)</td>
<td>.81</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6/24 (25)</td>
<td>28/107 (26)</td>
<td>.91</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10/24 (42)</td>
<td>54/107 (50)</td>
<td>.44</td>
</tr>
<tr>
<td>Hepatitis B surface Ag positive</td>
<td>2/17 (12)</td>
<td>5/60 (8)</td>
<td>.66</td>
</tr>
<tr>
<td>Hepatitis B core Ab positive</td>
<td>6/16 (38)</td>
<td>10/50 (20)</td>
<td>.155</td>
</tr>
<tr>
<td>Hepatitis C positive</td>
<td>1/17 (6)</td>
<td>1/56 (2)</td>
<td>.36</td>
</tr>
<tr>
<td>Tumor size &gt;5 cm</td>
<td>2/13 (15)</td>
<td>1/51 (2)</td>
<td>.041</td>
</tr>
<tr>
<td>Surgical resection</td>
<td>9 (36)</td>
<td>36/107 (32)</td>
<td>.71</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>61.2</td>
<td>71.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>30.6</td>
<td>24.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean tumor size (cm)</td>
<td>3.90</td>
<td>2.20</td>
<td>.040</td>
</tr>
</tbody>
</table>

|                                      |                  |       |         |
| **Intrahepatic cholangiocarcinoma**  | \( n = 15 \)     | \( n = 103 \) |         |
|                                      |                  |       |         |
| Age 60 years or older                | 10 (67)          | 68 (66) | .96    |
| Male                                 | 9 (60)           | 59 (57) | .84     |
| BMI greater than 30                  | 7/12 (58)        | 15/62 (18) | .002   |
| Smoking                              | 7 (47)           | 56 (54) | .58     |
| Alcohol history                      | 6 (40)           | 27/102 (26) | .28    |
| Diabetes mellitus                    | 5 (33)           | 24/100 (24) | .44    |
| Hypertension                         | 10/67            | 62/100 (62) | .73    |
| Hepatitis B surface Ag positive      | 3 (20)           | 17/90 (19) | .92    |
| Hepatitis B core Ab positive         | 5/14 (36)        | 22/76 (29) | .61    |
| Hepatitis C positive                 | 1 (7)            | 9/91 (10) | .69     |
| Tumor size >5 cm                     | 8/13 (62)        | 66/90 (73) | 0.38   |
| Single tumor                         | 9/13 (69)        | 85/91 (93) | .006   |
| Surgical resection                   | 2 (13)           | 26 (25) | .31     |
| Mean age (years)                     | 61.4             | 64.3 | .44     |
| Mean BMI                             | 32.8             | 25.6 | <.001   |
| Mean tumor size (cm)                 | 5.93             | 7.51 | .180    |

Abbreviations: BMI, body mass index.

*For some characteristics, percentage represents the numerator divided by total number in subgroup.

bTotal sample size (N=137).

cTotal sample size (N=118).
ICC

Of the 118 patients with ICC, 15 patients were PI, and 103 were Asian. The ICC cohort had 58% men and a mean age of 63.9 years, with 66% over 60 years. Risk factors and comorbidities included obesity (23%), smoking (53%), alcohol use (28%), diabetes mellitus (25%), hypertension (63%), HBV (19%), and HCV (9%). Tumor characteristics in this cohort include 90% of patients with a single tumor, a mean tumor size (largest lesion) of 7.33 cm, and 31% with surgical resection of tumors. Table 2 compares the risk factors, comorbidities, laboratory studies, and tumor characteristics between PIs and Asians with ICC. The only notable differences were that PIs were more likely to be obese (58% vs 18%; \( P = .002 \)) and have fewer presentations with a single tumor than multiple tumors compared to Asians (69% vs 93%; \( P = .006 \)).

**Predictors of Surgical Resection**

Table 3 describes the odds ratios of risk factors, comorbidities, and laboratory values as predictors of undergoing surgical resection. Factors predictive of undergoing surgical resection on univariate and multivariate analysis included having a single tumor and having ECC (compared with ICC). Elevated CA 19-9 and CEA were predictive of not receiving surgical resection.

**Survival**

Risk factors, comorbidities, and laboratory values were analyzed as predictors of 1-year survival in the total CCA cohort (Table 4). Being male significantly predicted 1-year survival, while hypertension was associated with less 1-year survival on univariate and multivariate analyses.

As shown in Figure 1, the median survival for PIs in the overall CCA cohort (18 months; 95% CI, 15–27 months) was similar to Asians (17 months; 95% CI, 16–20 months). When divided into ECC and ICC, PIs and Asians had no significant difference in median survival in both ECC (19 months; 95% CI, 13–31 months vs 17 months; 95% CI, 15–19 months) and ICC cohorts (18 months, 95% CI, 14–34 months vs 19 months; 95% CI, 16–27 months).

### Table 3. Predictors of Undergoing Surgical Resection in the Cholangiocarcinoma Cohort\(^ab\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crude Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 60 years or older</td>
<td>0.58 (0.24-1.37)</td>
<td>0.59 (0.32-1.20)</td>
</tr>
<tr>
<td>Male</td>
<td>1.57 (0.68-3.64)</td>
<td>1.24 (0.59-2.59)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>0.79 (0.27-2.32)</td>
<td></td>
</tr>
<tr>
<td>BMI above 30</td>
<td>0.91 (0.34-2.49)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>0.56 (0.25-1.30)</td>
<td></td>
</tr>
<tr>
<td>Alcohol history</td>
<td>2.02 (0.82-4.97)</td>
<td>1.52 (0.68-3.38)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.99 (0.41-2.40)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.83 (0.38-1.83)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.09 (0.44-2.69)</td>
<td></td>
</tr>
<tr>
<td>Presence of a second cancer</td>
<td>0.43 (0.15-1.26)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B surface Ag positive</td>
<td>0.76 (0.22-2.63)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B core Ab positive</td>
<td>0.52 (0.17-1.54)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C positive</td>
<td>4.14 (0.67-25.5)</td>
<td></td>
</tr>
<tr>
<td>Elevated CA 19-9</td>
<td>0.35 (0.14-0.86)</td>
<td>0.31 (0.14-0.72)</td>
</tr>
<tr>
<td>CA 19-9 &gt;1000 units/mL</td>
<td>0.36 (0.11-1.17)</td>
<td>0.35 (0.11-1.05)</td>
</tr>
<tr>
<td>Elevated CEA</td>
<td>0.30 (0.10-0.92)</td>
<td>0.38 (0.14-0.99)</td>
</tr>
<tr>
<td>Tumor size &gt;5 cm</td>
<td>0.68 (0.21-2.24)</td>
<td>0.90 (0.32-2.62)</td>
</tr>
<tr>
<td>Single tumor</td>
<td>4.50 (1.19-17.02)</td>
<td>3.73 (1.11-12.61)</td>
</tr>
<tr>
<td>ICC (vs ECC)</td>
<td>0.73 (0.17-3.31)</td>
<td>0.11 (0.03-0.39)</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, alpha fetoprotein; BMI, body mass index; CA, Carbohydrate Antigen; CEA, Carcinoembryonic Acid; CI, confidence interval; ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma.
\(^a\) Total sample size (N=255).
\(^b\) Bolded values are significant to \( P < .05 \).
Table 4. Predictors of One-Year Survival in the Cholangiocarcinoma Cohort$^a,b$

