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SARS-CoV-2 Variants in Rhode Island; May 2022 Update

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ABSTRACT

BACKGROUND: Genomic surveillance allows identification of circulating SARS-CoV-2 variants. We provide an update on the evolution of SARS-CoV-2 in Rhode Island (RI).

METHODS: All publicly available SARS-CoV-2 RI sequences were retrieved from https://www.gisaid.org. Genomic analyses were conducted to identify variants of concern (VOC), variants being monitored (VBM), or non-VOC/non-VBM, and investigate their evolution.

RESULTS: Overall, 17,340 SARS-CoV-2 RI sequences were available between 2/2020–5/2022 across five (globally recognized) major waves, including 1,462 (8%) sequences from 36 non-VOC/non-VBM until 5/2021; 10,565 (61%) sequences from 8 VBM between 5/2021–12/2021, most commonly Delta; and 5,313 (31%) sequences from the VOC Omicron from 12/2021 onwards. Genomic analyses demonstrated 71 Delta and 44 Omicron sub-lineages, with occurrence of variant-defining mutations in other variants.

CONCLUSION: Statewide SARS-CoV-2 genomic surveillance allows for continued characterization of circulating variants and monitoring of viral evolution, which inform the local health force and guide public health on mitigation efforts against COVID-19.

KEYWORDS: COVID-19, SARS-CoV-2, variants, genomic sequencing, Rhode Island

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic, resulting from the spread of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has caused significant global morbidity and mortality. As of May 17, 2022, the COVID-19 pandemic has resulted in at least 519,766,413 infections and 6,268,690 deaths worldwide, of which at least 81,682,634 infections and 992,415 deaths were in the United States alone. However, despite the ongoing public health mitigation efforts – including travel bans, social distancing, and stay-at-home orders – and the availability of vaccines, COVID-19-related morbidity and mortality continue to rise.

Since publication of its first genomic sequence, SARS-CoV-2 has accumulated numerous mutations throughout its genome, with gradual predominance of those conferring selective advantage in human hosts. These mutations are natural to the viral life cycle and, as seen in SARS-CoV-2, often result from an error-prone replication process, yielding viruses with novel mutations termed variants. In SARS-CoV-2, such mutations commonly occur in the receptor binding domain (RBD) of the spike protein, which interacts with the angiotensin-converting enzyme 2 (ACE2) human cellular receptor and facilitates viral fusion and entry into host cells.

Enhanced genomic surveillance efforts since the end of 2020, when the first clinically significant SARS-CoV-2 Alpha variant was recognized, have noted the continued emergence of multiple lineages and sub-lineages in different parts of the world, some of which have shared attributes that justified close monitoring and public health actions. The United States Centers for Disease Control and Prevention (CDC) continues to define variants being monitored (VBM; associated with severe disease or increased transmission but circulating at low levels); variants of interest (VOI; associated with changes to receptor binding, reduced antibody neutralization, reduced treatment efficacy, or increased transmissibility); variants of concern (VOC; associated with significantly reduced antibody neutralization, reduced treatment/vaccine efficacy, increased transmissibility, increased disease severity, or diagnostic detection failures); and variants of high consequence (VOHC; associated with significantly reduced effectiveness of prevention measures or medical countermeasures). The current CDC-defined variant classifications, as well as the related World Health Organization (WHO) nomenclature, are provided in Table 1.

Since the first reported case of SARS-CoV-2 in China in December 2019, five major COVID-19 waves have occurred in RI, in parallel to the global trends. These waves and the associated predominant variants, discussed further below, include the (i) Wuhan-Hu-1 strain from February 2020 to July 2020 [peak incidence in April 2020], (ii) D614G variant from June 2020 to February 2021 [peak incidence in November 2020], (iii) Alpha variant from January 2021 to July 2021 [peak incidence in April 2021], (iv) Delta variant from April 2021 to February 2022 [peak incidence in September 2021], and (v) Omicron variant from November 2021 to present [peak incidence in January 2022] (see Figure 1A, see Appendix for all Figures).
In September 2021, we reported on SARS-CoV-2 variants in RI, describing the state’s genomic surveillance program, circulating lineages, and independent mutation evolution, covering the state’s first three waves. Since then, similar to the rest of the world, RI has seen a significant upsurge in COVID-19-related infections, morbidity and mortality, along with an influx of new variants replacing the previously dominant strains, within the fourth and fifth waves. As of May 17, 2022, RI has seen a total of 384,187 SARS-CoV-2 infections (up by 252% from our prior report) and 3,559 associated deaths (up by 130% from our prior report), of which many were caused by the more recent Delta and Omicron variants and their sublineages. In this manuscript, we provide an update on SARS-CoV-2 variants in RI, and discuss their continued potential implications on public health mitigation efforts. Such local characterization of variants can continue to guide regional public health mitigation measures, and offer educational opportunities for health providers, public health officials, and the general public.

**METHODS**

**Collection of SARS-CoV-2 samples**

Diagnostic clinical laboratories across RI have been collecting specimens from individuals who were hospitalized, reside or work at long-term care or correctional facilities, study or work at educational facilities including K–12 schools, colleges and universities, as well as the general population, and testing them for SARS-CoV-2. Selected specimens were submitted to the RI State Health Laboratory (RISHL), which coordinates SARS-CoV-2 sequencing in the state and aggregates genomic data from collaborating laboratories, including the CDC, the Broad Institute, the Kantor Laboratory, and its own internal sequencing capacity. Deidentified sequences were submitted to the public database Global Initiative on Sharing All Influenza Data (GISAID). The present paper continues to utilize sequences originating from RI residents that were aggregated from GISAID since the beginning of the COVID-19 pandemic.

**SARS-CoV-2 sequencing and sequence analysis**

At the RISHL, for specimens with low (<30) cycle thresholds (Ct), RNA was extracted, reverse transcribed and amplified, and the entire SARS-CoV-2 genome was sequenced by next generation sequencing (NGS) using the Illumina platform. Alignment and variant-designation of sequences against the Wuhan-Hu-1 reference sequence (NCBI accession number MN908947) were conducted at the Kantor laboratory with a pipeline that combines available tools for SARS-CoV-2 sequence analysis. This pipeline is available under an open-source license from https://github.com/kantorlab/covid-pipeline. The classification of SARS-CoV-2 variants as VOC, VBM, or non-VOC/non-VBM was performed by Phylogenetic Assignment of Named Global Outbreak Lineages (Pangolin, https://cov-lineages.org/resources/pangolin.html), according to the current CDC classification.

**Analysis of SARS-CoV-2 variant diversity**

To further evaluate viral evolution within and beyond designated variants, we first characterized the diversity within the recent Delta and Omicron waves in RI, by examining their designated common sub-lineages since the beginning of the pandemic. We then identified the key mutations that distinguish those sub-lineages from the Wuhan-Hu-1 reference sequence and from their parent lineages (NCBI accession number MN908947) were conducted at the Kantor laboratory with a pipeline that combines available tools for SARS-CoV-2 sequence analysis. This pipeline is available under an open-source license from https://github.com/kantorlab/covid-pipeline. The classification of SARS-CoV-2 variants as VOC, VBM, or non-VOC/non-VBM was performed by Phylogenetic Assignment of Named Global Outbreak Lineages (Pangolin, https://cov-lineages.org/resources/pangolin.html), according to the current CDC classification.
Analysis of SARS-CoV-2 mutations

To further investigate the continued development of viral mutations beyond their designated lineages, we examined the occurrence of the five most common amino acid mutations that have been associated with the parent Delta lineage but that occurred at least once in sequences designated as Omicron, and the occurrence of the five most common amino acid mutations that have been associated with the parent Omicron lineage, but that occurred at least once in sequences designated as Delta.

Phylogenetic analysis

To provide a continued snapshot of the phylogenetic spectrum of the available RI SARS-CoV-2 sequences from the start of the COVID-19 pandemic, we created a maximum likelihood tree using RAxML. This phylogenetic tree includes [i] the earliest and latest RI non-VOC/non-VBM sequences since the start of the pandemic; [ii] the earliest and latest Delta sequences detected in RI; [iii] the earliest and latest five common Delta AY lineage sequences detected in RI; [iv] the earliest and latest Omicron sequences detected in RI; [v] the earliest and latest Omicron BA lineage sequences detected in RI; [vi] the earliest and latest VBM sequences detected in RI [besides Delta, which is included above]; [vii] one reference sequence for each of the VOC/VBM (Alpha B.1.1.7, GISAID accession number EPI_ISL_683466; Beta B.1.351, EPI_ISL_678615; Gamma P.1, EPI_ISL_792683; Delta B.1.617.2, EPI_ISL_1663516; Epsilon B.1.427, EPI_ISL_730092, Eta B.1.525, EPI_ISL_1035819; Iota B.1.526.1, EPI_ISL_801973; Kappa B.1.617.1, EPI_ISL_1372093; Mu B.1.621, EPI_ISL_4369031; Omicron BA.1, EPI_ISL_12327737; and Omicron BA.2, EPI_ISL_8212418); and [viii] the original SARS-CoV-2 sequence from Wuhan. The number of sequences included was limited to allow for a reasonable tree resolution.

RESULTS

In our previous report we included genomic surveillance efforts since the first COVID-19 case on 2/28/20 until the end of the B.1.1.7 (Alpha) variant wave on 7/27/21 in RI. Since then, there has been a marked increase in genomic surveillance of SARS-CoV-2 within the state, particularly due to the recent uptick in Omicron cases [Figure 1A]. As of mid-May 2022, the number of SARS-CoV-2 specimens successfully sequenced from RI residents has increased by over 4-fold to 17,340 sequences (Figure 1B).

Table 1 lists cases identified as VOCs and VBM lineages in RI. The earliest reported variant (then VOC; currently VBM) in RI was Iota (B.1.526 lineage), first detected on 1/7/21. The most frequently detected VBM has been Delta (B.1.617.2 and its AY lineages; see below), first sampled on 4/20/21. Other common VBM lineages include Alpha (B.1.1.7 and its Q sub-lineages), Iota (B.1.526), and Gamma (P.1 and its sub-lineages), first detected on 1/19/21, 1/7/21, and 3/3/21, respectively. Omicron (B.1.1.529 and its BA sub-lineages; see below), the only current VOC, was first detected on 11/30/2021.

Phylogenetic analysis of SARS-CoV-2 variants in RI demonstrated expected clustering of local variants with reference sequences, as well as the continued viral evolution over time, with earlier sequences in the COVID-19 pandemic being closer to the root [left in the figure] of the tree and more recent sequences [right of the tree] being more distal to the Wuhan-Hu-1 strain (Figure 2). Similarly, within variants, more recent sequences have evolved further as compared to reference and earlier sequences, indicating continued development of new mutations over time.

Multiple VOC, VBM, and non-VOC/non-VBM lineages have been circulating in RI. Non-VOC/non-VBM lineages predominated till December 2020, followed by the appearance of VBM lineages in January 2021 and their predominance till December 2021, and finally by the appearance of VOC, which overtook the landscape to become the predominant variant in RI thereafter (Figure 3A).

