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HAWAI‘I JOURNAL WATCH 3
Karen Rowan MS

A RARE CASE OF METASTATIC ESOPHAGEAL ADENOCARCINOMA PRESENTING AS AN ISOLATED CEREBELLAR LESION 4
Ankur Jain MD, FACG and Shilpa Jain MD, FACG

ESCHERICHIA COLI AS A POTENTIAL RESERVOIR OF ANTIMICROBIAL RESISTANCE GENES ON THE ISLAND OF O‘AHU 9
Michael A. Washington PhD; Chris R. Taitt PhD; Jauchia Blythe PhD; Kalei Hering; and Jason Barnhill PhD

MEDICAL SCHOOL HOTLINE 15
Hidden Jewel: The Hyperbaric Treatment Center of the University of Hawai‘i
Susan Steinemann MD, FACS
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The aim of the Hawaiʻi 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 Hawaiʻi and the Pacific region.

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**Hawai‘i Journal Watch**

**Karen Rowan MS**

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

**Diabetes Education Program Blends Family/Friend Support with Technology**

In under-resourced, rural communities in Hawai‘i, a diabetes self-management (DSM) program that taps into friend-and-family support can lead to improved knowledge, self-care behaviors, and hemoglobin A1C levels. Researchers including Joanne R. Loos PhD, of the School of Nursing and Dental Hygiene, piloted a 9-month DSM program on Moloka‘i with 7 participant dyads, each including 1 patient with type 2 diabetes and 1 family member or friend for support. The program involved diabetes education sessions delivered via telehealth, Bluetooth-enabled glucometers, community health services, and mobile technologies to activate and support the program. Participants demonstrated increased diabetes knowledge and all increased their glucose monitoring frequency. Most participants reported increased exercise and increased medication adherence, and some reported increased daily foot exams. The researchers concluded the findings support the utility of leveraging social capital to promote cost-effective, community-centric diabetes management in these settings.


**How SARS-CoV-2 Spreads Through the Air**

Airborne transmission of SARS-CoV-2 is largely governed by physicochemical factors, such as the size of aerosols, the momentum of their motion, and their interactions with various surfaces. In a new review article, researchers led by Yi Y. Zuo PhD, of the John A. Burns School of Medicine and the UH Department of Mechanical Engineering, synthesized the literature on airborne transmission of SARS-CoV-2. The review showed that there is a high likelihood that SARS-CoV-2 spreads via aerosols, and that while large aerosols in inhaled air tend to be deposited in the nose, throat, or bronchi, small particles may penetrate to the furthest alveolar regions of the lungs, where fewer clearance mechanisms are at work and rapid onset of severe infection can begin. Further study of the mechanics of COVID-19 aerosol transmission could lead to science-based ventilation protocols, antiviral materials and coatings, and even new therapeutic interventions, the researchers concluded.


**Utilizing the Social Determinants of Health Framework During COVID-19**

As COVID-19 continues to disproportionately affect older adults, social workers can utilize the social determinants of health (SDH) conceptual framework to guide their care. Yeonjung Jane Lee PhD, of the Myron B. Thompson School of Social Work, identified issues of heightened inequality due to COVID-19. Older adults who live in poverty may face food insecurity or have inadequate access to health care. Older adults with disabilities are at elevated risk of COVID-19 exposure. The pandemic has increased social isolation, which is associated with negative outcomes for older adults with heart disease or problems with psychological well-being or cognitive health. To better support older adults, social workers can facilitate pandemic preparedness and social networking via apps or other safe platforms and provide support to care givers. Lee concluded that the application of the SDH framework can strengthen the response to the pandemic.


**Diabetes Prevention Programs in Hawai‘i Include Many Cultural Adaptations**

In Hawai‘i, diabetes prevention programs based on standardized curricula benefit from the inclusion of culturally appropriate adaptations. Evaluators including L. Brooke Keliikoa DrPH, of the Office of Public Health Studies, described the adaptations made by staff members running programs at 7 federally qualified health centers (FQHCs) in Hawai‘i. The evaluation team conducted a document review and interviewed FQHC staff members. Results showed there were 61 adaptations across the 7 FQHCs, with each FQHC adding 4 to 16 adaptations to the existing curricula. The adaptations included incorporating hula, Zumba, and beach clean-ups as physical activity, featuring foods commonly consumed in Hawai‘i in discussions about diet, and building in social support through a dyadic recruitment strategy. Such adaptations require staff time and creativity, and help to make the programs salient to local communities, which is important in retaining participants in the program.


**Gender Differences in Diet Analysis in a Multiethnic Cohort**

Diet studies often use food frequency questionnaires (FFQs), but often do not account for gender differences in portion sizes in their analyses. Researchers led by Minji Kang PhD, of the University of Hawai‘i Cancer Center, examined FFQ and mortality data from 156,434 participants in the Multiethnic Cohort Study, which includes African American, Native Hawaiian, Japanese American, Latino, and non-Hispanic white participants. The researchers assessed participants’ total daily energy intake based on 2 calculations of portion sizes – one that did not differ by gender, and one that did. Results showed differences between the calculations. For example, women’s mean daily energy intake was 1979 kcal based on the original calculation, but 1595 kcal based on the gender-specific calculation. Moreover, small differences were seen in the associations between total energy intake and all-cause, cardiovascular disease, and cancer mortality. The researchers concluded that studies that use absolute energy intake may benefit from calculating gender-specific portion sizes.