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crude Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 60 years or older</td>
<td>0.74 (0.37-1.52)</td>
<td>0.75 (0.30-1.88)</td>
</tr>
<tr>
<td>Male</td>
<td>2.57 (1.39-4.74)</td>
<td>3.27 (1.42-7.51)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>1.63 (0.65-4.13)</td>
<td></td>
</tr>
<tr>
<td>BMI above 30</td>
<td>1.44 (0.59-3.55)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.31 (0.72-2.39)</td>
<td></td>
</tr>
<tr>
<td>Alcohol history</td>
<td>1.78 (0.88-3.60)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.06 (0.53-2.14)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.53 (0.28-0.99)</td>
<td>0.38 (1.57-0.91)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.05 (0.50-2.20)</td>
<td></td>
</tr>
<tr>
<td>Presence of a second cancer</td>
<td>0.90 (0.41-1.96)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B surface Ag positive</td>
<td>0.66 (0.27-1.65)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B core Ab positive</td>
<td>0.45 (0.20-1.00)</td>
<td>0.44 (0.19-1.03)</td>
</tr>
<tr>
<td>Hepatitis C positive</td>
<td>3.76 (0.47-29.9)</td>
<td></td>
</tr>
<tr>
<td>Elevated CA 19-9</td>
<td>0.86 (0.40-1.84)</td>
<td></td>
</tr>
<tr>
<td>CA 19-9 &gt;1000 units/mL</td>
<td>0.73 (0.36-1.51)</td>
<td></td>
</tr>
<tr>
<td>Elevated CEA</td>
<td>1.40 (0.66-2.95)</td>
<td></td>
</tr>
<tr>
<td>Tumor size &gt;5 cm</td>
<td>0.98 (0.49-1.97)</td>
<td></td>
</tr>
<tr>
<td>Single tumor</td>
<td>0.31 (0.04-2.50)</td>
<td></td>
</tr>
<tr>
<td>ICC (vs ECC)</td>
<td>1.04 (0.57-1.90)</td>
<td></td>
</tr>
<tr>
<td>Surgical resection</td>
<td>1.51 (0.76-3.01)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AFP, alpha fetoprotein; BMI, body mass index; CA, Carbohydrate Antigen; CEA, Carcinoembryonic Acid; CI, confidence interval; ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma.

$a$Total sample size (N=255).

$b$Bolded values are significant to $P < .05$.

Figure 1. Kaplan-Meier Survival Comparing Pacific Islanders and Asians

Abbreviations: ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; PI, Pacific Islander.
Discussion

In this study, the team determined PIs to have a slightly different presentation compared to Asians, but this did not prevent them from the opportunity for surgical resection. Though the “Asian Pacific Islander” group is documented to have a generally lower cancer incidence relative to whites, the consistent aggregation of Asians and PIs may be masking the disparities between these 2 populations. The unique ethnic makeup in Hawai‘i, with an Asian population of 38% and Pacific Islander population of 10%, and the high incidence of CCA in Asians suggests the utility of the comparison between Asians and PIs in this study. Prior studies have demonstrated that PIs have disparities in risk factors for all cancers, including a higher prevalence of obesity, smoking, alcohol use, diabetes mellitus, and cholesterol intake compared to Asians. These disparities, along with their underutilization of cancer prevention services, may contribute to PIs’ higher incidence of cancer compared to Asians.

Particularly in HCC, our team has previously reported that PIs presented with a significantly higher mean BMI, younger age, and significantly fewer liver transplantations compared to Asians. Consistent with those risk factors, this study found PIs were significantly younger and more likely to be obese than Asians; however, this did not correlate to fewer curative surgeries in this CCA cohort.

Though well established as a risk factor for HCC, viral hepatitis has been considered in fewer studies as a strong risk factor for CCA and more so for ICC. Our team has previously identified higher rates of HCV in the PI population compared to Asians in an HCC population. The present study did not find HBV or HCV to be higher in PIs in this CCA population. Over a third of PIs were positive for HBV core antibody—a prevalence non-significantly higher than Asians. The small sample size, especially of PIs with ICC, may be contributing to these findings. It is possible that younger PIs were more likely to have been vaccinated for HBV than older PIs, and patients with only partial PI ethnicity may have had less vertical transmission.

Our cohort also demonstrated that both Asians and PIs had more ECC than ICC. The ratios of ECC:ICC of Asians in this CCA cohort closely correlated with recently reported incidence ratios in East Asia, which was close to 1:1. Florio et al analyzed the global trends of ECC and ICC incidence from 1993 to 2012 and demonstrated the ECC:ICC ratios of the US, China, Japan, and South Korea to be 0.79:1, 0.9:1, 0.9:1, and 0.79:1, respectively.