Figure 3B provides further breakdown of the non-VOC/non-VBM lineages in RI. Around the end of 2020, as SARS-CoV-2 genomic surveillance intensified, multiple non-VOC/non-VBM lineages were observed. However, only few have made up substantial numbers at any one time. Until October 2020, B.1 dominated the non-VOC/non-VBM cases. Beginning in November 2020, an increase in prevalence of lineages like B.1.2, B.1.375, and B.1.517 was observed. By the end of May 2021, the non-VOC/non-VBM variants were overtaken by the VBM lineages and their prevalence remains low to this day.

Figure 3C provides further breakdown of the VOC/VBM lineages in RI. Around the start of 2021, RI, like the rest of the world, saw the emergence of several VBMs, mostly Iota and Alpha, which rose in numbers and quickly dominated the variant landscape till June 2021. In July 2021, Delta (then VOC; currently VBM) supplanted the other VBMs and became the sole variant in RI, until the emergence of VOC Omicron in November 2021 and its subsequent, and current, predominance.

As has been observed with all SARS-CoV-2 variants, further analysis of both the VBM Delta and the VOC Omicron sequences revealed continued accumulation of mutations, with subsequent evolution into sub-lineages. Among the 71 sub-lineages of Delta seen in RI, AY.103 [n=1266], AY.3 [n=1206], AY.44 [n=914], AY.25.1 [n=787], and AY.25 [n=744] were noted to comprise the majority of the sequences...
designated as Delta at any time during the Delta wave between July and December of 2021 [Figure 3D].

Similarly, among the 44 sub-lineages of Omicron seen in RI, BA.1.1 (n=2,464), BA.2 (n=1,171), BA.1 (n=474), BA.1.15 (n=319) and BA.1.17.2 (n=169) were noted to comprise the majority of the sequences designated as Omicron at any time during the Omicron wave between December 2021 and May 2022 [Figure 3E].

These sub-lineages represent continued viral evolution and are differentiated from their parent variants and from the Wuhan-Hu-1 strain by various mutations seen throughout their genomes [Figure 4]. The original Delta sequence [B.1.617.2] differs from the Wuhan-Hu-1 sequence by 29 amino acid mutations, and the most common Delta AY sub-lineages outlined above have additional 1-4 mutations, which further define them [Figure 4A].

The original Omicron sequence [B.1.1.529] differs from the Wuhan-Hu-1 sequence by 33 amino acid mutations, and the most common Omicron BA sub-lineages outlined above have additional 20–24 mutations which further define them [Figure 4B]. The extent of this large number of mutations, as compared to Delta, can also be seen on the tree in Figure 2 indicating more evolved phylogenetic branches of the Omicron lineages.

Further exploration of the mutation development in the most common recent VOC (Omicron) and VBM (Delta) variants demonstrated that mutations that define each variant are not necessarily characteristic of that specific variant only, indicating continued viral evolution beyond conventional variant definitions. For instance, five of the amino acid mutations that define Delta and five of the amino acid mutations that define Omicron, are the same mutations. Of the remaining unique 24 Delta amino acid mutations, nine mutations were noted in at least one RI sequence designated as Omicron. Figure 5A demonstrates the frequencies of the five most common Delta mutations/deletions, that were noted in 26 RI Omicron sequences, and which decrease over time. Of the remaining unique 28 Omicron amino acid mutations, eleven mutations were noted in at least one RI sequence designated as Delta. Figure 5B demonstrates the frequencies of the five most common Omicron mutations, that were noted in 108 RI Delta sequences, and which generally increase over time, as the Omicron predominance continues.

**DISCUSSION**

Following our previous report on SARS-CoV-2 variants in RI published in September 2021, as the Delta variant was emerging globally, this paper presents current data on SARS-CoV-2 variants in RI as of mid-May 2022. We demonstrate enhanced genomic surveillance efforts in RI since our first SARS-CoV-2 infection on February 28, 2020, similar to other states and countries across the world.30–33 Through these efforts, we have noted the emergence and disappearance of multiple statewide SARS-CoV-2 variants, representing expected viral evolution. Some variants predominated in more substantial waves, likely driven by epidemiological, immunological, or clinical factors that provide them with selective advantage to dominate over others variants. Such changes in variant landscape are concerning and highlight the need for continued local characterization of SARS-CoV-2 variants in order to capture the tremendous clinical and public health impact of COVID-19. At the same time, they increase awareness of the overall burden of the pandemic, and guide current and future public health mitigation efforts.

SARS-CoV-2 variants accumulate mutations through an error-prone, intra-host replication process,4 resulting in the multitude of lineages and sub-lineages that are observed in RI and elsewhere. The significance of the lineages and sub-lineages that rapidly appear is unclear and should not be over interpreted. Such diversity represents continued viral evolution and, owing to the enhanced genomic surveillance efforts, has been unprecedentedly witnessed in near-real time throughout the pandemic, in RI and elsewhere. Even at the time of this writing, newer Omicron sub-lineages continue to occur (e.g. by mid-June 2022, BA.4 and BA.5 were identified in 8 and 10 RI patients, respectively, and BA.2.12.1 was the most common recently sequenced Omicron sub-lineage).5 We should acknowledge and recognize this process as we continue to characterize the evolution of SARS-CoV-2, and monitor the linkage of viral evolution to clinical and epidemiological data.

Lineages and sub-lineages that end up predominating, even if temporarily, usually have some selective advantage. As discussed here, the VBM Delta, responsible for the fourth COVID-19 wave in RI, has about 30 mutations, and the VOC Omicron, responsible for the fifth wave, has about 50 mutations that distinguish them from the Wuhan-Hu-1 strain. Although few mutations are common across lineages, both Delta and Omicron have mutations in the open reading frame [ORF] 1a/1b [thought to encode a polyprotein involved in viral processing and immune evasion],44 and in the spike [S] protein [crucial for viral interaction with host ACE2 receptor and entry into host cells].55 The sub-lineages of these variants rapidly accumulate additional mutations in the ORFs and S protein domains,56,57 possibly enabling increased infectivity,56,59 breakthrough infections,40 immune evasion,41,42 and enhanced morbidity and mortality.43

The mutations that define the predominant variant in each wave are not necessarily exclusive to that variant and may be observed in other variants at varying frequencies over time. Omicron’s genome, for instance, while drastically different from the Wuhan-Hu-1 strain, contains mutations that are also seen in some RI Delta sequences, and vice versa for Delta’s genome. Though this currently only occurs in a minority of sequences, rising proportions of such variant-defining mutations in other variants justifies increased
awareness, as they highlight the potential convergence of mutations from multiple variants known to have clinical or epidemiological advantages into novel ‘super-variants’.\textsuperscript{44,45} The cross-occurrence of ‘Delta mutations’ in Omicron and of ‘Omicron mutations’ in Delta, such as those noted in the ORF and S protein domains of RI sequences, suggest the need for increased and careful genomic surveillance for tracking viral genomic evolution and mitigating the public health impact of SARS-CoV-2.

Genomic sequencing and surveillance of variants is, however, challenging and not without limitations. The nomenclature and SARS-CoV-2 lineage delineation is constantly evolving and undergoes relatively frequent modifications, including re-definition of VOC and VBM. As a result, variant classifications have changed even since our recent paper, and continue to change with the emergence of novel variants, which can impact genomic analyses and interpretations. This can be further complicated with changing selection pressures like vaccines and treatment options, which impact viral genomic evolution. Additionally, the generated sequences may not necessarily reflect the actual variant landscape of SARS-CoV-2, as not all COVID-19 infections are sampled and sequenced. Finally, delays in the sequencing process also create lags between generated results and actual spread of the evolving virus, delaying, at times needed, real-time clinical and public health decisions.

In conclusion, SARS-CoV-2 has continued to evolve since its emergence, with and without epidemiologic impact, despite substantial scientific advances and mitigation efforts. Most recently, the VOC Omicron has become the predominant lineage in RI, the United States, and globally, attributed to its increased transmissibility compared to previous SARS-CoV-2 variants. While Omicron’s case burden has declined substantially from peak levels, it continues to persist in RI despite the public health mitigation efforts and high vaccination rates (>80% fully vaccinated). The impact of continued SARS-CoV-2 evolution on public health remains to be determined as we travel within the spectrum of “end games” that may constitute the resolution of the COVID-19 pandemic.\textsuperscript{46} As such, enhanced genomic surveillance, which allowed for the quick identification of Delta and Omicron waves, and local and global vaccination efforts must be pursued to return to pre-pandemic lives.

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Disclaimer

The views expressed herein are those of the authors and do not necessarily reflect the views of the Rhode Island Department of Health.

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SARS-CoV-2 Variants and Their Clinical Significance: An Update as of May 2022

ELEFHERIOS MYLONAKIS, MD, PhD

SARS-CoV-2 has demonstrated a remarkable ability to mutate and evade the human immune system. In this issue of the Rhode Island Medical Journal [RIMJ], Dr. Rami Kantor and his group provide an especially important update on COVID-19 variants in RI. Dr. Kantor’s group examines variants of concern (VOCs) in our area, and helps us understand the dynamics of the pandemic while forming some important projections. The report highlights the dramatic increase in cases that coincided with the Omicron wave that spread quickly throughout the globe in December 2021 and January 2022, followed by a secondary wave in April 2022 that coincided with Omicron subvariants.

Omicron variants and lineages are antigenically distinct compared to early SARS-CoV-2 variants (614G, Alpha, Beta, Gamma, Zeta, Delta, and Mu). Months-long COVID-19 infections probably facilitate new variants and the mutations and viral lineages have significant biological effect because they allow the virus to evade antibody responses, either from the vaccine or previous infection. The genetic, antigenic, fitness and clinical variability is now continuing with the Omicron subvariants as the BA.4 and BA.5 sub-lineages are spreading.

In Portugal and other countries, BA.5 is quickly becoming the dominant SARS-CoV-2 variant resulting in a surge in COVID-19 cases. The growth advantage reported for BA.4 and BA.5 suggests that these variants will become dominant, resulting in an increase in COVID-19 cases in the coming weeks. Notably, there are significant differences between different Omicron lineages. For example, the Omicron BA.2 spike protein differs from that of BA.1 and the fusion peptide in BA.2 spike protein is less accessible to antibodies than in BA.1.

Mutations such as L452R and F486V play a key role in the ability of BA.4 and BA.5 to escape immune response and these subvariants resist neutralization by triple-dosed vaccine serum more than BA.1 and BA.2. As a result, vaccine efficacy or effectiveness against the Delta variant is 82.8% (95% prediction interval: 68.7–96.0) using the mRNA vaccine platform. Among the sub-lineages of Omicron, the predicted vaccine efficacy or effectiveness against infection seems to be only up to 33.3%. Also, the rapid evolution of the virus has resulted in declining efficacy of monoclonal antibodies against SARS-CoV-2. Natural immunity, and even passive immunotherapy through monoclonal antibodies seems to have not been able to keep up with the rapidly evolving virus.

