

# Hawai‘i Journal of Medicine & Public Health

A Journal of Asia Pacific Medicine & Public Health

August 2015, Volume 74, No. 8, ISSN 2165-8218

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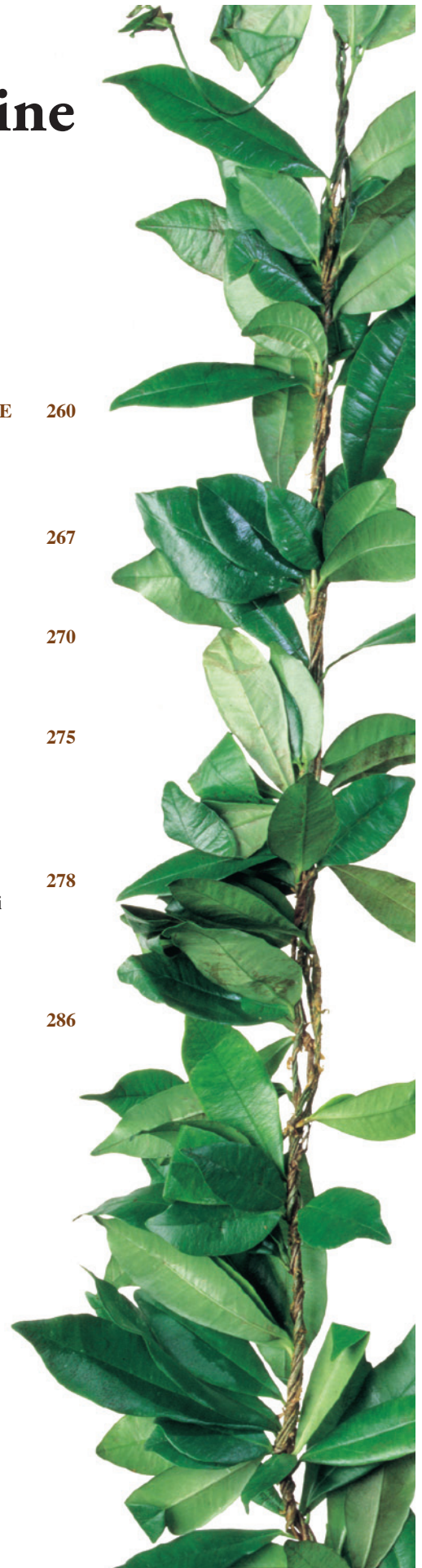
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A Journal of Asia Pacific Medicine & Public Health

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

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

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

Hawai'i Journal of Medicine & Public Health  
677 Ala Moana Blvd., Suite 1016B  
Honolulu, Hawai'i 96813  
<http://www.hjmph.org>; Email: [info@hjmph.org](mailto:info@hjmph.org)

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

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# Lemierre's Syndrome Caused by *Klebsiella pneumoniae* in a Diabetic Patient: A Case Report and Review of the Literature

Alan Chuncharunee MD and Thana Khawcharoenporn MD, MSc

## Abstract

Lemierre's syndrome is characterized by an oropharyngeal infection with internal jugular vein thrombosis followed by metastatic infections in other organs. This infection is usually caused by *Fusobacterium* spp. In this report, we present a rare case of *Klebsiella pneumoniae*-associated Lemierre's syndrome in a patient with poorly-controlled diabetes mellitus. The infection was complicated by septic emboli in many organs, which led to the patient's death, despite combined antibiotics, anticoagulant therapy, and surgical intervention. Therein, a literature review was performed for reported cases of Lemierre's syndrome caused by *Klebsiella pneumoniae* and the results are summarized here.

## Keywords

*Klebsiella pneumoniae*, Lemierre's syndrome, diabetes mellitus, review, complications

## Introduction

Lemierre's syndrome is a rare and almost forgotten, yet potentially life-threatening, disease. The disease is commonly characterized by an oropharyngeal infection resulting in internal jugular vein thrombophlebitis and subsequent metastatic infections.<sup>1</sup> This infection is commonly caused by *Fusobacterium necrophorum* and *F. nucleatum*. However, with the increase in variety of comorbidities, use of immunosuppressive agents and prevalence of drug resistance bacteria, Lemierre's syndrome has been reported with atypical pathogens and presentations.<sup>2</sup> We report a rare case of Lemierre's syndrome caused by *Klebsiella pneumoniae* in a diabetic patient.

## Case Report

A 51-year-old woman with hypertension, recently-diagnosed type 2 diabetes mellitus (DM) was admitted to a community hospital after 2 weeks of fever and localized pain and swelling at her right neck area. As the symptoms progressed, she had difficulty moving her neck. She denied history of trauma to the neck, night sweats, weight loss, history of intravenous drug use, history of alcoholic drinking, or recent dental procedures. Physical examination revealed: temperature 38°C, blood pressure 124/62 mmHg, heart rate 104/min, respiratory rate 20/min, pulse oxygen saturation 95% on room air, and marked erythema and swelling at the right upper neck area. Laboratory data showed a white blood cell count of 18,400 cells/mm<sup>3</sup> (79.4% neutrophils, 10.7% lymphocytes, and 9.0% monocytes), hemoglobin level of 9.4 g/dl, platelet count of 407,000 cells/mm<sup>3</sup>. Computed tomography (CT) of the neck was performed and revealed a large rim-enhancing multilocular cystic mass 6x3x8 cm in size occupying the right parapharyngeal space and likely to be right parapharyngeal abscess. The patient underwent incision and drainage of the right neck abscess

along with intravenous ceftazidime at the dose of 2 grams every 8 hours as empirical therapy. *Klebsiella pneumoniae* was detected from the pus culture. The organism was susceptible to penicillins with beta-lactamase inhibitors, cephalosporins, carbapenams, fluoroquinolones, and aminoglycosides and was resistant to ampicillin only. Intravenous ceftazidime was then deescalated to ampicillin-sulbactam. Despite the treatment, she developed worsening shortness of breath on day 5. Her chest radiograph showed new patchy infiltration at right middle lung and pleural effusion at the left lower lung field. Sputum culture grew *Klebsiella pneumoniae* with the same resistance pattern as that from the pus culture. No organism was recovered from any blood culture specimens. On day 8 of the antibiotic treatment the patient was transferred to our hospital due to the suspicion of inadequate drainage of the right neck abscess. Neck and chest CT at our hospital revealed an irregular-shaped hypodense lesion with rim enhancement along right carotid space likely to be a residual abscess (Figure 1A) with thrombosis of right internal jugular vein up to the right sigmoid sinus (Figure 1B and 1C) associated with multiple various size nodules and cavitary consolidations in both lungs likely to be septic emboli (Figure 2A, 2B and 2C). All of the findings were consistent with Lemierre's syndrome. On the third day after the transfer, the patient underwent extensive incision and drainage of the abscess. Anticoagulant therapy with enoxaparin was started and antibiotic therapy was changed to meropenem at the dose of 1 gram intravenously every 8 hours to cover for other nosocomial infections and emerging drug-resistant *K. pneumoniae*. Despite all of the treatments, the patient had persistent fever and required mechanical ventilator support. Repeated CT chest revealed multiple air-fluid containing cavities various in size and scattering in both lungs, left loculated pleural effusion, consolidation with areas of necrosis and bronchiectasis in both lower lobes suggesting necrotizing pneumonia. Pleural fluid was aspirated and showed culture-negative exudative profile with polymorphonuclear predominance. Her condition did not improve despite no evidence of carbapenem-resistant bacterial infection. On the 23rd day after admission to our hospital, her hospital course was complicated by multidrug-resistance *Acinetobacter baumannii*-associated pneumonia and septic shock. Colistin 300 mg intravenous loading followed by 150 mg intravenously every 12 hours was added to her antibiotic regimen. However, due to multiple organ failure from septic shock, the patient died on the 26th day after admission to our hospital.



Figure 1

- 1A. Axial view neck computed tomography showing an irregular-shaped hypodense lesion with rim enhancement along the right carotid space (arrow)
- 1B. Coronal view neck computed tomography showing thrombosis of the right internal jugular vein up to the right sigmoid sinus (arrow)
- 1C. Sagittal view neck computed tomography showing thrombosis of the right internal jugular vein up to the right sigmoid sinus (arrow)



Figure 2

- 2A. Chest radiograph showing alveolar infiltration at the right middle lung area and pleural effusion at the left lower lung area (arrows)
- 2B. Axial view chest computed topography showing multiple nodules in various sizes with cavitation (white arrows) in both lungs likely to be septic emboli, and pleural effusion (arrowheads).
- 2C. Coronal view chest computed topography showing multiple nodules in various sizes with cavitation (white arrows) on both lungs likely to be septic emboli, and pleural effusion (arrowheads).

## Discussion

Lemierre's syndrome is a rare disease with a prevalence of 0.6-2.3 per 1,000,000 population and a mortality rate between 4%-18% in the world.<sup>1</sup> In 1936, Dr. Andre Lemierre published a case series of 20 patients and described the term "Lemierre's syndrome" as the syndrome with development of septic thrombophlebitis of the tonsillar and peritonsillar veins secondary to pharyngotonsillitis or peritonsillar abscess formation. The rapidly progressive thrombophlebitis would then spread to involve the internal jugular and facial veins with the subsequent development of metastatic emboli to the respiratory tract and ultimately the remaining end points of circulation.<sup>2,3</sup> Most cases were caused by *Fusobacterium necrophorum* which accounted for 81% while other *Fusobacterium* species, such as *F. nucleatum* accounted for 11% of the cases. In addition, several organisms have been identified as causes of Lemierre's syndrome in many case reports and case series, such as *Streptococcus spp.*, *Bacteroides spp.*, *Eikenella corrodens*, *Enterococcus spp.*, *Peptostreptococci*, *Proteus mirabilis* and many more.<sup>4</sup>

We performed a Pubmed literature search for English-language articles published from the inception to January 2015 using the search term "*Klebsiella pneumoniae*" and "Lemierre's syndrome". There have been 9 case reports of *K. pneumoniae* associated Lemierre's syndrome (KLS) including our case, in the English literature (Table 1). *Klebsiella pneumoniae* associated Lemierre's syndrome occurred in middle-aged adults (age ranging from 44 to 68 years) with no sex predominance. Eight of the nine patients (89%) with KLS had poorly-controlled DM with hemoglobin A1C ranging from 9.9% to 14.2% and random serum glucose ranging from 197 to 843 mg/dl upon presentation. Among the eight DM patients, 3 (38%) were newly diagnosed of DM within one month. These findings implicate the strong correlation between DM and *K. pneumoniae* associated infections and are consistent with those reported in an observational study from Singapore which found that *K. pneumoniae* was responsible for a higher proportion of deep neck infections among people with DM compared to the general population (50% vs 26%).<sup>5</sup> Impaired phagocytosis of neutrophils due to hyperglycemia has been described as an important factor associated with increased risk of infections caused by *K. pneumoniae*, especially the capsular serotype K1 and K2 strains.<sup>6</sup> In addition, patients with KLS were older than those with classic Lemierre's syndrome (44-68 vs. 10-35 years old).<sup>4</sup> This may be explained by the higher prevalence of DM among the older population.<sup>6,7</sup> All nine KLS patients presented with fever, eight patients (89%) had neck swelling and pain, while three (33%) had symptoms in the oropharynx, such as sore throat and dysphagia. Metastatic infections were found in six patients (67%). The common distantly affected organs included lungs (56%) and brain (11%). Lungs were the most common infected metastatic sites in KLS similar to those in the classic Lemierre's syndrome.<sup>8</sup> Hemagglutinin of the causative bacteria has been identified as an important factor that promotes platelet aggregation, thrombophlebitis, and subsequent septic emboli metastasis in classical Lemierre's syndrome.<sup>9</sup> In KLS, the hema-

glutinin is found in type 3 pilli, a virulent factor responsible for adhering to endothelial cells of *K. pneumoniae*.<sup>10</sup> In addition, septic emboli formation and septic metastasis in KLS may be facilitated by MagA gene-associated hypermucoviscosity property of *K. pneumoniae*. This enables the bacteria to form an exopolysaccharide web to cover itself and be able to avoid serum complement activation and phagocytic ingestion.<sup>11</sup> In our review, two of the nine KLS patients (22%) were infected by extended-spectrum beta-lactamase (ESBL)—producing *K. pneumoniae*. Given that no risk factors associated with infections due to ESBL-producing *K. pneumoniae* were identified in both cases, the occurrence of these drug-resistant infections was most-likely due to the high prevalence of ESBL-producing strain of *K. pneumoniae* in the areas of these two reported cases.<sup>12,13,14</sup> Other drug resistant strains of *K. pneumoniae*, such as carbapenam-resistant Enterobacteriaceae *K. pneumoniae* (CRE-KP) and K1/K2 serotypes were not detected in any of the case reports. However, the infections caused by this drug-resistant strain were associated with prolonged hospital stay and increased cost (Table 1).