PIs also presented with more advanced CCA at diagnosis. PIs with ECC were more likely to have larger tumors, and PIs with ICC had more multifocal disease. Despite this, PIs were just as likely to receive definitive surgical resection. On the multivariate analysis, multifocality, ICC, and elevated tumor markers were predictive of not receiving surgical resection. Other studies have shown large tumors were associated with worse survival outcomes after surgical resection, as they have been associated with higher positive tumor resection margins and poor differentiation. Multifocality is also associated with higher recurrence rates and shorter overall survival after curative-intent surgical treatment of ICC. Previous studies by our group have shown a more advanced presentation of HCC in PIs, which affected candidacy for transplant and ultimately their survival.

Regardless of their more advanced presentation of CCA at diagnosis, PIs demonstrated comparable surgical resection as well as 5-year survival outcomes compared to Asians. Early survival was better in men and worse in patients with hypertension; PI ethnicity did not affect early survival. It is unclear why men had better early survival in our study, but there were no sex differences in overall survival. Other studies have suggested that women, younger age, nonsmoking status, and ECC were associated with better prognosis. Many studies found that the outcome in ECC is mostly dependent on treatment, with surgical resection offering the best chance of long-term survival, but this study did not find surgical resection to be predictive of early survival.

This study is limited in that it is a single-center study with relatively small sample size. This study also spans nearly 3 decades, and data from the earliest cases were not complete, especially concerning the tumor markers and survival information. In addition, treatment has likely improved and changed over time. Greater awareness of hepatobiliary cancers and development of expertise may have allowed for an earlier referral to this tertiary center allowing for more surgical treatment in the more recent years.

Despite these limitations, this is likely one of the largest studies of this rare cancer in this particular ethnic group. PIs represent the fastest-growing ethnic group—increasing in size 3 times faster than the rest of the US population. This study assesses this understudied population whose CCA presentation has not previously been characterized. PIs have been previously documented to have a higher risk factor profile for CCA and have been grouped with Asians to represent the racial group with the highest CCA and HCC in the nation, but are rarely studied separately. The results of this study indicated that PIs with CCA presented at a younger age and had a higher prevalence of obesity, but they are just as likely to receive potentially curative surgery and survive as Asians. Larger studies in this population will be needed to develop more definitive conclusions and strategies to promote earlier detection of CCA. However, health care providers should consider CCA in the differential diagnosis of jaundice or a newly discovered liver mass and recognize that this may occur at a younger age in PIs.
A Case Report of Wound Botulism — Rare Disease on the Rise with the Opioid Crisis

Miki Kiyokawa MD and William Haning MD

Abstract

Wound botulism is a rare, underrecognized life-threatening illness caused by a toxin produced by Clostridium botulinum, a spore-forming anaerobic bacterium. Approximately 20 cases are reported in the United States each year, mostly from California. Most wound botulism cases occur in drug injectors, particularly among those using black tar heroin. The initial presentation of botulism may overlap with other diagnoses, including opioid intoxication and pre-existing neurological disease, making accurate diagnosis difficult. A healthy 40-year-old patient with a history of injecting black tar heroin presented to an emergency department complaining of generalized weakness and throat discomfort. He was given antibiotics and was sent home. The next day, the patient presented to another emergency department with additional complaints of slurred speech and blurring of vision. He was admitted for a possible cerebrovascular injury. In the absence of positive findings from laboratory or imaging studies, botulism was considered. The patient decompensated and was intubated. Botulinum antitoxin was given, and the patient eventually recovered. Prompt decision-making based on clinical suspicion and an informed presumptive diagnosis, administration of botulinum antitoxin, and aggressive provision of supportive care can arrest the progression of paralysis and be life-saving. With the rise of opioid use in the United States, leading to a reversion to heroin as a cheaper form of opioids, cases of wound botulism may be on the rise. Clinician attentiveness to obtaining substance history and being aware of botulism presentation may lead to life-saving treatments for these patients.

Keywords

Botulism, black tar heroin, intravenous drug users, Botulinum antitoxin

Abbreviations and Acronyms

BAT = botulinum antitoxin
BoNT = botulinum neurotoxin
CDC = US Centers for Disease Control and Prevention
ED = emergency department

Introduction

Botulism occurs when spores of Clostridium botulinum germinate to toxin-producing bacilli in an anaerobic environment.1,2 Botulinum neurotoxin (BoNT) is readily formed and released, binding to the presynaptic nerve ending, causing irreversible blockage of acetylcholine release, a primary neurotransmitter at the neuromuscular junction, resulting in muscle paralysis.3,4 There are 5 main kinds of botulism: foodborne, infant, adult intestinal toxemia, iatrogenic, and wound.4,5 Wound botulism is a rare, reportable, life-threatening disease that occurs mostly in drug injectors, especially among those using black tar heroin in conjunction with skin popping (subcutaneous and inadvertent intradermal injection).3 We report here a case of wound botulism in a 40-year-old intravenous black tar heroin user whose initial presentation was non-specific.

Case Report

A 40-year-old heroin user with no pertinent past medical history initially presented to an emergency department (ED) with subjective complaints of generalized weakness, difficulty swallowing, dysphonia, and sensation of something “stuck” in his throat for 1 day. The patient’s significant other reported that the patient was walking, talking, and eating as usual despite the above complaints. The patient was subsequently sent home with antibiotics.

On the next day, his condition worsened despite taking the prescribed antibiotics. He presented to a different ED with additional complaints of slurred speech and double and blurry vision. In ED, the patient was not in acute distress with a blood pressure of 110/80, temperature of 98.6°F, and respiratory rate of 18 with oxygen saturation of 95%. He was noted to have rotary nystagmus, dysarthria, and motor strength of 4/5 in all extremities but no pronator drift. The extremity exam was notable for track marks bilaterally on the arms and hands, with an abscess on the left forearm. He had symmetrical facies, intact light touch, 2/4 deep tendon reflexes on all extremities, and physiologic plantar reflexes bilaterally. Computed tomography of the head, electrocardiography, chest X-ray, complete blood count, and comprehensive metabolic panel were all unremarkable. A urine drug screen was positive for opiates, and he reported using black tar heroin intravenously almost daily for the past 6 months, including recent skin popping. The patient was admitted for management of a possible cerebrovascular injury and was treated with an aspirin suppository. The left forearm abscess was drained later that day, and a culture was sent. The patient was continued on antibiotics.