This is particularly concerning since effective antiviral therapy options are extremely limited, and for advanced disease in hospitalized individuals an effective antiviral remains only a goal. For example, nirmatrelvir is only effective during early stages of the disease among outpatients and recrudescence after nirmatrelvir/ritonavir has been reported. As we move forward, it is likely that we need to expand monitoring for mutations substitutions, such as L50F, E166A and L167F in SARS-CoV-2 that have been linked to resistance to nirmatrelvir.

Importantly, the Omicron subvariants have shown substantial resistance to vaccine-induced and infection-induced serum neutralizing activity and the new BA.2.12.1, BA.2.13, BA.4, and BA.5 subvariants that contain Leu452 substitutions show more infectious potential. As a result of this increased ability of the virus to evade immune responses, along with the decrease in public health measures such as masking, and a decrease in booster adoption and waning of immunity, the potential for ongoing waves over the coming winter months is increasing. These changes even alter the Omicron entry process towards a TMPRSS2-independent fusion.

Vaccines provide significant protection from severe infection, hospitalization, and death. In this regard, we are expecting the need for additional booster vaccinations and the use of the upcoming Omicron-based vaccine. However, even BA.1-derived vaccine boosters may not achieve broad-spectrum protection against new Omicron variants and future surveillance needs to monitor if Omicron (or other emerging variants) evolve further to evade the humoral immunity.

This environment is particularly concerning for those who are immunosuppressed, individuals of older age, and those with comorbid conditions. For example, immunological changes after infection in aged individuals, along with the inability to mount a proper anti-viral response, can exacerbate disease severity in older patients. Surveillance is also needed in order to monitor for any increase in cases in the population, especially with the decrease in adherence to infection prevention policies, the increase in travel, and the waning immunity to initial vaccinations.

Surveillance data need to be correlated with clinical metrics on admissions and disease severity. Even though Omicron variant infections are associated with substantially
reduced risk of progression to severe clinical outcomes relative to time-matched Delta (B.1.617.2) variant infections, the concerning possibility is that future variants with large antigenic distance from currently circulating and vaccine strains will not necessarily display the lower intrinsic severity seen during Omicron infection. Also, reinfections need to be monitored as previous infection seems to alter the immune response to newer variants. For example, infection with the earlier B.1.1.7 (Alpha) variant may have resulted in less durable binding antibody against Omicron. The impact in post-acute (“long”) COVID-19 should also be monitored. Even though risk of long-COVID-19 appears to be lower with Omicron, the high number of cases could have extensive clinical and social ramifications.

Specific surveillance should monitor COVID-19 case rates among the more vulnerable groups, as well as severity indicators and the interconnection between different viral waves. Studies in animals suggest that co-infection with SARS-CoV-2 and the influenza virus is associated with altered disease severity and tissue tropism, as well as hematological changes, compared to infection with either virus alone.

As we continue to work on new antiviral agents, immunomodulatory treatments, and pan-β-coronavirus and intranasal vaccines, for the immediate and midterm future we should prepare for ongoing evolution of the virus with upcoming waves for the forthcoming winter months. The public, as well as those working in health care, are exhausted and our lives have been disrupted. However, the end of the pandemic and the return to normalcy is not a decision we can make. The summer should help control case numbers, but the fall and winter months are likely to bring another wave of cases. Complex decisions will need to consider the health of the community and the most vulnerable populations, the economy, and the long-term ramifications from post-acute (“long”) COVID-19. Improving COVID-19 vaccine uptake [including appropriate boosters] remains a priority. It is expected that additional booster doses will be needed at least for those at higher risk of severe disease. Ongoing adherence to vaccination protocols and early diagnosis and infection prevention measures provide what we need in order to fight the COVID-19 pandemic over the next few months.

Monitoring for SARS-CoV-2 lineages and sub-lineages is going to be important to actionable information so that we can project waves, prepare our health care facilities, and inform those who are more vulnerable from COVID-19. In this regard, for our state the monitoring is based on the collaboration between the Rhode Island Department of Health, hospitals, health centers, laboratories, and academic groups such as Dr. Kantor’s, and this collaboration provides important, actionable information that should continue to inform our decisions and protect our community. The extent of the increase in future cases will depend on vaccination coverage, previous SARS-CoV-2 pandemic waves, and our ability to leverage surveillance to actionable information and sensible infection-prevention policies.

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Celiac Artery Thrombosis and Splenic Infarctions: A Rare Complication in Unvaccinated COVID-19 Patient

OSAMA BATAYNEH, MD; HOUDA ABDELRAHMAN, MD; AHMAD TOUMAR, MD; RATIB MAHFOUZ, MD; JOSEPH PLAKYIL, MD

ABSTRACT
COVID-19 has been highly linked to a hypercoagulable state among affected patients. This case highlights that COVID-19 associated thrombotic incidents are not exclusive to venous circulation and include atypical arterial thrombosis. Here, we report a case of celiac artery thrombus in self-limited outpatient COVID-19 illness as a rare thrombotic complication of COVID-19 infection.

KEYWORDS: celiac artery thrombosis, splenic infarction, COVID-19 hypercoagulability, COVID-19 arterial thrombosis

CASE REPORT
A 76-year-old male nonsmoker with history of hypertension on amlodipine, unvaccinated for COVID-19 due to personal preference, presented to the emergency department with sharp and severe lower abdominal pain of sudden onset two days prior to arrival. The pain was constant, non-radiating, and not relieved by simple analgesics (such as acetaminophen and ibuprofen). He tested positive for COVID-19 two weeks prior to the onset of abdominal pain and reported mild symptoms, including fever (Tmax 102°F), productive cough, and shortness of breath. His lowest home oxygen saturation measurement was 90%. He remained stable and completed quarantine at home until resolution of these symptoms. He had no known family history of blood disorders, blood clots, or cancers.

On presentation, he was nonobese (BMI 24), afebrile and normotensive, saturating 93% on ambient air. He was not distressed. Lung exam demonstrated decreased air entry bilaterally with bibasilar crackles. His abdomen was soft and nondistended with left-sided tenderness to palpation.

Laboratory results are noted in Table 1. CT Abdomen/Pelvis with contrast revealed a partially occlusive thrombus in the distal celiac artery extending into common hepatic artery and multifocal ischemic splenic infarcts without perisplenic hematoma (Figure 1). Echocardiogram was negative for right heart strain or evidence of thrombus.

He was started on intravenous heparin for therapeutic anticoagulation. On hospital day 2, hematology was consulted due to the atypical site of thrombus formation and warfarin was initiated due to concern for underlying coagulopathy, including antiphospholipid syndrome. However, coagulopathy work-up returned negative except for only a positive phospholipid (Cardiolipin) Ab, IgM, making antiphospholipid syndrome less likely and not meeting the criteria for diagnosis. The patient was then transitioned to and discharged home on apixaban. Coagulopathy work-up results are noted in Table 2.

At the one-month follow-up in the hematologic clinic, cardiolipin IgM titer had notably trended down to 22.7 MPL.

Table 1. Laboratory Results at time of hospital admission

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>9x10^9/mcL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>15.2 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>41.7%</td>
</tr>
<tr>
<td>Platelet</td>
<td>272x10^3/mcL</td>
</tr>
<tr>
<td>Glucose</td>
<td>109</td>
</tr>
<tr>
<td>BUN</td>
<td>11 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.73 mg/dL</td>
</tr>
<tr>
<td>Sodium</td>
<td>131 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.6 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>97 mmol/L</td>
</tr>
<tr>
<td>Carbon Dioxide</td>
<td>23 mmol/L</td>
</tr>
</tbody>
</table>

Figure 1. Yellow arrow points toward the partially occlusive thrombus in the distal celiac artery extending into the common hepatic artery. Red arrow points toward the splenic infarctions.

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>8.5 mg/dL</td>
</tr>
<tr>
<td>Covid 19 PCR</td>
<td>Detected</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>1.0 mg/dL</td>
</tr>
<tr>
<td>AST</td>
<td>36 Intnl Unit/L</td>
</tr>
<tr>
<td>ALT</td>
<td>57 Intnl Unit/L</td>
</tr>
<tr>
<td>Total protein</td>
<td>7.1 g/dL</td>
</tr>
<tr>
<td>Lipase</td>
<td>31 Intnl Unit/L</td>
</tr>
<tr>
<td>Alkaline phosphate</td>
<td>127 Intnl Unit/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.1 g/dL</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>1.3 mmol/L</td>
</tr>
<tr>
<td>Troponin</td>
<td>&lt; 0.01 ng/mL x3</td>
</tr>
</tbody>
</table>
DIC biology in critical illness. 1 The endothelial damage trig-
mal coagulation resulting in acquired thrombophilia due to
hypoxemia in severe COVID-19 infection, and 3) abnor-
and venous systems, 2) increased blood viscosity secondary
with extensive endothelial dysfunction in both the arterial
for thromboembolism include 1) systemic inflammation
which COVID-19 infection intrinsically increases the risk
remains under investigation. The main mechanisms by
underlying mechanism behind this hypercoagulable state
provides a case report of a COVID-19 patient with thrombo-
edema (Tibial Thrombosis). The patient was a 61-year-old
male with a history of hypertension and severe COVID-
19 disease who presented with acute onset of left leg pain.

The decision regarding total duration of anticoagulation was
deferred to the next visit in the hematology clinic. A pre-
liminary plan was set for a total of 3-6 months based on the
everal coagulant factors (protein C, anti-thrombin III) that
normal coagulant factors (ie. platelet activating factor and
vasoconstricting, pro-thrombotic physiology that promotes
coagulation, increases expression of adhesion molecules
for leukocytes and platelets, and antagonizes anticoagulant
factors. 3, 7

The prevalence of venous thromboembolism in COVID-
19 patients reaches up to 30%. 2, 4 Overall, arterial thrombosis
is less common with an incidence rate of approximately 4% in
critically ill patients, the majority of whom are symptom-
atic with involvement of multiple arteries in approximately
18% of patients. 5, 9 The involvement of intra-abdominal vas-
cular arteries is even more rare. Celiac artery thrombosis and
splenic infarction are only reported in a few cases. 10, 11 Higher
frequency of thrombotic events seems to be present more in
severely ill patients, in particularly those admitted to inten-
sive care unit. 11 In mild COVID-19 cases, thrombotic events
were less common but reported even with absence of lung
parenchymal infiltrates, but with lower incidence rate than
severely ill patients. 13, 14 One explanation for the nondiscrim-
inatory thrombi formation in both arterial and venous cir-
culatory beds is acquired antiphospholipid antibodies seen
in COVID-19 and potentially leading to antiphospholipid
syndrome that leads to endothelial dysfunction.

Few cases of celiac artery thrombosis and splenic infarc-
tion were reported after administration of Oxford vaccine 15
and after ChAdOx1 nCoV-19 vaccine (Vaxzevria, Astra-
Zeneca). 16 However, thrombophilia work-up was negative
including APLs in these cases.

