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Aim:

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

History:

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

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

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The HJH&SW is financially supported by the academic units within the UH College of Health Sciences and Social Welfare, the UH Office of the Vice Chancellor for Research, the Hawai‘i State Department of Health, and by advertising. However, the journal’s editorial board maintains editorial independence from these entities for the acceptance and publication of research articles. All editorial decisions regarding the selection and editing of research articles are made by the members of the journal’s editorial board. The decisions of the editorial board are not influenced by nor subject to the approval of these entities.

The aim of the columns of the HJH&SW is to provide a space for the entities that financially support the HJH&SW to diseminate information regarding their research, programs, goals, or current issues facing their respective fields. Columns are edited by the HJH&SW contributing editors, who are employees of the agencies that support the HJH&SW.

The aim of the Hawai‘i Journal Watch is to highlight recent research of the entities that finacially support the HJH&SW. The research articles that are covered in the Hawai‘i Journal Watch are selected by both the HJH&SW and by researchers in the units that support the HJH&SW. The researchers whose articles are covered in the Hawai‘i Journal Watch are given the opportunity to fact check the news brief.

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Hawai'i Journal Watch

Karen Rowan MS

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

Healthy Beverage Options for Children at Hawai'i Restaurants

Hawai'i's "healthy default beverage law" went into effect in January 2020, requiring restaurants to offer a drink such as water, low-fat milk, or 100% juice as a default beverage option with children's meals. Researchers led by Meghan McGurk MPH, with the Thompson School of Social Work & Public Health, examined menus from restaurants across Hawai'i during November and December 2019, before the law went into effect. The researchers looked at 64 restaurants offering children's meals from a random sample of 383 establishments with food permits. Results showed that just 2 restaurants complied with the law before they were required to do so. About 12% offered some default beverages that were healthy, but also offered default beverages that were not healthy. More than 60% of restaurants with children's meals offered a sugar-sweetened beverage, such as soda or flavored milk, as a default beverage. The findings suggest that such laws may improve the beverage options included in children's meals.

- McGurk MD, Cacal SL, Vu U, et al. Baseline assessment of children's meals and healthy beverage options prior to a state-level healthy default beverage (HDB) law. *Journal of Healthy Eating and Active Living*. 2021;1(2):53-63.

Resilience in Native Hawaiian and Micronesian Families Who Have Regained Stable Housing

Factors that help Native Hawaiian and Micronesian families who were once houseless but succeeded in regaining stable housing include receiving support and taking initiative. Researchers including Francie J. Julien-Chinn PhD, of the Thompson School of Social Work & Public Health conducted narrative interviews with 4 Native Hawaiian and Micronesian families living on O'ahu who had experienced unstable housing but were living in stable housing at the time of the study. The interviews revealed that the families' protective factors included formal supports such as food stamps and section 8 housing, as well as informal support from family and friends. The families also developed insights into their situations and took initiative to make changes. Spiritual beliefs also played a role, such as the Native Hawaiian concepts of *lōkahi* (harmony) with *Akua* (gods and spirit), *'āina* (land), and *kānaka* (family). In interventions aimed at helping houseless families, it will help to focus on the factors that contribute to resilience.

- Julien-Chinn FJ, Park MLN. Understanding the connection between the 'Āina, strengths, and houselessness among previously houseless Native Hawaiian and Micronesian families. *Journal of Human Behavior in the Social Environment*. https://doi.org/10.1080/10911359.2021.191478

Proteins Linked with Endometrial Cancer Risk

Researchers have identified new proteins that may be linked with women's risk of endometrial cancer. Researchers led by Jingjing Zhu PhD, of the University of Hawai'i Cancer Center, examined data from the genomes of 12906 women with endometrial cancer and 108979 women without this cancer. The study utilized findings from previous genome-wide association studies that had identified 17 specific places in the genome linked to endometrial cancer risk; the new study looked at 1434 proteins in the blood whose circulating levels can be predicted by genetic variants. Results revealed nine proteins that may be linked to endometrial cancer risk, including proteins involved in DNA repair and immunity. The findings could improve the assessment of women's endometrial risk as well as the understanding of endometrial tumor development.

- Zhu J, O'Mara TA, Liu D, et al. Associations between genetically predicted circulating protein concentrations and endometrial cancer risk. *Cancers*. 2021;13(9):2088. doi:10.3390/cancers13092088.

Compounds from Southeast Asian Plant Linked to Pain Relieving Effects

Compounds called triterpenes from a plant called *Vernonia patula*, which grows in Southeast Asia and used medicinally, may be responsible for the plant's effects on pain and sedation. Researcher Md Afjalus Siraj PhD, of the Daniel K. Inouye College of Pharmacy along with his co-authors conducted simulation studies to examine the binding of six triterpenes isolated from *Vernonia patula* with human cannabinoid type 1 (CB1) receptor. Results revealed that three of the compounds — called friedelin, α-amyrin, and epifriedelanol — showed a strong binding affinity for the CB1 receptor. The results suggest these compounds may contribute to the pain relieving and sedative effects of the plant.

- Afjalus Siraj M, Rahman MS, Tan GT, Seidel V. molecular docking and molecular dynamics simulation studies of triterpenes from *Vernonia patula* with the Cannabinoid Type 1 Receptor. *Int J Mol Sci*. 2021;22(7):3595. doi:10.3390/ijms22073595

Long Non-coding RNA Molecules Could Hold Clues to Lung Cancer

Molecules called long non-coding RNAs (lncRNAs) may play valuable roles in diagnosing and treating lung cancer. In a review paper, researchers led by Yu Chen, of the John A. Burns School of Medicine, explain that lncRNAs have a well-established role in regulating gene expression in cells. In addition, some of these molecules may also serve as predictors of the sensitivity of lung cancer cells to chemotherapy, targeted therapy, and radiation treatments. A panel of lncRNAs could serve as a screening marker in the diagnosis of lung cancer; the current method of screening with low-dose CT scans yields many false positives. Other lncRNAs could serve as markers of prognosis of lung cancer patients. Because the molecules remain stable in the blood, they represent an area ripe for further research in the treatment of lung cancer.

- Chen Y, Zitello E, Guo R, Deng Y. The function of LncRNAs and their role in the prediction, diagnosis, and prognosis of lung cancer. *Clin Transl Med*. 2021;11(4):e367. doi:10.1002/ctm2.367

Rapid Implementation of a Statewide Observational Surveillance System to Monitor Wearing of Face Masks in Public Spaces

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Abstract

This report describes the rapid implementation of a statewide observational surveillance program to monitor the public's wearing of face masks in public spaces during community spread of Coronavirus disease 2019 (COVID-19). It describes how the Hawai'i State Department of Health partnered with University of Hawai'i faculty to develop and implement the surveillance program. The surveillance program involved organizing volunteers to conduct weekly direct observations in designated locations. A smartphone application (app) was created to record real-time observational surveillance data. From September 5, 2020, to March 13, 2021, a total of 84 577 observations were conducted across the state. Eighty-three percent of those observed were correctly wearing a face mask, 7% were wearing a face mask incorrectly, and 10% were not wearing a mask. Following the 2-week pilot phase of the project, volunteers were surveyed regarding facilitators and barriers for conducting observations and motivations for volunteering. Feedback was used to refine project procedures. With few states having implemented such a surveillance program, the information reported in this article may inform communities interested in tracking mask-wearing behaviors in the context of the COVID-19 pandemic.

Keywords

COVID-19, SARS-CoV-2, Face Mask, Hawaii, Public Health Surveillance, Smartphone

Abbreviations and Acronyms

CDC = Centers for Disease Control and Prevention
COVID-19 = Coronavirus disease 2019
DOH = Department of Health
RSL = Resolve to Save Lives
UH = University of Hawai'i

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic has severely impacted the State of Hawai'i, resulting in hundreds of lives lost, thousands infected, and major disruption to the livelihoods of Hawai'i residents. Although the number of daily cases statewide has decreased since hitting a peak of 353 cases per day in August 2020, the persistent threat of a "third wave" remains a major concern for the state. With COVID-19 vaccines in short supply, public health interventions have continued to rely upon strategies to limit transmission of the virus. Wearing a face mask is 1 of 3 key actions, along with handwashing and maintaining physical distancing, that people can take to prevent the spread of COVID-19.[1] To reduce the risk of COVID-19 transmission, the Centers for Disease Control and Prevention (CDC) recommends that all people over the age of 2 years wear masks in public places when around people outside of their household, especially in settings where social distancing cannot be maintained.[2]

Real-time data are an essential tool for informing decision-making for infectious disease control. Metrics to assess adherence to public health measures are useful to inform the response to COVID-19. "Observed mask-wearing" has been identified by Resolve to Save Lives (RSL) as 1 of 15 essential indicators for effective COVID-19 response. RSL recommends that all states report the percentage of people wearing masks correctly in public settings (eg, mass transit, shopping) using a standard, consistent method by week. Few states in the United States routinely report this metric.[3] As Hawai'i State Department of Health (DOH) state emergency managers and elected officials sought to develop metrics for use by decision-makers, this RSL metric was identified as essential for assessing ongoing community prevention activities. This article describes how a statewide observational surveillance system was developed to monitor the public's wearing of face masks in public spaces. The program was rapidly implemented to track face mask usage patterns by the general public. Although the State of Hawai'i mandates the use of face masks in public areas,[4] little was known regarding mask-wearing behaviors in Hawai'i before the launch of this project.[5]

Methods

Faculty at the University of Hawai'i (UH), under the guidance of the Hawai'i State DOH, worked collaboratively to design and rapidly implement a statewide observational surveillance system to monitor the wearing of face masks in public spaces. Methodology for observation sampling was guided by RSL recommendations.[6] The program was piloted on two days: September 5, 2020, and September 12, 2020. The pilot involved 79 volunteers conducting observations in all 4 Hawai'i state counties. Adjustments were made based on the volunteers' feedback after the pilot.

Once per week, teams of 2 volunteers observed people in designated areas and recorded face mask usage. Observations were recorded at the same time and day each week. Each volunteer

observed people for 2 hours or until 100 observations were recorded. Observations were recorded as: "Wearing Correctly," "Wearing Incorrectly," or "No Mask." "Wearing Correctly" was defined as wearing a face mask that completely covered the wearer's nose and mouth.[2] "Wearing Incorrectly" was defined as wearing a face mask in any other way, such as having the wearer's nose exposed, wearing the mask around the neck, or hanging from 1 ear. Volunteer pairs were instructed to initially observe the same people together to establish inter-rater reliability before recording observations. Once inter-rater reliability was established, volunteers were instructed to observe different people to avoid duplication of observations. For example, volunteers were instructed to conduct observations on opposite sides of the street or walkways from their partner or position themselves to observe different areas from their partner. Per CDC recommendations regarding mask-wearing in public spaces, volunteers observed individuals who appeared aged 2 years or older. Designated areas for observations were outdoor commercial zones selected with input from county health officials and members of the project team. Observation sites were spread out on each island to include multiple regions of each county each week. Sites were revisited weekly or every other week. Observations were limited to outdoor spaces because of the scarcity of public indoor spaces on all islands. Commercial zones were selected over areas like parks and beaches to minimize the effect of people engaged in activities, such as exercise, for which they would not be expected to wear a mask. Commercial zones, in general, involve people going into and out of indoor retail facilities, and therefore mask-wearing behavior is of more significance from a disease control perspective. Data was recorded using a smartphone application (app) or paper form. Data collected were aggregated by county and reported weekly as a community prevention metric for the DOH COVID-19 data dashboard.[7]

Smartphone App

The smartphone app was developed by UH engineering staff to facilitate the recording of observations. Desired qualities driving the development of the app were that it (1) be simple to use with minimal training, (2) be able to be used discreetly by observers, and (3) generate real-time data that could be sorted by zip code for seamless integration into the DOH COVID-19 data dashboard. A beta version was tested by project coordinators and refined with input regarding usability and functionality. A "web app" format avoided the need for downloading the app onto a cell phone before use. It also allowed developers to make rapid updates.