A Rare Case of Metastatic Esophageal Adenocarcinoma Presenting as an Isolated Cerebellar Lesion 5 Years After Treatment

Ankur Jain MD, FACG and Shilpa Jain MD, FACG

Abstract

Isolated brain metastasis (IBM) as a recurrence of primary esophageal adenocarcinoma (AC) has rarely been reported in the literature and typically manifests within a short period of time after diagnosing the primary lesion. We present here an unusual case of an IBM presenting nearly 5 years after neoadjuvant chemoradiation therapy and surgical resection of a primary distal esophageal tumor with no interval evidence of recurrence. A 53-year-old man presented to our gastroenterology clinic with progressive dysphagia and weight loss. On upper endoscopy, the patient was found to have a large obstructing distal esophageal mass with biopsies reported as moderately differentiated AC. Subsequent computed tomography (CT) chest/abdomen/pelvis (C/A/P) and magnetic resource imaging (MRI) brain were negative for any distant metastases. The patient received preoperative chemotherapy and radiation therapy, followed by distal esophagectomy with findings of stage IIIB disease. He did well after surgery and was monitored closely by his oncologist with no evidence of recurrence on interval imaging or follow-up endoscopy. Several years after his diagnosis, however, the patient developed new neurologic symptoms, and an MRI brain revealed a solitary cerebellar lesion with surrounding edema concerning for metastatic disease. Positron emission tomography and CT C/A/P were negative for any other new lesions. The tumor was resected, and pathology was confirmed as metastatic AC of esophageal origin. To our knowledge, this is the first case of recurrent esophageal AC presenting as an isolated cerebellar lesion 5 years after treatment of the primary tumor.

Keywords

Esophageal adenocarcinoma, neoadjuvant chemoradiation therapy, isolated brain metastasis

Abbreviations and Acronyms

AC = adenocarcinoma  
CT C/A/P = computed tomography scan chest/abdomen/pelvis  
GEJ = gastroesophageal junction  
IBM = isolated brain metastasis  
MRI = magnetic resonance imaging  
SCC = squamous cell carcinoma

Introduction

Esophageal cancer is the eighth-most common cancer and the sixth-most common cause of cancer death worldwide. The majority of esophageal cancers worldwide are squamous cell (SCC), but the incidence of adenocarcinoma (AC) arising out of Barrett’s esophagus has risen dramatically, particularly among white males. AC is now more prevalent than SCC in the United States and Western Europe. There are several known risk factors for esophageal AC, but a history of smoking, higher body mass index, gastroesophageal reflux disease, and a low fiber diet carry the highest attributable risk, accounting for almost 80% of cases in the United States.

According to the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program database, approximately 18% of patients with esophageal cancer are found to have localized disease on presentation, 33% have spread to regional lymph nodes, and 39% have distant metastases, with the remaining 10% not being staged. AC most frequently metastasize to intrabdominal sites (liver, peritoneum), while metastases from SCCs are usually intrathoracic. From most to least common, the sites of distant metastases in patients with esophageal cancer are reported to be liver, distant lymph nodes, lungs, bones, adrenal glands, and brain.

Survival in patients with esophageal cancer depends on the stage of the disease; patients with metastases detected in lymph node and solid organs have the lowest survival rates. The overall 5-year survival rate is approximately 19.9%. The 5-year survival rate for patients with localized disease is 47.1%, for those with regional metastases, survival is 25.2%, and for those with distant metastases, survival is 4.9%. The median survival of a patient with distant metastasis is only 6 to 12 months. SCC and AC, stage-by-stage, appear to have equivalent survival rates. Neoadjuvant chemoradiotherapy followed by surgical resection has become the standard of care for non-metastatic esophageal cancer, with the highest survival among those who have achieved a complete pathologic response (absence of viable residual tumor) at the time of surgery.

Brain metastases have been considered uncommon in patients with esophageal cancer, with a published incidence of less than 5%. The median time to diagnosis of brain metastasis is approximately 12 months, and the majority of these are supratentorial. We present here an unusual case of an isolated brain metastasis (IBM) presenting nearly 5 years after treatment of a primary distal esophageal tumor with no interval evidence of recurrence.

Case Report

A 53-year-old Japanese man presented to our outpatient gastroenterology clinic in Honolulu, Hawai’i, with progressive dysphagia to solids and liquids. He also reported a weight loss of 10 pounds over the past month. He denied any history
of gastroesophageal reflux disease, smoking, or heavy alcohol use. Upper endoscopy revealed a large friable, ulcerated, fungating mass at 38 cm, causing near complete obstruction of the esophageal lumen (Figure 1). The scope could not be advanced beyond the mass. Multiple biopsies were taken, and pathology revealed moderately differentiated AC.

A staging work-up by oncology including computed tomography (CT) chest/abdomen/pelvis (C/A/P), positron emission tomography scan, and magnetic resonance imaging (MRI) brain was negative for any obvious lymphadenopathy or distant metastases. After receiving pre-operative chemotherapy and radiation therapy, the patient underwent laparoscopic Ivor-Lewis esophagectomy with creation of a neo-esophagus. He was found to have a 4.8-cm tumor at the gastroesophageal junction (GEJ) with lymph-node positive disease, and his final pathologic diagnosis was reported as Siewert II, stage G3T3N2M0 (IIIB) poorly differentiated esophageal adenocarcinoma. The patient did well after surgery without any dysphagia, and he began to gain weight steadily. He was followed closely by oncology, and CT C/A/P done every 6 months after surgery showed no evidence of metastasis. A follow-up upper endoscopy performed 2 years later was also normal, and the patient was felt to be in clinical remission.