The clinical utility of aPLs levels in COVID-19 patients is
still not well established. Some studies suggest correlation
with disease severity and higher incidence of thrombotic
events, as patients with multiple APLs were found to have a
significantly higher incidence of cerebral infarction. 6, 7 How-
ever, despite the prevalence of APLs in COVID-19 patients,
studies suggest low utility for correlating their presence to
thrombotic events as they are non-specifically positive in
the absence of thrombotic disease and may later test nega-
tive as acute illness resolves. In a study of 31 ICU patients,
16 of 22 patients (72%) without thrombosis were aPL pos-
itive and 9 of 10 retested APLs-positive patients were neg-
ative on a second test after discharge. 17 This suggests that
aPL positivity in COVID-19 patients may not be the sentinel
feature predisposing to thrombotic events. In our case, the
positive Cardiolipin IgM down-trended at the one-month
follow-up, suggesting transient aPL antibody positivity as

Table 2. Coagulation Work-Up Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>13.8 sec</td>
</tr>
<tr>
<td>INR</td>
<td>1.2</td>
</tr>
<tr>
<td>PTT</td>
<td>37.2 sec</td>
</tr>
<tr>
<td>Protein S Activity</td>
<td>77.9%</td>
</tr>
<tr>
<td>Protein S Antigen free</td>
<td>73%</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>72%</td>
</tr>
<tr>
<td>Lupus anticoagulation INR</td>
<td>1.2</td>
</tr>
<tr>
<td>Activated Partial Thromboplast Time, P</td>
<td>35 sec</td>
</tr>
<tr>
<td>DRVVT screen ratio</td>
<td>1.08</td>
</tr>
<tr>
<td>Beta 2 Glycoprotein 1 Antibodies (IgM)</td>
<td>&lt;9.4 U/mL</td>
</tr>
<tr>
<td>Beta 2 Glycoprotein 1 Antibodies (IgG)</td>
<td>&lt;9.4 U/mL</td>
</tr>
<tr>
<td>Phospholipid (Cardiolipid) Ab, IgG</td>
<td>&lt;9.4 GPL unit</td>
</tr>
<tr>
<td>Phospholipid (Cardiolipid) Ab, IgM</td>
<td>74.0 MPL</td>
</tr>
<tr>
<td>Factor V Leiden (R506Q) mutation, B</td>
<td>Negative</td>
</tr>
<tr>
<td>Paroxysmal Nocturnal Hemoglobinuria</td>
<td>Negative</td>
</tr>
<tr>
<td>JAK2 V617F Mutation Detection, Bld</td>
<td>Negative</td>
</tr>
</tbody>
</table>

The degree of inflammatory markers’ elevation on initial
presentation is predictive of coagulation-associated com-
pliations among COVID-19 patients, with D-dimer above
2,500ng/mL, platelet count >450x10^9/mcL, CRP>100mg/L,
and ESR>40mm/h conferring high risk of thrombosis. 2 The
only available parameter from our patient’s case to compare
to these values is the platelet count, measured to be 272,000/
mcL on admission, two weeks after his initial infection.

Antiphospholipid antibodies (aPLs), anti-cardiolipin, anti-
β2-glycoprotein, and lupus anticoagulant, emerge after
vaccination or infection when self-antigens cross-react
with vaccine/viral antigens. Thrombotic events have been
reported in recipients of the adenoviral vector or mRNA-
based COVID-19 vaccines. 3 aPLs lend endothelial cells a
vasoconstricting, pro-thrombotic physiology that promotes
coagulation, increases expression of adhesion molecules
for leukocytes and platelets, and antagonizes anticoagulant
factors. 3, 7

DISCUSSION

Though the high incidence of thrombotic events in COVID-
19 patients is increasingly reported in the literature, the
underlying mechanism behind this hypercoagulable state
remains under investigation. The main mechanisms by
which COVID-19 infection intrinsically increases the risk
for thromboembolism include 1) systemic inflammation
with extensive endothelial dysfunction in both the arterial
and venous systems, 2) increased blood viscosity secondary
to hypoxemia in severe COVID-19 infection, and 3) abnor-
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feature predisposing to thrombotic events. In our case, the
positive Cardiolipin IgM down-trended at the one-month
follow-up, suggesting transient aPL antibody positivity as
most likely an acute phase reactant, rather than marker of true anti-phospholipid disease. Positivity of aPLs during COVID-19 infection is not uncommon and repeat testing at follow-ups is needed before relating these levels to anti-phospholipid disease.

Risk of thromboembolism for COVID-19 patients may persist even after initial presentation. Delayed onset of thrombosis has been reported and seen as late as 4–8 weeks after initial COVID-19 insult.14,18,21 Unlike venous thrombosis where risk decreases with time since COVID-19 infection, the risk of arterial thrombosis appears to remain stable after infection.22 The mechanism behind persistent delayed risk of thrombosis in COVID-19 is still not well understood, but presumably attributed to the body’s prolonged response to the virus rather than a primary process triggered by the virus itself.

A recent randomized controlled trial included 320 patients comparing post-discharge thromboprophylaxis with Rivaroxaban for patients at high risk on discharge [high risk defined as IMPROVE score ≥ 2 or 2–3 with a D-dimer >500 ng/mL] versus no extended thromboprophylaxis approach on discharge, revealed improved clinical outcomes with less risk of symptomatic or fatal thrombotic events within 35 days [3% risk of thrombotic events in Rivaroxaban group versus 9% in patients with no post-discharge thromboprophylaxis].23 The evidence for post-discharge thromboprophylaxis with antiplatelet therapy, on the other hand, remained lacking with mixed evidence and findings from the current studies.24-26

The development of APLs post-COVID-19 vaccination remains one of the theories behind thrombotic events seen after vaccines administration in otherwise healthy individuals. Despite the rare incidence of thrombotic events reported after COVID-19 vaccines, the morbidity and mortality associated with severe COVID-19 infection, including occurrence of thrombotic events, is such that the benefit of COVID-19 vaccination outweighs the risks in order to decrease severity of infection and associated complications.

CONCLUSION

This case of self-limited, non-severe COVID-19 infection with subsequent development of major arterial thrombosis alerts physicians to consider the extent of thrombotic events in patients with even mild COVID-19 infection. Furthermore, thrombotic events are not limited to venous thrombosis and include various sites within the arterial system. However, prophylactic anticoagulation to protect against thromboembolic events in the outpatient settings is still not formally recommended by major society guidelines in the absence of complete randomized control trials.

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CASE REPORT

Fatal Babesiosis in an Immunocompetent Patient
TYLER SELIG, MD; SULEMAN ILYAS, MD; CHRISTOPHER THEROUX, MD; JISOO LEE, MD

ABSTRACT

Human babesiosis is an emerging infectious disease with a progressively rising number of cases in the Northeast over the last few decades. We report a case of fatal babesiosis in a 48-year-old male without significant risk factors for a severe presentation. Clinicians should be aware that even in patients without the classic risk factors of asplenia, advanced age, and immunocompromised status for severe presentations of babesiosis, a deadly case can present. There is a need for further research regarding optimal treatment options for severe babesiosis considering the questionable efficacy of red blood cell exchange (RCE) transfusion in patients who do not improve on the current first-line antimicrobials.

KEYWORDS: babesia, babesiosis, red cell exchange, exchange transfusion, therapeutic apheresis

ABBREVIATION: RCE: red blood cell exchange

INTRODUCTION

Babesiosis is an intraerythrocytic infectious disease caused by the protozoa of the genus Babesia. The parasitic infection results in hemolysis of red blood cells (RBCs) with infection severity ranging from asymptomatic to mild-moderate characterized by a febrile hemolytic illness, and severe fulminant disease which can ultimately lead to death. It is typically transmitted by an arthropod vector, most commonly the *Ixodes scapularis* tick, but can also be transmitted uncommonly by blood transfusion, organ transplantation, and transplacentally. *Babesia microti* is the principal species causing the human disease in the United States, which is primarily seen in the northeastern and upper midwestern states.1

Severe human babesiosis is characterized by a parasitemia ≥4%, pronounced laboratory abnormalities, and complications that can include hemodynamic instability, encephalopathy, renal failure, disseminated intravascular coagulation (DIC), hepatic failure, acute respiratory distress syndrome (ARDS), myocardial infarction (MI), and death. The main risk factors for severe babesiosis are asplenia, an immunocompromised state including those with HIV/AIDS, malignancy, chronic kidney disease, on immunosuppressive therapy, and individuals age >50.2-4 Current first-line treatment entails a dual antimicrobial regimen of azithromycin and atovaquone. In the minority who do not respond to antimicrobials, RCE transfusion is weakly recommended by the Infectious Disease Society of America (IDSA) for severe babesiosis, often with parasitemia >10% or with mild/moderate parasitemia with severe hemolytic anemia (hemoglobin <10 g/dL), and/or severe renal, pulmonary, or hepatic impairment.5

Here, we present a case of severe babesiosis that proved fatal in an individual lacking significant risk factors, who did not receive an RCE.

CASE REPORT

A 48-year-old male with a past medical history of type 2 diabetes (recent hemoglobin A1c of 13.5%), obesity, and mild intermittent asthma presented to the emergency department (ED) in July with a two-week history of worsening fatigue, generalized weakness and intermittent subjective fevers. The patient endorsed headaches, vision changes, nausea, nonbloody emesis, nonbloody diarrhea, and dark urine. He denied chest pain, dyspnea, abdominal pain, arthralgias, myalgias, rashes or chills. Of note, the patient worked as a landscaper. He denied any known recent tick or animal exposures, any recent travel, or previous blood transfusions.

On arrival to the ED, the patient was tachycardic, afebrile, and normotensive. Physical exam was notable for an ill-appearing male who was fully oriented with jaundiced skin,
CASE REPORT

icteric sclera, clear lungs, soft abdomen without organomegaly, and no rashes. Blood parasite smear returned with small ring-form parasites [Figure 1] with 25% RBCs infected consistent with babesiosis [Figure 2]. Complete blood count revealed a hemoglobin of 11.1 g/dL, white blood cell count of 12.4 x10^9/L, and platelet count of 11x10^9/L. Basic metabolic panel was notable for creatinine of 5.96 mg/dL (patient’s baseline creatinine was 0.9–1.0 mg/dL), blood urea nitrogen of 108 mg/dL, and anion gap of 20. Hepatic function panel was remarkable for aspartate aminotransferase of 314 IU/L, alanine transaminase of 107 IU/L, alkaline phosphatase of 137 IU/L. Lactate was 5.8 mEq/L. Azithromycin and atovaquone were started for babesiosis treatment, as well as doxycycline to cover possible co-infection with Lyme disease and anaplasmosis [both later returned negative].

Following admission to the medical intensive care unit, the patient was tachypneic and hypoxic, requiring supplemental oxygen. Repeat parasite blood smear two hours following the initial smear returned with 17.5% of RBCs infected. The Transfusion Medicine service was then consulted for RCE consideration, who recommended deferring an exchange transfusion.