Unique features of the app facilitate rapid data collection and reporting. Data collected by volunteers were uploaded instantaneously to the app's website. Upon starting the app, users were prompted to input their name, zip code, and location code to ensure all data generated include the name of the data collector and location where each observation was made. Observations were tallied and displayed in real-time so that volunteers could note the total number of observations as well as the number in each category of "Wearing Correctly," "Wearing Incorrectly," or "No Mask" during their shift. A clicking noise sounded each time an observation was recorded to assure volunteers their data were noted. Finally, when volunteers recorded 100 observations, a notification displayed stating that the quota had been reached. Volunteers unable to use the app on a cell phone could manually input tallies into the app's website using a computer.

Volunteer Training

Each volunteer was required to complete a 15-minute live or recorded virtual training session. The training session discussed the project's purpose, instructions on conducting and recording observations, and safety precautions. The DOH provided volunteers with a letter to show authorities if questioned while conducting observations. Following the first 2-week pilot run of the project, volunteers were sent an 8-question survey regarding their role as a volunteer. Five items assessed the clarity of instructions provided, the sufficiency of knowledge that volunteers had to serve as data collectors, perception of safety while conducting observations, ease of use of the observation application, and perceived confidence in the ability to accurately collect data. These survey items used a 5-point Likert scale, with 1 being "Strongly Disagree" and 5 being "Strongly Agree." Two open-ended questions asked volunteers about facilitators and barriers encountered while collecting data in the field. Finally, volunteers were also asked about their motivations for volunteering.

Results

Between September 5, 2020, and March 13, 2021, a total of 202 volunteers affiliated with the UH, the Hawai'i State Medical Reserve Corps, and other community groups participated in the project. Volunteers recorded 84 577 observations at 58 sites on 5 Hawaiian islands. Observation data showed that statewide during this period, 83% of people wore masks correctly, 7% wore masks incorrectly, and 10% wore no mask (Table 1). Figure 1 illustrates trends regarding persons observed correctly wearing a mask by county by week. Although variation can be seen each week across the 4 counties, the overall percentage of the population observed wearing a mask correctly across the state increased since the beginning of the observation period. Kaua'i County exhibited lower mask-wearing percentages than other counties.

Table 1. Face-Mask Usage Observations Collected in Hawai'i, September 5, 2020–March 13, 2021 (N=84 577)

Observations	n	%
Wearing mask correctly	70 376	83
Wearing mask incorrectly	5554	7
No mask	8647	10

Of the 79 volunteers that participated in the pilot, 41 (51.9%) responded to the survey. Feedback was overwhelmingly positive regarding clarity of instruction (mean, 4.6), sufficiency of knowledge to serve as a data collector (4.7), perception of safety (4.8), ease of use of the app (4.5), and confidence in ability to collect accurate data (4.6). Responses are summarized in Table 2.

Volunteers provided various motivations for volunteering, including receiving college credit (n=16; 39%), wanting to serve the community (n=13; 22%), self-gratification for volunteering (n=5; 12%), and other reasons (n=7; 17%). Responses are summarized in Table 3. Qualitative comments provided insight into volunteers' experiences recording observations. Some comments focused on the app's functionality (eg, occasionally froze or lagged). One participant remarked how despite being skeptical of using an app, observation collection went very smoothly. Other comments pertained to methodology. Volunteers commented that they needed greater clarity regarding who to observe and at what point to record their observations. For example, volunteers noted that persons walking to and from the ocean and those stepping in and out of cars were not wearing masks at the time of observation but donned masks after being observed. Volunteers requested greater guidance regarding how to avoid counting the same individuals as their partners. Feedback regarding the designated locations was also provided. Some sites were sparsely populated at the time of observation. Volunteers suggested changing the locations or the time of day that observations were conducted to be in areas with more foot traffic. Volunteers noted that because many of the sites were located in commercial shopping areas, mask-wearing behaviors may differ in other types of settings, such as parks and beaches.

Table 2. Facilitators and Barriers Reported By Volunteers Piloting Mask Observation Study in Hawai'i, September 2020 (N=41)

Question[a]	Mean (SD)	Median
The instructions provided were clear.	4.6 (0.6)	5
I have sufficient knowledge to serve in the role of data collector.	4.7 (0.5)	5
I felt safe while in the field collecting data.	4.8 (0.5)	5
The face mask observation application was easy to use.	4.5 (0.8)	5
I am confident that I will be able to collect data in an accurate manner.	4.6 (0.7)	5

Abbreviation: SD, standard deviation.
[a] Survey items used a 5-point Likert scale, with 1 being "Strongly Disagree" and 5 being "Strongly Agree."

Table 3. Volunteer Motivations for Participating in Pilot Face Mask Observation Study in Hawai'i, September 2020 (N=41)

Volunteer motivations for participating in the study	n (%)
College course credit	16 (39.0)
Want to serve my community	13 (31.7)
Self-gratification for volunteering	5 (12.2)
Other[a]: Interest in the success of COVID-19 public health measures Learn more about collecting public health data It looks good on a resume Interested in public health & public health nursing	7 (17.1)

Abbreviation: COVID-19, Coronavirus disease 2019.
[a] "Other" motivations represent write-in responses

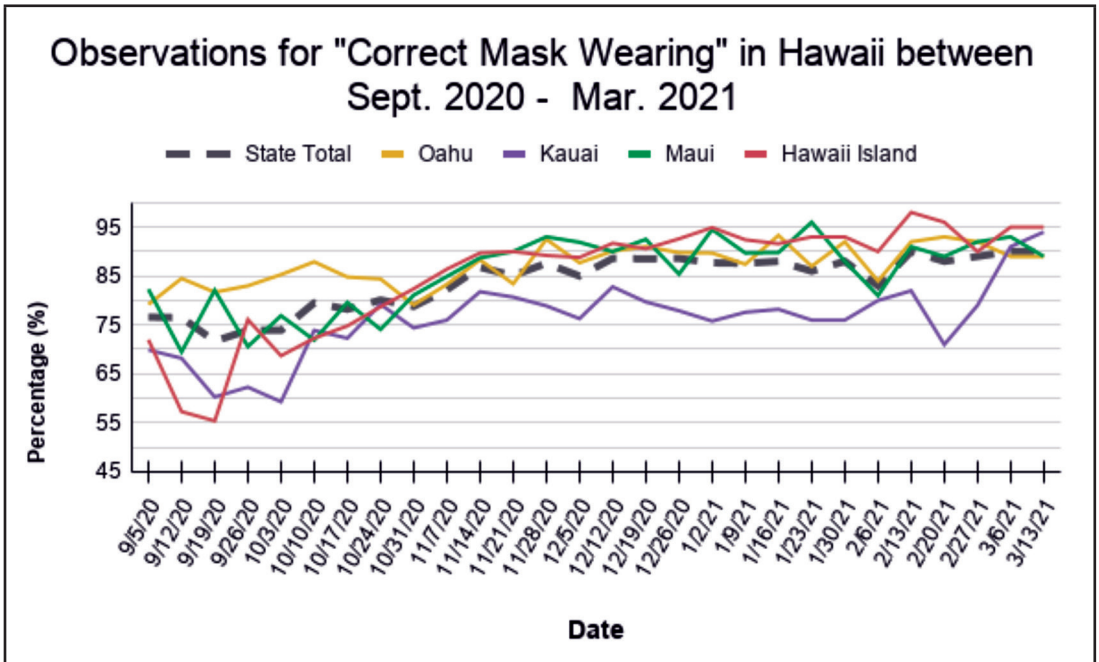

Figure 1. Percentage of People Observed Wearing a Face Mask Correctly in Hawai'i Between September 5, 2020–March 13, 2021 (N=84 577)

Discussion

Mitigating the spread of infections is critical to protecting public health and decreasing the strain on healthcare resources. Widespread use of masks in community settings can prevent the transmission of respiratory diseases caused by coronaviruses and other respiratory viruses.[8] By developing an observational surveillance program to track face mask-wearing, patterns of usage can be more readily identified. The methodology described in this report can be used to assess mask-wearing behavior in relation to local mandates and other changing conditions in a community. Changes in mask usage can be assessed regarding the resumption of in-person learning at schools, increases in tourism, social or holiday season activities, and changes in disease activity. Such information can inform public health education efforts and lead to more targeted messaging and outreach to populations at risk for COVID-19. For example, on October 15, 2020, the State of Hawai‘i initiated its pre-travel testing program, allowing all airline passengers arriving from out of state to be exempt from the 14-day mandatory quarantine with a negative test result within 72 hours of departure. This policy resulted in a higher number of visitors to the state. Having the observational surveillance program in place before this policy change allowed emergency planners the ability to assess mask-wearing behavior as tourism activity rose in each county. Similarly, following an emergency proclamation by the governor on November 16, 2020, that established a single statewide mask mandate for the islands,[4] the impact on mask-wearing behaviors in public areas following this critical policy change could be tracked.

Following the program pilot, various adjustments were made. Volunteer feedback was incorporated into the program's protocols. Improvements were made to the app to enhance the user experience and streamline data reporting. Volunteers were provided clarifying instructions on who to include in their observations and when to record their observations. For example, volunteers were instructed to exclude persons actively eating, drinking, smoking, or exercising. Such instructions aligned with mask-wearing guidelines provided by state and county governments.[7] Observation site selection was refined to provide greater standardization of the data collected. The pilot phase of the project included a mixture of commercial areas and recreational areas (eg, parks, beaches). After the pilot stage of the project, the focus shifted to commercial areas. Furthermore, 1 airport was included as an observation site due to the importance of tourism in the local economy.