Approximately 5 years after surgery, the patient developed persistent nausea, dizziness, and vertigo and was noted to be losing weight again. He was found on MRI brain to have a new 4.0 × 2.9 × 3.5-cm well-circumscribed cerebellar lesion with surrounding edema and mass effect concerning for metastasis (Figure 2). Positron emission tomography scan/CT C/A/P was negative for any other new lesions. The patient underwent surgical resection of the lesion with findings confirming metastatic AC of esophageal origin with features similar to the GEJ tumor (Figure 3). He is now awaiting post-operative stereotactic radiosurgery and will continue to be followed closely by the oncology and neurosurgery services.
Figure 2. Magnetic Resonance Imaging of Brain with Mass in Cerebellum

Coronal view of cerebellar tumor with dimensions of $4.0 \times 2.9 \times 3.5$ cm-enhancing lobulated well-circumscribed mass of central right cerebellum and cerebellar vermis containing hemorrhagic products with moderate surrounding edema and mass effect greater on the right.

Figure 3. Imaging of Metastatic Adenocarcinoma Cells in the Brain

Cerebellar tumor (20x magnification) - metastatic adenocarcinoma with features similar to the gastroesophageal junction tumor.
Discussion

Epidemiology

Current consensus-based guidelines for staging, such as those published by the National Cancer Comprehensive Network and European Society for Medical Oncology, do not recommend routine pretreatment brain imaging for patients with esophageal or esophagogastric junctional cancers since brain metastasis is considered uncommon in these patients.\(^{13-14}\) It is not considered to be cost-effective or necessary as part of the initial staging evaluation or subsequent surveillance unless symptoms or signs raise suspicion for brain metastases. Brain metastases are now being encountered more commonly than previously appreciated however, perhaps due to improved survival in patients with esophageal cancer as well as advanced neuroimaging techniques.\(^{15}\)

In more contemporary esophageal cancer cohorts with higher percentages of AC, the incidence of brain metastases has been reported to be as high as 13%.\(^{16}\) In a large retrospective study by Harada and others, the rate of brain metastases in upper gastrointestinal cancer was highest among patients with proximal esophageal AC. Siewert type I lesions (epicenter of lesion 1 to 5 cm above GEJ) and presence of lymph node metastases were independent risk factors for brain metastases in these patients.\(^{17}\) Our patient initially presented with a distal esophageal AC (Siewert type II, epicenter of lesion up to 1 cm above and 2 cm below GEJ) but was found to have lymph node metastases at the time of surgery which likely increased his risk of brain metastases.

Nobel and her colleagues defined IBMs as truly isolated recurrences of esophageal cancer in patients who have achieved complete pathologic response after neoadjuvant therapy or the first observed site of widespread distant metastases in those with residual nodal disease.\(^{18}\) They further suggested that patients who receive neoadjuvant therapy and achieve a complete pathologic response would benefit most from brain imaging, both preoperatively and with routine surveillance, due to the increased likelihood of IBM.\(^{19}\) Our patient was found to have lymph node-positive disease after neoadjuvant therapy, but a CT C/A/P at the time of his brain metastasis did not reveal any evidence of concurrent systemic metastases. This finding supports the suggestion that these patients should receive brain imaging, both preoperatively and with routine surveillance.

Welch and others reported that the median time to diagnose brain metastasis from the original diagnosis of esophageal cancer was 11 months.\(^{11}\) In another study by Kothari et al, the median latency after primary diagnosis was 14 months, ranging from 0 to 70 months.\(^{12}\) The majority of these lesions (60%) were supratentorial, which includes the cerebrum.\(^{12}\) In a case report by Tuna and others, a patient developed a cerebellar metastasis from esophageal cancer within 2 years of her primary diagnosis.\(^{15}\) Interestingly, our patient developed neurologic symptoms and a new cerebellar lesion almost 5 years after his original diagnosis.

Prognosis

Nobel and her colleagues found that the median overall survival of patients with isolated brain metastases was approximately 0.95 years, but was significantly higher for those with a pathologic complete response to neoadjuvant therapy than those without (median , 1.56 vs 0.66 years).\(^{18}\)

In their study, Harada and others found that the median overall survival of patients with brain metastases was only 1.16 years but was more favorable for patients with a solitary brain lesion with no other distant metastasis and who underwent surgery or stereotactic radiosurgery for treatment of the lesion.\(^{17}\) Welsh and colleagues observed that survival was superior for patients who initially had surgical resection of brain lesions compared to patients treated with whole-brain radiotherapy or stereotactic radiosurgery alone.\(^{11}\) Song and others also reported that a solitary brain lesion and surgical treatment of the lesion provide a good prognosis.\(^{19}\)

Although our patient had residual nodal disease after neoadjuvant therapy, he did present with a solitary brain lesion which was surgically treated and had no concurrent systemic metastases, which are all better prognostic indicators.