The next day, the patient required endotracheal intubation with mechanical ventilation after developing altered mental status and worsening tachypnea. A chest X-ray was obtained and revealed multifocal bilateral airspace opacities suggestive of pulmonary edema [Figure 3], consistent with a diagnosis of ARDS. Total bilirubin returned at 24.4 mg/dL, direct bilirubin at 19.6 mg/dL, and phosphorus at 10.2 mg/dL. The patient soon became hypotensive and required vasoressor support. Transfusion Medicine and Infectious Disease services recommended against RCE due to the patient’s hemodynamic instability and RCE’s limited efficacy. Shortly after, the patient was started on continuous venovenous hemofiltration due to his renal failure, worsening acidemia and hemodynamic instability.

The patient’s hemodynamics continued to deteriorate, requiring three vasopressors to maintain adequate perfusion pressures. This was further complicated by episodes of atrial fibrillation with rapid ventricular response, requiring synchronized cardioversion. During this time, the patient developed worsening hemolytic anemia, worsening acidemia and new acute liver failure, despite a reduction in parasitemia [10%]. At this point, the patient’s family requested that he be transitioned to comfort measures only and the patient passed soon after.

A few days following the patient’s death, babesia studies returned with PCR positive for *B. microti* and positive antibody findings (IgG 1:128 and IgM 1:160) confirming the babesiosis diagnosis.

DISCUSSION

Human babesiosis is an emerging infectious disease with a progressively rising number of cases in the Northeast, including Rhode Island, over the last few decades. The incubation period of *B. microti* following a tick bite is typically between one to four weeks. Tick-borne babesiosis in the United States is predominantly seen between May and September. Patients whose daily lives require frequent
exposure to high grass, such as our patient, should be educated on the importance of wearing long sleeves and using tick repellant for primary prevention of tick-borne illness.

Severe human babesiosis from *B. microti* is typically seen in an adult with at least one of the three main risk factors: asplenia, immunosuppressed state, or age >50. Notably, our patient did not have any of these risk factors. In regard to babesiosis, an immunosuppressed state has been previously defined as one due to an immunodeficiency disorder, malignancy with or without active chemotherapy, immunosuppressive therapy for solid-organ or stem-cell transplantation, or tumor necrosis factor-alpha inhibitors. While the patient did have a history of poorly controlled diabetes mellitus, diabetes has not previously been shown to be a significant risk factor for severe babesiosis. Chronic medical conditions have been shown to be a significant risk factor for transfusion-associated babesiosis but are not associated with the tick-associated disease.

Complications of severe babesiosis include hemodynamic instability, encephalopathy, renal failure, DIC, hepatic failure, ARDS, and MI. These complications most commonly occur in those with severe anemia (hemoglobin <10 g/dL) and in those with parasitemia ≥10%. Our patient developed acute renal failure, septic shock, acute liver failure and ARDS during his hospitalization.

Treatment is not recommended for asymptomatic *B. microti* infections. For both mild/moderate and severe cases, current first-line treatment entails a dual antimicrobial regimen of azithromycin and atovaquone. Severe babesiosis requires hospitalization. Prior to the IDSA guideline change in 2020, clindamycin plus quinine was recommended for severe infections. The new guidelines recommend azithromycin plus atovaquone for both mild/moderate and severe infections, with clindamycin plus quinine as an alternative regimen in cases of treatment failure. While treatment is effective for the vast majority of *B. microti* infections, there remains a dearth of safe, proven adjunctive treatments for severe presentations. Currently, RCE is weakly recommended (low-quality evidence) by the IDSA for severe babesiosis presenting with parasitemia >10% or with mild/moderate parasitemia with severe hemolytic anemia (hemoglobin <10 g/dL), and/or severe renal, pulmonary, or hepatic impairment. Although our patient presented with high-grade parasitemia with end-organ dysfunction, it was thought he presented too late in his illness for RCE to have an effect. Pigment nephropathy from hemolytic anemia was thought to be a large contributor to his severe renal failure, which would not be corrected with RCE. It should also be noted that our hospital system typically avoids RCEs. A previous paper that also studied hospitalized patients in Rhode Island had reported four deaths out of 19 patients who received an RCE as opposed to no deaths out of nine patients who received antimicrobials alone. Conversely, a recent retrospective analysis, at another large tertiary northeastern hospital that used parasitemia >10% to determine need for RCE, showed that parasitemia levels are closely associated with disease severity, and the authors concluded the use of parasitemia >10% seemed to be a reasonable indicator for RCE. Their review found that increasing parasitemia was associated with an increased severity of the most common complications of babesiosis – hematologic, pulmonary, renal, and hepatic impairment. Nineteen patients received RCE, 17 of whom met AFSA/IDSA clinical indicator criteria of parasitemia >10%. The mortality rates were 10.5% (2/19) and 1.4% (1/72) in the RCE and non-RCE groups, respectively. However, given that the patients treated with RCEs were generally more ill, no definitive conclusions could be made regarding which treatment was more efficacious. Based on the conflicting evidence of RCE in babesiosis compared to antimicrobials alone, it is possible that our patient would have expired even if one or multiple RCEs were performed.

**CONCLUSION**

In conclusion, we report a case of fatal babesiosis in a 48-year-old male without significant risk factors for a severe presentation. Despite recent treatment guideline changes, further research is needed for alternative treatment options who do not respond to the current first-line antimicrobials considering the lack of strong evidence supporting RCE. Given the rare nature of severe presentations, this could best be accomplished with a registry of patients with severe illness treated with and without RCE.

**References**


CASE REPORT


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Malignant Variant of Calcifying Epithelial Odontogenic Tumor with Neuroendocrine Differentiation

YIGIT BAYKARA, MD; YAMAC AKGUN, MD; LANCE VAN TRUONG, DO; MEL CORBETT, MB, BCh, BAO; SEAN M. HACKING, MB, BCh, BAO

ABSTRACT

A 60-year-old female presented with asymptomatic failing mandibular dental implants. Computed tomography (CT) showed a partially calcified, hypointense lesion within the soft tissues, measuring 1.3 x 0.8 x 1.0 cm along the buccal cortex. Incisional biopsy demonstrated a basaloïd type of tumor composed of sheets of cells with plump ovoid nuclei, distinct nucleoli, and scant eosinophilic cytoplasm. Mitoses were present, averaging about 2 per 10 high power fields with scattered individual apoptotic cells. Numerous laminated calcified bodies (Liesegang rings) were observed with confluence of these bodies to form larger foci of dystrophic mineralization. These features clearly established the malignant nature of this tumor. Immunohistochemically, the tumor was positive for synaptophysin, focally positivity for CAM 5.2 and had a Ki-67 proliferation index of approximately 25%. This is the first report of a tumor with features of a malignant variant of calcifying epithelial odontogenic tumor and neuroendocrine differentiation.

KEYWORDS: calcifying epithelial odontogenic tumor, neuroendocrine, malignant variant, dental implant

CLINICAL PRESENTATION

A 60-year-old female with a past medical history of hypertension, hyperlipidemia, and type II diabetes mellitus was found to have a gingival lesion during dental implant follow-up examination. Her family history was non-contributory. Intraoral examination revealed firm redundant gingival tissue around a failing implant of the right posterior mandible. A clinical diagnosis of granulation tissue was favored with a need to rule out malignancy. Cone-beam computed tomography (CT) of the mandible showed a hypointense lesion with punctate loci of mineralization within the soft tissues measuring 1.3 x 0.8 x 1.0 cm (Figure 1). There was deformity and scalloping of the adjacent buccal cortex. The lesion abutted the anterior border of the masseter muscle.

PATHOLOGY FEATURES

Biopsy revealed a tumor consisting of sheets of primitive basaloïd type cells with some cells demonstrating scant eosinophilic cytoplasm (Figure 2). Many of the tumor cells...
had multiple nucleoli. Individual cell necrosis and apoptotic bodies were noted. Mitoses were readily identified and number about 2/10 high power fields (HPF’s). Abundant psammomomatoid calcifications were noted throughout the tumor.

Tumor cells were positive for synaptophysin and demonstrated focal positivity for CAM 5.2. The Ki-67 proliferation index was approximately 25%. The following immunohistochemical stains were negative: CK7, CK20, AE1.3, S-100, SOX-10, chromogranin, CD56, PAX-8, CA125, CDX2, TTF-1, PR, ER, and WT-1. The tumor was diagnosed as a malignant epithelioid neoplasm, consistent with a high-grade neuroendocrine carcinoma.

Two months after initial biopsy, the patient underwent wide right composite mandibular resection under general anesthesia. The specimen consisted of a 5.1 x 3.3 x 2.0 cm composite resection of the right mandible (Figure 3).

Histological examination of the lesion showed cytologic features identical to those seen in the biopsy. A distinctive feature of this tumor (not seen in the biopsy) was the presence of numerous scattered laminated calcified bodies (Liesegang rings); these bodies confluence to form larger foci of dystrophic mineralization (Figure 4).

Small nests of the tumor cells were seen to infiltrate underlying cortical bone. In addition, the tumor produced a 0.2 cm intra-lymphatic metastasis immediately adjacent to an otherwise uninvolved lymph node (Figure 5). These features clearly established the malignant nature of this tumor.

Additional immunohistochemical examination performed on the resection specimen demonstrated focal positivity for GFAP. Congo red stain for amyloidosis was negative.

**DISCUSSION**

Calcifying epithelial odontogenic tumor (CEOT) is a rare benign odontogenic tumor first described by Jens Jørgen Pindborg in 1955. Since then, it is often eponymously referred to as “Pindborg tumor”. CEOT accounts for <1% of odontogenic tumors, and are most frequently observed in the mandible, with 80% being in the premolar or molar region.

CEOT is composed of nests of polyhedral neoplastic cells, with eosinophilic cytoplasm, nuclear pleomorphism and prominent nucleoli. A distinct feature of this tumor is the presence of stromal amyloid deposition with concentric calcific deposits called Liesegang ring.

A malignant form of this tumor is exceedingly rare, only seven cases have been reported in the literature (Table 1). These tumors exhibit nuclear pleomorphism, frequent mitotic figures and vascular invasion, as well as increased proliferative activity assessed by immunostaining for Ki-67.

Definitive resection of the lesion with tumor-free surgical margins and long-term follow-up is the recommended therapy.

Several features in this case suggest a diagnosis of malignant variant of CEOT. The pattern of calcification in the form of concentric ‘Liesegang rings’ closely resembles the calcifications seen in COET. The deep submucosal gingival location near cortical bone is consistent with derivation from odontogenic epithelium. Immunohistochemical positive staining for low molecular weight cytokeratin (CAM 5.2) and GFAP are consistent with the diagnosis. The absence of any amyloid-like protein deposition is unusual for a diagnosis of a usual CEOT, while the characteristic
polyhedral epithelial cells with distinct cellular outlines and intercellular bridges preclude a diagnosis of benign CEOT. Neuroendocrine carcinoma (NEC) constitutes a heterogeneous group of tumors with varying clinical manifestations, histologic appearances, degrees of differentiation, biologic behaviors, and prognoses. Thus far, only a small number of such tumors have been reported in the oral cavity. In this case, the morphologic and immunohistochemical findings were suspicious for NEC. The lesion consisted of small basaloid tumor cells compatible with a small cell neuroendocrine carcinoma. Individual necrotic cells were present. Immunohistochemistry in this case was positive for synaptophysin and the Ki-67 proliferation index was approximately 25%. The atypical location of the lesion, presence of psammomatoid calcifications and the absence of additional neuroendocrine immunohistochemical markers, mitigates against the diagnosis of a typical NEC.