On the second hospital day, the patient underwent brain magnetic resonance imaging, which showed no abnormality. The patient’s neurological symptoms persisted with no improvement. A neurologist was consulted, and Guillain-Barre syndrome, myasthenia gravis, and botulism were considered. Lumbar puncture showed no albuminocytologic dissociation for Guillain-Barre syndrome or any other abnormalities. A myasthenia gravis panel was sent to a laboratory in the continental United States, but results were not expected for at least a week—ultimately, these were negative. The Hawai‘i State Department of Health and the Centers for Disease Control and Prevention (CDC)
were notified and consulted for assistance in managing possible botulism. Following the discussion, the CDC authorized the release of botulism antitoxin (BAT). For further diagnostic purposes, a sample of the patient’s blood was sent to the CDC.

On the third hospital day, the patient started to experience dyspnea, which subsequently required intubation. The BAT arrived and was administered, and the patient was transferred to a facility supporting a higher level of care.

On the fourth hospital day, anti-GQ1b IgG antibody was sent for possible Miller-Fisher syndrome, a variant of Guillain-Barre syndrome, before empiric treatment of intravenous immunoglobulin for Guillain-Barre syndrome was initiated. The result came back a few weeks later and was negative. Nerve conduction studies and electromyography showed changes consistent with a presynaptic neuromuscular defect as seen in botulism. Supportive care was continued.

The patient was extubated on his ninth day in the hospital. He recovered steadily; however, the patient continued to fail the swallow test and was discharged home with a gastrostomy feeding tube after 2½ weeks of hospitalization.

The patient’s cultures from the left arm abscess, spinal fluid, blood, urine, and sputum were all negative. A report from the CDC was received almost 50 days after the patient was tested, indicating the presence of BoNT type B.

**Discussion**

BoNT is produced by *Clostridium botulinum* and is recognized as one of the most lethal poisons by the World Health Organization and poses a major bioweapon threat. Assuming an average weight of 70 kg per person for the 5.6 billion people in the world, only 39.2 g of pure BoNT would be sufficient to eradicate humankind. There are 7 types of BoNT, toxins A-G, where toxins A, B, E, and rarely F can cause botulism in humans. All the serotypes of BoNT interfere with neural transmission by irreversibly blocking the release of acetylcholine, which is the principal neurotransmitter at the neuromuscular junction, thus causing muscle paralysis.

**Epidemiology**

The CDC warns that botulism is frequently misdiagnosed. Wound botulism is rare, and only approximately 20 cases are reported every year in the United States. According to National Survey on Drug Use and Health, the number of heroin users has been on the rise since 2007 with a slight decrease in 2017; however, no overall increase in the wound botulism cases between 2001 and 2017 has been noted. Any type of botulism is a reportable disease to the CDC, and in Hawai‘i, to the state health department. During 2001–2016, 353 wound botulism cases were reported to the CDC, of which 291 cases (82%) were from California. Botulism is rarely reported outside California, but this may represent underdiagnosis elsewhere.

In Hawaii, only 1 case of wound botulism was reported during 2001–2017.

**Risk Factors**

One of the major risk factors for wound botulism is intravenous drug use and skin popping. *Clostridium botulinum* spores, which are not killed by heat, germinate and produce BoNT in an anaerobic environment, such as puncture wounds from heroin injection and necrotic tissue created by skin popping. Another risk factor is intravenous administration of black tar heroin, which is usually made in Mexico and is, cheaper than regular heroin due to its adulteration and lower purity (average purity, 27.1%). It is unclear how black tar heroin becomes contaminated.

From 2005 to 2017, 93% (222 out of 239) of the wound botulism cases in the United States were noted to be from injection drug users. In a wound botulism outbreak in San Diego County, California, which occurred between 2017 and 2018, there were 9 wound botulism cases reported; all 9 patients reported using intravenous heroin. Of these, 7 patients (78%) used black tar heroin, and 6 patients (67%) admitted to skin popping. The patient in this case report was a black tar heroin user who acknowledged skin popping.

**Signs and Symptoms**

According to Rao et al, there were 332 botulism cases reported in the United States between 2002 and 2015; most had descending paralysis (93%), subjective muscle weakness (85%), shortness of breath (65%), and cranial palsies such as dysphagia (86%), blurred vision (80%), and slurred speech (78%). Autonomic dysfunction such as dry mouth and fluctuating blood pressure and heart rate may also be present. Botulism usually progresses to symmetric descending flaccid paralysis and ultimately respiratory muscle paralysis and may result in death.

Initial presentation of botulism may be non-specific, such as generalized weakness and throat discomfort like in this patient. This type of non-specific presentation might lead to confusion with other diagnoses. Peak and colleagues noted that the symptoms of wound botulism often overlap with the symptoms of opioid intoxication or neurologic syndromes such as Guillain-Barré syndrome. In this patient, Miller Fisher syndrome and myasthenia gravis were also considered.

Myasthenia gravis is an autoimmune disease that presents a variable combination of weakness of the extraocular, bulbar, limb, and respiratory muscles, which is similar to our patient’s presentation. A hallmark of myasthenia gravis, however, is the presence of fluctuating muscle weakness that improves with rest, which our patient did not have. The patient’s myasthenia gravis panel also came back negative.
Patients with Guillain-Barre syndrome suffer from a flaccid, fairly symmetrical ascending paralysis, depressed deep tendon reflexes, and, at times, autonomic dysfunction, such as extreme hypertension or hypotension. Guillain-Barre syndrome is often seen after gastrointestinal infection with Campylobacter jejuni and respiratory infection, such as with Epstein-Barr virus. Lumbar puncture shows elevated protein, known as albuminocytologic dissociation, in 50% to 75% of patients. In this patient, deep tendon reflexes remained normal, and he denied having a recent infection before the onset of symptoms. Lumbar puncture results were also normal.