Among a variety of characteristics of Lemierre's syndrome, the diagnosis is based on the hallmark features, which include (1) history of a painful illness or compatible clinical findings, (2) evidence of either metastatic lung lesions or metastatic lesions in other sites, and (3) either evidence of internal jugular vein thrombophlebitis or isolation of *F. necrophorum* or *Fusobacterium spp.* from blood cultures or a normally sterile site.<sup>4</sup> The evidence of internal jugular vein thrombophlebitis is one of the criteria required for the diagnosis. Retrograde venography is the gold standard for diagnosis of venous thrombosis but this procedure is invasive.<sup>15,16,17</sup> Thus, many non-invasive investigation tools such as CT venography, magnetic resonance venography (MRV), ultrasonography have been used to detect the venous thrombosis. CT with venous enhancement can reveal low attenuation intraluminal filling defects and adjacent soft tissue anatomy, benefiting in the approach for surgical interventions. Magnetic resonance imaging (MRI) combined with MRV has the highest sensitivity (97%) to detect thrombosis.<sup>18</sup> With better depiction on brain parenchyma, MRI is recommended to perform in the case with suspicion of intracerebral venous thrombosis.<sup>19</sup> However, due to MRI's high cost and limited availability, CT is generally recommended as the primary investigation tool for evidence of the thrombosis.<sup>20</sup> Ultrasonography shows benefit of the least expensive cost and no radiation and contrast exposure. However, because of its difficulty seeing the fresh thrombus with low echogenicity and the anatomy of the area beneath the clavicle, it is rather used in the follow-up examinations, which the early diagnosis and anatomical structure have been successfully investigated.<sup>21</sup>

Based on the standard practice, the microbiological studies should consist of pus Gram's staining for morphology study, pus cultures and blood cultures in both aerobic and anaerobic conditions, and, if available, gas-liquid chromatography to detect butyric acid produced by *Fusobacterium spp.*<sup>4</sup> Due to difficulty culturing the causative organisms, the real time

Table 1. Summary of Cases of <i>Klebsiella pneumoniae</i> -associated Lemierre's Syndrome Reported in the Literature.				
Article	Bhagat ,et al <sup>39</sup>	Tsai, et al <sup>40</sup>	Phua, et al <sup>41</sup>	Our case
Age (year)/Sex	44/F	45/F	50/M	51/F
Comorbidities	DM	DM	DM*	HT,DM*
History of alcoholic drinking	NR	NR	NR	No
Location	New York, US	Taipei, Taiwan	Singapore	Pathumthani, Thailand
Area prevalence of DRS <sup>Ref</sup> (ESBL/CRE-KP/K1/K2) (%)	7.6 <sup>42</sup> /8 <sup>43</sup> /NR/NR	28.4 <sup>44</sup> /1.2 <sup>45</sup> /27.5 <sup>46</sup> /15.7 <sup>46</sup>	38 <sup>47</sup> / $<1^{45}$ /7.7 <sup>46</sup> / 19.2 <sup>46</sup>	56.9 <sup>48</sup> /5.1 <sup>49</sup> /0 <sup>46</sup> /8.6 <sup>46</sup>
Clinical Presentation	Fever, sore throat, vomiting	Fever with chill, sore throat, productive cough, dysphagia, odynophagia, neck pain and swelling	Fever with chill, neck swelling, syncope	Fever, neck swelling, neck pain
Duration from onset to presentation (days)	7	3	8	5
Primary infectious source	Acute pharyngotonsillitis	Neck cellulitis	Retroclavicular abscesses	Parapharyngeal abscess
Thrombosis	IJV	IJV, Sigmoid sinus	IJV, Sigmoid sinus, Transverse sinus	IJV
Complications	Lung metastasis	Lung metastasis	None	Lung metastasis, HAP
Culture-positive specimen	Blood	Blood and pus	Blood and pus	Pus and sputum
Multidrug-resistant strain	No	No	No	No
Glycemic control				
BS upon admission(mg/dl)	843	206	220	NR
HbA1C (%)	14.2	11.6	12.1	9.4
Surgical treatment				
I&D (times)	No	Yes (1)	Yes (1)	Yes (2)
IJV ligation	None	None	None	None
Further operations	None	None	None	Debridement
Anticoagulants				
Type	UFH	LMWH	LMWH	Warfarin
Duration (days)	NR	42	90	20
Antibiotics				
ATB prior admission	Oral penicillin	None	None	Ceftazidime
Initial ATB after diagnosis	Ampicillin, cefotaxime, metronidazole	Ceftriaxone, gentamicin	Ceftazidime, cloxacillin, clindamycin	Ampicillin-sulbactam
After known culture result	Ampicillin, cefotaxime, metronidazole	Flomoxef	Cefazolin	Meropenem
Duration (days)	42	42	42	26
Outcomes				
Duration to clinical response (day)	7	2	NR	None
Hospital stay (day)	NR	15	NR	26
Resolution of infection	Yes	Yes	NR	No
Resolution of thrombosis	Yes	NR	NR	Yes
Survival	Survived	Survived	Survived	Died

Table 1. Summary of Cases of <i>Klebsiella pneumoniae</i> -associated Lemierre's Syndrome Reported in the Literature. (Continued)					
Article	Lee, et al <sup>50</sup>	Lim, et al <sup>51</sup>	Nguyen, et al <sup>52</sup>	Garbati, et al <sup>53</sup>	Singapore-walla, et al <sup>54</sup>
Age (year)/Sex	56/F	57/M	63/M	63/M	68/M
Comorbidities	None	DM*	HT, DM,DLP	DM, Asthma	DM
History of alcoholic drinking	NR	NR	NR	NR	NR
Location	Taipei, Taiwan	Penang, Malaysia	Kuala Lumpur, Malaysia	Riyadh, Saudi Arabia	Singapore
Area prevalence of DRS <sup>Ref</sup> (ESBL/ CRE-KP/K1/K2) (%)	28.4 <sup>44</sup> /1.2 <sup>45</sup> / 27.5 <sup>46</sup> /15.7 <sup>46</sup>	38 <sup>55</sup> /4.05 <sup>56</sup> / 12.5 <sup>57</sup> /1.6 <sup>57</sup>	38 <sup>55</sup> /4.05 <sup>56</sup> / 12.5 <sup>57</sup> /1.6 <sup>57</sup>	55 <sup>58</sup> /1.17 <sup>59</sup> / NR/NR	38 <sup>47</sup> / $<1.45$ /7.7 <sup>46</sup> / 19.2 <sup>46</sup>
Clinical Presentation	Fever, headache, neck swelling	Neck swelling	Fever with chill, neck pain and swelling	Fever, neck pain and swelling, dysphagia, odynophagia, change of voice	Fever, neck pain and swelling
Duration from onset to presentation (days)	5	7	7	5	7
Primary infectious source	Neck abscess	Parotid gland abscess	NF at neck	Right carotid space abscess	Neck cellulitis
Thrombosis	IJV	IJV	IJV	IJV, sigmoid sinus, transverse sinus	IJV
Complication	Brain metastasis	Lung metastasis	Lung metastasis	None	None
Culture-positive specimen	Blood and pus	Pus	Blood and pus	Pus	Blood and pus
Multidrug-resistant strain	ESBL	No	ESBL	No	No
Glycemic control					
BS upon admission (mg/dl)	NR	NR	NR	230	398
HbA1C(%)	NR	12.7	NR	9.9	NR
Surgical Treatment					
I&D (times)	Yes(1)	Yes(1)	Yes(1)	Yes(1)	Yes(1)
IJV ligation	None	None	None	None	None
Further operations	None	None	Debridement	None	Debridement
Anticoagulants					
Type	NR	Warfarin, LMWH	None	Warfarin	None
Duration (Days)	NR	56	None	42	None
Antibiotics					
ATB prior admission	Ceftazidime, metronidazole	Penicillin, cloxacillin	NR	None	None
Initial ATB after diagnosis	Ceftazidime, amikacin	Ceftriaxone, metronidazole	Ceftriaxone, metronidazole, ciprofloxacin	Clindamycin cefuroxime	Ceftriaxone, metronidazole
After known culture result	Fosfomycin, meropenem	Amikacin	Meropenem, amoxicillin-clavulanate	Clindamycin, cefuroxime	Amoxicillin-clavulanate
Duration (days)	56	42	56	35	35
Outcomes					
Duration to clinical response (day)	NR	NR	7	NR	NR
Hospital stay (day)	60	NR	56	NR	NR
Resolution of infection	Yes	Yes	Yes	Yes	Yes
Resolution of thrombosis	NR	NR	NR	Yes	Yes
Survival	Survived	Survived	Survived	Survived	Survived

Abbreviations : ATB, antibiotics; BS, blood sugar; CRE-KP, carbapenem-resistant Enterobacteriaceae- *Klebsiella pneumoniae*; DLP, dyslipidemia; DM, diabetes mellitus; DRS, drug resistant strain; ESBL, extended-spectrum beta-lactamases; F, female; HAP, hospital acquired pneumonia; HT, hypertension; IJV, internal jugular vein; I&D, incision and drainage; K1, K1 capsular serotype of *Klebsiella pneumoniae*; K2, K2 capsular serotype of *Klebsiella pneumoniae*; LMWH, low molecular weight heparin; M, male; No., number of patients; NR, not recorded; UFH, unfractionated heparin.

\* newly diagnosed DM within 1 month.



polymerase chain reactions (PCR), such as PCR targeting on *rpoB* sequence in the classic Lemierre's syndrome and PCR targeting on 16s rRNA gene in cases suspected of having *K. pneumoniae* infection, have been used.<sup>22</sup>

The mainstay treatment of Lemierre's syndrome is the combination of antibiotic therapy and surgical intervention.<sup>23</sup> For classic Lemierre's syndrome, a beta-lactamase resistant beta-lactam antibiotic is recommended as empirical therapy since there have been reports of treatment failure with penicillin and beta-lactamase producing *F. necrophorum*.<sup>24,25</sup> The treatment drugs include ampicillin-sulbactam and piperacillin-tazobactam. Antibiotics should be tailored according to culture and susceptibility data when available. An alternative option is clindamycin or metronidazole if the organism is found susceptible.<sup>4,19,26,27,28</sup> For patients suspected to have KLS, the empirical regimen should be antibiotics that can be used for classic Lemierre's syndrome and are also active against *K. pneumoniae* based on the local susceptibility data and the risk of acquiring the ESBL-producing strain. These antibiotics include ampicillin-sulbactam or piperacillin-tazobactam while a carbapenem should be used in cases with risks for ESBL-associated infections.<sup>29</sup> In the setting where CRE-KP is prevalent, combination therapy with tigecycline and colistin should be considered as empirical therapy.<sup>30</sup> The definitive antibiotic for KLS patients should be based on the susceptibility results. Commonly-used antibiotics that are active against *K. pneumoniae* are ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam, cephalosporins, fluoroquinolones, and carbapenems.<sup>29</sup> The duration of therapy should be prolonged (2–6 weeks) to allow for antibiotic penetration through fibrin clots and prevention of relapse.<sup>28</sup>

Surgical management is often performed in order to gain primary source control in patients with refractory sepsis and/or multiple septic metastasis, respiratory distress due to pulmonary thrombus metastasis and in those with intracerebral or mediastinal extension of thrombus.<sup>31</sup> Surgical interventions may include incision and drainage of the infected sites and excision of the affected vein and its tributaries if incision and drainage alone cannot adequately remove the septic focus and bacteremia persists.<sup>32</sup> Anticoagulant therapy in patients with Lemierre's syndrome is controversial. The therapy may be considered in cases with thrombophilia, the thrombosis extending into the cerebral sinuses, and/or poor improvement of the symptoms within 72 hours despite adequate antibiotics and surgical interventions.<sup>9,27,33,34</sup> Previous reports suggest giving the anticoagulant for 4 weeks to 6 months depending on the patients' responses.<sup>27,34</sup> In our review of the nine KLS cases, anticoagulant drugs were given to six patients (67%) due to intra-cerebral thrombosis (3 cases) and poor responses after antibiotic therapy (3 cases). In these six cases, the median duration of anticoagulant therapy was 16.5 days (range 7–26 days).

The mortality rates of the classic Lemierre's syndrome were reported to be 4.9% in cases with septic metastasis and up to 18% in some case series.<sup>1,4,26</sup> In our review, the mortality rate of KLS patients was 11% while the mortality rate in cases

with septic metastasis was 17%. The overall mortality rate of KLS was higher than the classic Lemierre's syndrome, while both group had no difference in the rates of septic metastasis. The possible explanation may be the higher incidence of beta-lactam-resistance among *K. pneumoniae* (51%) compared to that of *Fusobacterium spp.* (41.1 %) which might have led to inappropriate initial empirical therapy.<sup>35,36</sup> The previous studies of classic Lemierre's syndrome indicated that a delay in antibiotic treatment, multiple metastatic sites, advanced age and persistent fever were associated with mortality.<sup>8,37,38</sup> In this report, our KLS patient was at high-risk for death due to the delayed antibiotic treatment (5 days after the onset of infection), having lung metastasis and persistent fever for 26 days.