An additional differential was that of a minor salivary gland tumor, although most minor salivary gland tumors occur in the palate. Salivary gland carcinomas displaying exclusively myoepithelial differentiation, known as myoepithelial carcinoma (MYEC), are rare. A malignant minor salivary gland tumor with a predominant myoepithelial cell component was considered in the differential diagnosis of this case. This was, in part, due to sheets of uniform cells with plump, ovoid nuclei and eosinophilic cytoplasm, which can be seen in a MYEC. This tumor was located on the alveolar ridge, a locus devoid of minor salivary gland, excluding a diagnosis of a salivary gland tumor. Additionally, the neoplastic cells failed to demonstrate positive staining for calponin and AE1/AE3 which are positive in 93% and 63% of MYECs respectively.

In summary, the findings in this case most likely represent a malignant COET with neuroendocrine differentiation. This is supported by the morphological findings of scattered laminated calcified bodies (COET) and positivity for synaptophysin.

### References

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ABSTRACT
Isolated angioedema of the small intestine is a rare adverse event in patients taking angiotensin-converting enzyme inhibitors. Here, we present a case of visceral angioedema in a 32-year-old woman who presented with left upper quadrant pain, nausea, vomiting, diarrhea, and characteristic radiographic signs of small bowel angioedema, six months after starting lisinopril. Her symptoms improved within 48 hours of withholding the offending agent and with supportive care. We discuss the epidemiology, pathophysiology, diagnosis, and management of angiotensin-converting enzyme inhibitor-induced angioedema.

KEYWORDS: ACE inhibitor, visceral angioedema, abdominal pain

INTRODUCTION
Angiotensin-converting enzyme inhibitors (ACEi) are commonly prescribed for the management of hypertension, kidney disease, and heart failure. Although this class of medications is typically well tolerated, they are associated with distinctive adverse effects, including dry cough, hyperkalemia, and angioedema. ACEi-induced angioedema commonly affects the lips, tongue, face, and upper airway, which poses an increased risk of life-threatening airway obstruction. However, isolated visceral angioedema rarely occurs, and a limited number of cases have been reported. These patients typically present with diffuse abdominal pain, diarrhea, vomiting, and ascites. Symptoms are often non-specific and may mimic an acute abdomen. ACEi-induced angioedema is currently under-recognized, which could lead to increased morbidity as well as unnecessary testing and interventions. We discuss the epidemiology, pathophysiology, diagnosis, and management of ACEi-induced intestinal angioedema.

CASE PRESENTATION
A 32-year-old woman with essential hypertension presented to the emergency department with five days of worsening left upper quadrant pain and subjective lip swelling. The patient reported nausea, vomiting, diarrhea, and poor oral intake. New medications included lisinopril within six months of presentation and an oral estrogen and progesterone contraceptive pill three days before the onset of her symptoms. Her vital signs were notable for tachycardia to 100 beats per minute and a blood pressure of 156/94 but were otherwise within normal limits (Table 1). She was uncomfortable

Table 1. Vital Signs on Presentation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°F)</td>
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</tr>
<tr>
<td>Blood Pressure (mmHg)</td>
<td>156/94</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>100</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>20</td>
</tr>
<tr>
<td>O2 Saturation (%)</td>
<td>99</td>
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Table 2. Clinical Laboratory Data on Admission

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<tr>
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<tr>
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<td>135–145</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
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<td>3.6–5.1</td>
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<td>Chloride (mmol/L)</td>
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<td>98–110</td>
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<td>Bicarbonate (mmol/L)</td>
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</tr>
<tr>
<td>Alanine Aminotransferase (IU/L)</td>
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<td>6–45</td>
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<tr>
<td>Alkaline Phosphatase (IU/L)</td>
<td>53</td>
<td>34–104</td>
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<tr>
<td>Total Bilirubin (mg/dL)</td>
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<tr>
<td>Complement factor 4 (mg/dL)</td>
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<td>15–57</td>
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<tr>
<td>C1 Esterase Inhibitor (mg/dL)</td>
<td>32</td>
<td>21–38</td>
</tr>
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Figure 1. Axial view of computed tomography of the abdomen and pelvis with contrast demonstrating loops of dilated, thickened small bowel, most prominent in the left upper quadrant (labeled with red arrows).

Figure 2. Coronal view of computed tomography of the abdomen and pelvis with contrast demonstrating loops of dilated, thickened small bowel (labeled with red arrows) as well as a small amount of free fluid in the paracolic gutters and pelvis.

appearing, with mild lower-lip edema, and an abdominal exam revealing left upper quadrant tenderness to palpation without rebound tenderness or guarding. She had no peripheral edema or rash on extremity and skin exam. Laboratory studies, including a complete metabolic panel, complete blood count with differential, and lipase, were within normal limits. C-reactive protein and erythrocyte sedimentation rate were mildly elevated. Complement factor 3 (C3), complement factor 4 (C4), and C1 esterase inhibitor were all within normal limits (Table 2).

Abdominal computed tomography with intravenous contrast showed dilated, thickened small bowel loops with a small amount of free fluid in the paracolic gutters and pelvis (Figures 1 & 2). There was no pneumatosis, enteric vessel pathology, or abscess. Given the patient’s history of lisinopril use, intestinal angioedema was determined to be the most likely culprit. Following discontinuation of lisinopril and the administration of intravenous corticosteroids with antihistamines, her symptoms improved. She returned twice to the emergency room in the subsequent two weeks after discharge with similar symptoms that resolved with supportive care.

DISCUSSION
Angioedema is a well established, albeit infrequent, complication of ACEi therapy with an estimated incidence between 0.1% and 0.7%. A vast majority of ACEi-induced angioedema cases present with non-pitting edema of the lips, tongue, face, upper airway, and larynx, requiring ventilatory support in up to 7% of cases. Rarely, patients develop predominantly visceral angioedema instead. These patients typically present with a diffuse abdominal pain, vomiting, diarrhea, and ascites. In one review of 34 cases of ACEi-induced angioedema, 100% of patients reported vomiting, 76% emesis and 47% diarrhea. Simultaneous orofacial involvement is uncommon, but has been reported. Up to 54% of reported cases of ACEi-induced intestinal angioedema present within three days of initiation of an ACEi, but patients have also been diagnosed after up to nine years of ACEi treatment. Because symptoms are non-specific and typically resolve within 24–48 hours, many patients have multiple, recurrent episodes before a diagnosis is made. While most cases of angioedema have been reported in patients taking lisinopril, other ACEi have been implicated, including enalapril, captopril, and benazepril. In a study of 111 patients with ACEi-induced angioedema, 46% were found to have recurrence of angioedema after discontinuing the ACEi, typically within the first month. Female sex has been reported as a risk factor for ACEi-induced angioedema broadly, and 85% of patients with ACEi-induced angioedema of the small bowel have been female.

Given its non-specific presentation, there is a broad differential diagnosis for patients presenting with intestinal...
angioedema relating to ACEi treatment. The acute onset of abdominal pain, nausea, vomiting, and diarrhea can mimic many causes of a surgical abdomen, including appendicitis, cholecystitis, small-bowel obstruction, and acute mesenteric ischemia. Symptoms can also resemble gastrointestinal infections, inflammatory bowel disease, vasculitis, and obstructing lymphomas. Many cases of intestinal angioedema have undergone surgical exploration or endoscopic biopsy prior to reaching the final diagnosis.11-13 Beyond ACEi, there are a number of other causes of angioedema including allergic angioedema, hereditary angioedema with C1 deficiency, hereditary angioedema with normal C1, acquired angioedema, and NSAIDs.14

Work-up includes a complete blood count, complete metabolic panel, stool antigen and infectious assays, and complement studies (C3, C4, and C1 esterase inhibitor) to rule out hereditary or acquired angioedema.4,8 Ultrasound and computed tomography (CT) are non-invasive, useful tools to investigate ACEi-induced angioedema, as they can demonstrate supportive findings and rule out other etiologies. Characteristic CT findings include dilated bowel loops, thickened mucosal folds, ascites, and mesenteric edema resembling a “stacked coin” or “doughnut.”11,15 Ascites has been reported in 59% of cases.8 The jejunal followed by the ileum and duodenum are most commonly affected,11 but involvement of the distal antrum and pylorus of the stomach have been reported as well.11 Proposed diagnostic criteria for ACEi-induced intestinal angioedema include the following: 1) Use of an ACEI (regardless of dose or duration), 2) Non-specific abdominal complaints with the presence of bowel edema, 3) Resolution of symptoms upon discontinuation of the ACEI, and 4) Absence of alternative diagnoses for abdominal symptoms.17

There is no standardized treatment of ACEI-induced intestinal angioedema. Once a diagnosis has been established, the most important intervention for the resolution of symptoms is cessation of the ACEI. Additional supportive care measures include intravenous fluids, bowel rest, pain management, and anti-emetics. Most cases resolve within 48 to 72 hours with conservative measures. Corticosteroids, antihistamines, and epinephrine are the mainstays of treatment in histamine-mediated angioedema and anaphylaxis, and, as in our patient, are often administered empirically in cases of ACEI-induced angioedema. Unfortunately, these interventions have shown minimal efficacy in bradykinin-driven cases of angioedema.14,18,19 Symptoms are typically isolated to the small bowel, although simultaneous small bowel and oral-facial involvement has been reported, and physicians should also monitor for signs of facial edema and impending airway collapse.5 Several agents used in the treatment of hereditary angioedema have been investigated for ACEI-induced angioedema, including tranexamic acid, icatibant [bradykinin B2 receptor antagonist], ecallantide [kallikrein inhibitor], berinert (C1 inhibitor concentrate), and fresh frozen plasma. Although these agents should theoretically be effective in the treatment in bradykinin-mediated angioedema, they have shown conflicting efficacy in ACEI-induced angioedema and remain under investigation. Currently, their use is mainly recommended in severe cases with worsening angioedema threatening the airway, particularly when the etiology has not been definitively established.14,19 Following an episode of ACEI-induced angioedema, patients should be switched to other agents. Of note, although previous studies had linked angiotensin II receptor blockers (ARBs) to an increased risk of angioedema, more recent large-scale meta-analyses and cohort studies have found these agents to be safe alternatives.20,21 Angioedema has also been reported with direct renin inhibitors [i.e., aliskiren].22

CONCLUSIONS
Given its rarity and non-specific symptoms, there are no studies characterizing the incidence of ACEI-induced intestinal angioedema and therefore it is likely underdiagnosed.24 A careful history and physical examination as well as laboratory studies and imaging can help establish this diagnosis while ruling out other similarly presenting etiologies. This condition typically resolves with supportive care within 48-72 hours of discontinuation of the offending ACEI; however, symptoms frequently recur. Increased awareness is essential to prevent repeated occurrences of gastrointestinal symptoms, rehospitalizations, and potentially unnecessary endoscopic or surgical interventions.