Global studies provide evidence for an association between community mask mandates and improved COVID-19 outcomes.[9] To date, little is known regarding adherence to state mandates regarding the use of face masks in public spaces in the United States. Similarly, little is known about the extent to which mask-wearing is becoming a social norm in the context of the COVID-19 pandemic. An observational study conducted in Wisconsin found that approximately 41% of shoppers wore a mask when entering retail stores in June 2020; mask-wearing behavior increased to over 90% in July and August following the enactment of mask mandates in the state.[10] A statewide survey conducted in August 2020 asked Hawai‘i residents about self-reported mask-wearing behavior. The survey found that 84% reported wearing face masks all or most of the time while outside in a public space.[11] A separate survey conducted in October 2020 asked Hawaii residents how often they wear a mask outside the home, to which 90% reported "multiple times in the past month."[12] An observational study of face mask usage in outdoor public spaces in Honolulu, Hawai‘i found that of the 200 individuals observed, 77% used face masks correctly; in contrast, 23% were incorrectly masked or not masked. [4] Observation data collected by this project during September 5, 2020, and March 13, 2021, showed that 83% of people wore masks correctly, 7% wore masks incorrectly, and 10% wore no mask while out in public spaces. While there is an overall positive trend in mask-wearing across the state, Kaua‘i County exhibited lower percentages of correct mask-wearing than other counties. Kaua‘i County had consistently had lower disease rates than the other counties, potentially contributing to a lower level of concern about disease transmission. RSL recommends that the target metric for people wearing masks correctly in public areas be at least 80% or greater.[3] In Hawai‘i, there is still room for improvement.

A strength of the project has been that it provided citizens with the opportunity to engage in and contribute to the COVID-19 public health response in their communities. Volunteers described being motivated by a desire to serve their community, a sense of self-gratification for volunteering, and a willingness to learn about public health. Establishing a role for general citizens to contribute to the public health response to a crisis can promote social connectedness and may ultimately contribute to community resilience.[13] Understanding volunteer motivation for participating helped inform the project team's volunteer recruitment and retention efforts.

The study has multiple limitations. Mask-wearing behaviors recorded by the study may not be representative of the overall population. Behaviors may differ if observations were recorded at different times or locations. Observers did not have knowledge of persons who could not wear masks for personal health or other reasons. It is important to note that the goal of the study was to assess changes in behavior and social norms in regards to mask-wearing in Hawai‘i rather than to assess compliance with regulations. Observations were independent of mask-wearing rules, as the observation is of behavior, not of compliance. Independent of local rules, national guidance recommend that mask-wearing is protective and should be done in a wide variety of settings.

Mask-wearing behaviors are influenced by how often people observe others wearing them.[14] Regular reporting of mask-wearing

behaviors may serve as a means for encouraging the uptake of healthy behaviors in the community through public messaging. Mask-wearing is an indicator for which individuals can take action to make a difference. Other indicators for COVID-19 response, such as ongoing dashboard reporting of case rates or lab positivity rates, or hospital bed availability, are of great interest to the public health response but are not necessarily empowering for the general public. Ongoing dashboard mask-wearing data, in contrast, is something each individual has the power to change through their daily behavior. Implementation of a sound mask-wearing behavior monitoring system provides essential information to the DOH and the public.

Conflict of Interest

None of the authors identify a conflict of interest.

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References

1. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19). Coronavirus Disease: Protect Yourself. Available from: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html. Published October 28, 2020. Accessed November 2, 2020.
2. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19). Coronavirus Disease: Considerations for Wearing Masks. Available from: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-to-wear-cloth-face-coverings.html. Published August 7, 2020. Accessed September 16, 2020.
3. Resolve to Save Lives. Tracking COVID-19 in the United States. Available from: https://preventepidemics.org/wp-content/uploads/2020/07/Tracking-COVID-19-in-the-United-States-Report.pdf. Published July 21, 2020. Accessed September 12, 2020.
4. Officer of the Governor State of Hawaii. Fifteenth Proclamation Related to the COVID-19 emergency. Available from: https://governor.hawaii.gov/wp-content/uploads/2020/11/2011051-ATG_Fifteenth-Proclamation-Related-to-the-COVID-19-Emergency-distribution-signed.pdf. Published November 16, 2020. Accessed January 12, 2021.
5. Tamamoto KA, Rousslang ND, Ahn HJ, Better HE, Hong RA. Public Compliance with face mask use in Honolulu and regional variation. *Hawaii J Health Soc Welf*. 2020;79(9):268–271.
6. Resolve to Save Lives. Promoting Mask-Wearing During the COVID-19 Pandemic: A Policymaker's Guide, Annex II: Mask-Use Adherence Measurement Technical Reference. Available from: https://preventepidemics.org/wp-content/uploads/2020/08/Annex-II-technical-reference-for-monitoring.pdf#:~:text=Annex%20II%3A%20Mask-Use%20Adherence%20Measurement%20Technical%20Reference.%20This,that%20can%20be%20used%20to%20inform%20decision%20making. Published August 27, 2020. Accessed September 12, 2020.
7. Hawaii State Department of Health. (n.d.) What You Should Know: Get The Facts About COVID-19. Available from: https://health.hawaii.gov/coronavirusdisease2019/what-you-should-know/current-situation-in-hawaii/. Accessed January 19, 2021.
8. MacIntyre CR, Chughtai, AA. A rapid systematic review of the efficacy of face masks and respirators against coronaviruses and other respiratory transmissible viruses for the community, healthcare workers and sick patients. *Int J Nurs Stud*. 2020; 108:103629. https://doi.org/10.1016/j.ijnurstu.2020.103629
9. Leffler CT, Ing E, Lykins JD, Hogan MC, McKeown CA, Grzybowski A. Association of country-wide Coronavirus mortality with demographics, testing, lockdowns, and public wearing of masks. *Am J Trop Med Hyg*. 2020;103(6):2400–2411. doi: 10.4269/ajtmh.20-1015
10. Haischer MH, Beilfuss R, Hart MR, et al. Who is wearing a mask? Gender-, age-, and location-related differences during the COVID-19 pandemic. *PLOS One*. 15(10):e0240785. https://doi.org/10.1371/journal.pone.0240785
11. Moore C, Hayashi S, Lanfranchi R. Hawai'i during COVID-10: A Community Impact Survey. Available from: https://drive.google.com/file/d/1F2gfvRKwbUvkbw_cfCewS6JUEnmlQDNG/view. Published September 21, 2020. Accessed October 30, 2020.
12. SMS Research & Marketing Service Inc. Community Pulse Survey. Available from: https://www.smshawaii.com/studies/community-pulse-survey. Accessed January 19, 2021.
13. National Biodefense Science Board. Community Health Resilience Report. Available from: https://www.phe.gov/Preparedness/legal/boards/nbsb/meetings/Documents/nbsb-chrreport.pdf. Published April 23, 2013. Accessed January 13, 2021.
14. Barile JP, Guerin RJ, Fisher KA, et al. Theory-based behavioral predictors of self-reported use of face coverings in public settings during the COVID-19 Pandemic in the United States. *Ann Behav Med*. 2021;55(1):82–88. doi:10.093/abm/kaa109

A Case Report of Antibiotic-Induced Aseptic Meningitis in Psoriasis

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Abstract

Although frequently prescribed, certain antibiotics such as trimethoprim-sulfamethoxazole carry the risk of a rare yet life-threatening adverse effect, termed drug-induced aseptic meningitis. Morbidity can be avoided if the medication is identified and discontinued. Patients in reported cases tend to be female and have an autoimmune disease or prior adverse reaction to the offending agent. As a rare and poorly characterized condition, the subset of patients using antibiotics at risk for aseptic meningitis remains unclear; hence, cataloging these adverse events remains critical for better elucidating the disease. Here, we report a 62-year-old man with psoriasis and no prior history of sulfa allergy, who presented with a sudden onset of fever, chills, vomiting, and muscle aches 5 hours after taking single doses of trimethoprim-sulfamethoxazole and ciprofloxacin. Common infectious causes were ruled out, and his medications were discontinued. Despite initial symptom resolution with discontinuation, the patient neurologically deteriorated over the next two days before eventually recovering with supportive care. This case highlights the variable presentation of drug-induced aseptic meningitis. In contrast to previous reports of drug-induced aseptic meningitis, our patient was male, older than the median age of 40 years, and did not have a prior adverse reaction to the antibiotic. Furthermore, to the best of our knowledge, we report a possible case of antibiotic-induced aseptic meningitis in a patient with psoriasis. Lastly, the case emphasizes not only the value of a thorough medication history but also the importance of recognizing that patients may deteriorate in the first 48 hours before resolution.

Keywords

Trimethoprim, sulfamethoxazole, aseptic meningitis, drug-induced, adverse effect, TMP-SMX, meningitis, drug reaction

Abbreviations and Acronyms

ADR = adverse drug reaction
CIAM = ciprofloxacin-induced aseptic meningitis
CSF = cerebrospinal fluid
DIAM = drug-induced aseptic meningitis
ED = emergency department
HIV = human immunodeficiency virus
IQR = interquartile range
NSAID = nonsteroidal anti-inflammatory drugs
PCR = polymerase chain reaction
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
SLE = systemic lupus erythematosus
TMP-SMX = trimethoprim-sulfamethoxazole
TNFα = tumor necrosis factor α
TSIAM = trimethoprim-sulfamethoxazole-induced aseptic meningitis

Introduction

First recorded in 1925 as a syndrome involving the acute onset of meningeal irritation, abnormal cerebrospinal fluid content with absence of bacterial involvement, and a brief clinical course, aseptic meningitis has since become recognized as an all-encompassing term for non-pyogenic meningitides.[1,2] Aseptic meningitis can be further stratified as infectious (often viral) or non-infectious, with non-viral etiologies including drugs, neoplasms, and autoimmune diseases.[1-6] Drug-induced aseptic meningitis (DIAM) is a rare condition that disproportionately affects females. It is most commonly documented as secondary to nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, intravenous immunoglobulins, monoclonal antibodies, and intrathecal agents.[3-7] The median age of presentation is 40 years (interquartile range [IQR], 28–58 years).[7] In particular, NSAID- and antibiotic-induced DIAM have been strongly associated with specific autoimmune and connective tissue diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis, Crohn's disease, and Sjogren's syndrome.[8-16] Of the antibiotics, trimethoprim-sulfamethoxazole (TMP-SMX) is the most frequently reported agent associated with DIAM.[4,5] The median age of those affected is 41 years (IQR, 24.5–61 years), and, consistent with DIAM, females are disproportionately affected. Patients tend to have an autoimmune disease, previous exposure to the precipitating agent, or immunocompromise.[4,5,7] Ciprofloxacin-induced aseptic meningitis (CIAM) is an even rarer condition with few recorded cases to draw significant epidemiological trends.[6,7] Notably, in a series of 192 cases of DIAM, 36% were antibiotic-induced, and, of these, 3% were associated with ciprofloxacin. In contrast, 46% were associated with TMP-SMX.[6] In another series of 329 cases of DIAM, 11% were antibiotic-induced, of which 16% were associated with TMP-SMX and none were associated with ciprofloxacin.[7]

Case Report

A 62-year-old Japanese American man with a history of psoriasis and benign prostatic hyperplasia was brought by his wife to the emergency department (ED) with fever, chills, vomiting, and muscle aches. One day prior, he visited his urologist and received a prostate massage as part of the examination. Five hours prior to his presentation, he took his first doses of ciprofloxacin 500 mg and TMP-SMX 800–160 mg orally as prophylaxis for an upcoming prostate biopsy. Over several hours, he developed fever, chills, vomiting, dizziness, and muscle aches.