Conclusion

This case illustrates the potential for esophageal adenocarcinoma to present as an isolated brain metastasis several years after treatment of the primary lesion and subsequent clinical remission. The overall incidence of esophageal cancer-related brain metastases appears to be rising. Further studies are needed to determine whether MRI brain should now be considered part of routine staging and surveillance protocols for esophageal adenocarcinoma after diagnosis of a primary tumor.
Table 1. Siewert-Stein Classification of Esophageal Adenocarcinoma

<table>
<thead>
<tr>
<th>Siewert-Stein Classification Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Adenocarcinoma of the distal esophagus (epicenter of lesion 1 to 5 cm above gastroesophageal junction [GEJ])</td>
</tr>
<tr>
<td>Type II</td>
<td>Adenocarcinoma of the cardia (epicenter of lesion up to 1 cm above and 2 cm below GEJ)</td>
</tr>
<tr>
<td>Type III</td>
<td>Sub-cardial type adenocarcinoma (epicenter of lesion 2 to 5 cm below GEJ)</td>
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</table>


Table 2. TNM Staging System for Esophageal Adenocarcinoma

<table>
<thead>
<tr>
<th>TNM Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor (T)</td>
<td>Has the tumor grown into the wall of the esophagus?</td>
</tr>
<tr>
<td>Node (N)</td>
<td>Has the tumor spread to the lymph nodes?</td>
</tr>
<tr>
<td>Metastasis (M)</td>
<td>Has the cancer spread to other parts of the body?</td>
</tr>
</tbody>
</table>


Table 3. Cancer Staging System for Esophageal Adenocarcinoma

<table>
<thead>
<tr>
<th>Esophageal Adenocarcinoma stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Stage 0</td>
<td>The cancer is only in the epithelium (top layer of cells lining the esophagus)</td>
</tr>
<tr>
<td>Stage I</td>
<td>The cancer is growing into the lamina propria or muscularis mucosa (tissue under the epithelium, submucosa, or muscularis propria (thick muscle layer))</td>
</tr>
<tr>
<td>Stage II</td>
<td>The cancer is growing into the muscularis propria and is poorly differentiated (high grade), has spread to 1 or 2 nearby lymph nodes, or is growing into the adventitia (outer layer of the esophagus)</td>
</tr>
<tr>
<td>Stage III</td>
<td>The cancer has spread to no more than 6 lymph nodes or is growing into the pleura (the thin layer of tissue covering the lungs), the pericardium (the thin sac surrounding the heart), or the diaphragm (the muscle below the lungs that separates the chest from the abdomen) and has spread to no more than 2 nearby lymph nodes.</td>
</tr>
<tr>
<td>Stage IV</td>
<td>The cancer is growing into the trachea (windpipe), the aorta (the large blood vessel coming from the heart), the spine, or other crucial structures and has spread to no more than 6 nearby lymph nodes or has spread to 7 or more nearby lymph nodes</td>
</tr>
</tbody>
</table>


Conflict of Interest

None of the authors identify a conflict of interest.

Acknowledgment

Dr. Thomas Namiki (Pathologist, Hawai’i Pathologists’ Laboratory)
Escherichia coli as a Potential Reservoir of Antimicrobial Resistance Genes on the Island of O‘ahu

Michael A. Washington PhD; Chris R. Taitt PhD; Jauchia Blythe PhD; Kalei Hering; and Jason Barnhill PhD

Abstract

The problem of antimicrobial-resistant bacteria has not been adequately explored in the tropical island environment. To date, there has not been a systematic investigation into the prevalence and distribution of antimicrobial resistance determinants in the Hawaiian Islands. Urinary isolates are the most common bacterial pathogens encountered in the clinical laboratory. Therefore, the antimicrobial resistance determinant profiles of these organisms can serve as a sentinel for the overall antimicrobial resistance situation in a localized patient population. In this study, 82 clinical isolates of Escherichia coli derived from 82 distinct patients were collected at a large medical center on the island of O‘ahu. Each isolate was evaluated for the presence of antimicrobial resistance genes using a microarray-based approach. A total of 36 antimicrobial resistance genes covering 10 classes of antimicrobial compounds were identified. Most isolates were found to harbor between 3 and 5 antimicrobial resistance genes. Only a few isolates were found to harbor more than 12 genes. Significantly, a high rate of phenotypic resistance to one of the first-line treatments for uncomplicated urinary tract infection (sulfamethoxazole) was identified. This phenotype was correlated to the presence of sulfonamides and trimethoprim resistance determinants. Since E. coli is one of the most encountered pathogens in the hospital environment, the presence of clinically relevant resistance determinants in isolates of this organism from a clinical setting on O‘ahu is a significant finding that warrants further investigation.

Keywords

antimicrobials, antimicrobial resistance determinants, E. coli, microarray

Abbreviations and Acronyms

AMR = antimicrobial resistance
ARDM = antimicrobial resistance determinant microarray
AST = antimicrobial sensitivity testing
ESBL = extended-spectrum β-lactamase
SXT = sulfamethoxazole
TAMC = Tripler Army Medical Center

Introduction

Antimicrobial resistance is a serious threat to the continuation of modern antibacterial chemotherapy. Bacterial populations can develop antibacterial resistance by various mutational events on the chromosome that result in increased survivability of the population in the presence of an antibacterial agent. They can also develop resistance by acquiring exogenous genes that travel from cell to cell on mobile genetic elements or plasmids or by becoming infected by bacterial phages or other viruses that ferry various antibacterial resistance genes from strain to strain. Since the genes carried on the bacterial chromosome are typically non-mobile, they are not likely to spread to nearby populations of bacteria, while genes carried on mobile genetic elements, plasmids, or viruses can be readily spread between populations. It is, therefore, important to identify the number and types of antibacterial resistance genes that are present in a local bacterial population and to identify whether or not they reside on the chromosome to inform the rational development of clinical interventions and preventive measures. Although numerous bacterial species cause human disease, it is impractical to study them all simultaneously. Therefore, it is essential that sentinel or indicator organisms be used to monitor the development and spread of antibacterial resistance.