In conclusion, KLS is a rare and emerging condition associated with poorly-controlled DM. Although the clinical presentations of KLS are similar to the classic Lemierre's syndrome, additional coverage with antibiotics that are active against *K. pneumoniae* is needed. In cases with risk factors for acquiring multidrug-resistant *K. pneumoniae*, such as ESBL-producing strains and CRE-KP, empirical antibiotic regimens should be adjusted accordingly. Early control of infection at the primary site with appropriate empirical antibiotics and surgical interventions remains the critical strategy to prevent metastasis, achieve clinical responses and reduce mortality among KLS patients.

## Conflict of Interest

None of the authors identify a conflict of interest.

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# Improving the Utilization of Human Papillomavirus and Cervical Cytology Co-testing for Cervical Cancer Screening in an Obstetrics and Gynecology Resident Clinic

Kurt Yoshino MD; Maxine Karimoto MD; Christina Marzo MD; Bliss Kaneshiro MD; and Mark Hiraoka MD

## Abstract

*Human Papillomavirus (HPV) testing in combination with cervical cytology (HPV co-testing) has been recommended for cervical cancer screening for women 30 to 65 years of age. In several studies, HPV co-testing increased sensitivity for detecting high grade dysplasia and resulted in cost-savings. This retrospective cohort study assessed the prevalence of HPV co-testing in an obstetrics and gynecology resident clinic before and after a brief educational intervention which was designed to reinforce current cervical cancer screening recommendations. The intervention consisted of a short presentation that was given to all residents and medical assistants in October 2011. The proportion of women age 30-65 years of age who had cervical cancer screening with HPV co-testing as compared to cervical cytology alone was compared before and after the intervention using chi-square tests. The goal of the intervention was to increase the percentage of patients receiving co-testing from 0.5% to 7.8%. Each arm (pre- and post-intervention) required 130 subjects to achieve 80% power with a significance of  $P = .05$ . No significant differences in demographics including age, insurance type, and cytology were noted. HPV co-testing increased from 0% to 55% ( $P < .001$ ). Of the 72 subjects who had co-testing, 58 (80%) will not need cervical cancer screening for another 5 years. HPV co-testing represents an underutilized cervical cancer screening modality for women 30 years and older. This brief educational intervention, adaptable to any clinical setting, significantly increased co-testing at the clinical site.*

## Introduction

An increased risk of cervical cancer following infection with high-risk human papillomavirus (HPV) subtypes has been well documented.<sup>1</sup> In February 2003, the Food and Drug Administration approved the use of HPV testing in association with routine cervical cytology (HPV co-testing) as a screening modality for cervical cancer. In March 2003, the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP) released cervical cancer screening guidelines which recommended HPV co-testing every five years as the preferred cervical cancer screening tool for women 30 to 65 years of age.<sup>2</sup> When compared to cytology alone, HPV co-testing resulted in improved sensitivity (95% to 99%) for detecting high grade cervical dysplasia.<sup>3</sup> Additionally, although the up-front cost of HPV co-testing is higher, health care costs are overall significantly decreased because of a longer screening interval for those with negative tests (5 years).<sup>4</sup>

In 2011, few providers at the University of Hawai'i obstetrics and gynecology resident clinic had incorporated HPV co-testing as the recommended screening modality for cervical cancer. This mirrored what was occurring nationally; a 2010 survey of primary care physicians revealed that 19% of providers still recommended screening every three years even when women

had normal cytology and a negative HPV test.<sup>5</sup> To promote adherence to cervical cancer screening recommendations, a ten-minute educational intervention for resident providers and clinic staff was designed. The purpose of this study was to assess the efficacy of this educational intervention in increasing co-testing rates for women 30 to 65 years of age in an outpatient obstetrics and gynecology resident clinic.

## Methods

This study was deemed exempt by the Institutional Review Board of Hawai'i Pacific Health. A ten-minute educational intervention consisting of eight slides was designed. The slides briefly reviewed the data supporting the evidence and indications for HPV co-testing. Examples of the co-testing order form and the ordering procedure were included. The presentation concluded with a five-minute question and answer session and printed copies of the presentation were available upon request. No HPV co-testing supports were added into the existing electronic medical record.

A retrospective cohort study was performed to compare HPV co-testing before and after the intervention. We examined the medical records of all women between the ages of 30 and 65 years who were screened for cervical cancer at the Kapi'olani Medical Center Women's Outpatient Clinic. This clinic serves as the primary clinic for the University of Hawai'i Obstetrics and Gynecology resident physicians. The study period spanned from July 2011 through January 2012, which included the three-month period before and after the intervention. The principal investigator gave the presentation to all residents and medical assistants in the clinic in October 2012. Collected data included whether HPV co-testing was performed, cervical cytology and HPV results, and demographic information including patient age and insurance type.

The primary outcome was the difference in HPV co-testing before and after the educational intervention. At baseline we estimated approximately 0.5% of eligible patients were co-tested for HPV. Based on HPV co-testing data from John Hopkins University,<sup>6</sup> an increase to 7.8% was determined to represent a clinically meaningful difference. A sample size of 130 subjects in each arm, 260 subjects total, was necessary to achieve 80% power with an alpha of 0.05. To achieve this sample size with our clinic volume, a six month data collection period spanning three-months before the intervention and three months after the intervention was required.

Chi-squared tests were used to determine the significance of association for categorical variables. Continuous variables were compared with a t-test. Sample size calculations were performed with Power and Sample Size (PASS) 2008 (NCSS LLC, Kaysville, Utah). All analyses were performed with Statistical Package for the Social Sciences (SPSS) version 16.0 (Chicago, Illinois). If differences in demographic characteristics were noted between patients presenting before and after the intervention, multiple logistic regression was planned.

## Results

Two hundred thirty eight patients were eligible for HPV co-testing during the pre-intervention period and 131 were eligible during the post-intervention period. The two study groups were similar with respect to age and insurance type. Median age was 37 years in both groups (Table 1). No statistical difference was noted between groups with respect to cervical cytology diagnoses. A negative result was the most common cervical cytology finding in both groups (91%) (Table 2). Following the intervention, HPV co-testing significantly increased from 0% prior to the intervention to 55% after the intervention ( $P < .0001$ ) (Table 3). Of the 72 women who had HPV co-testing, 58 had a negative result for both cervical cytology and HPV testing. Thus, no further cervical cancer screening will be needed for five years for these 58 women.

## Discussion

HPV co-testing is an effective means of cervical cancer screening in women between 30 and 65 years of age. The usual diagnostic procedure following an abnormal screening test involves performing a colposcopy which involves examining the cervix through a magnifying scope. The most common treatment procedure of high grade cervical dysplasia is a loop electrode excisional procedure (LEEP) which removes a portion of the cervix with a heated wire device. Both procedures are invasive and often cause some patient discomfort, and the LEEP can increase the risk of preterm delivery.<sup>7</sup>

HPV infection is critical in the natural history of cervical cancer.<sup>1</sup> After the release of the 2012 ASCCP guidelines, the recognition of the significance of HPV infection in the detection of cervical cancer increased among women's health care providers. More physicians recommended more frequent follow-up in patients with a positive HPV test compared to patients with a negative HPV test.<sup>8</sup> A subsequent decrease in the number of colposcopy and LEEP procedures occurred.<sup>9,10</sup> Despite fewer procedures, an increase in cervical cancer was not noted. Instead, HPV testing became a successful adjunct to cervical cancer screening; a decrease in the incidence of cervical cancer was noted after the advent of HPV vaccination.<sup>11</sup> A need still exists to increase both the implementation of these practices among physicians, as well as the speed at which these practices are adopted. This study demonstrated that a simple intervention was successful in increasing HPV co-testing among a select group of providers.

Patient Demographics	Pre-Intervention	Post-Intervention	P-value
Age (mean)	37.92 (n=248)	37.13 (n=131)	.37
Insurance Type			
Medicaid and Medicare	62.9% (156/248)	53.4% (70/131)	.11
Private	30.6% (76/248)	35.1% (46/131)	
No Insurance	6.5% (16/248)	11.5% (15/131)	

Cytology result	Pre-Intervention	Post-Intervention	P-value
NEG	91.1% (226/248)	90.8% (119/131)	0.39
ASCUS	5.2% (13/248)	7.6% (10/131)	
LSIL	2.0% (5/248)	1.5% (2/131)	
HSIL	1.6% (4/248)	0% (0/131)	

NEG=negative result. ASCUS= Atypical squamous cells of unknown significance. LSIL = Low-grade squamous intraepithelial lesion. HSIL = High-grade squamous intraepithelial lesion.

Co-Testing Performed	Pre-Intervention	Post-Intervention	P-value	OR (95% CI)
Yes	0% (0/248)	55% (72/131)	< .001	301.4 (41.0-2213.6)
No	100% (248/248)	45% (59/131)		

OR=odds ratio. CI=confidence interval

Several factors contributed to the success of the study. First, the intervention was simple, short (one session), and inexpensive. These qualities mean that the intervention can be easily reproduced and disseminated to other women's health care providers to increase HPV co-testing at multiple health access points. Second, the intervention was done in a select group of providers and staff practicing in the same clinic. This allowed the quick administration of the intervention. The practice pattern in the clinic changed rapidly since all providers and staff were introduced to HPV co-testing concepts in a short period of time. Although this intervention could be implemented on a larger scale with an increased number of physicians in different settings, a longer time period may be necessary to achieve similar results.

Several limitations should be noted. The study intervention was conducted in a group of resident physicians and it is unclear whether the results are generalizable to other providers. Due to a relatively short time in practice, residents may not be as attached to practice patterns as attending physicians who may have longstanding practice patterns. Resident physicians are accustomed to discussing and adjusting practices based on

information they provide to each other. The observed effect may have been due to this type of inter-resident discussion rather than the actual study intervention itself. Based on information provided in the intervention, residents would have been able to determine that part of the intent of the study was to increase HPV co-testing. Hence, it is possible that social desirability bias may have affected the results. Because the study took place in two sequential three-month time periods, it is unclear whether providers would have incorporated HPV co-testing regardless of the intervention. Additionally, the post-intervention study period was short and it is unknown whether the increase in HPV co-testing will be sustained. Olomu, et al, demonstrated that quality improvement measures implemented by physicians resulted in only a percentage of providers continuing the desired practice one year post-intervention suggesting that additional intervention measures should be performed at regular intervals.<sup>12</sup> Further study of this group of clinicians would be helpful to determine if the improved screening behavior was continued, or if additional interventions are warranted.

Due to rapidly emerging scientific data regarding the natural history of HPV and cervical dysplasia, the 2012 ASCCP guidelines will likely not be the last cervical screening guideline revision. Recently HPV testing alone has been offered as an alternative primary screening test to HPV co-testing and may soon replace HPV co-testing as the recommended primary screening test.<sup>13</sup> Determining the best method to disseminate information rapidly into the larger medical community consisting of many independent practices would be a recommended area of future study. One possible alternative, publication in major medical journals, does seem to be effective in dictating physician behavior if given enough time.<sup>14</sup> Other possible options include using the electronic medical record or other electronic health applications. Previous work by White and Kenton in 2013 suggested that the electronic medical record could be effective at increasing physician compliance with changing screening recommendations.<sup>15</sup>

In conclusion, a simple educational intervention can be a cost-efficient, effective method to improve the use of HPV co-testing in a resident clinic setting. Additional work is required to determine whether the improved screening behavior will be sustained in this population of physicians, as well as determining the best method for communicating ever-changing and complex guidelines to the medical community at-large.

### Conflict of Interest

None of the authors identify a conflict of interest.