Miller Fisher syndrome is a variant of Guillain-Barre syndrome, which can present with the clinical triad of ophthalmoplegia, ataxia, and areflexia and, to a lesser degree, with mild motor weakness and bulbar palsies as in this patient. It accounts for between 1% and 5% of all Guillain-Barre cases in Western countries and twice as common in men than women with the median age of onset in the fifth decade. Anti-GQ1b IgG antibody can be used for diagnosis, which is present in 85% of the patients and was negative in this patient. Although Miller Fisher syndrome usually follows a self-limiting course, the usual treatment for Guillain-Barre syndrome, such as intravenous immune globulin and supportive care, may be used to hasten recovery.

Diagnosis

Diagnosing wound botulism can be challenging due to the lack of an immediately-confirmatory test and the presence of confounding symptoms that overlap with other neurologic syndromes or opioid intoxication. Confirmatory diagnosis requires growth of Clostridium botulinum from stool or wound cultures or the presence of toxin in the serum or other body fluid. The latter test is performed by the CDC or another designated lab depending on the state. As the confirmation test may take weeks to months, a high index of clinical suspicion, including a history of intravenous drug use and neurologic symptoms, should prompt early treatment and administration of BAT, rather than waiting for lab results. Patients suspected of having wound botulism who fit the clinical picture but without laboratory confirmation should still be considered as having probable wound botulism because the sensitivity of the mouse lethality bioassay, the gold standard to confirm botulism, is only 68%.

Treatment

BoNT causes paralysis by binding on the presynaptic neuron of the neuromuscular junction and irreversibly blocking acetylcholine release. Treatment for botulism is BAT to neutralize free BoNT in the bloodstream and stop the progression of the paralysis. Recovery of BoNT affected neurons occurs by the sprouting of nerve terminals and the formation of new synaptic contacts, which usually takes 2 to 3 months. Prompt diagnosis is essential in treatment for botulism and can be life-saving. When botulism is suspected, the state health department and the CDC should be contacted. If clinical consultation with both agencies supports botulism, BAT can be obtained. BAT is available only from the CDC due to its limited use and relatively short expiration date. The antitoxin is stored at the CDC Quarantine Stations located in major airports around the nation. In our case, BAT was available in 1 day.

Prognosis

During 1975–2009, mortality from wound botulism in the United States was approximately 5%, but recently, mortality from this disease decreased to about 1.5% (2010–2017). Mortality depends on various factors, including the type of toxin, where type F has the higher mortality while type B toxin (as in this patient) has lower mortality. The sequelae of wound botulism are similar to other types of botulism. Some who survive may have fatigue and shortness of breath for years. Fortunately, many people recover fully, but it may take months, and patients may require extended rehabilitation therapy.

Conclusion

Wound botulism is a rare disease that may be fatal if untreated, with approximately 20 cases per year reported in the United States. It is even rarer in the state of Hawai‘i, where only 1 wound botulism case has been reported between 2001 and 2017. Its association with the use of black tar heroin has been long known. Botulism’s initial presentation can be non-specific and may be misdiagnosed as opioid intoxication or another neurological disease. The treatment is supportive care and BAT, which needs to be given promptly to have any significant effect. Obtaining an accurate substance use history and an awareness of the characteristic botulism presentation may lead to prompt diagnosis, administration of BAT, and provision of supportive care and ultimately may be life-saving. In injection drug users, generalized weakness, blurry vision, slurred speech, paralysis, or dyspnea should prompt the clinician to strongly consider the possibility of wound botulism. Despite the syndrome’s rarity, the rise in the national use of heroin can be expected to produce an associated rise in such co-morbidities.

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References

Pre-Surgical Screening and Incidence of COVID-19 Infection at the Shriners Hospitals for Children — Honolulu

Dayne Fujimoto PharmD; Brandi Blair MD; Robin (Rob) H. Miyamoto PhD

Introduction

As the COVID-19 pandemic continued to impact healthcare facilities across the United States during the spring of 2020, and with the implementation of Centers for Disease Control and Prevention (CDC) precautions, Shriners Hospitals for Children – Honolulu (SHC HON) resumed elective surgeries in May 2020. In an effort to provide further insight into the efficacy of infection control measures, best care practices, and the well-being of our pediatric patient population and larger community, the incidence of COVID-19 was examined among asymptomatic patients scheduled for elective outpatient or inpatient surgery.

On March 23, 2020 (effective 12:01 am, March 24), Governor Ige issued the statewide stay-at-home/work-at-home order due to the rising number of COVID-19 cases. On that day, Hawai‘i’s total number of confirmed coronavirus cases was 77 (37.5% increase from previous day) and the first COVID-related death had occurred three days before. There was an average of 1.0 newly reported cases per day for every 100 000 residents statewide for the 7-day period ending on March 23. Consequently, on May 5, 2020, COVID-19 restrictions were eased and some essential businesses were allowed to reopen as the average of newly reported cases per day for every 100 000 residents statewide decreased to 0.2 (625 confirmed cases and 17 deaths).

Pre-Surgical COVID-19 Testing

Accordingly, SHC HON ceased having elective surgeries on March 24, which resumed on May 11. Prior to admission for elective surgery, all scheduled patients were tested for COVID-19 and their results were recorded. If a patient had a positive test result and/or was symptomatic before or after testing, his/her surgery was rescheduled for a later date in accordance with CDC guidelines (eg, asymptomatic for 14 days, negative test result before rescheduled surgery).

The electronic medical records of patients who had a COVID-19 test between May 18 to July 22, 2020 and were scheduled for elective orthopedic or dental surgery were reviewed. The variables of interest included the result, type (eg, polymerase chain reaction [PCR]) and date of the patient’s COVID-19 screening test, age, sex, ethnicity, date, and type of surgery, and COVID-19-related symptoms (ie, if positive test result). There were 131 patients tested for COVID-19 and/or scheduled for elective surgery during this 10-week period, and none of them tested positive. Table 1 presents the patients’ demographic and related information.

Conclusion

The finding of 0 COVID-19 positives suggests that these patients and families are to be commended for keeping the prevalence of COVID-19 low among our hospital’s pediatric population, which is comprised of children from various racial and socioeconomic backgrounds, as well as within the larger community. For example, for every 100 000 residents statewide aged 0-17 years, there were averages of 0 and 6 new coronavirus cases during the weeks ending on May 16 and July 25, respectively. During this 10-week period, and across all ages, the total number of cases increased from 637 to 1490 (1.2% positivity rate based on 73 009 tests) and related deaths went from 17 to 26. In addition, over 45% of the patients reviewed were of Native Hawaiian/Pacific Islander descent, who, as a group, was reported to be disproportionately impacted by COVID-19 in contrast to other racial groups in Hawai‘i. However, the incidence rate found herein is very much lower, and infectivity appears to be similar, or non-existent, among these pediatric patients despite racial differences.