References


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Posterior Scleritis: A Unique Sequela of Cogan Syndrome

NICOLE LIFSON, MD; VIREN RANA, DO; LEWENA MAHER, MD; LORY SNADY-MCCOY, MD

KEYWORDS: Cogan syndrome, Cogan’s syndrome, posterior scleritis

CASE REPORT
A 42-year-old female with a history of Cogan syndrome, sensorineural hearing loss, and coronary vasculitis presented with three days of deep, boring, right-eye pain and photophobia. Visual acuity was 20/200 on the right and 20/20 on the left. Pupils were without an afferent pupillary defect. Extraocular movements were limited in all positions of gaze. Examination revealed scleral injection (Fig.1), pain with extraocular movements, and 3 mm of proptosis of the right eye. Dilated fundus exam showed chorioretinal folds (Fig. 2). Ophthalmic B-scan ultrasound of the right eye showed thickening of the sclera with fluid in tenon’s space (Fig. 3). Left eye appeared normal. A diagnosis of posterior scleritis was made and the patient was treated with intravenous steroids. She was transitioned to oral prednisone, infliximab, and methotrexate with resolution of her ocular symptoms and improvement of visual acuity to 20/40 of the right eye.

Figure 1. External photograph of the right eye with scleral injection and deep corkscrew vessels. Mid-peripheral cornea with interstitial corneal deposits without an associated epithelial defect.

Figure 2. Fundus photograph of the right eye demonstrates chorioretinal folds emanating from the optic nerve head (green arrow).

Figure 3. Ophthalmic B-scan ultrasound of the right eye shows thickening of the sclera (blue arrowheads) and fluid in tenon’s space (red arrowheads).
DISCUSSION

Cogan syndrome is a chronic inflammatory disease typically seen in young adults that often leads to sensorineural deafness and ocular inflammation by a presumed autoimmune etiology.\(^1\) Ocular manifestations may vary but typically involve interstitial keratitis.\(^1\)

In addition to vision and hearing deficits, systemic involvement is present in up to 80% of Cogan syndrome patients including coronary vasculitis, headache, fever, arthritis, and myalgias.\(^1\) Atypical ocular presentations of Cogan syndrome include episcleritis, choroiditis, uveitis, optic disc edema, angle closure glaucoma, and central vein occlusion.\(^1\) There are few reported cases of posterior scleritis related to Cogan syndrome.\(^2,3\) This rare finding presented in our patient with ocular pain, vision loss, proptosis, choroidal folds, and scleral thickening noted on B-scan.

CONCLUSION

Cogan syndrome should be considered in those with ocular inflammation and hearing loss. Diagnosis is often delayed given the lack of definitive testing and the fact that auditory symptoms and keratitis commonly do not present simultaneously, often occurring several months to years apart.\(^1\) Given the vision and life-threatening sequelae of Cogan syndrome, it is critical for providers to be aware of the various ocular and systemic manifestations.

References

Sustained Ankle Clonus in Multiple Sclerosis

WALEED TARIQ SIDDIQUI, MD, MPH

CASE PRESENTATION

A 35-year-old-man presented to the emergency department with acute onset of right lower extremity weakness. He had a history of multiple sclerosis (MS) and had been frequently admitted to our facility with MS exacerbations. On neurological exam, there was severe spasticity and hyperreflexia of the legs with hyperreflexia. Babinski signs were present bilaterally. Ankle dorsiflexion elicited marked, sustained clonus bilaterally (See Video). The findings of upper neuron lesion (spasticity, hypertonia, clonus) were not new and had been present for many years. There was diminished sensation to light touch on the right leg and decreased strength. Cranial nerve and cerebellar function were intact. Laboratory evaluation was unremarkable. A contrast enhanced MRI of the brain showed chronic encephalomalacia and volume loss in the deep white matter region of the left middle cerebral artery. These findings were unchanged compared to his prior imaging. We attributed the leg weakness secondary to an exacerbation of multiple sclerosis.

DISCUSSION

Clonus is a typical sign of spasticity. It manifests as involuntary, rhythmic contractions in response to a sudden sustained stretch. Unsustained clonus [few beats] may be a normal finding. However, sustained clonus is a pathological finding, indicating a lesion or injury to the upper motor neuron fibers of the lateral corticospinal tract.1,2 In multiple sclerosis, demyelination of upper motor neurons produces upper motor neuron signs which can include synkinesias, co-contraction, hyporeflexia of superficial reflexes, hyperreflexia of deep tendon reflexes, spasticity and clonus. An injury to the descending pyramidal tracts can cause loss of inhibitory activity resulting in disinhibition of spinal reflex circuits. This can lead to hyperreflexia in the form of rhythmic, involuntary contractions known as clonus. These contractions occur at frequencies between 5 and 7 Hz and are a response to abruptly applied stretch stimuli. Brisk dorsiflexion is applied to evoke ankle clonus,2,3 but clonus may be seen at the knees, wrist, or even the jaw. The patient was treated with a five-day course of high dose intravenous corticosteroids and physical therapy. On discharge, his leg weakness had improved significantly, however, the spasticity and clonus remained unchanged.

References


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Thrombosis in COVID 2022: An Updated Narrative Review of Current Literature and Inpatient Management

ARUN MUTHIAH, MD; SARAH OHNIGIAN, MD; JOHN L. REAGAN, MD; ANDREW HSU, MD

ABSTRACT

Early in the pandemic, it was recognized that infection with COVID-19 was associated with an increased incidence in both venous and arterial thrombotic events leading to poor patient outcomes. Given the rapid rise of the pandemic, anticoagulation strategies were initially based upon retrospective and observational data with few high-quality randomized control trials to help direct strategies regarding the use of thromboprophylaxis during hospitalization, empiric therapeutic anticoagulation, and extended-duration thromboprophylaxis after discharge. Over the past year, several randomized control trials have now been published evaluating these strategies. In this article, we hope to review the current literature surrounding the use of intermediate-dose thromboprophylaxis, empiric therapeutic anticoagulation, and the use of extended-duration thromboprophylaxis for patients hospitalized with COVID-19.

KEYWORDS: Coronavirus 2022, COVID-19, COVID-19 coagulopathy, thrombosis, anticoagulation

INTRODUCTION

Early literature regarding Coronavirus 2019 (COVID-19) described derangements in coagulation parameters which were associated with poorer patient outcomes. Furthermore, post-mortem examination of patients who died from COVID-19 demonstrated direct viral infection of the endothelial cells leading to diffuse endothelialitis, microvascular dysfunction, and widespread thrombotic microangiopathy, raising suspicion that these derangements were markers of thrombotic complications rather than bleeding risk. Clinically, patients hospitalized with COVID-19 were observed to have an increased incidence of venous thromboembolism (VTE) – pulmonary embolism (PE) and deep vein thrombosis (DVT) – and an increased incidence of arterial thromboembolism (ATE) – strokes (CVAs), myocardial infarctions, systemic arterial embolism, and acute limb ischemia.

The recognition that thrombosis was a common complication of patients hospitalized with COVID-19, which resulted in poorer patient outcomes, led to the rapid development of strategies to help mitigate thrombotic complications to improve patient outcomes. Tang et al demonstrated improvement in mortality in patients hospitalized with COVID-19 who received thromboprophylaxis with either low-molecular-weight heparin (LMWH) at 40-60mg daily or subcutaneous unfractionated heparin (UFH) at 10,000-15,000 IU daily. This early finding led to the global adoption of prophylactic anticoagulation in the management of patients hospitalized with COVID-19; however, this practice varied between countries and between institutions as some preferred higher intensity thromboprophylaxis, empiric therapeutic anticoagulation for certain populations, and/or extended-duration thromboprophylaxis after discharge. These practices have continuously evolved throughout the pandemic and were initially based upon retrospective and observational data; however, as the pandemic has continued in 2022, results from multiple randomized control trials (RCTs) have emerged to help shape these various practices. The aim of this review is to summarize the most current literature surrounding the management and prevention of thrombosis in patients hospitalized with COVID-19.

INTERMEDIATE-DOSE PROPHYLAXIS

During the start of the pandemic, the use of intermediate-dose thromboprophylaxis was based upon retrospective studies and meta-analyses examining its use in settings outside of COVID-19. A meta-analysis by Eck et al examined 70 randomized trials investigating intermediate-dose LMWH versus placebo and showed a small but statistically significant improvement in all-cause mortality; however, this benefit was at the cost of an increased rate of major bleeding. Rannucci et al conducted a prospective observational study of 16 ICU patients with COVID-19 and obtained lab work one week after increasing their thromboprophylaxis from standard-dose to intermediate-dose LMWH. Results showed time-related decreases in fibrinogen levels (p=0.001), D-dimer (p=0.02) and improved viscoelastic testing. Another study investigating coagulation profile retrospectively assessed 468 patients with severe COVID-19 who received intermediate-dose prophylaxis [LMWH 40mg twice daily or UFH 7500 IU three times daily] and showed stable or decreasing D-dimer levels in comparison to those who received standard-dose prophylaxis [p<0.001] and an improved 30-day mortality [p=0.045] without differences in bleeding [p=0.1].
There has been a scarcity of new RCTs specifically evaluating the merits of intermediate-dose prophylaxis within the past year. Previously, the INSPIRATION trial was a randomized study examining intermediate-dose LMWH (defined as 1mg/kg daily) versus standard-dose prophylaxis in 660 patients hospitalized with COVID-19 in the intensive care unit (ICU). Intermediate-dose was not associated with benefit – there was no significant difference in 30-day mortality [43.1% vs 40.9%; p=0.50]; development of VTEs [3.3% vs 3.5%; p=0.94]; ATEs in the form of CVAs [0.3% vs 0.4%; p=0.97]; ventilator-free days [30 vs 30 days; p=0.50]; or length of ICU stay [5 vs 6 days; p=0.14]. Furthermore, there was an increased rate of major bleeds (2.5% vs 1.4%) but did not meet the noninferiority criteria.14

Over the past year, INSPIRATION remains the only RCT directly examining the use of intermediate-dose prophylaxis. However, intermediate-dosed prophylaxis has been indirectly examined in other RCTs. HEP-COVID was a trial that evaluated high-risk patients receiving therapeutic LMWH versus intermediate-dose LMWH (30 mg twice daily, 40mg twice daily, or 0.5 mg/kg twice daily) versus standard-dose of LMWH/UFH. The study’s primary efficacy outcome (VTE, ATE, or any cause death) and rate of thromboembolism were reduced in non-ICU patient receiving therapeutic dose anticoagulation without differences in rates of major bleeding. The control group was comprised of 38.7% receiving intermediate-dose LMWH, but there was no data specifically comparing the outcomes of those who received intermediate-dose LMWH versus standard-dose LMWH/UFH.15