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# Autoimmune Hepatitis in Hawai'i

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## Abstract

*Autoimmune Hepatitis (AIH) is a poorly understood disease. There has been a paucity of reports on the epidemiology and clinical course of AIH in multiethnic populations. The aim of this study is to examine the clinical and serologic features of AIH in the multiethnic population of Hawai'i. This was a retrospective, cross-sectional study of a cohort of patients seen between 2010-2013 in a tertiary referral center in Hawai'i. All 32 patients were diagnosed according to International Autoimmune Hepatitis Group (IAIHG) criteria. The mean (SD) age of diagnosis was 49.4 (17.5) years, 75% of patients were female, 72% were Asian, 19% were Caucasian, 6% were Pacific Islander, and 3% were African American. When compared to Caucasians, Asians had lower transaminase levels and international normalized ratio (INR), and were more likely to have anti-nuclear antibody (ANA) seropositivity at presentation. Asians were also older at diagnosis and more likely to achieve complete or partial remission. Patients diagnosed before the age of 40 had higher levels of total bilirubin at presentation compared to those diagnosed after the age of 40. No significant differences were observed between genders. Asian patients with type I AIH present later in life with more favorable laboratory values, and have a superior treatment response compared to Caucasians. Diagnosis before the age of 40 is associated with less favorable laboratory values at diagnosis. Further studies are necessary to validate these findings and determine the reason for the ethnic differences.*

## Introduction

Autoimmune hepatitis (AIH) is a disease of unknown etiology characterized by a loss of immune tolerance to the liver, resulting in chronic hepatocellular inflammation, autoantibodies, and hypergammaglobulinemia.<sup>1,2</sup> Despite its discovery in the 1950's, the pathogenesis underlying AIH and many of its clinical features remains unclear.<sup>3</sup>

The diagnosis of AIH is based on the criteria established by the International Autoimmune Hepatitis Group (IAIHG), established in 1993 and revised in 1999.<sup>1</sup> The disease is classified into two types based on the presence of circulating autoantibodies. Type 1 is defined by the presence of anti-nuclear antibody (ANA) and/or anti-smooth muscle antibody (SMA). Type 2 is defined by the presence of anti-liver/kidney microsomes (LKM-1) and/or anti-liver cytosol antigen (LC-1).<sup>1</sup> Treatment for AIH is based on the 2010 American Association for the Study of Liver Disease (AASLD) Practice Guidelines, which recommend a regimen of prednisone with azathioprine or prednisone monotherapy. Treatment results in the remission of disease in 65%-80% of patients.<sup>2,4</sup> However, up to 86% of patients experience a relapse after withdrawal of corticosteroids, thus potentially reverting to the natural history of AIH of progressive liver dysfunction.<sup>1,5</sup>

AIH has a strong female predominance, and commonly occurs in concurrence with other autoimmune diseases including thyroiditis, inflammatory bowel disease, and systemic lupus erythematosus.<sup>1,3,6,7</sup> AIH presents with a bimodal distribution and a variable clinical presentation that ranges from asymptomatic to acute liver failure.<sup>2,5,8-10</sup> Prevalence rates differ between

ethnicities, with previous studies reporting a prevalence rate of 1 in 5,000 to 10,000 in Western countries compared to much lower rates in Japanese populations.<sup>11-12</sup> Current data suggests that many of the characteristics of AIH vary between ethnicities. Several studies have found that Japanese have a milder form of the disease with a later onset when compared to Caucasians.<sup>8,13-14</sup> Despite these reports, overall epidemiologic data of AIH remain sparse, especially in the United States. The multiethnic population of Hawai'i provides a unique opportunity to elucidate differences in the characteristics of AIH between ethnic groups and will allow clinicians to better diagnose and manage this disease. Thus, the aim of this retrospective study is to investigate the clinical and serological features of AIH and treatment response in the multiethnic population of Hawai'i.

## Methods

In this retrospective, cross-sectional study, medical records of 32 patients clinically determined to have AIH were reviewed. These patients presented to our tertiary referral center from January 1, 2010 through August 31, 2013. Patients with concurrent primary biliary cirrhosis were excluded. All patients were diagnosed with AIH according to the IAIHG scoring system.<sup>2</sup>

Data including age, gender, and self-identified ethnicity were obtained from patient charts. Laboratory data was obtained at presentation and throughout treatment, and included alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), total bilirubin, international normalized ratio (INR), albumin, gamma-glutamyl transferase (GGT), ANA, and SMA. Reference ranges for these are as follows: ALT is 0-41 IU/L, AST 0-40 IU/L, total bilirubin is 0-1.2 mg/dl, INR is  $\leq 1$ , GGT is 8-61 IU/L, ANA is  $\leq 40$ , and SMA is  $< 20$ .

Presentation of disease was stratified into three categories: acute, insidious, or asymptomatic. Acute included persons with features of icteric hepatitis. Insidious included persons with vague or non-specific symptoms (eg, fatigue, malaise, nausea, abdominal pain). Asymptomatic included persons who presented with abnormal liver function tests in the absence of symptoms.

Treatment response at one year was stratified into three categories: complete, partial, or no remission. Complete remission was defined as the normalization of liver function tests below 40 IU/L. Partial remission was defined as ALT less than two times the upper limit of normal. No remission was defined as the lack of normalization such that ALT was greater than two times the upper limit of normal (80 IU/L).

Determination of histology consistent with AIH was based on liver biopsy. Histology consistent with AIH was defined as the presence of interface hepatitis, lobular hepatitis, rosettes, or plasma cell infiltration.<sup>2,11</sup>

The study was approved by the University of Hawai'i Human Studies Program CHS #20525 and The Queen's Medical Center RA-2014-050.

One-way analysis of variance was used to test the differences in the means of continuous variables, and chi-squared tests were used to test differences between categorical variables. Statistical analyses were performed with SPSS, Version 21 (SPSS Inc, Chicago IL).

## Results

The study population consisted of 32 patients, diagnosed according to criteria issued by the IAIHG. The clinical, serological, immunological, and histological features at presentation are reported in Table 1. The mean (SD) age at diagnosis was 49.4 (17.5) years, and the majority of patients were female (75%). Most patients identified as Asian (72%), followed by Caucasian (19%), Pacific Islander (including Native Hawaiian) (6%), and African American (3%). Of those who identified as Asian, the majority were Japanese or Okinawan (47%).

Concomitant autoimmune diseases were present in 25% of patients. Four patients had hypothyroidism, two patients had hyperthyroidism, and two patients had psoriatic arthritis. Other reported autoimmune disorders included one patient with thrombocytopenia not related to portal hypertension and one patient with systemic lupus erythematosus.

Table 2 stratifies patients by ethnicity. Due to the limited patient population, only Caucasians and Asians were analyzed. Compared to Caucasians, Asians were more likely to be diagnosed at a later age, and present with lower levels of ALT, AST, and GGT, and significantly higher levels of albumin. Additionally, Asians had significantly higher proportion of ANA seropositivity compared to Caucasians (93% and 40%). Lastly, treatment response in Asians was associated with higher rates of remission compared to Caucasians.

To determine the effect of age at diagnosis on disease course, patients were grouped into two categories—those diagnosed before the age of 40, and those diagnosed after the age of 40 (Table 3). Patients diagnosed before the age of 40 had significantly higher levels of total bilirubin (9.4 mg/dL and 7.0 mg/dL) and GGT (117 IU/L and 95.8 IU/L) compared to those diagnosed after the age of 40. Improved treatment response in patients diagnosed before the age of 40 compared to those diagnosed after the age of 40 was numerically higher but not statistically significant ( $P = .09$ ).

No statistically significant gender differences were observed (data not shown)

## Discussion

We describe the clinical and serological features as well as clinical course of a multiethnic cohort of 32 patients diagnosed with type I AIH at a tertiary referral center in Hawai'i. The majority of the patients were Asian, and had a milder form of the disease compared to Caucasians. More specifically, Asians had milder presenting symptoms, more favorable laboratory values, and higher remission rates compared to Caucasians. Asians

**Table 1. Cohort Characteristics of Patients with Autoimmune Hepatitis at Presentation**

	Cohort
N	32
Mean age at diagnosis, years, (SD)	49.4 (17.5)
Female gender, no. (%)	24 (75%)
Ethnicity, no. (%)	
Caucasian	6 (19%)
Asian	23 (72%)
African American	1 (3%)
Pacific Islander	2 (6%)
Concomitant autoimmune disease, no. (%)	8 (25%)
ALT, IU/L, Mean (SD)	501.6 (595.7)
AST, IU/L, Mean (SD)	484.4 (640.0)
Total bilirubin, mg/dL, Mean (SD)	7.6 (13.1)
INR, Mean (SD)	1.2 (0.2)
Albumin, g/dL, Mean (SD)	4.1 (0.4)
GGT, IU/L, Mean (SD)	101.4 (128.1)
ANA positive, no. (%)	17 (77%)
SMA positive, no. (%)	8 (47%)
Histology consistent with AIH, no. (%)	18 (86%)
Cirrhosis present on biopsy, no. (%)	16 (50%)
Presentation, no. (%)	
Acute	7 (28%)
Insidious	12 (48%)
Asymptomatic	6 (24%)
Treatment response, no. (%)	
Complete remission	24 (75%)
Partial remission	5 (16%)
No remission	3 (9%)

Abbreviations: standard deviation (SD), alanine aminotransferase (ALT), aspartate aminotransferase (AST), International normalized ratio (INR), gamma-glutamyl transferase (GGT), anti-nuclear antibody (ANA), smooth muscle antibody (SMA), autoimmune hepatitis (AIH).

were diagnosed at a later age and were more likely to have a positive ANA. A comparison of age at diagnosis also revealed significant differences. A diagnosis before the age of 40 was associated with higher bilirubin and GGT values, while older patients were more likely to report ANA positivity. Lastly, no statistically significant differences were found between genders.

AIH has a strong female predominance. The current study found that 75% of the patients were female, concordant with previous reports that 75% of persons with AIH are female.<sup>1-3,15</sup> Concomitant autoimmune disorders are commonly associated with AIH, and 25% of the patients in our population reported extra-hepatic autoimmune disorders, with thyroid disorders being the most common. This is consistent with previous studies, reporting extra-hepatic autoimmune disease in 20% of AIH patients.<sup>3,16</sup> Furthermore, thyroid disorders were the most commonly concurrent extra-hepatic autoimmune disease.<sup>3,13</sup>

Table 2. Clinical, Serologic, and Histologic Characteristics by Ethnicity			
	Caucasian	Asian	P-value
n	6	23	
Age at diagnosis, years, Mean (SD)	36.2 (14.3)	54.9 (15.2)	.013
Female gender, no. (%)	5/6 (83%)	18/23 (78%)	.79
Concomitant autoimmune disease, no. (%)	2/6 (33%)	5/23 (22%)	.55
ALT, IU/L, Mean (SD)	1137.5 (525.0)	409.7	.033
AST, IU/L, Mean (SD)	1285.3 (883.8)	337.4	.008
Total bilirubin, mg/dL, Mean (SD)	6.6 (7.6)	6.2 (13.1)	.95
INR, Mean (SD)	1.4 (0.1)	1.1 (0.0)	.067
Albumin, g/dL, Mean (SD)	3.7 (0.4)	4.3 (0.3)	.004
GGT, IU/L, Mean (SD)	230.0 (199.3)	65.1 (78.0)	.011
ANA positive, no. (%)	2/5 (40%)	14/15 (93%)	.004
SMA positive, no. (%)	2/4 (50%)	6/11 (54%)	.88
Histology consistent with AIH, no. (%)	4/4 (100%)	12/14 (85%)	.42
Cirrhosis present on biopsy, no. (%)	2/4 (50%)	6/16 (37%)	.92
Presentation, no. (%)			.185
Acute	2/5 (40%)	4/17 (23%)	
Insidious	3/5 (60%)	7/17 (41%)	
Asymptomatic	0/5 (0%)	6/17 (35%)	
Treatment response, no. (%)			.014
Complete remission	3/6 (50%)	19/23 (82%)	
Partial remission	1/6 (16%)	4/23 (17%)	
No remission	2/6 (33%)	0/23 (0%)	

Abbreviations: standard deviation (SD), alanine aminotransferase (ALT), aspartate aminotransferase (AST), International normalized ratio (INR), gamma-glutamyl transferase (GGT), anti-nuclear antibody (ANA), smooth muscle antibody (SMA), autoimmune hepatitis (AIH).

The three patients whose ethnicities were not identified as Caucasian or Asian were excluded from this analysis. One-way analysis of variance was used to test the differences in the means of continuous variables, and chi-squared tests were used to test differences between categorical variables.

Most patients presented with an insidious onset, following previous data that demonstrated that the majority of patients initially present with vague, non-specific symptoms.<sup>14,15</sup> However, it is important to note that nearly a quarter of our patients presented acutely, while nearly a quarter of patients were asymptomatic. Thus, nearly half our patients presented with vague, nonspecific symptoms, making it important to keep autoimmune hepatitis in the differential diagnosis of any patient with acute hepatitis, acute liver failure or elevated liver function tests, as clinical manifestations may vary widely. However, these results may be biased as we are a tertiary referral center with a liver transplant program.

Differences between ethnicities were investigated due to the diverse, multiethnic population of Hawai'i. Although AIH is an overall rare disease, rates of disease have been found to differ by ethnicity, with Caucasians having a higher incidence than Asians.<sup>17</sup> Incidence rates in Japan have been reported at 0.15

cases per 100,000 people per year, in contrast with Western countries such as England, reporting incidence rates of 3.0 cases per 100,000 people per year.<sup>12,13</sup> In this study, the majority of patients diagnosed with AIH were Asian, likely reflecting the large Asian population in Hawai'i. The majority of Asians identified as Japanese or Okinawan.