Escherichia coli is a ubiquitous organism that can often lead to fatal infections in immunocompromised humans. The abundance of this organism in the clinical laboratory makes it an ideal subject for surveying the antibacterial resistance landscapes of small clinics, community hospitals, and surrounding populations. Although it has been historically investigated as an indicator of human fecal contamination, E. coli can propagate in the environment outside of a human host and colonize numerous animal species. Further, it is a naturally competent organism that can incorporate extracellular DNA in the ambient conditions present in environmental waters. Regional temperature variation has been associated with increases in the rates of E. coli infection in the Pacific region, and it has been suggested that global warming may lead to further increases in overall infection rates.

The propensity for E. coli to serve as a reservoir for antimicrobial determinants genes has been previously demonstrated. Indeed, macrolide resistance genes that have been found to hinder the treatment of Shigella infections have been identified in E. coli, and the horizontal of these genes have led to recent increases in the detection of macrolide resistance in Shigella species. In addition, sulfonamide resistance genes have been detected in E. coli strains that harbor the transmissible genetic structures that facilitate the dissemination and integration of these genes into a wide range of bacterial pathogens. It is suspected that these strains may eventually lead to an increase in the overall levels of antimicrobial resistance in currently circulating bacterial communities. These properties of E. coli indicate that it has the potential to serve as a sentinel or indicator of the overall antimicrobial resistance profile of a localized patient population in the community hospital and large medical center setting.
The prevalence and distribution of antimicrobial resistance genes have not been adequately characterized in the Pacific region, and there have been no recent antimicrobial resistance studies on the island of O‘ahu. This island is characterized by a warm and humid tropical environment, the presence of numerous recreational and coastal waters, and a large military population. Since seawater can serve as a source of multidrug resistant E. coli, it is expected that residents and visitors may be exposed to one or more of the environmental reservoirs of this pathogen at some point during their time on the island. Exposure can occur during recreational activities, by contact with miscellaneous surfaces in public and non-public spaces, and by iatrogenic exposure in clinics and hospitals. The goal of this study was to determine the potential for E. coli to serve as a reservoir for antimicrobial resistance genes on O‘ahu by evaluating 82 clinical isolates that were obtained from urinary cultures collected between 2014 and 2015, analyzed between 2016 and 2017, and evaluated between 2018 and 2019.

Materials and Methods

Patient Population

This study was conducted at the Tripler Army Medical Center (TAMC) on the island of O‘ahu, in the state of Hawai‘i (21.4389°N, 158.0001°W). TAMC is the only federal medical center in the Pacific Basin; it serves a patient population of 200,000 military beneficiaries annually, including active duty and retired military, their families, and members of a variety of indigenous Pacific Islander groups. Significantly, TAMC regularly receives samples and patients from throughout the Pacific region to include the Republic of the Marshall Islands, the Republic of Palau, and the Federated States of Micronesia.

Bacterial Isolates

Since urine samples are the most common samples submitted to the clinical laboratory and since E. coli is the most common isolate with a potential to serve as a sentinel species, a total of 82 urinary isolates of E. coli were obtained from the pathology laboratory at TAMC. They consisted of pre-existing, anonymous, clinical diagnostic isolates that were stripped of all identifiers. All isolates were obtained from urine collected as part of the routine care of patients with suspected urinary tract infections. The clinical laboratory procedure for the isolation of bacterial pathogens from urine is as follows: after collection, the urine was transported to the clinical laboratory where it was used to inoculate blood agar and MacConkey plates. The plates were then incubated aerobically at 35°C for 24 hours, and the resulting isolates were collected and re-streaked onto blood agar plates. The isolates were then supplied to the research group as pure colonies on blood agar plates. To avoid skewing our results, isolates were selected only based on their identification as E. coli and not based on phenotypic antimicrobial susceptibility patterns or demonstrated resistance criteria.

Antimicrobial Sensitivity Testing

Antimicrobial sensitivity testing (AST) was performed on a total of 22 out of 82 isolates due to the availability of materials and instrument availability using the Vitek 2 (bioMérieux, Inc.: Hazelwood, MO). All testing was performed following the manufacturer’s instructions.

DNA Isolation and Microarray Hybridization

DNA was extracted from all 82 bacterial isolates using the MasterPure DNA and RNA Complete Purification Kit (Epicenter Biotechnologies: Madison, WI) and quantified using the Qubit fluorimeter (Invitrogen/Life Technologies: Grand Island, NY). Extracted DNA was whole genome amplified, fragmented using DNase I, biotin-labeled, and hybridized on the Antimicrobial Resistance Determinant (ARDM) Microarray (version 2 [v.2]) as previously described. Microarray pre-hybridization and hybridization were performed at 60°C in a rotisserie incubator, followed by washing and labeling with polymeric streptavidin horseradish peroxidase (S104PHR, Fitzgerald Industries: North Acton, MA). ARDM interrogation was accomplished using the ElectraSense Reader (CustomArray: Woodinville, WA). The ARDM v.2 comprises 2,240 probes, corresponding to 236 antimicrobial resistance determinant genes. Content of the microarray is described in Taitt, et al.

Data Analysis

Signal processing and evaluation of the signal to noise ratio was accomplished utilizing previously established algorithms. Briefly, 2 signal thresholds were established: a high stringency threshold resulting from the mean of the lowest 2,128 probes with 3 standard deviations and a low stringency threshold resulting from the mean of the lowest 2016 probes with 3 standard deviations. A gene detection was considered positive if at least half the probes for that gene were above the high stringency threshold, or 70% of the probes were above the low stringency threshold. A chi-square test with a significance level set at $P < .05$ was used to evaluate possible correlations between bacterial genotype and antimicrobial resistance phenotype.