He denied having headache, neck stiffness, visual symptoms, focal neurologic symptoms, ataxia, abdominal pain, or sore throat. No seizures were noted by family members. Aside from ciprofloxacin and TMP-SMX, he did not take any other of his medications that day.

The patient's medical history was significant for psoriasis, hypertension, hyperlipidemia, and benign prostatic hyperplasia. His medications included amlodipine, losartan, atorvastatin, coenzyme Q10 supplements, calcipotriene, betamethasone, and triamcinolone ointments. He took these medications for several years without adverse reactions. Although he reported mild muscle aches with atorvastatin, it was resolved with coenzyme Q10 supplementation. Of note, he was not taking any tumor necrosis factor α inhibitors at this time. Medication allergies included erythromycin, from which he experienced a rash and low-grade fever, and penicillin and ampicillin, from which he experienced hives. His immunizations were up-to-date. He did not travel recently and did not have any sick contacts. The patient worked in his garden and water lily pond daily but does not recall mosquito bites and has not had significant exposure to fresh water.

His vitals in the ED were as follows: temperature 39.4°C, blood pressure of 136/91 mm Hg, heart rate of 111, and respiratory rate of 22 per minute. The patient was only noted to have mild tenderness in the left lower back to palpation on physical examination. Initial laboratory included a complete blood count notable for leukocytosis of $10.5 \times 10^3/\mu L$ with a neutrophil predominance at 82% and lactic acid elevated to 3.3 mmol/L. The differential diagnosis at this time included gastroenteritis, sepsis secondary to his recent prostate massage, pyelonephritis, and discitis and osteomyelitis. Blood cultures and a urinalysis were obtained along with severe acute respiratory syndrome coronavirus 2, better known as SARS-CoV-2, and influenza polymerase chain reaction (PCR) tests. A chest x-ray, computed tomography of the abdomen and pelvis, and magnetic resonance imaging of the brain and thoracic spine were obtained. His daily medications and antibiotics were held, and he was empirically treated with cefepime and acetaminophen. His urinalysis, influenza, and imaging results returned negative and, after seven hours, his fever resolved, thus he was discharged home with ondansetron. He received a discharge diagnosis of back pain, nausea and vomiting, and fever, unspecified. His SARS-CoV-2 test was negative.

The next morning, he was found in a confused state upon awakening, along with fever, chills, nausea, vomiting, and muscle aches. He was again brought to the ED. A review of symptoms in the emergency department was negative for focal weakness, numbness, seizures, visual loss, dizziness, and difficulty walking. The patient did not restart any of his antibiotics. He had a fever of 39.6°C and was given acetaminophen. A lumbar puncture was then performed. Cerebrospinal fluid (CSF) analysis revealed a pleocytosis of $63/mm^3$ with polymorphic neutrophils at 28%, monocytes at 60%, red blood cell count of $468/mm^3$, elevated total protein at 76 mg/dL, and normal glucose levels at 58 mg/dL, which was consistent with meningitis. CSF cultures and gram stain were obtained, along with a meningitis/encephalitis PCR panel for *Escherichia coli*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, enterovirus, herpes simplex viruses 1 and 2, human herpesvirus 6, human parechovirus, varicella zoster virus, cytomegalovirus, and *Cryptococcus neoformans/gattii*. Also, separate rapid plasma reagin, herpes simplex viruses, and cryptococcal antigen tests were obtained. Blood cultures were again drawn, and computed tomography of the head was obtained, which was shown to be unremarkable. Because the patient had a known allergy to ampicillin, empiric treatment with vancomycin, meropenem, and acyclovir was started, and the patient was admitted for meningitis.

On hospitalization day 1, he developed a headache and continued to have altered mental status, fever, nausea, and myalgia. Both infectious disease and neurology teams were consulted for further management of meningitis. On hospitalization day 2, symptoms persisted, and an electroencephalography revealed mild global dysfunction suggestive of encephalopathy but no seizures or epileptic abnormalities. His symptoms and neurologic status started to improve on hospitalization day 3, and empiric antibiotics were discontinued after cultures, rapid plasma reagin, PCR, and antigen tests were shown to be negative. At this time, the neurology team suggested DIAM as a possible diagnosis. On hospitalization day 4, the patient markedly improved and was discharged with a diagnosis of aseptic meningitis. Two weeks after discharge, he continued to have fatigue, but his cognition returned to baseline, and he denied having any other symptoms from his initial presentation. Two months since admission, the patient has not experienced any recurrence of symptoms or adverse effects from the disease; he returned to baseline and resumed his normal daily activities. Although an outpatient follow-up for a drug rechallenge was scheduled, the patient eventually decided not to undergo the test.

Discussion

Epidemiology

DIAM is predominantly observed in women and those with comorbid autoimmune disease.[3-7] TSIAM is additionally associated with previous TMP-SMX exposure and functional immunocompromise, such as human immunodeficiency virus (HIV) infection.[3-6] In TSIAM, the more frequent observation in female patients is thought to be due to higher rates of urinary tract infection, which is commonly treated with TMP-SMX, while the more frequent observation in HIV-infected patients is thought to be due to the use of TMP-SMX for prophylaxis against opportunistic infections.[5] In addition, one series of 41 TSIAM cases identified 20% having comorbid autoimmune disease.[5]

The patient in our case is notable in that he is a male, older than the typical age of most DIAM patients, and has a history of psoriasis. Although comorbidity with psoriasis is consistent with the association between DIAM and autoimmune disease in general, the association between any antibiotic-induced aseptic meningitis and psoriasis, in particular, has not been reported in the literature to the best of our knowledge.

Etiology

NSAIDs are the most commonly documented cause of DIAM, followed by antibiotics, of which TMP-SMX is most frequently described.[3-5,7] Other commonly reported causes of DIAM include intravenous immunoglobulins, monoclonal antibodies, intrathecal agents, and vaccines.[3-6] Monoclonal antibodies that inhibit tumor necrosis factor α (TNFα) may be used to treat severe psoriasis.[17] Several cases have documented an association between TNFα inhibitors and severe psoriasis or psoriatic arthritis, leading to the entity termed TNFα inhibitor-associated aseptic meningitis.[18-20] Of note, while there was no prior history of TNFα inhibitor use, our patient was exposed to several antibiotics during his clinical course.

As symptoms are initiated upon taking TMP-SMX and ciprofloxacin, these medications are implicated as the causative agents by temporal association. A series of 329 cases reported that, of antibiotic-induced cases of aseptic meningitis, 16% were associated with TMP-SMX, while none were associated with ciprofloxacin.[7] Another series of 192 cases of DIAM showed that, of all those involving antibiotics, 46% involved TMP-SMX, while only 3% involved ciprofloxacin.[6] By extrapolation, TMP-SMX would be the most likely cause of aseptic meningitis in our patient. Notably, the series further identified 16% of cases to involve trimethoprim alone, with 1% sulfamethoxazole only, suggesting that trimethoprim may be the more common cause of TSIAM.[4,6] However, as clinical interests precluded the ability to conduct confirmatory tests, we cannot definitively exclude other administered antibiotics for contributing to the patient's disorder (ie, the aseptic meningitis in this case). While thought to be likely due to TMP-SMX, this reaction could have also been caused by ciprofloxacin, trimethoprim alone, sulfamethoxazole alone, or even another unidentified trigger.

As the definitive diagnosis of adverse drug reactions (ADRs) remains challenging, several semi-quantitative measures of causality have been developed.[21-28] Utilizing a ten-question survey published in 1981 by Naranjo et al, our patient was deemed to have had a *possible ADR*.[22] While useful for reducing inter-rater disagreements and categorizing the probability of ADRs, ultimately, these algorithms do not confirm causality nor accurately measure the likelihood of an ADR.[22,28] Moreover, many questions in these algorithms rely on a drug rechallenge test, which is usually clinically impractical and often unethical.[21] Hence, by nature of the questions (ie, use of arbitrary weights per question and requirement of a drug rechallenge), the causality grades of these algorithms are practically limited to no higher than *possible ADR*.[22,28]

Pathophysiology

The two commonly hypothesized mechanisms of DIAM include either a direct irritation of the meninges, particularly with intrathecal administration of drugs, or an immunologic hypersensitivity reaction with systemic administration.[3,4] The association of DIAM with autoimmune disease favors an immune-mediated mechanism, especially in our patient, as intrathecal drugs were not administered. Sulfonamide antibiotics such as TMP-SMX are commonly associated with hypersensitivity reactions.[20] Hypersensitivity reactions to TMP-SMX are generally not mediated by type I hypersensitivity and tend to be non-immediate in presentation.[4,5,29] In addition, type II hypersensitivity only would occur if the drug or metabolites are introduced into the CSF.[3-5] Therefore, in our patient, a type III or IV hypersensitivity mechanism is most likely. A series of 41 cases of TSIAM showed that the onset of symptoms generally occurred in the order of hours to days, consistent with type III or IV.[5] In addition to hypersensitivity, the recently described concept of p-i interactions may also have a role in TSIAM.[5,29] In this concept, drugs may bind directly to receptors on T cells, activating them.[5,29] As psoriasis is also a T cell-mediated disease, the meningitis in our patient may have been T cell-mediated as well.[30] T cells are also the major mediator of cutaneous manifestations of TMP-SMX hypersensitivity, such as Stevens-Johnson syndrome and toxic epidermal necrolysis.[29]

While the relation between psoriasis and DIAM is only a conjecture, other studies have linked DIAM with other autoimmune diseases.[4] Moreover, autoimmune diseases are often are comorbid with each other—psoriasis, in particular, has been found to be associated with SLE, rheumatoid arthritis, Crohn's disease, celiac disease, multiple sclerosis, and autoimmune thyroid disease.[31,32] By extension, DIAM—an immune-mediated inflammation of the meninges—may potentially also be linked to psoriasis. Indeed, psoriasis has been found to be associated with increased odds of meningitis.[33]

Clinical Manifestations

Previous reports of TSIAM have shown that the onset of symptoms generally occurs within hours to days after TMP-SMX ingestion; however, a few reported cases have an onset after 3 months.[5,6] The presentation is similar to that of other meningitides: fever, headache, altered mental status, nausea, vomiting, and signs of meningismus, though many other manifestations may occur.[1-6] Alarming manifestations such as hypotension, seizures, and coma have also been reported.[4,5] However, initial presentations can be vague, as in the patient in our case, who presented with flu-like symptoms without headache. Even with discontinuation of the offending agent, patients may continue

to deteriorate clinically as the drug continues to be absorbed.[5] A series of 41 cases of TSIAM noted patients that deteriorated within the first 24 hours after discontinuation and recovered within 3 days.[4] This is highlighted in our case, in which our patient was initially stabilized in the ED, sent home, only to present once more with deteriorating clinical status. This potential to worsen is hypothesized to be due to accumulation of the drug in body tissues, while resolution represents clearance of the drug.[5] The observed recovery time within 3 days may be explained by the pharmacokinetics of TMP-SMX. As the half-life of TMP-SMX is 10 hours, recovery within 3 days correlates with 5 to 7 half-lives, which correlates to 95% to 99% of drug clearance.[4] Our patient was noted to improve on hospital day 3 and markedly improved on day 4, which is in concordance with the pattern suggested by TMP-SMX's pharmacokinetics.