Asians were also diagnosed at a later age and had higher rates of remission compared to Caucasians. This follows with previous studies reporting a later diagnosis and improved treatment response in Asians compared to Caucasians.<sup>2,8,11,18</sup> Asians had significantly lower serum levels of GGT and INR, as well as lower serum levels of ALT, AST, and albumin. The milder laboratory values correlate with the trend toward the insidious and asymptomatic presentations observed in Asians, although this was not statistically significant. These features may also indicate a less severe form of the disease, which correlates with the greater rates of remission observed in the



Table 3. Clinical, Serologic, and Histologic Features by Age at Diagnosis			
	Diagnosis <40 years of age	Diagnosis >40 years of age	P-value
n	10	19	
Female gender, no. (%)	9/9 (90%)	12/19 (63%)	.124
Ethnicity, no. (%)			
Caucasian	5/10 (50%)	1/19 (5%)	.63
Asian	3/10 (30%)	17/19 (90%)	
African American	1/10 (10%)	0/19 (0%)	
Pacific Islander	1/10 (10%)	1/19 (5%)	
Concomitant autoimmune disease, no. (%)	4/10 (40%)	3/19 (16%)	.148
ALT, IU/L, Mean (SD)	527.4 (607.6)	527.8 (655.7)	.71
AST, IU/L, Mean (SD)	606.9 (863.5)	445.0 (545.5)	.46
Total bilirubin, mg/dL, Mean (SD)	9.4 (13.9)	7.0 (13.6)	.026
INR, Mean (SD)	1.3 (0.2)	1.1 (0.0)	> .99
Albumin, g/dL, Mean (SD)	3.9 (0.5)	4.2 (0.4)	.56
GGT, IU/L, Mean (SD)	117.4 (134.6)	95.8 (138.5)	.004
ANA positive, no. (%)	5/9 (55%)	11/12 (92%)	.019
SMA positive, no. (%)	2/7 (29%)	5/9 (56%)	.28
Histology consistent with AIH, no. (%)	5/7 (71%)	13/14 (93%)	.186
Cirrhosis present on biopsy, no. (%)	4/7 (57%)	5/12 (42%)	.52
Presentation, no. (%)			
Acute	1/8 (13%)	5/16 (31%)	.60
Insidious	5/8 (63%)	7/16 (44%)	
Asymptomatic	2/8 (25%)	4/16 (25%)	
Treatment response, no. (%)			
Complete remission	5/8 (63%)	13/18 (72%)	.093
Partial remission	2/8 (25%)	3/18 (17%)	
No remission	1/8 (13%)	2/18 (11%)	

Abbreviations: standard deviation (SD), alanine aminotransferase (ALT), aspartate aminotransferase (AST), International normalized ratio (INR), gamma-glutamyl transferase (GGT), anti-nuclear antibody (ANA), smooth muscle antibody (SMA), autoimmune hepatitis (AIH). Three patients had an unknown age of diagnosis and were excluded from this analysis.

One-way analysis of variance was used to test the differences in the means of continuous variables, and chi-squared tests were used to test differences between categorical variables.

Asian patients compared with Caucasians. All Asian patients responded to treatment with at least partial remission, while 33% of Caucasians had no remission of their disease, consistent with previous reports from Miyake, et al, showing that Japanese patients had superior treatment response from corticosteroids compared to Caucasians.<sup>18</sup> Treatment response is integral in the prevention of severe liver-related complications, and these results suggest that patients with AIH, especially Caucasians, should be monitored closely in their response to treatment. Interestingly, ANA seropositivity was higher in Asians (93%), compared to Caucasians (40%). Low prevalence of ANA in our Caucasian population may be due to the small sample size.<sup>19,20</sup> The etiology for the differences in presentation and treatment response is still unclear, but may be due to underlying genetic factors. Several studies have suggested that differing human

leukocyte antigen (HLA) alleles are correlated with gender, ethnicity, and prognosis.<sup>19,21-23</sup> Patients with HLA DR3 and HLA DR4 are at increased risk for type 1 AIH.<sup>19</sup> HLA DR4 has also been associated with increased response to treatment compared to DR3, and is the dominant HLA allele in Japanese patients with type 1 AIH.<sup>13</sup> As HLA alleles have been shown to be associated with AIH in various forms, it is possible that they may also explain the differences observed between ethnicities in this study. HLA genotyping was not available in our study, and it certainly should be incorporated in future studies. It is also possible that differing intestinal microbiomes may play a role in the pathogenesis of AIH in a manner similar to other autoimmune diseases such as diabetes mellitus type 1 and rheumatoid arthritis.<sup>24,25</sup> However, these features have not been investigated in patients with autoimmune hepatitis to our knowledge.

Age of diagnosis varied widely in the present study, with the youngest patient diagnosed at 18 years, and the oldest at 80 years. A bimodal distribution was not observed, but the sixth and fourth decades of life were the most common age at diagnosis. Interestingly, a diagnosis of AIH after the age of 40 was associated with higher bilirubin and GGT levels, and lower rates of ANA seropositivity. Presentation of AIH did not differ by age, which was consistent with previous reports.<sup>8,26</sup> While not reaching the level of statistical significance, in this study, patients with an older age at diagnosis appeared to have higher rates of remission (79% achieved complete remission and 13% partial remission compared to 63% and 25%, respectively among their younger counterparts,  $P = .09$ ). This is in contrast with previous studies that reported persons over the age of 50 with a worse treatment response.<sup>15,27</sup> These results may be explained by the finding that 90% of those diagnosed over the age of 40 were Asian, compared to 30% under the age of 40, with Asians showing a good response to treatment. Patients under the age of 20 have been reported to have a particularly poor treatment response and prognosis.<sup>15</sup> Among the thirty-two patients in our study, three were diagnosed before age 20, of which two had evidence of cirrhosis on biopsy at the time of diagnosis.

The effect of gender on the clinical features of AIH remains controversial. In the present study, no significant differences were found between genders, supporting previous evidence that gender is independent of clinical characteristics of AIH.<sup>7,19,28-31</sup> However, Czaja, et al, suggested that some differences between genders may be mediated by differing HLA status.<sup>19</sup>

The limitations of our study include the small sample size, the fact that this data was collected at a tertiary referral center, and lack of longitudinal data due to the recent establishment of this referral center. Further studies with a larger number of patients are necessary to validate the current findings.

## Conclusion

The results of our study indicate that clinical and serological features of AIH were significantly different between Asians and Caucasians. Asians were diagnosed at a later age, had better laboratory values, and higher rates of remission compared to Caucasians. Patients diagnosed before the age of 40 had worse serologic values compared to those diagnosed after the age of 40. Finally, gender was not significantly associated with differences in clinical, serological, and prognostic features of AIH.

## Conflict of Interest

None of the authors identify a conflict of interest.

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# MEDICAL SCHOOL HOTLINE

## **Celebrating 15 Years of the Area Health Education Center at the John A. Burns School of Medicine**

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

The Area Health Education Center (AHEC) debuted in the (then named) Hawai'i Medical Journal in November 2000, with a Medical School Hotline article titled *The Role of AHEC in Medical Education*. This article described an emerging AHEC program with two regional community-based centers in Hilo and Lihue. These centers worked to provide the entire State of Hawai'i with health careers recruitment for K-12 students, support for continuing education, community-based education, and training of health care professional students in interprofessional teams. They strove to meet the federal mandate of the AHEC Program: to enhance access to high quality, culturally competent health care through academic-community partnerships to ultimately improve the distribution, diversity, and supply of the primary care health professions workforce who serve in rural and underserved health care delivery sites. Fifteen years later, we can reminisce about AHEC's humble (yet ambitious) beginnings and speculate about our future growth.

The main goal of the Hawai'i/Pacific Basin AHEC (HPB AHEC) is to improve the health of the underserved through education. The program has been working toward this goal with assistance from a long-term federal grant that has been in Hawai'i since 1995 (and in the United States since 1972, with AHEC Programs already established in 45 other states). Over time, however, the HPB AHEC has diversified its activities and funding to reach more people than ever before. The HPB AHEC program now has nine centers that have provided health careers recruitment activities for more than 40,000 students, training for more than 3,000 health professions students, and over 100,000 person-hours of continuing and community education. HPB AHEC centers are still located in Hilo and Lihue, but the program has also expanded to Wai'anae, Waimanalo, Kaunakakai, Koror (Palau), Pago Pago (American Samoa), Saipan (Commonwealth of the Northern Mariana Islands) and Yap (Federated States of Micronesia). Additionally, the HPB AHEC collaborates with the Guam AHEC, which services Guam; the Republic of the Marshall Islands; and Pohnpei, Kosrae, and Chuuk (the three states of the Federated States of Micronesia not served by Hawai'i AHEC). This broad geographic distribution of locations ensures that all of Hawai'i and the US Affiliated Pacific Islands jurisdictions have access to AHEC resources.

So what *exactly* does the HPB AHEC do? In 2014 alone, the program provided health careers recruitment activities for 3,433 students. The HPB AHEC also organized health careers training for 432 students, including 53 students who trained in the Pacific Basin. A total of 8,000 hours of Continuing Medical Education (CME) were administered for over 2,000 providers, which included hosting the annual Hawai'i Health Workforce Summit on healthcare transformation and provider satisfaction. The upcoming September 2015 Summit will include speakers on career satisfaction, using technology for the progress of telehealth, how to start a practice, and many other topics. The Summit also consists of a job fair that matches students and residents (including groups near retirement age) with practices and groups in need of future providers. The Summit is free to all participants and it is anticipated that over 500 providers, residents, and students will attend.

In addition, AHEC provides resources to recruit the next generation to health careers, including the Speaker's Bureau, which was created so that all Hawai'i schools can request health career speakers to visit their school, and to provide support for K-12 students to travel to health career schools such as JABSOM. The HPB AHEC also provides summer enrichment programs, school-based health awareness programs, and support for the Department of Education Career and Technical Education programs across the region. Student support also continues after they are accepted to a health professions school to promote retention within the field. To provide a model for future practice types, the HPB AHEC funds training for students in underserved areas to work as part of interprofessional teams. For example, in collaboration with Hawai'i Veterans Affairs program, the HPB AHEC coordinates the annual Rural Health Training Initiative that sends up to 40 public health, medical, nurse practitioner, and social work students to Guam and American Samoa for interprofessional clinical and community-based experiences. The HPB AHEC also supports travel for hundreds of students from all health professions to train in areas of need across the Pacific Region. Travel funds are available for students who are interested in gaining rural clinical experiences with the hope that they will elect to service these locations as professionals. Furthermore, the HPB AHEC provides mentoring and research

opportunities to students of all ages. The newest program is the Health Careers Corps, a Hawai'i Pipeline program for high school and college students to learn about health careers, receive mentoring and be a part of a group support system. Students who participate in any AHEC activities will be invited to join this group, and it is expected that students will remain actively engaged in the program for an average of four years, or at least until they graduate from health professions school. Typical activities include career awareness, campus visits, mentoring, research, and provider shadowing. We currently have eight members and expect to expand to 40 members by the end of the year. Please contact [AHEC@hawaii.edu](mailto:AHEC@hawaii.edu) to sign up!

AHEC's most satisfying (yet challenging) program has been the creation and administration of Hawai'i's State Loan Repayment Program. This program is made possible through support from HMSA, Queens Medical Center, AlohaCare, University Health Alliance, Lana'i Community Health Center, Ohana Healthcare, other local funders, and a federal grant award. As a direct result of this program, there are 19 physicians, nurse practitioners, and psychologists receiving loan repayment while working in underserved areas across Hawai'i. These individuals dedicate themselves to those in need for at least two years in Hawai'i's poorest and most rural areas. As compensation, the HPB AHEC uses federal and local funds to directly pay down educational debt (tax free!). It is hoped that the program will also gain support of the State legislature and continue for years to come.

Many of the HPB AHEC outreach activities are made possible through broad partnerships. Some of the wonderful collaborations for health careers recruitment activities are with student-run programs such as the Health Occupations Students of America (HOSA) Future Health Professionals, a national organization with dozens of local groups in Hawai'i and one in American Samoa. HPB AHEC also assists with the registration for the 200 students who qualify to compete in activities and challenges related to a variety of health topics at the annual Hawai'i HOSA

conference. Another partnership is with Teen Health Camp, a program started five years ago by three Medical and Public Health students, which is now run by a diverse group of medical/public health/nursing/pharmacy students who conduct day long health career awareness activities. The Teen Mentorship Academy is also associated with these camps, which currently involves five medical students who visit underserved students at their high school to provide health curriculum suggestions and mentoring services. Another outstanding student-run partnership is the Medical Student Mentorship Program that provides guidance to 183 college students across the state of Hawai'i who are interested in pursuing medical school.