Previous studies of patients from other children’s hospitals located on the continental United States have reported high variability in the prevalence of COVID-19 dependent on geography, with an average rate of 0.65%. Comparable data from
other Shriners hospitals located in states with very high rates of COVID-19 will be analyzed with regard to geographical differences, or the possibility that pediatric patients (and their families) might be locally unique in (dis)similar ways.

From a public health perspective, Hawai‘i’s overall response to COVID-19 was proactive given our state government’s timely enactment of restrictions (eg, face mask wear, social distancing, no/limited social gathering, and monitored travel) and Hawai‘i residents’ civil adherence to them, due to increasing COVID-19 positivity rates statewide and the evolving pandemic across the United States. Within the control and prevention milieu that emerged in response to the COVID-19 pandemic, it is conceivable, perhaps expected, that certain regions and/or groups will vary in their ratification of and adherence to government-mandated restrictions. The 0 positivity rate provided support for the effectiveness of the public health initiatives authorized by local officials in response to COVID-19, which, in turn, was dependent upon the statewide community’s endorsement of them.

Comparable information about Hawai‘i’s general pediatric patient population or that from other children’s hospitals were limited and/or not readily accessible, which reduced the extent to which contrasts with the current data could be made. This finding of 0 positives may have been solely due to the fact that the children presenting for elective surgery at SHC HON during this time period represented an exception with regard to their observance of COVID-19 precautions. Or, it could purely be reflective of the cautious demeanor of these children, or moreover, the protective efforts of their parents given their vulnerable health condition(s) (typically comorbid), as witnessed at SHC HON on a daily basis.

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References
Hawai‘i Nurses Play Major Role in COVID-19 Pandemic Response

Laura Reichhardt MS, APRN, AGPCNP-BC

The Spotlight on Nursing is a recurring column from the University of Hawai‘i at Mānoa’s School of Nursing and Dental Hygiene (UHM SONDH). It is edited by Mary G. Boland DrPH, RN, FAAN, Dean of UHM SONDH; Kristine Qurashi PhD, RN, CEN, PHNA-BC, FAAN, Associate Dean of Research for UHM SONDH and HJH&SW Contributing Editor; and Joanne R. Loos PhD, Science Writer for UHM SONDH.

Note: This Spotlight on Nursing column has been adapted from The Hawai‘i State Center for Nursing 2020 Annual Report. Please visit https://www.hawaiicenterfornursing.org/ for the full report.

The Hawai‘i State Center for Nursing (HSCN) has a mission to provide accurate nursing workforce data for planning, disseminate nursing knowledge to support excellence in practice and leadership development, promote a diverse workforce, and advocate for sound health policy in the state of Hawai‘i. In 2019, the HSCN reported that although the state’s nursing workforce was sufficient to meet the needs of Hawai‘i, there existed a shortage of specialty nurses. The 2020 COVID-19 pandemic created a need for a larger number of nurses, including those with specialties in critical fields such as emergency, acute medical/surgical, critical care, nephrology, and others, and a need to fill the surge capacity demands across the state. Currently, Hawai‘i’s nursing workforce is insufficient to meet current and future “surge-capacity” nursing workforce needs.

During pandemics, the needs for health care workers become urgent across all communities affected by the event. Despite the fact that the United States has more than 4 million nurses, there are still critical shortages of nurses with the skills required for COVID-19 pandemic response. Such has happened in the State of Hawai‘i. During the summer of 2020, hospitals in the state activated 80 National Guard health care workers (including nurses), hired travel nurses from other states, and transferred patients to other facilities due to shortages of nurses. As discussed in oral communication with the Healthcare Association of Hawai‘i (HAH) and hospital administrators in August 2020, as active cases increased across the state and hospitalization rates reached full-capacity, the HSCN and the HAH undertook an urgent effort to assess hospital staffing needs, identify local nurse and health care provider availability, and request for federal support. In addition, to further augment the nursing workforce, the state waived license requirements during an emergency proclamation period to allow new nursing graduates to work with full scope of practice upon graduation, before taking the national licensure exam.

Therefore, it is essential that the state of Hawai‘i prepare for future surge nursing workforce needs. Such preparation includes increased numbers of nurses and systems for rapid cross-training for the various roles that nurses may fill. For the COVID-19 pandemic, such needs have included: management of patients in respiratory failure, COVID-19 testing and surveillance, and a variety of roles in mass vaccination endeavors.

The nursing deficit the state experienced during the second half of 2020 was multifactorial. For instance, our state opened additional beds to accommodate COVID-19 patients, decreased the nurse-to-patient ratio, for example, from 6 patients per nurse to as few as 2 patients in medical surgical units for COVID-19 patients, and created special COVID-19 units with nurses and hospital staff who were dedicated to those units, as stated in oral communication with HAH in August 2020. These measures all necessitated additional nursing staff who were not readily available. This was coupled with the demand for nurses with expertise in high-acuity medical-surgical, telemetry, critical care, and nephrology specialties. However, the state lacked the capacity to expand this workforce. The state also experienced sudden nursing workforce shortages in long-term care and residential care settings when COVID-19 cases entered those facilities, according to oral communication with the Hawai‘i Provider Surge Capacity Taskforce in August 2020. At the same time, Hawai‘i nursing education programs experienced devastating losses of clinical placement opportunities for both entry-level and advanced practice nursing students. This occurred for a variety of reasons, including a lack of personal protective equipment across the state, the need to direct the attention of the existing nursing workforce toward COVID-19 endeavors, and the need to limit the numbers of persons in the facilities in order to prevent the spread of the disease, as stated in oral communication various oral communication between HSCN and its Hawai‘i Centralized Clinical Placement Collaborative from March 2020 through the present. Recent graduates experienced delays in being able to register to take the national licensing exam due to closures and a reduction of testing centers, as reported in oral communication with state schools of nursing in June 2020. Further, according to oral com-
munication with the Hawai‘i Provider Surge Capacity Taskforce in August 2020, nurses reported experiencing personal fears of contracting the COVID-19 virus through peer or patient contact, a lack of adequate personal protective equipment, and burnout from protracted periods of overtime, emotional, and physical exhaustion.\(^\text{10}\)

The HSCN was able to directly respond. Notably, the HSCN used workforce data to inform strategy, workforce planning, and crisis mitigation, while leveraging partners such as government, hospitals, schools of nursing, and professional associations to actualize HSCN-led strategies and plans. In addition to responding to COVID-19, the HSCN maintained or adjusted operations and programs to the constrained working environment that the pandemic presented. The HSCN carried out specific assessment and intervention activities in response to the COVID-19 pandemic (Table 1).