Diagnosis

DIAM is a diagnosis of exclusion.[3-5] Patients present with aseptic meningitis characterized by pleocytosis, elevated proteinorrhachia, and normal glycorrhachia in the CSF, though these findings are nonspecific.[3-5] Importantly, routine cultures will be negative.[3-5] However, the differential diagnosis of potential pathogens causing aseptic meningitis is extensive.[34] A limitation of our case is that, while workup for viral pathogens was performed, only pathogens specifically included in the panel tests were excluded. However, the meningitis panel used in this case was relatively sensitive, with a very high negative predictive value.[35] Thus, the most common viral causes were most likely ruled out, and viral meningitis was thought to be less likely. In practice, a detailed history of medications, onset of symptoms, and observing recovery after discontinuation are key components of the diagnosis.[3-6]

The most reliable method of diagnosing DIAM is by drug rechallenge.[3-6] However, this may be unethical or impractical for many patients, particularly in this case's patient, in whom the neurologic manifestations were severe and distressing. In addition, empiric antibiotics are often started after obtaining cultures and CSF samples in patients presenting with meningitis.[4,5,36-39] While the patient's CSF findings of mild pleocytosis with a monocytic predominance, normal glucose, and mildly elevated protein rule against bacterial meningitis, it should be noted that a limitation of our study is that the patient took ciprofloxacin, TMP-SMX, and cefepime upon presenting for his first ED visit. This may have caused the sterile CSF cultures collected during his second ED visit and may have also dampened potentially markedly abnormal CSF findings that would have been present before antibiotic use. Thus, the collection of CSF before empiric antibiotic therapy is essential, as it can be difficult to distinguish DIAM from an incompletely treated bacterial meningitis.[3-5,40] However, given that TSIAM is more common, in addition to the overall presentation of recent TMP-SMX use in a patient with autoimmune disease, negative tests for common infectious causes, CSF findings suggestive of aseptic meningitis, the improvement after discontinuation, TSIAM was thought to be the most likely cause of the patient's aseptic meningitis.

Management and Prognosis

Discontinuation of the offending drug is the mainstay of treatment for DIAM.[3,5,6] In practice, many patients with suspected meningitis are treated with empiric antimicrobial agents, as in this case.[5,36-39] Otherwise, management is primarily supportive.[3,5] With discontinuation of the offending drug, resolution of both symptoms and CSF abnormalities typically occurs within days.[3] In TSIAM, symptoms resolve within 2–3 days, which correlates with enough half-lives of TMP-SMX for near-complete drug elimination.[5] Ultimately, full recovery is expected for most patients, though many patients will experience a recurrence if re-administered TMP-SMX, and thus should be advised to avoid TMP-SMX.[5] In this case, the patient, began improving on day 3, with discharge by day 4, which generally agrees with the concept of drug elimination as the mechanism of recovery. The patient was fully recovered within 2 months. The delay in complete recovery may be caused by residual inflammation from the acute phase of the condition.

Conclusion

In summary, we report a possible case of antibiotic-induced aseptic meningitis in a patient with psoriasis. As our patient diverged from the common epidemiologic trends, this case highlights the variable presentation of DIAM. Despite antibiotic discontinuation, the patient neurologically deteriorated over 48 hours before eventually recovering with supportive care. Furthermore, while autoimmune disease has been observed to increase risk, aseptic meningitis caused by antibiotics in patients with psoriasis, in particular, has yet to be reported in the literature. Lastly, in patients presenting with aseptic meningitis, this case emphasizes the value of a thorough medication history. When DIAM is suspected, clinicians should remain aware that patients may experience an initial period deterioration, depending on the implicated drug's pharmacokinetics.

Conflict of Interest

None of the authors identify any conflict of interest.

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References

1. Adair, CV, Gauld RL, Smadel JE. Aseptic meningitis, a disease of diverse etiology: clinical and etiologic studies on 854 cases. *Ann Intern Med*. 1953;39(4):675–704. doi:10.7326/0003-4819-39-4-675.
2. Wright WF, Pinto CN, Palisoc K, Baghli S. Viral (aseptic) meningitis: a review. *J Neurol Sci*. 2019;398:176–183. doi:10.1016/j.jns.2019.01.050.
3. Yelehe-Okouma M, Czmil-Garon J, Pape E, Petitpain N, Gillet P. Drug-induced aseptic meningitis: a mini-review. *Fundam Clin Pharmacol*. 2018;32(3):252–260. doi:10.1111/fcp.12349.
4. Jolles S, Sewell WA, Leighton C. Drug-induced aseptic meningitis. *Drug Saf*. 2000;22(3):215–226. doi:10.2165/00002018-200022030-00005.
5. Bruner KE, Coop CA, White KM. Trimethoprim-sulfamethoxazole-induced aseptic meningitis-not just another sulfa allergy. *Ann Allergy Asthma Immunol*. 2014;113(5):520–526. doi:10.1016/j.anai.2014.08.006.
6. Morís G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis revisited. *JAMA Intern Med*. 2014;174(9):1511–1512. doi:10.1001/jamainternmed.2014.2918.
7. Bihan K, Weiss N, Théophile H, Funck-Brentano C, Lebrun-Vignes B. Drug-induced aseptic meningitis: 329 cases from the French pharmacovigilance database analysis. *Br J Clin Pharmacol*. 2019;85(11):2540–2546. doi:10.1111/bcp.14073
8. Kremer I, Ritz R, Brunner F. Aseptic meningitis as an adverse effect of co-trimoxazole. *N Engl J Med*. 1983;308(24):1481. doi:10.1056/NEJM198306163082415.
9. Biosca M, de la Figuera M, García-Bragado F, Sampol G. Aseptic meningitis due to trimethoprim-sulfamethoxazole. *J Neurol Neurosurg Psychiatry*. 1986;49(3):332–333. doi:10.1136/jnnp.49.3.332.
10. Streiffer RH, Hudson JG. Aseptic meningitis and trimethoprim-sulfamethoxazole. *J Fam Pract*. 1986;23(4):314.
11. Bernstein RF. Ibuprofen-related meningitis in mixed connective tissue disease. *Ann Intern Med*. 1980;92(2 Pt 1):206–207. doi:10.7326/0003-4819-92-2-206.
12. Horn AC, Jarrett SW. Ibuprofen-induced aseptic meningitis in rheumatoid arthritis. *Ann Pharmacother*. 1997;31(9):1009–1011. doi:10.1177/106002809703100911.
13. Samuelson CO Jr, Williams HJ. Ibuprofen-associated aseptic meningitis in systemic lupus erythematosus. *West J Med*. 1979;131(1):57–59.
14. Hedlund J, Aurelius E, Andersson J. Recurrent encephalitis due to trimethoprim intake. *Scand J Infect Dis*. 1990;22(1):109–112. doi:10.3109/00365549009023129.
15. Derbes SJ. Trimethoprim-induced aseptic meningitis. *JAMA*. 1984;252(20):2865–2866.
16. Gilroy N, Gottlieb T, Spring P, Peiris O. Trimethoprim-induced aseptic meningitis and uveitis. *Lancet*. 1997;350(9071):112. doi:10.1016/S0140-6736(05)61813-2.
17. Kim WB, Jerome D, Yeung J. Diagnosis and management of psoriasis. *Can Fam Physician*. 2017;63(4):278–285.
18. Wang DY, Chong WS, Pan JY, Heng YK. First case report of aseptic meningitis induced by adalimumab administered for treatment of chronic plaque psoriasis. *J Investig Allergol Clin Immunol*. 2017;27(3):183–185. doi:10.18176/jiaci.0148.
19. Kluger N, Girard C, Gonzalez V, Guillot B, Bessis D. Efalizumab-induced aseptic meningitis. *Br J Dermatol*. 2007;156(1):189–191. doi:10.1111/j.1365-2133.2006.07594.x.
20. Matsuura-Otsuki Y, Hanafusa T, Yokozeki H, Watanabe K. Infliximab-induced aseptic meningitis during the treatment of psoriatic arthritis. *Case Rep Dermatol*. 2017;9(2):26-29. Published 2017 May 22. doi:10.1159/000458405.
21. Jones JK. Adverse drug reactions in the community health setting: approaches to recognizing, counseling, and reporting. *Fam Community Health*. 1982;5(2):58–67. doi:10.1097/00003727-198208000-00009
22. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245. doi:10.1038/clpt.1981.154
23. Kramer MS, Hutchinson TA. The Yale algorithm. Special workshop--clinical. *Drug Inf J*. 1984;18(3–4):283–291. doi:10.1177/009286158401800315
24. Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. *Clin Pharmacol Ther*. 1977;21(3):247–254. doi:10.1002/cpt1977213247
25. Bégaud B, Evreux JC, Jouglard J, Lagier G. Imputabilité des effets inattendus ou toxiques des médicaments. Actualisation de la méthode utilisée en France [Imputation of the unexpected or toxic effects of drugs. Actualization of the method used in France]. *Therapie*. 1985;40(2):111–118.
26. Mashford ML. The Australian method of drug-event assessment. Special workshop--regulatory. *Drug Inf J*. 1984;18(3–4):271–273. doi:10.1177/009286158401800313
27. Koh Y, Yap CW, Li SC. A quantitative approach of using genetic algorithm in designing a probability scoring system of an adverse drug reaction assessment system. *Int J Med Inform*. 2008;77(6):421–430. doi:10.1016/j.ijmedinf.2007.08.010
28. Michel DJ, Knodel LC. Comparison of three algorithms used to evaluate adverse drug reactions. *Am J Hosp Pharm*. 1986;43(7):1709–1714.
29. Dorn JM, Alpern M, McNulty C, Volcheck GW. Sulfonamide drug allergy. *Curr Allergy Asthma Rep*. 2018;18(7):38. Published 2018 Jun 6. doi:10.1007/s11882-018-0791-9.
30. von Csiky-Sessoms S, Lebwohl M. What's new in psoriasis. *Dermatol Clin*. 2019;37(2):129–136. doi:10.1016/j.det.2018.11.001.
31. Somers EC, Thomas SL, Smeeth L, Hall AJ. Are individuals with an autoimmune disease at higher risk of a second autoimmune disorder?. *Am J Epidemiol*. 2009;169(6):749–755. doi:10.1093/aje/kwn408
32. Hsu LN, Armstrong AW. Psoriasis and autoimmune disorders: a review of the literature. *J Am Acad Dermatol*. 2012;67(5):1076–1079. doi:10.1016/j.jaad.2012.01.029
33. Hsu DY, Gordon K, Silverberg JI. Serious infections in hospitalized patients with psoriasis in the United States. *J Am Acad Dermatol*. 2016;75(2):287–296. doi:10.1016/j.jaad.2016.04.005
34. Wright WF, Pinto CN, Palisoc K, Baghli S. Viral (aseptic) meningitis: A review. *J Neurol Sci*. 2019;398:176–183. doi:10.1016/j.jns.2019.01.050.
35. Agabawi S. Trimethoprim-sulfamethoxazole-induced aseptic meningitis: a rare presentation of commonly used antibiotic. *Case Rep Infect Dis*. 2019;2019:4289502. Published 2019 Dec 11. doi:10.1155/2019/4289502.
36. Vincent JJ, Zandotti C, Baron S, et al. Point-of-care multiplexed diagnosis of meningitis using the FilmArray® ME panel technology. *Eur J Clin Microbiol Infect Dis*. 2020;39(8):1573–1580. doi:10.1007/s10096-020-03859-y
37. Jha P, Stromich J, Cohen M, Wainaina JN. A rare complication of trimethoprim-sulfamethoxazole: drug induced aseptic meningitis. *Case Rep Infect Dis*. 2016;2016:3879406. doi:10.1155/2016/3879406.
38. Ni Lochlainn M, Gooi HC, Ogese MO, Naisbitt DJ, Jafar-Mohammadi B. Trimethoprim-induced aseptic meningism. *Br J Hosp Med (Lond)*. 2017;78(2):108–109. doi:10.12968/hmed.2017.78.2.108.
39. Wambulwa C, Bwayo S, Laiyemo AO, Lombardo F. Trimethoprim-sulfamethoxazole-induced aseptic meningitis. *J Natl Med Assoc*. 2005;97(12):1725–1728.
40. Jaijakul S, Salazar L, Wootton SH, Aguilera E, Hasbun R. The clinical significance of neutrophilic pleocytosis in cerebrospinal fluid in patients with viral central nervous system infections. *Int J Infect Dis*. 2017;59:77–81. doi:10.1016/j.ijid.2017.04.010