In addition to student and professional outreach opportunities, the HPB AHEC offers to perform extensive research on the health career workforce and physician shortage in Hawai'i. The Physician and Physician Assistant Workforce Assessment for Hawai'i research data has demonstrated a workforce disparity in Hawai'i of over 600 fewer physicians and 100 fewer physician assistants when compared to a similar population and composition on the US mainland. Therefore, activities to recruit and retain medical providers are paramount to our mission. An example of this is the Ho'okipa Welcome Wagon program, a collaboration with the Hawai'i Rural Health Association, in which local community members pick up health careers students, interviewees and new hires at the airport to share Hawai'i's Aloha Spirit. Additionally, the Doc Jobs initiative program advertises all known Hawai'i physician job opportunities on the HPB AHEC's webpage, sends notices to providers on the mainland who may be interested in relocating to Hawai'i, and participates in the Hawai'i Physician Recruiter group to maximize job attractiveness within the island chain (including promoting business support and low interest loans). The HPB AHEC is working with this group to provide resources so that all of Hawai'i's local residents can be aware of job opportunities, enhance interview skills, receive advice on how to design CVs and provide experience with contract negotiations. The

What is in it for you?		
Health Career Level of Individual	Programs Available	Where to Find More Information
High school student interested in Health careers	1) Health Careers Navigator book 2) Teen Health Camps 3) Teen Mentorship Academy 4) Health Careers Corps Research opportunities 5) AHEC summer camps	<a href="http://www.ahec.hawaii.edu">www.ahec.hawaii.edu</a>
Undergraduate student interested in Health careers	1) Health Careers Navigator book 2) Prehealth Career Corps	<a href="http://www.ahec.hawaii.edu">www.ahec.hawaii.edu</a>
Health professions student wanting to perform rotation in a rural or underserved area	1) Rural Health Training Initiative 2) Travel support	Call AHEC at 808-692-1060
Resident nearing end of residency looking for jobs or guidance on how to set up practice	1) Hawai'i Healthcare Jobs 2) Support for practice start up	<a href="http://www.ahec.hawaii.edu">www.ahec.hawaii.edu</a>
Social Worker, Nurse Practitioner, Psychologist, Physician, or Physician Assistant looking for loan repayment	Hawai'i State Loan Repayment Program	<a href="http://www.ahec.hawaii.edu">www.ahec.hawaii.edu</a>
Anyone looking for continuing education	Hawai'i Health Workforce Summit	<a href="http://www.ahec.hawaii.edu">www.ahec.hawaii.edu</a>
Physician, Nurse Practitioner or Physician Assistant looking for a job	Hawai'i Healthcare Jobs	<a href="http://www.ahec.hawaii.edu">www.ahec.hawaii.edu</a>
New provider, interviewing provider, visiting student	Ho'okipa Welcome Wagon	<a href="http://www.hawaii.stateruralhealth.org">www.hawaii.stateruralhealth.org</a>

HPB AHEC regularly organizes focus groups with providers to assess career satisfaction and offers to perform exit interviews with doctors choosing to leave Hawai'i.

Looking forward, the HPB AHEC is developing exciting new projects that will be showcased in 2015. The HPB AHEC will be publishing the first-ever health careers pathway book for Hawai'i. This book (*Hawai'i Health Navigator*) is a 150-page resource for all students, career counselors, and science and health teachers in Hawai'i that will provide information on joining the workforce in a health-related career. A first-draft version of the *Hawai'i Health Navigator* is available on the HPB AHEC website. The goal is to turn the book into an interactive web-based tool. HPB AHEC welcomes advice and input during this revision period. Another initiative for 2015 is to expand medical education resources in Hawai'i by incorporating open source software for regular teleconferencing that will allow providers that are working directly with patients to share their knowledge with providers who are located in rural areas, and therefore may have limited resources. This program will

emphasize case presentations and mentoring on specific topics such as treatment for addiction, hepatitis C, chronic pain, and end of life care. The HPB AHEC's aim is to assist in replicating a New Mexico based project called Project ECHO™, a tele-mentoring program for providers in rural areas to learn the skills to care for remote, challenging, or hard-to-reach patients. This allows patients to be treated within their community in lieu of having to travel great distances to receive the care they require. Additionally, this flexibility helps providers remain satisfied in practice and connects them to other providers with similar interests across the state.

The past 15 years of AHEC in Hawai'i have been very rewarding and the program looks forward to many more years of service to the health community. The HPB AHEC program continues to welcome your participation, ideas, and feedback. Please email [ahec@hawaii.edu](mailto:ahec@hawaii.edu) or call 808-692-1060 for more information.

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## **Protecting Public Health Through Governmental Transparency: How the Hawai'i Department of Health's New "Stoplight" Placarding Program is Attempting to Influence Behavioral Change in Hawai'i's Food Industry**

Peter Oshiro BS

*Insights in Public Health is a monthly solicited column from the public health community and is coordinated by HJMPH Contributing Editors Tetine L. Sentell PhD from the Office of Public Health Studies at John A. Burns School of Medicine and Donald Hayes MD, MPH from the Hawai'i Department of Health in collaboration with HJMPH Associate Editors Tonya Lowery St. John MPH and Lance K. Ching PhD, MPH from the Hawai'i Department of Health.*

### **Abstract**

*Reducing the occurrence of and influencing the rapid correction of food illness risk factors is a common goal for all governmental food regulatory programs nationwide. Foodborne illness in the United States is a major cause of personal distress, preventable illness, and death. To improve public health outcomes, additional workforce was required due to long standing staffing shortages and was obtained partially through consolidation of the Hawai'i Department of Health's (HDOH) two food safety programs, the Sanitation Branch, and the Food & Drug Branch in July 2012, and through legislation that amended existing statutes governing the use of food establishment permit fees. Additionally, a more transparent food establishment grading system was developed after extensive work with industry partners based on three possible placards issued after routine inspections: green, yellow, and red. From late July 2014 to May 2015, there were 6,559 food establishments inspected statewide using the placard system with 79% receiving a green, 21% receiving a yellow, and no red placards issued. Sufficient workforce to allow timely inspections, continued governmental transparency, and use of new technologies are important to improve food safety for the public.*

### **The Problem of Major Food Safety Violations in Hawai'i's Food Industry**

It is estimated that food illnesses in the United States cause approximately 3,000 deaths, 128,000 hospitalizations, and 48 million illnesses annually. The occurrence of approximately 1,000 reported disease outbreaks (local, regional, and national) each year highlights the challenges of preventing these maladies.<sup>1</sup>

The HDOH investigated 247 foodborne illnesses in the State of Hawai'i in 2014.<sup>2</sup> Symptoms of food illnesses can range from slight gastric discomfort to severe bouts of bloody diarrhea, vomiting, fevers, and organ failure that may result in hospitalizations, permanent disabilities, or even fatalities. Nearly all causes of foodborne illness are preventable if proper care is taken with food employee personal health and hygiene; maintenance of proper temperature controls regarding cooking, storing, cooling, and reheating of potentially hazardous foods; proper sanitizing and cleaning of food equipment and utensils; and ensuring that food is obtained from approved food sources. HDOH rules and regulations are designed to prevent or mitigate

the causes and occurrences of foodborne illnesses by controlling these food illness risk factors.

The Food Safety Program is currently a consolidation of the Sanitation Branch and the Food and Drug Branch. The program belongs to the Environmental Health Services Division (EHSD) of the Hawai'i Department of Health. The food safety program regulates the food industry through Hawai'i Administrative Rules (HAR), Title 11, Chapter 50, Food Safety Code, and is authorized by section § 321-11 of the Hawai'i Revised Statutes (HRS).

Food establishments include: restaurants, caterers, lunch wagons, push carts, markets, liquor establishments, convenience stores, hotel banquet and room service kitchens, food manufacturers, institutional kitchens (schools, hospitals, prisons), day care centers, homeless feeding, temporary food sales events, food demos, fundraisers, etc, and are legally defined as;

- (1) Any place or portion thereof, maintained, used, or operated for the purpose of storing, preparing, serving, manufacturing, packaging, transporting, or other otherwise handling food at the retail or wholesale level;
- (2) Any place used for cleaning food equipment or utensils in support of another food establishment; or
- (3) Any operation that is conducted in or in conjunction with a mobile, stationary, temporary or permanent facility, or location where food is served, or provided to the public, with or without charge, regardless of whether the food is consumed on or off the premises.<sup>3</sup>

In 2009, the Sanitation Branch conducted 2,691 routine inspections of food establishments on O'ahu.<sup>4</sup> This represented only 46% of the 5,800 food establishments on O'ahu at the time and resulted in an inspection frequency of over 2 years for each food facility. These routine inspections resulted in over 2,400 critical violations and over 2,800 non-critical or good

manufacturing practices (GMP) violations.<sup>5</sup> Only 20% of the 2,691 inspections had no violations, the other 80% had multiple violations. Critical violations are defined as foodborne illness risk factors that the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) has identified as the practices and behaviors that are the contributing factors to foodborne illness outbreaks within food service and retail food establishments.<sup>6</sup> The risk factors are;

- Food from unsafe sources
- Poor personal hygiene
- Inadequate cooking
- Improper Holding/Time and Temperature
- Contaminated equipment/Protection from contamination

The 2,400 critical violations observed is extremely high and the multiple critical violation rate observed during routine inspections ranged from 40% to nearly 80% of all routine inspections in certain geographical areas.<sup>4</sup> A multiple critical violation rate as low as 11% is achievable for world class food safety programs like Sacramento County, who in 2008, won the Crumbine Award for Excellence in Food Protection. Sacramento County was able to reduce the “yellow” placard rate to 11% during their routine inspections.<sup>7</sup> The Crumbine Award is given annually to local environmental health jurisdictions that demonstrate unsurpassed achievement in providing outstanding food protection services to their community.

The critical violation rate observed during routine inspections was disconcerting, so it was imperative that the HDOH improve its food safety program. One of the main contributing factors to the high occurrence of food illness risk factors is the poor inspection frequency due to a lack of food inspectors. In 1999, the Sanitation Branch evaluated the inventory of food establishments statewide and categorized them into three risk categories that were based on the number of food operations present in the food establishment that impact public health. Eight operations (e.g. receiving, cold storage, hot storage, thermal processing, etc.) were identified to determine the complexity of the food establishment and the fees for the permit. Risk Category 3 (\$50) food establishments, had 1-3 of the food operations. The Category 2 (\$100) establishments had 4-5 and Category 1 (\$150) establishments had 6-8 operations.<sup>8</sup> The risk categories were also created to inspect the highest risk facilities more often than the lower risk facilities, but in FY 2010, O’ahu had a ratio of 590 food establishments per inspector. This resulted in an inspection frequency of one inspection every 2 to 2½ years for each food establishment regardless of risk category as there were so few inspectors available. According to FDA recommendations, the ideal workload for food inspectors is 150 food establishments per inspector.<sup>9</sup> This ideal staffing ratio would allow a food regulatory program that has 3 risk categories to inspect the Category 1 food establishments 3 times a year, the Category 2 establishments 2 times per year, and the Category 3 establishments once per year.

To achieve a ratio closer to the ideal 150 food establishments

per year, the program would need to hire at least 20 more inspectors (from the existing 10 in 2010) to achieve a ratio of 200:1 as there were approximately 5,900 food facilities in FY 2010.

## Resolving Staffing Shortages

It was very apparent that from 2002-2008, the competition between the Food Safety program and all other State departments for General Fund appropriations, coupled with the administrations political philosophy of not increasing the number of government employees would not produce any gains in the number of food safety inspectors.

The Food Safety Program then decided to take a bold step to change section §321-27 Environmental Health Education Fund (EHEF), of the Hawai’i Revised Statutes (HRS) to allow the permitting fees to be used to “Conduct program activities and functions of the Sanitation Branch including permit issuance, inspections, and enforcement and the hiring of additional inspectors.”<sup>10</sup> To that end HB36 was introduced in the 2009 legislature outside of the DOH’s legislative package.<sup>11</sup> The bill easily passed the House and Senate chambers of the legislature, but was eventually vetoed by Governor Lingle.

In 2010, an identical bill to HB36 was introduced to the 2010 Legislature as HB2688 which again passed both chambers of the Legislature with no opposition and was signed into law by Governor Lingle.<sup>12</sup> HRS Section §321-27 was now the Sanitation and environmental health special fund. The annual ceiling on the fund was also increased from \$300,000 to \$1,500,000 to allow for the needed program support.