Results

Patient Population and Phenotypic Antimicrobial Resistance

This study was conducted on the island of O‘ahu at the only military tertiary medical facility in the Pacific Basin. The patient population consists of men and women who were active duty service members, retired service members, military family members, and indigenous Pacific Islanders from throughout the region. A total of 82 E. coli isolates were collected.

Phenotypic susceptibility testing was only performed on a subset of the isolates due to resource limitations (n=22). Over
half of those isolates produced extended-spectrum β-lactamases (ESBLs, 59%); a large number were found to be resistant to ampicillin (86%), and over half were resistant to first-, second-, third-, or fourth-generation cephalosporins. Resistance to fluoroquinolones and trimethoprim/sulfamethoxazole (SXT) was present in 40% of the isolates and was of concern as they have been used as a treatment for uncomplicated urinary tract infections in the past (Table 1).²¹

### Antimicrobial Resistance Gene Detection

A total of 36 unique antimicrobial resistance (AMR) genes were detected by the microarray within the tested population (Figures 1 and 2). These genes covered 10 classes of antimicrobials: β-lactams, aminoglycosides, macrolides, tetracyclines, phenicols, fluoroquinolones, quaternary amines, streptothricin, fluoroquinolones, sulfonamides, and trimethoprim. The number of genes detected in the tested population in this study was skewed, with most isolates harboring between 3 and 5 AMR genes and a small number of isolates harboring 10 or more AMR genes (Figure 3). There was an average of 4.4 and a median of 3 AMR gene detections per isolate. Five isolates harbored an astonishing 14 genes. The AMR determinants most detected were the chromosomal genes, *cmr* (70%), *mac*(A) (57%), *mac*(B) (48%), and *bla*TEM (29%).

Seven β-lactamase genes were detected throughout the isolate set. Twenty-four isolates harbored *bla*TEM, AST data were available for half of the *bla*TEM-positive strains, and all but 1 was resistant to both ampicillin and ampicillin/sulbactam (data not shown), suggesting that these isolates harbored inhibitor-resistant TEM-type β-lactamases. One isolate carrying *bla*TEM was susceptible to ampicillin and all other β-lactam antibiotics, suggesting that the *bla*TEM gene was not transcribed or that the gene product was non-functional. Significantly, 24 isolates were found to carry genes from the *bla*CTX-M-1 (13%) or *bla*CTX-M-9 families of ESBLs. Members of this family are typically transmitted on plasmids, and carriage of these genes positively correlated with

#### Table 1. Antimicrobial Resistance Profile of Bacterial Isolates

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>n (%)</th>
<th>N=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBL Producer</td>
<td>13 (59%)</td>
<td></td>
</tr>
<tr>
<td>Ampicillin alone</td>
<td>19 (86%)</td>
<td></td>
</tr>
<tr>
<td>Ampicillin + Sulbactam</td>
<td>14 (64%)</td>
<td></td>
</tr>
<tr>
<td>Cefazolin (first generation)</td>
<td>14 (64%)</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime (third generation)</td>
<td>13 (59%)</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone (third generation)</td>
<td>14 (64%)</td>
<td></td>
</tr>
<tr>
<td>Ceftepime (fourth generation)</td>
<td>13 (59%)</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Ertapenem</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>9 (40%)</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>9 (40%)</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>9 (40%)</td>
<td></td>
</tr>
</tbody>
</table>

* ESBL., extended-spectrum β-lactamase

---

**Figure 1. Distribution of Antimicrobial Resistance Genes in Bacterial Isolates**

* n=82 isolates; * Beta-lactams and aminoglycoside genes
ESBL phenotype (chi-square $P=.008$). Notably, none of the 83 tested strains harbored any of the 8 additional ESBL or 15 carbapenemase genes included in the ARDM v.2 chip content: $bla_{BEL}$, $bla_{GES}$, $bla_{GIM}$, $bla_{IMP}$, $bla_{KPC}$, $bla_{NDM}$, $bla_{OXA-10/PSE}$, $bla_{OXA-23}$, $bla_{OXA-24}$, $bla_{OXA-48}$, $bla_{OXA-51}$, $bla_{PER}$, $bla_{SME}$, $bla_{SPM}$, $bla_{VEB}$, $bla_{VIM}$.

A total of 11 aminoglycoside resistance genes were detected, but these were not found in a large proportion of the population under study; two-thirds of the isolates did not harbor any aminoglycoside resistance genes. The most detected aminoglycoside AMR genes were $strB$ and $strA$ that were often found to occur together. One isolate positive for $aac(6)-ib$ was also resistant to ciprofloxacin and levofloxacin, suggesting that the detected $aac(6)-ib$ gene may indeed be the fluoroquinolone resistant variant, $aac(6)-ib-cr$. However, we did not attempt to sequence this gene or the quinolone resistance-determining regions of $gyrA$ and $parC$, most typically associated with high-level fluoroquinolone resistance. $QnrS$, observed in one isolate, typically confers only low-level fluoroquinolone resistance.
Although macrolides have reduced activity against gram-negative bacteria due to poor penetration of the outer membrane, it was noted that the mac(A)/mac(B) efflux pump genes were found in over 40% of the population. However, the mph(A)/mph(K) genes that confer resistance to azithromycin, which is clinically useful in certain situations, were found in 16% of the study population. Four tetracycline resistance genes were detected with a relatively low prevalence of 16%. Among these, the tet(A) gene was the most common (10%), followed by tet(B) (5%). The sulfonamide resistance genes, sul1 and sul2, were found in 12 and 10 isolates, respectively. Eighteen isolates harbored a trimethoprim resistance determinant, but none of them carried more than 1. Co-carriage of sul1 or sul2 with 1 of the trimethoprim resistance genes was observed in 13 strains and was correlated with phenotypic SXT resistance (P=.003). Two observations may be of particular concern to clinicians and epidemiologists. There was a high rate of carriage of CTX-M type ESBLs (29% overall), and there is a strong possibility that at least some of their genes are being carried on plasmids. The even higher rate of ESBL phenotypes (59% of the 22 isolates with AST results) may indeed portend the eventual failure of third- and fourth-generation cephalosporins within the local communities. The high rate of resistance to ciprofloxacin is also of great concern; ciprofloxacin is an alternative therapeutic for uncomplicated urinary tract infection in cases of known allergy to SXT or when resistance to SXT is suspected; SXT resistance was observed in 40% of our tested isolates. Increasing prevalence of fluoroquinolone resistance in a population with already high rates of SXT resistance would significantly limit the therapeutic options available to clinicians treating urinary tract infections.