Utility of Routine Testing for Chlamydia and Gonorrhea in the Setting of Preterm Delivery or Premature Preterm Rupture of Membranes

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Abstract

This study aimed to explore the rates of positive and negative Chlamydia trachomatis and Neisseria gonorrhoeae test results in patients screened for these infections and later experienced preterm delivery or preterm premature rupture of membranes. The team conducted a retrospective chart review of patients admitted for preterm premature rupture of membranes or who experienced preterm delivery between April 1, 2009, and April 30, 2015. Patients lacking chlamydia and gonorrhea screening before admission were excluded from the study. Four hundred and six patients met the inclusion criteria. The prevalence of chlamydia infection at initial prenatal screening before admission was 13.3%. Among those for whom the prenatal chlamydia test was negative, 1.7% of patients had a positive subsequent chlamydia test on admission screening. Among those for whom the prenatal chlamydia test was positive, 18.5% had a positive subsequent chlamydia test on admission screening. Positive prenatal test (P=.002) and age 25 years or less (P<.001) were associated with positive admission screening for chlamydia, though only a positive prenatal test remained significant in a logistic regression model (odds ratio, 8.56; 95% CI, 2.67–27.49; P=.003). The prevalence of gonorrhea was low at 0.2% of patients positive for gonorrhea at prenatal testing and 0.5% of patients positive for gonorrhea at admission testing. Our results suggest that individualization based on patient characteristics may be utilized to decrease re-testing. More research is needed to identify possible additional risk factors for new infection or re-infection and the most optimal timing for re-screening during the prenatal period.

Abbreviations and Acronyms

ACOG = American College of Obstetricians and Gynecologists
CDC = Centers for Disease Control and Prevention
KMCWC = Kapi'olani Medical Center for Women and Children
NICU = neonatal intensive care unit
PTD = preterm delivery
PPROM = preterm premature rupture of membranes
STI(s) = sexually transmitted infection(s)
US = United States

Background

In the United States (US), chlamydia and gonorrhea are the first and second most commonly reported sexually transmitted infections (STIs). In 2017, more than 1.7 million cases of chlamydia and more than 550 000 cases of gonorrhea were reported to the Centers for Disease Control and Prevention (CDC).[1] Chlamydia and gonorrhea result in urogenital infections, extragenital infections, and sequelae detrimental to fertility and neonatal outcomes. Males present with symptoms of urethritis and epididymitis, and females present with urethritis, cervicitis, and pelvic inflammatory disease. In both men and women, asymptomatic infection is common.[2,3] Preterm premature rupture of membranes (PPROM) complicates 3% of pregnancies, and in turn, is responsible for one-third of all preterm births.[4]

Studies exploring the role of chlamydia infection as a cause of preterm delivery (PTD) are mainly observational and yield mixed results, so the extent to which infection adversely affects pregnancy remains controversial.[5] Most studies suggest chlamydial infection increases the risk of PTD, PPROM, and low birthweight infants.[6-10] Rours et al noted the risk of PTD before 32 weeks was significantly higher among women with chlamydia than those who tested negative after adjustment for age and socio-economic background (odds ratio [OR], 4.35; 95% CI, 1.3–15.2).[15] Some studies, however, have not demonstrated an increased risk of these outcomes.[5,11-14] A recent large observational study of more than 100 000 women did not find an association between chlamydial infection and preterm birth, small for gestational age infants, or intrauterine fetal demise.[16] Neonates who acquire chlamydia at the time of delivery are at risk for conjunctival infections and *Chlamydia trachomatis* pneumonia.[2]

Similar to results of studies examining outcomes associated with maternal chlamydia infection, studies of outcomes associated with maternal gonococcal infection have yielded mixed results. Most studies of maternal gonococcal infection note associations with low birth weight and small for gestational age infants though some studies have also found a higher risk of PPROM and PTD in individuals with gonorrhea.[14,17-21] Studies also suggest associations of maternal gonococcal infection with spontaneous abortion, intrauterine growth restriction, and chorioamnionitis.[14,17-20] A recent study in Washington state found a significantly increased risk of low birthweight, but not of PTD, PPROM, chorioamnionitis, or infant admission into a neonatal intensive care unit (NICU).[22] If untreated, transmission of gonorrhea from mother to infant occurs in 30% to 50% of cases.[23] Neonatal complications include neonatal conjunctivitis, pharyngitis, and arthritis.[3]

The American College of Obstetricians (ACOG) recommends screening all pregnant women at the initial prenatal visit for chlamydia and re-screening women at risk for a new infection

in the third trimester. Patients are considered to be at a higher risk for a new infection if they have new or multiple sex partners, a sex partner with concurrent partners, or a sex partner who has a STI.[1,2] The CDC has more limited recommendations for screening than ACOG and recommends screening pregnant women who are 25 years of age or younger and women of any age who have risk factors for infection. ACOG and the CDC recommend gonorrhea screening during pregnancy in patients 25 years of age or younger, those with risk factors for infection (previous or coexisting STI, new or multiple sex partners, inconsistent condom use among persons not in mutually monogamous relationships, exchanging sex for money or drugs), and those living in high-morbidity areas.[24]

In the current study, patients at our institution admitted for PPROM or experienced PTD during the study period were routinely screened for gonorrhea or chlamydia regardless of whether they had been previously screened. This study was not based on any national recommendation but was performed at our institution for many years. We sought to evaluate the utility of this practice. Data regarding admission to the NICU, chorioamnionitis, and neonatal sepsis were collected to assess the prevalence of these outcomes in the setting of maternal chlamydia or gonococcal infection.

Materials and Methods

The primary objective of this retrospective, descriptive study was to determine the prevalence of chlamydia among patients admitted for PPROM or experienced PTD who had a negative chlamydia test earlier in pregnancy. PTD was defined as delivery before 37 weeks' gestation, and PPROM was defined as rupture of the amniotic membrane before 37 weeks without the onset of labor. We also sought to identify risk factors for chlamydia at the time of admission so that testing could be done more selectively. Gonorrhea and chlamydia testing are typically done at the same time, with the same sample. Specimens collected were tested for chlamydia and gonorrhea using the Aptima Combo 2 assay, with associated test sensitivity of 97.8% and specificity of 99.2%. Though we planned to describe the results of gonorrhea testing, we did not seek to identify risk factors for gonorrhea because of the suspected lower prevalence of gonorrhea in the current population.

Using *International Classification for Diseases, Ninth Revision* (ICD-9) codes, we identified patients who met our inclusion criteria at Kapi'olani Medical Center for Women and Children (KMCWC) between April 1, 2009, and April 30, 2015. We further limited our cohort to women who (1) had a chlamydia test result from a date before admission, which we termed "antenatal screening", and (2) had a screening for chlamydia at the time of admission, which we termed "admission screening." We excluded those who did not have prenatal screening for chlamydia before admission as these patients should have testing done at the time of admission per ACOG guidelines.[24,25] Charts were individually reviewed to verify diagnoses and test results.

In addition to gonorrhea and chlamydia test results, we collected demographic and clinical information. At KMCWC, race is self-reported and entered into the electronic medical record. An individual could identify with more than 1 race. If an individual identified with multiple races, they were analyzed by each race they best identified. Since individuals could be counted in more than 1 racial category, we did not compare any outcome between races (for example, Asian versus white) but compared single racial categories with the rest of the population (for example, Asian versus non-Asian) because of the increased presence of multiracial individuals in the study population. We reported demographic characteristics by race for all races for which more than 30 participants were identified. We described patients' demographic and clinical characteristics by frequency and percentage for categorical variables and mean and standard deviation for continuous variables. We evaluated associations between gonorrhea and chlamydia test results and other variables using chi-square or Fisher's exact tests. All analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC). A P value of less than .05 was considered statistically significant. We determined the proportion of patients who had admissions to the NICU and a diagnosis of chorioamnionitis or neonatal sepsis based on ICD-9 codes. This study was granted exempt status from Institutional Review Board approval by the Hawai'i Pacific Health Research Institute (HPHRI 2015-076).

Results

The demographics and clinical characteristics of the study population are presented in Table 1. Among the demographics listed in Table 1, a previous positive prenatal chlamydia test was the only factor significantly associated with a positive chlamydia test result upon admission screening. During the study period, there were 406 patients admitted for PPROM or resulting PTD who had both antepartum and admission test for chlamydia. Of the 406 patients who met our inclusion criteria, 352 patients (86.7%) had negative prenatal chlamydia tests, and 54 (13.3%) had positive prenatal chlamydia tests (Figure 1). Of the 352 patients who had negative prenatal chlamydia tests, 346 (98.3%) had negative chlamydia tests on admission, and 6 (1.7%) had positive chlamydia tests on admission. Of the 54 patients with positive prenatal chlamydia tests, 44 (81.5%) had negative chlamydia tests on admission, and 10 (18.5%) had positive chlamydia tests on admission. Regardless of prenatal chlamydia test results, of the 406 patients, 16 (3.9%) had positive chlamydia tests on admission, and 390 (96.1%) had negative chlamydia tests on admission.