The task was still not complete as revenue from the existing permit fee structure was approximately \$440,000 annually. This existing revenue would not be enough to allow the hiring of 20 new inspectors as well as transitioning from manually written inspection reports to a much needed electronic web-based inspection system. The program also wanted to introduce a new concept of a restaurant “grading” or placarding system that would be a major paradigm shift in the way the DOH regulated the food industry. The electronic web-based inspection system would allow immediate public access to food establishment inspection results. The placarding system would be a very high profile method of notifying the public the status of the most recent DOH inspection of the food facility by placing a highly visible, brightly colored 8 1/2” x 11” placard at the most visible location at the entrance to the food facility.

Once the authorization to allow the special fund to be used for all operational costs of the food safety program was approved by passage of Act 176/June 2010 (HB2688), the program began drafting a new HAR to effectuate the change in statutes. By summer of 2012, the DOH had a draft of HAR 11-50, Food Safety Code. The length of time taken to revise the rules took nearly two years as it involved a complete rewrite of the existing food rules known as HAR 11-12, Food Establishment Sanitation which was approximately 82 pages in length. HAR 11-50 ended up as a 171 page administrative rule as the program adopted the 2009 FDA Model Food Code as the basis for the new HAR. In addition to being the vehicle to generate additional revenue

and defining the “Stop-Light” food establishment placarding program, it was critical that the State’s new food safety rules reflected a nationally recognized standard as well as the most current scientific thought on the control of foodborne illnesses and emerging pathogens.

In the Summer of 2012, between the final draft of the rule and public hearings that were held in October 2013, the food safety program met multiple times with the major stakeholders that would be affected by the new rule. Meetings and discussions with the Executive boards of the Hawai’i Restaurant Association, the Hawai’i Hotel and Lodging Association, The Hawai’i Food Manufacturers Association and the Hawai’i Food Industry Association produced very fruitful and frank discussions to justify the new HAR to the food industry prior to any official public hearings. The goal of the food safety program was to get industry “buy-in” for a doubling of the regulatory burden which expanded an 82 page rule to 171 pages, a quadrupling of the average food establishment permit fee from \$46 to \$200 by changing the existing fee schedule in HAR, and the introduction of a high profile food establishment placarding program that would notify the public of the most recent inspection results of the food facility. The new HAR Title 11, Chapter 50, Food Safety Code was signed by Governor Abercrombie in February 2014.

### Implementation of Placarding — Chapter 50

The DOH recognized the fact that one of the biggest drivers of behavioral change in industry practices is governmental transparency. The placarding system was designed to greatly influence voluntary compliance with food safety regulations that protect public health. Prior to the implementation of Chapter 50, Food Safety Code, food establishments that were observed to have major violations typically needed multiple follow-up inspections and threats of permit suspensions or fines to completely resolve all critical violations. If the food establishment still did not come into compliance, the program would need to litigate the issue through lengthy, resource draining solutions by taking administrative actions that may include;

- Meetings with the offender to discuss why the food establishment is having difficulty complying with food safety regulations;
- Meetings with legal counsel (Deputy Attorney General) in obtaining a Docket No. and drafting and creating extensive legal documents that lead to creation of “Notice of Violations and Orders” (NOVO) that threaten permit suspensions and/or monetary penalties due to non-compliance;
- Scheduling and arranging formal Administrative Hearings with departmental hearings officers;
- Dealing with the outcomes of the hearings officers decisions which may not favor the DOH;
- Repeating the previous three bullet points in preparation for an appearance in Civil Court if the respondent contests the outcome of the Administrative Hearings.

The HDOH adopted a stop-light placarding system to alert the public to a food establishment’s performance as the model for government transparency. Brightly colored Green (Pass), Yellow (Conditional Pass) or Red (Closed) placards are posted by the food safety field staff in a highly visible location at the entrance of the food establishment upon completion of a routine inspection (Figure 1). An establishment is issued a Green (Pass) placard if one critical violation or less is observed and corrected or mitigated on site prior to the completion of the inspection (Table 1). If two or more critical violations are observed, a Yellow (Conditional Pass) placard is issued. The yellow placard indicates which of the 5 critical violations mentioned on page 2, which lead directly to food illnesses, plus rodent/insect infestation, were responsible for the issuance of a Conditional Pass placard. Although rodent and insect infestations are not known as a direct cause of food illness in the United States, the general public and the HDOH have a universal aversion to the presence of rodents or insects in restaurants and other food establishments which may adulterate or contaminate the food supply. A Closed - Red placard is issued if there are imminent health hazards occurring such as no water, no power, sewage overflowing in food prep areas, or an active foodborne outbreak is ongoing as determined by our epidemiologists at the DOH Disease Investigation Branch.<sup>13</sup>

Other States food safety jurisdictions have used a traditional letter grading system, (A, B, C, Fail) or numerical system that indicates the inspection score out of 100 points. We strongly believe that the “stop-light” (Green-Yellow-Red) system is su-



Figure 1. Food Establishment “Stoplight” Placards, State of Hawai’i



Conditions Observed	Placard Issued		
	Green "Pass"	Yellow "Conditional Pass"	Red "Closed"
	One critical violation or less. Violation must be corrected or mitigated prior to the conclusion of inspection.	Two or more violations. Requires a follow up inspection within 48 hours.	Imminent Health Hazard observed. (eg. active food illness outbreak ongoing, overflowing sewage, no power, no water.)

rior to either of these due to it being a zero-tolerance program for critical violations. ALL critical violations must be corrected if the food establishment is given a PASS-Green placard. It is difficult for the public to understand the difference between restaurants that received a "B" versus a "C" grade or what it means if a restaurant had a score of 83 versus 77.

The placarding system that Hawai'i has adopted is concerned with critical violations that are "Foodborne Illness Risk Factors", and not "Good Retail Practice" (GRP) violations such as unclean floors and walls which do not directly cause foodborne illnesses, but are still important factors in providing safe, wholesome and unadulterated food products.<sup>13</sup> The food establishment inspection report in use at present is the national standard and is divided into two sections. The top section is labeled "Food-borne illness risk factors and public health interventions" represented by the first 27 items listed on the report. The bottom half of the inspection report is labeled as "good retail practices" and are represented by items 28-54 on the inspection report (Figure 2).

The placarding system is designed to avoid or greatly minimize the occurrence of possible litigation by encouraging voluntary compliance of food safety regulations through the use of societal pressure through governmental transparency of food safety inspection results. If a Yellow – Conditional Pass is posted at the food facility, it clearly notifies the public which, and how many of the 5 critical violations plus rodent/insect infestation were observed during the last inspection. Public notification that poor personal hygiene, or foods being subject to contamination, or any of the other 4 categories of food safety violations is shown to have a very strong negative effect on potential customers.

Achieving national uniformity among regulatory programs responsible for retail food protection in the United States has long been a subject of debate among the industry, regulators and consumers. Adoption of the 2009 FDA Model Food Code at the state level has been a keystone in the effort to promote greater uniformity. However, a set of widely recognized standards for regulatory programs that administer the Food Code was lacking. To meet this need FDA has developed the "Voluntary National Retail Food Regulatory Program Standards" (Program Standards) through ideas and input from federal, state, and local regulatory officials, industry, trade and professional associations,

academia, and consumers on what constitutes a highly effective and responsive retail food regulatory program.<sup>14</sup>

Adopting national standards was a key component in obtaining "buy-in" from the regulated industry. The HDOH did not want to impose a local rule or philosophy that was divergent from a national standard. Hawai'i is a very large player in the food industry with numerous corporate mainland restaurants, fast food outlets, and convenient store chains. Hawai'i also is home to large national hotel chains like Sheraton, Hyatt, Four Seasons, Marriott, Disney, and others that, along with the restaurant chains, had already adopted either the 2005 or the 2009 FDA Model Food Code to use as their internal, corporate food safety quality control. The food industry was already ahead of the game prior to our introduction of HAR Chapter 50. The DOH needed to make sure that if it engaged in a high profile food establishment "grading" program, that could have implications on the commerce of the food establishments, that it would need to be a nationally recognized set of criteria that the HDOH were judging the food establishments on to be defensible.

The food establishment placarding system was created to:<sup>15</sup>

- Reduce the incidence of major violations in the food establishment, thus reducing the risk of the public contracting foodborne illnesses or being exposed to harmful contamination of the food supply;
- Allow patrons to make informed decisions regarding food safety prior to entering the food facility;
- Increase compliance with food safety laws while reducing the number of follow-up inspections;
- Convey meaningful inspection results to the public and the food service industry using a system that is easy to understand; and
- Reward the food establishment for excellence in food safety.

The HDOH halted all routine inspections of food establishments in January 2014 and began the "How To Get A Green Placard" (HTGAGP) campaign. The purpose of the campaign was for the food safety inspectional staff to visit ALL 10,000 plus food establishments statewide (5,900 on O'ahu) with active permits to issue them a folder that contained everything they need to know regarding what our food safety staff would be concentrating on during routine inspections, and to explain the placarding program directly to food establishment owners and managers.<sup>16</sup> The target date for completion on O'ahu was June 30, 2014. The HDOH also arranged meetings with over 30 chain and individual groups of food service operators/owners in lieu of site visits for those companies that wanted all of their key managers and line personnel to get the same message at once. Our program took great care to ensure that the food industry would not be surprised with the application and enforcement of our new food rules, which were a true paradigm shift in the way the State DOH would regulate food establishments. The placarding violations and how to prevent them were also available in multi-language hand-outs. Chinese, Korean, Japanese,

STATE OF HAWAII		<b>FOOD ESTABLISHMENT INSPECTION REPORT</b>				Page ____ of ____								
Establishment Name					Date: _____									
					Time In: _____									
					Time Out: _____									
Address			City	Zip Code	Telephone									
Permit #	Owner Name			Purpose of Inspection	Est. Type	Risk Category								
FOODBORNE ILLNESS RISK FACTORS AND PUBLIC HEALTH INTERVENTIONS														
Circle designated compliance status (IN, OUT, N/O, N/A) for each numbered item: IN=in compliance    OUT=not in compliance    N/O=not observed    N/A=not applicable				Mark "X" in appropriate box for: COS=corrected on-site during inspection    and/or    R=repeat violation										
Compliance Status		COS		R										
<b>Supervision</b>				<b>Potentially Hazardous Food (TCS food)</b>										
1	IN	OUT	Person in charge present, demonstrates knowledge, and performs duties											
<b>Employee Health</b>				<b>Consumer Advisory</b>										
2	IN	OUT	Management awareness; policy present		23	IN	OUT	N/A	Consumer advisory provided for raw or undercooked foods					
3	IN	OUT	Proper use of reporting, restriction & exclusion		<b>Highly Susceptible Populations</b>									
<b>Good Hygienic Practices</b>				<b>Chemical</b>										
4	IN	OUT	N/O	Proper eating, tasting, drinking, or tobacco use	25	IN	OUT	N/A	Food additives: approved and properly used					
5	IN	OUT	N/O	No discharge from eyes, nose, and mouth	26	IN	OUT	Toxic substances properly identified, stored, and used						
<b>Preventing Contamination by Hands</b>				<b>Conformance with Approved Procedures</b>										
6	IN	OUT	N/O	Hands clean and properly washed	27	IN	OUT	N/A	Compliance with variance, specialized process, and HACCP plan					
7	IN	OUT	N/A	N/O	Adequate handwashing facilities supplied and accessible									
<b>Approved Source</b>				<div style="border: 1px solid black; padding: 2px; font-size: small;">           Risk factors are food preparation practices and employees behaviors most commonly reported to the Centers for Disease Control and Prevention as contributing factors in foodborne illness outbreaks.  <b>Public health interventions</b> are control measures to prevent foodborne illness or injury.         </div>										
9	IN	OUT	Food obtained from approved source		<b>GOOD RETAIL PRACTICES</b>									
Good Retail Practices are preventative measures to control the introduction of pathogens, chemicals, and physical objects into foods.														
Mark "X" in box if numbered item is <b>not</b> in compliance.    Mark "X" in appropriate box for:    COS = corrected on-site during inspection    and/or    R = repeat violation														
Safe Food and Water		COS		R		<b>Proper Use of Utensils</b>					COS		R	
28	IN	OUT	Pasteurized eggs used where required		41	IN	OUT	In-use utensils: properly stored						
29	IN	OUT	Water and ice from approved source		42	IN	OUT	Utensils, equipment and linens: properly stored, dried, handled						
30	IN	OUT	Variance obtained for specialized processing methods		43	IN	OUT	Single-use/single-service articles: properly stored, used						
<b>Food Temperature Control</b>				44				Gloves used properly						
31	IN	OUT	Proper cooling methods used: adequate equipment for temperature control		<b>Utensils, Equipment and Vending</b>									
32	IN	OUT	Plant food properly cooked for hot holding		45	IN	OUT	Food and nonfood-contact surfaces cleanable, properly designed, constructed, and used						
33	IN	OUT	Approved thawing methods used		46	IN	OUT	Warewashing facilities: installed, maintained, used; test strips						
34	IN	OUT	Thermometers provided and accurate		47	IN	OUT	Nonfood-contact surfaces clean						
<b>Food Identification</b>				<b>Physical Facilities</b>										
35	IN	OUT	Food properly labeled; original container		48	IN	OUT	Hot and cold water available; adequate pressure						
<b>Prevention of Food Contamination</b>				49				Plumbing installed; proper backflow devices						
36	IN	OUT	Insects, rodents, and animals not present		50	IN	OUT	Sewage and waste water properly disposed						
37	IN	OUT	Contamination prevented during food preparation, storage, and display		51	IN	OUT	Toilet facilities: properly constructed, supplied, clean						
38	IN	OUT	Personal cleanliness		52	IN	OUT	Garbage/refuse properly disposed; facilities maintained						
39	IN	OUT	Wiping cloths: properly used and stored		53	IN	OUT	Physical facilities installed, maintained, and clean						
40	IN	OUT	Washing fruits and vegetables		54	IN	OUT	Adequate ventilation and lighting; designated areas used						
<b>REMARKS</b>														
Print name of Person in Charge: _____														
Signature of Person in Charge: _____											Date: _____			
Signature of Agent/Dept. of Health: _____					Follow-up: (Circle one)    YES    NO			Follow-up Date: _____						

SAN INSP FOOD 02/14

Figure 2. Food Establishment Inspection Report, State of Hawai'i

Ilocano and Tagalog, Thai, Vietnamese, and Spanish translated hand-outs were made available.