Several potential assemblages of antimicrobial resistance genes were detected. Sul1 was found to occur in combination with the quaternary amine resistance gene qacED1 in 12 isolates. These genes are often associated with the presence of class 1 integrons. One isolate was found to harbor dfrA1, aadA1/A2, and sat2, a combination often associated with class 2 integrons. Six isolates were found to harbor the same unique combination of 11 genes: aadA4, aph3/str(A), aph6/str(B), mac(A), mph(A)/mph(K), tet(A), cmr, qacED1, sul1, sul2, and dfrA17. While some members of these genes are typically chromosomal (cmr, mac(A)), others are often found on plasmids. It is also interesting to note that 5 of the 6 isolates also harbored blaCTX-M-1 (3 isolates) or blaCTX-M-9 (2 isolates), which are also typically plasmid-borne. These data suggest that there may be 1 or more multi-drug resistant plasmids circulating in Hawai‘i.

Discussion

To our knowledge, this is the first surveillance study of the prevalence and diversity of AMR determinants in the Hawaiian Islands. It is important to note that the only selection criteria used for the inclusion of isolates into this study was the identification of each isolate as E. coli. This limitation suggests that the data obtained in this study may be somewhat representative of the overall AMR status of urinary E. coli isolates in the overall patient population at the time of collection. It should also be noted that although several antimicrobial resistance determinants known to be transmitted by plasmids were identified, there was no effort to separate chromosomal DNA from plasmid DNA. Therefore, the localization of a particular determinant to an individual plasmid could not be demonstrated. Some of the AMR genes detected here are not clinically relevant, including mac(A), mac(B), and cmr. However, a significant number of isolates harbored genes considered of clinical importance. Significantly, there was a high level of phenotypic resistance (>40%) to SXT, which was correlated with co-carriage of sulfonamide and trimethoprim resistance determinants. Importantly, SXT is a first-line therapeutic agent for uncomplicated urinary tract infections.

Our overall sample size was small (n=82 for genotypic analysis, n=22 for phenotypic analysis), and therefore extrapolating this result to the general bacterial population in Hawai‘i is not appropriate. However, our results point to the potential for some alarming trends. Indeed, the level of horizontal transfer of resistance determinants within the geographic confines of a relatively small Pacific island should be monitored. The emerging concept of the “coalescence” of microbial communities suggests that horizontal gene transfer tends to occur because of environmental forces that bring communities of microorganisms into contact with one another. It is possible that the effects of human activity are amplified in small island environments due to the close association between the microbial, animal, fungal, and plant communities. The results presented here should be followed up with more in-depth studies involving larger numbers of isolates and plasmid analysis. These studies should aim at identifying the source of the antimicrobial resistance genes that were detected in this study, and an effort should be made to determine the spatial distribution and movement patterns of those genes on the island of O‘ahu and throughout the Pacific region so that the risks associated with antimicrobial resistance can be anticipated and mitigated.

Disclaimer: The views expressed herein are those of the authors and do not reflect the position of the United States Military Academy, the Department of the Army, the Department of the Navy, or the Department of Defense.

Conflict of Interest

None of the authors identify any conflicts of interest.

Acknowledgements

This work was funded by the Army Advanced Medical Technology Initiative of the US Army Medical Research and Development Command Telemedicine and Advanced Research Technology Center.
Walking past the nondescript building at the southeast corner of the Kuakini Medical Center (KMC) campus, people may not realize that it houses an essential resource for the state of Hawai‘i. The Hyperbaric Treatment and Wound Care Center (HTC), Hawai‘i’s “dive chamber,” has been providing life- and limb-saving hyperbaric oxygen therapy (HBOT) for over 37 years, now celebrating its 25th anniversary at its present location at KMC’s Hale Pulama Mau building. The unassuming facade belies its importance as the only emergency hyperbaric chamber in the state, serving the most critical patients in need of HBOT, and an essential safety net for military and commercial scuba dive operations. The chamber is owned by the University of Hawai‘i John A. Burns School of Medicine (JABSOM), and staffed and supported by University Health Partners, the faculty practice of JABSOM. The HTC has an illustrious history of research under Edward Beckman MD, Frank Farm, Jr., Robert Overlock MD, and Richard Smerz DO, PhD, including development of the novel “Hawaiian Deep Tables.” In addition to dive emergencies, the HTC treats a variety of medical conditions including radiation injury and problem wounds. The HTC serves also as a training site for medical students, residents, and fellows both local and international.