Looking ahead, the HSCN commits to identify, investigate, and address nursing workforce issues that pose challenges to assuring an adequate nursing workforce to provide access to care for all people in Hawai‘i. In particular, the HSCN plans to focus its efforts in the following areas:

- Clinical placement availability
- Faculty recruitment and retention
- Professional development and education support related to specialization in nursing in community-based settings and acute care locations
- Recruitment of nurses for certain areas, including licensed practical nurses, community-based nursing roles, and acute-care specialty areas
- The availability, or unavailability, of travel and out-of-state nurses in a time of national and global nursing demand surge
- The enhancement of the resilience of our own workforce in times of crisis

The HSCN continues to serve the calls to action that were set forth in 2003. It is committed to convening partners, building trust, delivering outcomes, and supporting innovation to ensure high-quality care is accessible to all the people of Hawai‘i.

Author’s Affiliation:
Hawai‘i State Center for Nursing, Honolulu, HI

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5. Avedaño E. Hawai‘i asks feds to send more nurses with the pandemic. Honolulu Civil Beat/August 24, 2020.

Table 1. Hawai‘i State Center for Nursing Assessment and Intervention Activities

<table>
<thead>
<tr>
<th>Focus</th>
<th>Activities</th>
</tr>
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<tbody>
<tr>
<td>Workforce Research</td>
<td>2019 workforce data indicated that new graduate nurses in Hawai‘i were employed at a similar rate compared to nurses nationally. However, new graduate nurses employed in Hawai‘i were more likely to be hired into long-term care or other settings. This rate is proportional to employment settings for the overall nursing population in Hawai‘i. Workforce research about enrolled nursing students and existing workforce was used to support surge staffing plans and estimate available workforce.</td>
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<td>Evidence-Based Practice (EBP)</td>
<td>EBP engagement across hospital and school of nursing programs was sustained despite constraints due to COVID-19. EBP workshops and writing workshops pivoted to a more accessible online format with success.</td>
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<td>Clinical Nursing Education</td>
<td>The Centralized Clinical Placement Collaborative program initiates weekly calls to address loss of and changes to clinical education access. The Center worked with the Governor’s Office, Hawai‘i Board of Nursing (HBON), National Council of State Boards of Nursing, Healthcare Association of Hawai‘i (HAH) and others to address severe lack of access for certified tests needed to apply for nursing licensure by examination.</td>
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<tr>
<td>Recruitment of Nurses</td>
<td>HSCN worked with community partners and the Hawai‘i Emergency Management Agency Emergency Support Function 8 (HIEMA ESF-8) to form a working group to identify scenarios and develop strategies for COVID-19 surge workforce shortages. Outcomes included working with Governor’s Office and HBON to enable newly graduated nurses to work with a license waiver, co-leading an initiative with HAH to identify available in-state nurses and nursing students and link them to employers facing urgent nurse and nurse aide shortages due to COVID-19 cases.</td>
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<td>Transition to Nursing Practice</td>
<td>Commitment to new-graduate transition to practice in hospital settings “residency programs” was reinforced, with a new national curriculum to be launched in 2021. The new curriculum enables expanded workforce development opportunities in specialty areas identified as needs prior to and intensified during the COVID-19 pandemic.</td>
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<tr>
<td>Preceptor Tax Credits</td>
<td>Preceptor tax credits were distributed for the first time after Act 43, SLH 2018 was enacted. Activities with academic partners and recruitment of preceptors continued in 2020 to promote and expand this program. Despite COVID-19 constraints, the Preceptor Tax Credits maintained the same volume of preceptor engagement in 2020.</td>
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<td>Professional Development</td>
<td>Nationally accredited nursing professional development opportunities related to Center priority areas, mandates, and COVID-19 were provided by the HSCN in support of nursing-required continuing competency requirements (Act 27, SLH 2015) and pressing nursing issues in 2020. HSCN partnered with UH Mānoa School of Nursing and Dental Hygiene and HAH to disseminate needed COVID-19 education to nurses, statewide. Nearly 6000 hours of continuing nursing education was distributed as an outcome of these partnerships.</td>
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Hawai‘i Journal of Health & Social Welfare
(HJH&SW)

Guidelines for Publication of HJH&SW Supplements

The Hawai‘i Journal of Health & Social Welfare (HJH&SW) partners with organizations, university divisions, and other research units to produce topic-specific issues of the journal known as supplements. Supplements must have educational value, be useful to HJH&SW readers, and contain data not previously published elsewhere. Each supplement must have a sponsor(s) who will work with the HJH&SW staff to coordinate all steps of the process. Please contact the editors at hjhsw@hawaii.edu for more information if you would like to pursue creating a supplement.

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 HJH&SW editorial staff to make certain the educational objectives and value of the supplement are optimized during the planning process.

2. Supplements should treat broad topics in an impartial and unbiased manner. They must have educational value, be useful to HJH&SW readership, and contain data not previously published elsewhere.