### Present Results

On July 21, 2014 the DOH issued a Media Advisory in an effort to showcase the results of the first placards being issued under the new placarding program.<sup>17</sup> Due to the media response, and the difficulty coordinating a surprise inspection for the media, the DOH had to settle for a last minute, arranged mock inspection at a local café that was closed for business. This had to be done to accommodate all three major news stations as well as the major newspaper. The Nielsen audience on the evening news that night was over 656,000 viewers through 24 news stories between 8:00 a.m. that morning on all the news shows until 10:00 pm that night.<sup>18</sup> The media focused on the poor food establishments that were shown getting a Yellow Conditional Pass placard and which of the food illness risk factors (critical violations) were found at the facility. The next evening presented more of the same with an estimated Nielsen audience above 500,000 on follow-up stories. On August 22, 2014, a restaurant at a major shopping center removed the Yellow - Conditional Pass placard issued to them a day after the inspection. HDOH did another press release on this event on Sept 29, 2014, and another 470,000 Nielsen viewers saw the negative publicity surrounding the event.<sup>19,20</sup> The restaurant paid the HDOH a fine of \$11,000 and indicated to the HDOH that they lost a significant amount of business immediately following the negative publicity.

As the one-year anniversary of the new placarding system and implementation of HAR, Chapter 50, Food Safety Code, approaches on July 23, 2015 some interesting, preliminary trends have unfolded (Table 2). In the first three months, from July

23 until October 31, 2014, 32% of all food establishments that underwent routine inspections, were issued Yellow Conditional Pass placards. This means that one out of three restaurants were operating with multiple foodborne illness risk factors present. The months of November and December saw significant decreases to 19% and 16% Yellow placards issued, then became very stable over the last five months, from January until May showing the following results 23%, 26%, 25%, 24%, and 23% of yellow placards issued respectively. The very preliminary results have shown a steady reduction from one in three facilities being issued yellow placards under the new HAR Chapter 50 inspections, to one in four facilities at present. These statistics are very promising for the new food safety rules in showing a significant drop in the occurrence of foodborne illness risk factors in the regulated community.

### Future Goals

The signing of Act 176/June 2010 was responsible for a staffing increase from 9 field staff in 2011 to 29 at present with only 2 more vacant positions that are actively being filled for a total of 31 field inspection staff. The full staffing levels that we have achieved will allow the HDOH to consistently inspect Hawai'i's food establishments at an optimum frequency of at least 1 to 3 times per year based on their risk factors. Only eleven of the twenty-nine field staff at present have greater than 4 years of food safety experience, so it will be another three years before the majority of the field staff will be at a level of being fully independent, capable of immediate field interpretations of all food safety regulations, and having reached a level of efficiency and competency to inspect all food establishments at the appropriate frequency. The food safety program fully expects to see the number of Yellow placards issued decline to further lows.

Table 2. Hawai'i Placard Issuance Results by County, Aug 2014-May 2015																
Date	Honolulu County				Hawai'i County				Maui County				Kaua'i County			
	G	Y	R	%Y	G	Y	R	%Y	G	Y	R	%Y	G	Y	R	%Y
<b>2014</b>																
AUG*	336	143	0	30												
SEP	298	161	0	35												
OCT	283	130	0	31												
NOV	240	58	0	19												
DEC	421	80	0	16	335	51	0	13	494	66	0	12	95	36	0	27
<b>2015</b>																
JAN	257	76	0	23												
FEB	322	112	0	26												
MAR	387	130	0	25	466	65	0	12	391	19	0	5	115	40	0	26
APR	379	120	0	24												
MAY	349	104	0	23												
<b>TOTAL</b>	<b>3,272</b>	<b>1,114</b>		<b>25</b>	<b>801</b>	<b>116</b>		<b>13</b>	<b>885</b>	<b>85</b>		<b>9</b>	<b>210</b>	<b>76</b>		<b>27</b>

\*Note: August time period for 2014 started on July 23, 2014

The next greatest influence to further reduce the occurrence of food illness risk factors will be the launching of our new web-based food safety inspection system. The HDOH recently awarded a contract to create and maintain a fully electronic web-based food safety inspection system. The main highlight of the system that the HDOH hopes to reduce food illness risk factors further, will be complete public access to all of our food establishment inspection results. The philosophy of transparent government being used to drastically change industry behavior for the better will literally be on display for the whole world to see. The new information technology vendor will introduce a public portal with easy drill down menus to access HDOH food establishment inspection reports online. The Green/Yellow/Red Placards may also be imbedded with a Quick Response (QR) code so any potential customer can wave their smart device/ phone over the placard and immediately see the results of the last inspection.

Technology combined with governmental transparency can be a powerful tool in influencing positive industry behavior to drastically reduce food illnesses or the adulteration of foods by eliminating the occurrence of food illness risk factors. The food industry in Hawai'i will never be the same (thankfully) due to the adoption of new food safety rules, new technologies and immediate public access to food establishment inspection results.

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## GLAUCOMA AND MEDICAL MARIJUANA.

Glaucoma is a disease of the optic nerve, the cable that carries messages from the visual system to the brain. With elevated pressure within the globe, the optic nerve will suffer injury that can lead to blindness. While we have medications, laser treatment, and sometimes surgery, in some patients the pressure is relentless and cannot be controlled. Marijuana is known to reduce the pressure within the eye and it has been suggested for therapy in these stubborn cases. Smoking THC (tetrahydrocannabinol) the active ingredient in marijuana can reduce the intraocular pressure. Alternatively, the drug can be taken orally or absorbed under the tongue to avoid possible damage to the lungs as may occur with smoking. However, the effect is limited; pressure rises again after three or four hours. Moreover there are systemic side effects of impaired judgment and drowsiness. To date, research has not been able to compound a topical medication with effective THC. In summary, appealing as the idea is, like many things medical, the art is painted in shades of grey.

## A RUDE AWAKENING

At Stanford University department of psychiatry, researchers conducted a survey to evaluate confusional arousal, a condition called sleep drunkenness. Some 19,000 adults eighteen years and older were studied to determine the incidence of this condition that occurs when the body beats the brain out of bed. Sufferers may awaken not knowing where they are, have trouble talking or try to answer the phone when the alarm is ringing. These events can occur to anyone with jet lag or fatigue, but for one in seven (15%) of those studied, they regularly inhabit this hazy world. Such episodes are sometimes linked with other sleep disorders, anti-depressant drug use, and mental illness, according to the journal *Neurology*.

## OUT OF AFRICA: HIV, EBOLA, WEST NILE FEVER... CHIKUNGUNYA.

Still another virus has migrated out of Africa, bringing suffering and often crippling pain. Chikungunya "to walk bent over" has established itself In Brazil, the Caribbean, India, SE Asia and the Pacific islands. This mosquito born disease comes on like the flu with fever, chills, headache and aching joints and typically lasts a week. Many patients later develop severe joint pain that can recur for months or years. Apart from settling in Southeast Asia in the late 1950s, previous sorties from Africa have fizzled. Not this time. In 2005 the virus migrated from Kenya and found its way to Reunion, an island off the coast of Africa. The island was overwhelmed and became the jumping off place for a mutated virus that swept through Madagascar, Mauritius, Comoros, and the Seychelles. It moved to India and hit the jackpot. With mutation the virus can inhabit *Aedes aegypti* and *Aedes albopictus* (the Asian tiger mosquito), both living in Hawai'i. The best thing that can be said is that unlike Dengue, Chikungunya confers lifetime immunity, but then once is enough.

## WOW, I NEED A DRINK. WHAT'S IN YOUR HANDBAG?

Last summer the US Food and Drug Administration jumped the gun with approval of a powdered alcohol compound that only needs water. The FDA reneged and ordered further study of Lipsmark LLC, and its revolutionary product. Following scientific review the Alcohol Tax and Trade Bureau approved labels for Palcohol, a compound that can easily become a lemonade drink. Because alcohol is regulated at the state level, once a product receives federal approval it can go on sale in most states. Several states have adopted pre-emptive bans and more are gearing up to ban powdered alcohol. Still, large states including California, Florida and New York have no laws that would limit its distribution. Since the compound will probably be sold in foil packets, there can be no doubt it will travel far and wide. Keep the breathalyzer handy.

## MERS IS ONE MORE SCARY DISEASE.

A 68 year-old man returned to Korea from the Middle East. Nine days after he first appeared with fever, cough and shortness of breath, doctors recognized he had MERS (Middle East respiratory syndrome). The vigor of this betacoronavirus derived from bats is frightening. One hundred eighty two patients have been found positive for MERS and thirty-one have died. In Arabia the fatality rate is estimated at 40%. It is not air borne, but rather is spread by personal contact. In an attempt to choke off the epidemic, Korean officials have temporarily closed over 2,000 schools including 20 universities. 2,467 have been placed in isolation at home or in facilities. Because one sick man can spread MERS so easily, it is evident that health facilities in Hawai'i and other destinations of Korean and Middle East traffic, must be super-alert for this disease.

## DOES MY CHIN MAKE ME LOOK FAT?

Activis recently changed its name to Allergan after purchasing that company. Focusing on the cosmetic market Activis (now Allergan) has made a generous offer to absorb Kythera, that markets Kybella, an injectable compound that breaks down the fat in sub-mental fullness also known as the double chin. Allergan is seeking to add Kybella to bolster its market-leading cosmetic medicine portfolio, anchored primarily by Botox. Kybella, approved by the FDA in April of this year, will give Allergan a product for the chin to go along with therapies for the forehead, eyes, cheek and nose. Some experts have forecast sales well below Kythera's estimate because treatment requires multiple injections. A typical double chin patient will need four sessions, each requiring dozens of shots. Patients are used to one or perhaps two visits and might be turned off with repeated trips. The double chin is a new target in the \$12 billion cosmetic market, and has the appeal of an undertreated defect affecting both men and women.

## A RARE EVENT: A CUSTOMER WINNING AGAINST BANK OF AMERICA.

In June 2011 the Bank of America wrongfully pursued payment for a house and lot in Naples, Florida. Warren and Maureen Nyerges had purchased the property with cash paid directly to the bank. After a frustrating struggle for more than a year, the bank finally admitted its error and thought the matter was forgotten. No, Warren and Maureen won a judgment of \$2,534 for expenses that the bank contemptuously ignored. The Nyergeses sought and obtained a seizure order, and two deputies backed a truck up to the local BA branch to confiscate computers and office furniture valued at \$2,534. After two hours of multiple phone calls with higher up bank officials, the branch manager wrote a check for payment in full.

## ADDENDA

- Drug overdose took the lives of 44,000 Americans in 2013, exceeding motor vehicle crashes. Over half of the deaths (52%) were caused by prescription drugs.
- Restaurant sign, "No. We do not have Wi-Fi. Talk to each other."
- Teach your children about taxes. Eat 30% of their ice cream.
- Jerry Seinfeld is kind of short, but he can always stand on his wallet.
- You do the dishes, sweep the floor and make the beds. In six months you have to do it all again. (Joan Rivers)
- I've been married so long I'm on my third bottle of Tabasco sauce.
- In sex as in banking there is a penalty for early withdrawal.

## ALOHA AND KEEP THE FAITH rts

*(Editorial comment is strictly that of the writer.)*



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