HBOT is the primary treatment for decompression illness (“the bends”) and arterial gas embolism, and reduces the mortality from acute carbon monoxide poisoning. Patients with these maladies can be critically ill, paralyzed or require ventilator support. The large multiplace HTC chamber enables care as it allows medical equipment and multiple clinicians to be in the chamber with the patient. It accommodates various patient positions, oral intake, and intravenous therapy. However, the HTC chamber also is very resource-intensive to operate, requiring constant maintenance and a minimum of 4 technicians and clinicians to treat a single patient. Economic pressures have made multiplace chambers an endangered species, less than 16% of hyperbaric facilities have multiplace chambers, and only 12% provide emergency services to high-acuity patients.

According to the Hawaiian Islands Recreational Scuba Association, an average of 1000 divers per day participated in recreational scuba diving activities in Hawai‘i waters in pre-pandemic times. Military, research, and commercial entities also engage in daily dive operations. Despite technological advances including dive computers and detailed safety protocols, HTC continues to treat approximately 2 dozen patients per year with serious dive-related injuries. Many of these patients that are treated for decompression illness adhered to their dive plan and dive computers, i.e. suffered an “unexplained hit,” or without obvious cause. Health care related events such as iatrogenic air embolism, and environmental exposures such as carbon monoxide poisoning, remain omnipresent and unpredictable risks. All of these patients require expedient evaluation and treatment, and the HTC is their lifeline. The next closest emergency chamber is in San Diego; inherent delays in treatment and risks of air transport would significantly increase morbidity in Hawai‘i patients.

Over 10% of Hawai‘i residents have diabetes, with an even greater prevalence among Native Hawaiians and Pacific Islanders. Diabetics have a roughly 1 in 5 chance of developing a foot ulcer, associated with an 11% annual mortality in Medicare beneficiaries. The American Diabetes Association consensus statement confirms: “Any ulcer present over four weeks is a cause for concern, as it is associated with worse outcome including amputation.” HBOT, in conjunction with comprehensive wound care, improves the odds of healing, achieving a significant improvement in amputation-free survival. Patients at the HTC receive intensive monitoring with glucose checks, daily wound care, and surgical wound debridement as needed.

Cancer survivors who have received radiation therapy may also benefit from HBOT. The late effects of radiation therapy include radiation cystitis, proctitis, osteoradionecrosis, and other soft tissue necrosis. About half of patients requiring oral surgery after high dose radiation therapy have complications including delayed healing, wound infection, and dehiscence. This risk can be diminished four-fold with the use of adjunct HBOT. Other approved indications for HBOT include refractory osteomyelitis, acute traumatic peripheral ischemia, crush injuries, necrotizing fasciitis, skin grafts, and actinomycosis.
Providers are encouraged to talk with hyperbaric physicians at the HTC, available 24/7, to discuss potential patients (808) 587-3425.

The logistics of treating patients living outside Honolulu are considerable but not insurmountable. Over a third of emergency cases are transferred from neighbor islands. Patients with elective conditions for HBOT (e.g. diabetic foot ulcer) have no restrictions on air travel, and typically remain on Oʻahu for their weekday treatments, returning home on the weekends. New patients receive a telehealth consultation, and educational videos orient the patient to the chamber environment and teach techniques of ear pressure equalization.

The SARS-CoV-2 (COVID-19) pandemic has raised valid concerns about the safety of a multiplace chamber environment, as patients and care providers are in a common enclosed space during HBOT. The Undersea & Hyperbaric Medicine Society (UHMS) provided guidelines for infection control, patient treatment, and staff safety in multiphase chambers. Patients are assessed and counseled regarding their risk for complicated COVID-19 infection and are repeatedly tested for COVID-19. HBOT protocols have been modified to allow for greater distancing in the chamber and all patients have their own personal oxygen and air intake and exhaust for the duration of HBOT, with the exception of the initial 2 minutes of chamber pressurization. Communication with mainland hyperbaric centers has confirmed no signs of increased virus transmission in the multiphase environment following appropriate protocols.

There are intriguing scientific hypotheses and ongoing clinical trials investigating the use of HBOT for patients with COVID-19 infection. HBOT can transiently ameliorate hypoxemia in patients. More durable benefits have been postulated from attenuation of the inflammatory response, repayment of accrued oxygen debt, and possible reduction in hypercoagulation.8 UHMS recommends treating COVID-19 patients only in the context of approved clinical trials. The HTC is not currently participating in any of these trials and, given its responsibility as the only emergency chamber in the region with limited resources for staffing, cannot absorb the risk inherent in trial participation. COVID-19 infection is considered a contraindication to elective HBOT at the HTC, and a relative contraindication to emergency treatments, with those patients evaluated on a case-by-case basis. However, the hyperbaric community anxiously awaits the results of national trials, which may inform practice in this realm.

The sustainability of the HTC, for economic viability and maintaining the unique skills of the hyperbaric staff, is dependent upon community referrals for wound care and elective HBOT. However, due to the high cost of maintaining 24/7 availability of a free-standing facility, there remain substantial costs that are not covered by clinical revenue. Philanthropic support of the HTC through the University of Hawaiʻi Foundation is encouraged. Members of the dive community remain philosophically supportive, but commercial dive operators have been hard hit financially by the pandemic. Appreciation and funding for Hawaii’s multiphase chamber facility and uniquely skilled staff cannot be subject to chance and circumstance. This essential emergency service and public health resource – a jewel of Hawaiʻi – deserves substantial and durable support from the government.

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References
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.

Examples of Hawaiian words that may appear in the HJH&SW:

‘āina  Mānoa
ali‘i  Māori
Hawai‘i  Moloka‘i
kūpuna  O‘ahu
Kaua‘i  ‘ohana
Lāna‘i  Wai‘anae
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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:

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   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.)

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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.

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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

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