3. Supplements must have a sponsor who will act as the guest editor of the supplement. The sponsor will be responsible for every step of the publication process including development of the theme/concept, peer review, editing, preliminary copy editing (ie, proof reading and first round of copy editing), and marketing of the publication. HJH&SW staff will only be involved in layout, final copy editing and reviewing final proofs. It is important that the sponsor is aware of all steps to publication. The sponsor will:
   a. Be the point of contact with HJH&SW for all issues pertaining to the supplement.
   b. Solicit and curate articles for the supplement.
   c. Establish and oversee a peer review process that ensures the accuracy and validity of the articles.
   d. Ensure that all articles adhere to the guidelines set forth in journal’s Instructions to Authors page, especially the instructions for manuscript preparation and the statistical guidelines.
   e. Obtain a signed Copyright Transfer Agreement for each article from all authors.
   f. Comply with all federal, state, and local laws, rules, and regulations that may be applicable in connection with the publication, including ensuring that no protected health information appears in any article.
   g. Work with the editorial staff to create and adhere to a timeline for the publication of the supplement.
   h. Communicate any issues or desired changes to the HJH&SW staff in a timely manner.

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   • Final date to submit a list of all articles, with working titles and authors
   • Final date for submitting Word documents for copy editing
   • Final date for submitting Word documents for layout
   • Final date to request changes to page proofs (Please note that changes to page proofs will be made only to fix any errors that were introduced during layout. Other editing changes will incur an additional fee of $50 per page.)

5. The cost of publication of a HJH&SW supplement is $5,000 for an 8-article edition with an introduction from the sponsor or guest editor. Additional articles can be purchased for $500 each with a maximum of 12 articles per supplement. This cost covers one round of copy editing (up to 8 hours), layout, online publication with an accompanying press release, provision of electronic files, and indexing in PubMed Central, SCOPUS, and Embase. The layout editor will email an invoice for 50% of the supplement to the designated editor for payment upon signature of the contract. The remaining will be due at the time of publication. Checks may be made out to UCERA.

6. The sponsor may decide to include advertisements in the supplement in order to defray costs. Please consult with the HJH&SW advertising representative Michael Roth at 808-595-4124 or email rothcomm@gmail.com for assistance.
7. Supplement issues are posted on the HJH&SW website (http://www.hawaiijournalhealth.org) as a full-text PDF (both of the whole supplement as well as each article). An announcement of its availability will be made via a press release and through the HJH&SW email distribution list. Full-text versions of the articles will also be available on PubMed Central.

8. It is the responsibility of the sponsor to manage all editorial, marketing, sales, and distribution functions. If you need assistance, please contact the journal production editor. We may be able to help for an additional fee.

9. The editorial board reserves the right of final review and approval of all supplement contents. The HJH&SW will maintain the copyright of all journal contents.

Sample Workflow and Timeline for a Supplement

1. The sponsor contacts the HJH&SW editors (hjhsw@hawaii.edu) to discuss the supplement topic, estimated timeline, length and cost. HJH&SW staff will review the journal requirements for articles and share our review process with the sponsor. **Time frame: 2 weeks**

2. The sponsor will complete the draft contract and pay a non-refundable deposit of $2500 or half the contract value. **Time frame: 3 days**

3. The sponsor will solicit articles for the supplement. **Time frame: 3-6 months**

   Articles must comply with:
   • Instructions for Manuscript Preparation and Submission of Research Articles
   • Instructions for Manuscript Preparation and Submission of Columns
   • HJH&SW Statistical Guidelines
   • HJH&SW Style Guide for Native Hawaiian Words and Phrases
   • AMA Manual of Style. A free summary can be found here.

4. The sponsor will oversee the article selection, peer review, and editing process. We recommend that time be allowed for at least two rounds of reviews for each article. **Time frame: 3-6 months**

   • Ensure that each article includes Institutional Review Board (IRB) review and approval, and a statement disclosing any conflicts of interest.
   • Obtain a Copyright Transfer Agreement signed by all authors for each article.

5. Optional: During this time, the sponsor can solicit advertisements for the supplement to help defray costs for publication and/or printing. To initiate this process, the sponsor will work the HJH&SW advertising representative Michael Roth at 808-595-4124 or roth-comm@gmail.com.

6. The sponsor or their designee will conduct a final review of each article to ensure adherence to HJH&SW guidelines and AMA style. **Time frame: 2 weeks**

7. For each article, the sponsor will submit the final Word document and Copyright Transfer Agreement to the HJH&SW journal production editor. The journal production editor will send the articles to the copy editor for final journal style review. Copyediting will be 8 hours per edition plus 1 hour per article for additional articles purchased. Any additional hours will be billed at $100 per hour. **Time frame: 2 weeks**

8. The sponsor will submit the final articles to the layout editor for formatting. **Time frame: 1 month**

   Acting in the role of guest editor, the sponsor will include a column introducing the supplement. **IMPORTANT:** All articles submitted for layout should be in their finalized form. Page proofs will be returned to the sponsor for their review and approval, but changes will only be made to fix any errors that were introduced during the layout process. Any editing or changes to the text or figures after the initial copy layout will incur a fee of $50 per page.

9. The sponsor will review the electronic copy from the layout editor and submit any final corrections. **Time frame: 5 working days**

10. The layout editor will make the final corrections and provide a finished electronic copy of the supplement to the sponsoring editors to allow time for printing.

11. The managing editor will work with the sponsor to draft a press release. Sponsors should contact the managing editor at least 30 days prior to the date of publication to plan and script the press release. Sponsors are encouraged to submit 1-2 photos to accompany the press release. Note that obtaining signed photo releases is the responsibility of the sponsor.

12. The supplement will be published online along with the press release. An electronic copy will be sent to our subscribers and circulation lists, and the edition will be forwarded to the National Library of Medicine for indexing and made available for no cost access to the public.

Revised 2/6/20
The HJH&SW encourages authors to use the appropriate diacritical markings (the 'okina and the kahakō) for all Hawaiian words. We recommend verifying words with the Hawaiian Language Dictionary (http://www.wehewehe.org/) or with the University of Hawai‘i Hawaiian Language Online (http://www.hawaii.edu/site/info/diacritics.php).

Authors should also note that Hawaiian refers to people of Native Hawaiian descent. People who live in Hawai‘i are referred to as Hawai‘i residents.

Hawaiian words that are not proper nouns (such as keiki and kūpuna) should be written in italics throughout the manuscript, and a definition should be provided in parentheses the first time the word is used in the manuscript.

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