Of the 54 patients with positive prenatal chlamydial tests, treatment was documented in the medical record for 46 (85.2%) of them. Of the 8 patients with positive prenatal chlamydial tests who did not have documented treatment, 1 (12.5%) tested positive, and 7 (87.5%) tested negative upon admission screening for chlamydia. The resolution of positive test results for patients without documented treatment is likely because of the incomplete nature of some medical records, as explained

Table 1. Demographics and Clinical Characteristics of the Study Population			
Characteristics	**Negative Admission Chlamydia (n=390) n (%)**	**Positive Admission Chlamydia (n=16) n (%)**	***P* Value[a]**
Positive antenatal test	44 (11.3)	10 (62.5)	<.001
Age, 25 years or younger	166 (42.6)	13 (81.3)	.002
PPROM at admission	126 (32.3)	2 (12.5)	.107
History of preterm delivery	39 (10.0)	0 (0.0)	.38
Insurance type			
Unknown/uninsured	2 (0.6)	0 (0.0)	.56
Public	187 (47.9)	11 (68.8)	
Private	185 (47.4)	5 (31.3)	
Military	16 (4.1)	0 (0.0)	
Gestational age at delivery, weeks			
Less than 24	10 (2.6)	0 (0.0)	.76
24 to 27+6[b]	47 (12.1)	3 (18.3)	
28 to 31+6[b]	62 (15.9)	3 (18.3)	
32 to 36+6[b]	271 (69.5)	10 (62.5)	
Race			
Filipino	181 (46.4)	8 (50.0)	.78
White	179 (45.9)	5 (31.3)	.25
Hawaiian	152 (39.0)	5 (31.3)	.53
Chinese	102 (26.2)	4 (25.0)	.92
Japanese	80 (20.5)	2 (12.5)	.43
Micronesian	27 (6.9)	4 (25.0)	.008

Abbreviations: PPROM, preterm premature rupture of membranes.
[a] *P* values <.05 considered to be statistically significant, reflecting an association with a positive chlamydia test.
[b] "+6" in reference to number of days of gestation, in addition to the previous value indicating weeks of gestation.

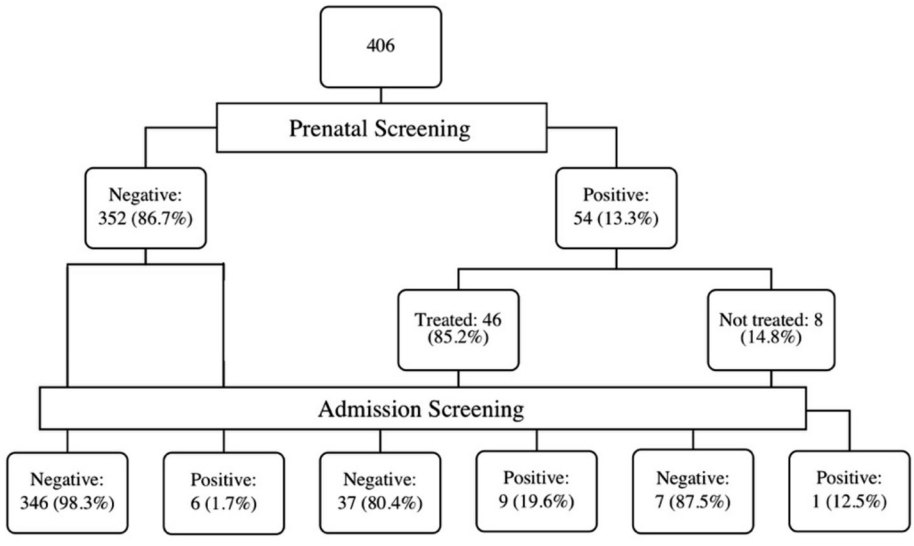

Figure 1. Chlamydia Prenatal Screening Results and Subsequent Admission Screening Results for Patients Admitted for PPROM or Experienced PTD.

Table 2. The Association of Chorioamnionitis, Neonatal Intensive Care Unit Admission, and Neonatal Sepsis Events with Chlamydia Test Results

Diagnosis	Negative Admission Chlamydia (n=390) n (%)	Positive Admission Chlamydia (n=16) n (%)	*P* Value[a]
Chorioamnionitis	43 (11.0)	3 (18.8)	.34
NICU admission	310 (79.5)	12 (75.0)	.66
Sepsis in newborn	46 (11.8)	1 (6.3)	.49

Abbreviations: NICU, neonatal intensive care unit.
[a] *P* values <.05 considered to be statistically significant, reflecting an association with a positive chlamydia test.

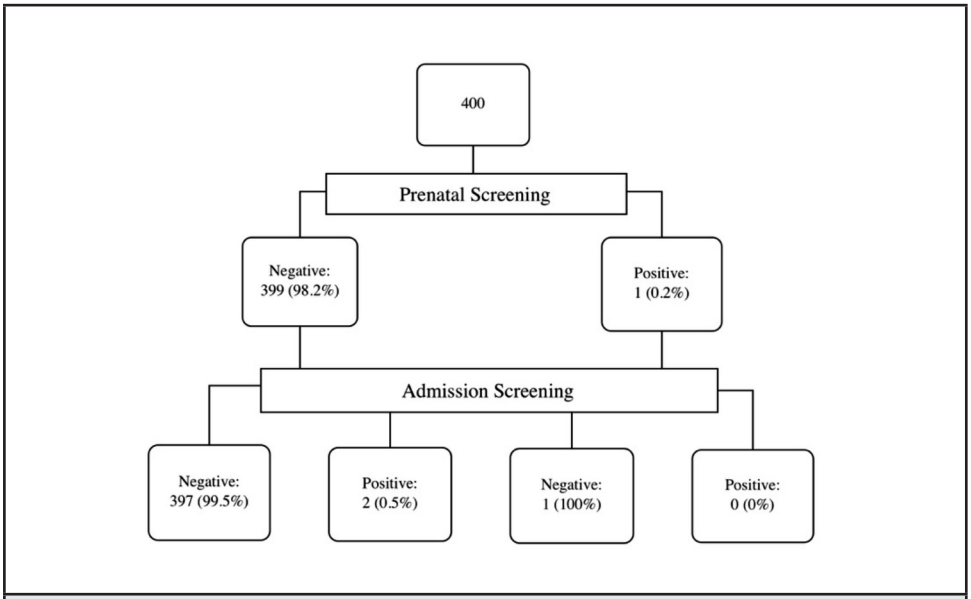

Figure 2. Gonorrhea Prenatal Screening Results and Subsequent Admission Screening Results for Patients Admitted for PPROM or Experienced PTD.

further in the limitations of the study. Patients also might have gone to different facilities or providers and received treatment that was not documented in the electronic medical record. Of the 46 patients with positive prenatal chlamydial tests who did receive treatment, 9 (19.6%) tested positive, and 37 (80.4%) tested negative upon admission screening for chlamydia. The higher rates of positive chlamydia results upon admission for patients with documented treatment might be related to incomplete treatment or re-infection.

Six patients who had antepartum tests and admission tests for chlamydia did not have concurrent gonorrhea tests, including 4 patients who did not have prenatal tests for gonorrhea and 2 patients who did not have admission tests for gonorrhea, leaving 400 patients available for the analysis of gonorrhea test results. We could not ascertain the reason for this testing discordance from reviewing the medical record. Of the 400 patients who had prenatal and admission tests for gonorrhea, 2 tested positive at admission (0.5%), as shown in Figure 2. One patient had a positive prenatal test (0.2%) but tested negative at admission.

The mean age of patients who tested positive for chlamydia on admission was 21.8 (standard deviation [SD], 4.9) years, compared to a mean of 27.2 (6.2) years for patients who tested negative on admission (*P*=.16). Mean gestational age on admission was no different in those who tested positive and those who tested negative for chlamydia on admission, with a mean (SD) of 229.9 (26.2) days versus a mean (SD) of 223.0 (24.3) days.

The 3 factors that showed significant association with a positive chlamydia test on admission were age 25 years or younger (OR, 5.85; 95% CI 1.64–20.85), a positive antepartum test for chlamydia (OR, 13.11; 95% CI, 4.54–37.82) and Micronesian race (OR, 4.48; 95% CI, 1.35–14.84) (Table 1). From a logistic regression model adjusting for the 3 significant variables, only a positive antepartum test for chlamydia remained significantly associated with a positive test on admission (OR, 8.56; 95% CI, 2.67–27.49; *P*=.003), while age 25 years or younger (*P*=.089) and Micronesian race (*P*=.650) were not significant.

If admission testing for chlamydia were done only in women who were 25 years of age or younger, we would have tested 179 individuals and detected 13 of 16 (81.3%) chlamydia infections. If we had tested only patients with a positive antepartum test and those who were 25 years of age or younger, we would have tested 192 individuals and detected 14 of 16 (87.5%) chlamydia infections on admission.

Table 2 reports the percentages of patients with positive and negative admission chlamydial tests who had chorioamnionitis, NICU admission, or a diagnosis of neonatal sepsis. A higher percentage of patients with positive chlamydia tests on admission had chorioamnionitis, though this was not statistically different (18.8% versus 11.0%; *P*=.34).

Discussion

During pregnancy, routine screening for chlamydia is recommended by ACOG and the CDC in women 25 years of age or younger and those with risk factors for infection.[24,25] These recommendations are important because most patients with chlamydia are asymptomatic, and most studies suggest a higher risk of neonatal morbidity when a pregnancy is complicated by infection.[2] At our institution, it was common to re-screen patients at the time of admission for PTD or PPROM regardless of risk factors or the results of screening earlier in pregnancy. Among those who were re-screened at the time of admission, 3.9% had a positive test for chlamydia, and 0.5% had a positive test for gonorrhea. Despite the abundance of STI statistics in non-pregnant women, there are minimal data reflecting the prevalence of STIs among pregnant women. In a study using self-reported data from the Pregnancy Risk Assessment Monitoring System in 5 states (Arkansas, Delaware, Mississippi, Missouri, and New York State), 2.4% of patients reported being diagnosed with a positive chlamydia result, and 0.5% of patients reported being diagnosed with a positive gonorrhea result.[26] In comparison, our population had a slightly higher percentage of chlamydia and a similar percentage of gonorrhea.

The CDC reports a rate of 542 chlamydia cases per 100 000 population in Hawai‘i, similar to the US average of 539 chlamydia cases per 100 000 population.[1] Reported rates of chlamydia are dependent on the actual burden of disease in a population and the likelihood of getting screened. Women's rate of chlamydia is twice that of men because of a higher likelihood of being screened (692.7 per 100 000 for US women versus 380.6 for US men).[1] Chlamydia infection also varies by age, with rates being highest in women ages 20 to 24 (4064 per 100 000) and ages 15 to 19 (3307 per 100 000).[1] As women get older, rates decline. The rate of chlamydial infection is 176.6 per 100 000 in US women ages 40 to 44 years.[1] In our cohort, we similarly noted that age was associated with having a positive admission screening test upon admission for PTD and PPROM. However, this was not significant after adjustment for having a previous test in pregnancy. This retrospective study suggests limiting re-screening to those who were 25 years of age or younger or had a positive test earlier in pregnancy would reduce the number of tests while identifying most patients with chlamydia. In this cohort, approximately half of patients would not have required re-testing, and still, the majority (87.5%) of positive cases would have been identified on admission. Based on results of past studies examining maternal chlamydia infection, missing 12% of maternal chlamydia infections by reducing re-screening could result in increased rates of associated adverse neonatal outcomes.[6-10] Further research is needed to identify better factors that could safely be used to select patients who would most benefit from re-screening.

Gonorrhea is less common than chlamydia, and this was also demonstrated in our population, with 1 patient testing positive during antepartum testing and 2 patients with positive tests on admission. The rate of gonorrhea in Hawai‘i is 105 per 100 000 population.[1] The lower rate of gonorrhea in this cohort limits the ability to make recommendations beyond those already established by national organizations. Both ACOG and CDC recommend re-screening patients for gonorrhea based on whether an individual has an ongoing risk of infection.[2,24] In clinical practice, gonorrhea and chlamydia tests are commonly conducted and processed from the same specimen, so it is often practical to do the tests simultaneously.

There are several limitations to this study. The data were limited to information available in the electronic medical record, so we were not able to ascertain information about some risk factors, particularly those that pertained to sexual partners. Prenatal records and test results for many patients were gathered through a review of prenatal records from outpatient offices and laboratories rather than from the hospital's electronic medical record because most physicians did not use the same electronic medical record system as the hospital. Some records were incomplete, which may explain why some patients who had a positive prenatal chlamydia test but did not have a documented treatment tested negative for chlamydia on admission. Incorporating risk factors (new or multiple sex partners, inconsistent condom use, STI identified in a sexual partner, persons not in mutually monogamous relationships, exchanging sex for money or drugs) outlined by the CDC for gonorrhea or chlamydia would have further enhanced our ability to identify those in whom screening on admission was warranted. The wide confidence intervals generated in our analysis are a reflection of the limited sample size. In particular, given limitations of sample size, particularly in the group of patients who tested positive for chlamydia on admission, conclusions cannot be drawn about the associations between a positive test for chlamydia and chorioamnionitis, NICU admission, and sepsis.

Findings from this study have implications for clinical practice. During the study period, patients at our institution admitted for PTD or PPROM were routinely screened for gonorrhea or chlamydia regardless of previous screening results or their age.

This study suggests that re-screening at the time of admission can be more personalized based on patient characteristics, and repeat testing in many individuals can be eliminated. Further studies are needed to determine the optimal timing and frequency of re-screening in high-risk populations.

Conflict of Interest and Disclosure Statement

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References

1. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2018*. Atlanta: U.S. Department of Health and Human Services; 2019. DOI: 10.15620/cdc.79370.
2. Kilpatrick SJ, Papile L, Macones GA, Watterberg KL, American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Antepartum Care. In: Kilpatrick SJ, Papile L, Macones GA, Watterberg KL, eds. *Guidelines for Perinatal Care.* 8th ed. Elk Grove Village, Chicago: American Academy of Pediatrics; 2017:149–226.
3. Kilpatrick SJ, Papile L, Macones GA, Watterberg KL, American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Perinatal Infections. In: Kilpatrick SJ, Papile L, Macones GA, Watterberg KL, eds. *Guidelines for Perinatal Care.* 8th ed. Elk Grove Village, Chicago: American Academy of Pediatrics; 2017:479–558.
4. Mercer BM. Preterm premature rupture of the membranes: current approaches to evaluation and management. *Obstet Gynecol Clin North Am.* 2005;32(3):411.28. DOI: 10.1016/j.ogc.2005.03.003.
5. Sweet RL, Landers DV, Walker C, Schachter J. Chlamydia trachomatis infection and pregnancy outcome. *Am J Obstet Gynecol.* 1987;156(4):824–833. DOI: 10.1016/0002-9378(87)90338-3.
6. Gravett MG, Nelson HP, DeRouen T, Critchlow C, Eschenbach DA, Holmes KK. Independent associations of bacterial vaginosis and Chlamydia trachomatis infection with adverse pregnancy outcome. *JAMA.* 1986;256(14):1899–1903.
7. Martius J, Krohn MA, Hillier SL, Stamm WE, Holmes KK, Eschenbach DA. Relationships of vaginal Lactobacillus species, cervical Chlamydia trachomatis, and bacterial vaginosis to preterm birth. *Obstet Gynecol.* 1988;71(1):89–95.
8. Martin DH, Koutsky L, Eschenbach DA, Daling JR, Alexander ER, Benedetti JK, Holmes KK. Prematurity and perinatal mortality in pregnancies complicated by maternal Chlamydia trachomatis infections. *JAMA.* 1982;247(11):1585–1588.
9. Andrews WW, Goldenberg RL, Mercer B, Iams J, Meis P, Moawad A, Das A, Vandorsten JP, Caritis SN, Thurnau G, Miodovnik M, Roberts J, McNellis D. The Preterm Prediction Study: association of second-trimester genitourinary chlamydia infection with subsequent spontaneous preterm birth. *Am J Obstet Gynecol.* 2000;183(3):662–668. DOI: 10.1067/mob.2000.106556.
10. Ryan GM Jr, Abdella TN, McNeeley SG, Baselski VS, Drummond DE. Chlamydia trachomatis infection in pregnancy and effect of treatment on outcome. *Am J Obstet Gynecol.* 1990;162(1):34–39. DOI: 10.1016/0002-9378(90)90815-o.
11. Gonçalves LF, Chaiworapongsa T, Romero R. Intrauterine infection and prematurity. *Ment Retard Dev Disabil Res Rev.* 2002;8(1):3–13. DOI: 10.1002/mrdd.10008.
12. Riggs MA, Klebanoff MA. Treatment of vaginal infections to prevent preterm birth: a meta-analysis. *Clin Obstet Gynecol.* 2004;47(4):796–807. DOI: 10.1097/01.grf.0000141450.61310.81.
13. Silveira MF, Ghanem KG, Erbelding EJ, Burke AE, Johnson HL, Singh RH, Zenilman JM. Chlamydia trachomatis infection during pregnancy and the risk of preterm birth: a case-control study. *Int J STD AIDS.* 2009;20(7). DOI: 10.1258/ijsa.2008.008388.
14. Donders GG, Desmyter J, De Wet DH, Van Assche FA. The association of gonorrhoea and syphilis with premature birth and low birthweight. *Genitourin Med.* 1993;69(2):98–101. DOI: 10.1136/sti.69.2.98.
15. Rours GIJG, Duijts L, Moll HA, Arends LR, de Groot R, Jaddoe VW, Hofman A, Steegers EAP, Mackenbach JP, Ott A, Willemse HFM, van der Zwaan EAE, Verkooijen RP, Verbrugh HA. Chlamydia trachomatis infection during pregnancy associated with preterm delivery: a population-based prospective cohort study. *Eur J Epidemiol.* 2011;26(6):493–502. DOI: 10.1007/s10654-011-9586-1.
16. Reekie J, Roberts C, Preen D, Hocking JS, Donovan B, Ward J, Mak DB, Liu B. Chlamydia trachomatis and the risk of spontaneous preterm birth, babies who are born small for gestational age, and stillbirth: a population-based cohort study. *Lancet Infect Dis.* 2018;18(4):452–460. DOI: 10.1016/S1473-3099(18)30045-8.
17. Liu B, Roberts CL, Clarke M, Jorm L, Hunt J, Ward J. Chlamydia and gonorrhoea infections and the risk of adverse obstetric outcomes: a retrospective cohort study. *Sex Transm Infect.* 2013;89(8):672–678. DOI: 10.1136/sextrans-2013-051118.
18. Elliot B, Brunham RC, Laga M, Piot P, Ndinya-Achola JO, Maitha G, Cheang M, Plummer FA. Maternal gonococcal infection as a preventable risk factor for low birth weight. *J Infect Dis.* 1990;161(3):531–536. DOI: 10.1093/infdis/161.3.531.
19. Johnson HL, Ghanem KG, Zenilman JM, Erbelding EJ. Sexually transmitted infections and adverse pregnancy outcomes among women attending inner city public sexually transmitted diseases clinics. *Sex Transm Dis.* 2011;38(3):167–171. DOI: 10.1097/olq.0b013e3181f2e85f.
20. Edwards LE, Barrada MI, Hamann AA, Hakanson FY. Gonorrhea in pregnancy. *Am J Obstet Gynecol.* 1978;132(6):637–641. DOI: 10.1016/0002-9378(78)90856-6.
21. Maxwell GL, Watson WJ. Preterm premature rupture of membranes: results of expectant management in patients with cervical culture positive for group B streptococcus or Neisseria gonorrhoeae. *Am J Obstet Gynecol.* 1992;166(3):945–949. DOI: 10.1016/0002-9378(92)91369-l.
22. Heumann CL, Quilter LAS, Eastment MC, Heffron R, Hawes SE. Adverse birth outcomes and maternal Neisseria gonorrhoeae infection: a population-based cohort study in Washington state. *Sex Transm Dis.* 2017;44(5):266–271. DOI: 10.1097/OLQ.0000000000000592.
23. Laga M, Meheus A, Piot P. Epidemiology and control of gonococcal ophthalmia neonatorum. *Bull World Health Organ.* 1989;67(5):471–477.
24. Centers for Disease Control and Prevention (CDC). STDs During Pregnancy – CDC Fact Sheet (Detailed). https://www.cdc.gov/std/pregnancy/stdfact-pregnancy-detailed.htm. Updated February 11, 2016. Accessed May 18, 2020.
25. The American College of Obstetricians and Gynecologists (ACOG). Routine Tests During Pregnancy. https://www.acog.org/patient-resources/faqs/pregnancy/routine-tests-during-pregnancy. Published November 2019. Accessed May 18, 2020.
26. Williams CL, Harrison LL, Llata E, Smith RA, Meites E. Sexually transmitted diseases among pregnant women: 5 states, United States, 2009-2011. *Matern Child Health J.* 2018;22(4):538–545. DOI: 10.1007/s10995-017-2422-9.

Hawai'i Journal of Health & Social Welfare (HJH&SW)

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- Final date for submitting Word documents for copy editing
- Final date for submitting Word documents for layout
- Final date to request changes to page proofs (Please note that changes to page proofs will be made only to fix any errors that were introduced during layout. Other editing changes will incur an additional fee of $50 per page.)

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

6. The sponsor may decide to include advertisements in the supplement in order to defray costs. Please consult with the HJH&SW advertising representative Michael Roth at 808-595-4124 or email rothcomm@gmail.com for assistance.

7. Supplement issues are posted on the HJH&SW website (http://www.hawaiijournalhealth.org) as a full-text PDF (both of the whole supplement as well as each article). An announcement of its availability will be made via a press release and through the HJH&SW email distribution list. Full-text versions of the articles will also be available on PubMed Central.

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

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

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Sample Workflow and Timeline for a Supplement

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

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

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

Articles must comply with:

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

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

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

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

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

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

8. The sponsor will submit the final articles to the layout editor for formatting. **Time frame: 1 month**
Acting in the role of guest editor, the sponsor will include a column introducing the supplement.
IMPORTANT: All articles submitted for layout should be in their finalized form. Page proofs will be returned to the sponsor for their review and approval, but changes will only be made to fix any errors that were introduced during the layout process. Any editing or changes to the text or figures after the initial copy layout will incur a fee of $50 per page.

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

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

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

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

Revised 2/6/20

Hawai‘i Journal of Health & Social Welfare (HJH&SW)

Style Guide for the Use of Native Hawaiian Words and Diacritical Markings

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

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

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

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

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

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