Both the REMAP-CAP for Critically Ill Patients and the ATTACC for the Non-critically Ill Patients trials were specifically investigating the utility of therapeutic-dose heparin, but also incorporated a portion of patients in their control arms who were received intermediate-dose prophylaxis (defined as LMWH 0.5mg/kg twice a day or 40mg twice a day, subcutaneous dalteparin 5000U once daily, UFH 7500 three times daily or 10000 twice daily, or tinzaparin 4500 unit twice daily). In the REMAP-CAP trial, 51.7% of the control group for critically ill patients versus 26.5% for non-critically ill patients in the ATTACC trial received intermediate-dose prophylaxis as per United Kingdom national practice guidelines and was posited as a reason that therapeutic-dose heparin did not show benefit in the critically ill population in the REMAP-CAP trial.16,17

Despite more than two years of the COVID-19 pandemic, there continues to be questions regarding the efficacy of intermediate-dose prophylaxis given the lack of prospective RCTs. The INSPIRATION trial demonstrated no improvement in outcomes in ICU patients with a numerical increase in major bleeding events. Given this continued paucity of data, societal guidelines (Table 1) from the American Society of Hematology (ASH) and American College of Chest Physicians (CHEST) continue to recommend against its routine use. Meanwhile, the International Society on Thrombosis and Haemostasis (ISTH) states that intermediate-dose could be considered in “high-risk” patients.18-20

### Table 1. Summary of Societal Recommendations for Thromboprophylaxis in COVID-1917-19

<table>
<thead>
<tr>
<th>American Society of Hematology (ASH)</th>
<th>International Society for Thrombosis and Haemostasis (ISTH)</th>
<th>American College of CHEST Physicians (ACCP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboprophylaxis (includes intermediate-dose and therapeutic anticoagulation)</td>
<td>1) Critically ill: standard prophylactic-doses over intermediate-intensity or therapeutic-intensity anticoagulation</td>
<td>Prophylactic-dose UFH or LMWH in acutely ill and/or critically ill COVID-19 patients after assessing bleeding risk. Intermediate-dose LMWH can be considered in high-risk patients. Obese patients defined by actual bodyweight or BMI should consider a 50% increase in the dose of thromboprophylaxis.</td>
</tr>
<tr>
<td></td>
<td>2) Non-critically ill: therapeutic-intensity over prophylactic-intensity anticoagulation</td>
<td>Prophylactic-dose anticoagulation in acutely ill and/or critically ill COVID-19 patients over intermediate or full treatment dosing.</td>
</tr>
<tr>
<td>Extended-Duration Thromboprophylaxis</td>
<td>No routine anticoagulation post-discharge</td>
<td>Should be considered in patients that meet high-risk criteria. Recommend use of LMWH or DOAC. Duration can be 14–30 days.</td>
</tr>
</tbody>
</table>

Red: updated recommendations; NR: no recommendation; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; “critically-ill” defined as patients suffering from a life-threatening condition who would typically be admitted to an intensive care unit (ICU).
was defined by the requirement of any ICU-level respiratory or cardiovascular support [i.e., high-flow nasal cannula, mechanical ventilation, extracorporeal life support (ECMO), vasopressors, or inotropes]. This trial enrolled 1098 patients who were administered therapeutic anticoagulation for 14 days or until recovery [defined as discharge or liberation of supplemental oxygen]. Ultimately, there was no difference between the experimental and control group in its primary endpoint of 21-day organ support-free days or survival to hospital discharge (40.1% vs 41.1%, respectively). Of note, the therapeutic arm was also associated with a higher percentage (3.8% vs 2.3%) of major bleeding events leading to the premature closure of the trial. Authors theorized that potential reasons for the lack of positive results included poor adherence to therapeutic anticoagulation in the treatment arm – only 77.6% of patients receiving therapeutic levels of anticoagulation. Furthermore, the authors noted that in the control arm, 51.7% patients receiving intermediate-dose anticoagulation, which may have comparatively limited the benefit of therapeutic anticoagulation. These results differed from an earlier randomized trial, HESACOVID, which was an open-label, phase II RCT examining the empiric use of therapeutic LMWH 1mg/kg twice daily versus standard prophylaxis [defined as subcutaneous UFH 5000 IU three times daily or LMWH 40 mg daily] in 20 mechanically ventilated COVID-19 patients and showed that therapeutic enoxaparin led to successful 28-day liberation from mechanical ventilation [p=0.031].

ATTACC for Non-critically Ill Patients enrolled 2219 patients with moderate COVID-19 [defined as requiring hospitalization without ICU-level respiratory or cardiovascular support] and were further stratified by D-dimer levels: “high” [defined as ≥ 2x upper limit of normal [ULN]] “low” [defined as < 2x ULN], or unknown. Like the REMAP-CAP trial, patients were administered therapeutic anticoagulation for 14 days or until recovery. However, unlike in the critically ill population, therapeutic anticoagulation showed an improvement in 21-day organ support-free days with a posterior probability of 98.6%. There was also greater survival until hospital discharge without organ support in the therapeutic arm. Patients with “high” D-dimer levels had a posterior probability for superiority of therapeutic anticoagulation of 97.3%, followed by 92.9% in the “low” cohort, and 97.3% unknown cohort. This suggested greater treatment benefit of therapeutic anticoagulation in non-ICU, COVID-19 patients with high D-dimer levels at time of enrollment. Of note, the average D-dimer level was 3.2x ULN and 1.1x ULN for the “high” and “low” subgroups, respectively. Unlike in REMAP-CAP, intermediate-dose anticoagulation only comprised 26.5% of the control arm.

Aside from the multiplatform ATTACC, REMAP-CAP, and ACTIV-4 trial, there were several other RCTs that examined the use of therapeutic anticoagulation in predominantly non-ICU, COVID-19 patients. The ACTION trial was an open-label trial evaluating 30 days of therapeutic anticoagulation [defined as rivaroxaban 20 mg daily for stable patients, or initial LMWH 1 mg/kg twice per day or IV UFH for unstable patients, followed by rivaroxaban to day 30] against standard-dose prophylaxis with LMWH/UFH. The trial enrolled 615 hospitalized patients with COVID-19 who had symptoms up to 14 days prior to randomization and an elevated D-dimer level at time of enrollment. Ninety-four percent of patients were considered non-critically ill and did not meet criteria for ICU admission. Furthermore, only 27% of patients had a D-dimer level > 3x ULN. The primary efficacy endpoints were time to death, duration of hospitalization, and duration of supplemental oxygen – none of which were different between the therapeutic and prophylactic arms [34.8% vs 41.3%, respectively; p=0.40]. However, in the therapeutic arm, there was a statistically significant increased rate of major or clinically relevant non-major bleeding [8% vs 2%, p=0.001].

The open-label RAPID trial investigated the role of therapeutic [defined as LMWH 1mg/kg twice daily or 1.5mg/kg daily, IV UFH, subcutaneous dalteparin 100U/kg twice daily or 200U/kg once daily, or tinzaparin 175U/kg once daily] versus standard-dose prophylaxis for 28 days or until discharge or death in hospitalized, non-ICU, COVID-19 patients. They were also required to either have both supplemental oxygen requirements and an elevated D-dimer level drawn within the first five days of admission, or just an isolated D-dimer level > 2x ULN. A total of 465 patients were enrolled to evaluate a primary composite outcome of death, invasive and non-invasive mechanical ventilation, or admission to ICU. There was no difference between the therapeutic arm and prophylactic in composite primary outcome (16.2% vs 21.9%), respectively; p=0.12). Furthermore, analysis of the secondary outcomes showed neither differences in composite of invasive/non-invasive mechanical ventilation [p=0.53] nor in ICU admission [p=0.34]. However, there was a decrease in all-cause death in the therapeutic group (1.8% vs 7.6%, p=0.006). Oddly, the most common cause of death was acute hypoxic respiratory failure and authors noted that there were no fatal thromboembolic events. Given these findings, it is unclear if the use of therapeutic anticoagulation contributed to the improvement in all-cause death.

HEP-COVID was a RCT that investigated therapeutic LMWH [1 mg/kg twice daily] versus standard and intermediate-dose prophylaxis [UFH up to 22500 IU subcutaneously divided into twice or thrice daily; LMWH 30 mg or 40 mg subcutaneously once or twice daily, or dalteparin, 2500 IU or 5000 IU once daily] in hospitalized ICU and non-ICU patients. Only 34.9% and 30.6% of the therapeutic and non-therapeutic arms, respectively, were ICU patients. In this trial, 253 patients were included if they required supplemental oxygen and either a D-dimer level > 4x ULN on admission or an ISTH sepsis-induced coagulopathy (SIC) score of at least 4. The majority of patients [249 [98.4%]] were enrolled using
the D-dimer criteria. The primary efficacy outcome of VTE, ATE, or death from any cause was decreased in the therapeutic group (p=0.03). This decrease appeared to be driven by thromboembolism (29.0% vs 10.9%, p<0.001) given there was no difference in death [p=0.28]. Authors noted that the treatment effect was largely observed within first 14 days of hospitalization. Furthermore, the benefit was seen in non-ICU patients [p=0.004], but not ICU patients [p=0.71]. There was no significant difference in major bleeding between the treatment arms, regardless of setting [p=0.12].

Overall, the above trials provide conflicting results regarding the empiric therapeutic anticoagulation. However, several themes do emerge from these multiple trials: 1) there appears to be benefit (21-day organ free support days [ATTACC] or decreased rates of thromboembolism [HEPROVIDE]) in hospitalized patients who do not require ICU level of care (i.e., high-flow nasal cannula, mechanical ventilation, ECMO, vasopressors, or inotropes); 2) the largest benefit occurs within the first 14 days of use of therapeutic anticoagulation; and 3) in the non-ICU setting, patients with elevated D-dimers garner the most benefit (though the exact degree of elevation remains unclear).

These themes and remaining questions are reflected in ASH’s updated guidelines as they continue to recommend standard-dose prophylaxis for critically ill COVID-19 patients (i.e., requiring ICU level of care), but have updated their guidelines for acutely ill COVID-19 patients (i.e., requiring hospitalization) to now recommending empiric therapeutic anticoagulation over prophylactic anticoagulation. Societal guidelines provided by CHEST and ISTH have not changed in lieu of these new prospective trials.16-20

## EXTENDED-DURATION PROPHYLAXIS

Given the increased incidence of thrombosis in COVID-19 patients while hospitalized, there was concern for thrombotic complications post-discharge leading to the use of extended-duration thromboprophylaxis. This strategy had been developed in non-surgical patients prior to the pandemic and led to the creation of the modified IMPROVE score (Table 2) which stratified patients into risk groups based upon several clinical factors. Patients deemed “high-risk” derived benefit from thromboprophylaxis after discharge.24,25

During the first year of the pandemic, data regarding the use of extended-duration thromboprophylaxis was limited to two retrospective studies which observed that patients hospitalized with COVID-19 were not at increased risk for development of VTE when compared to historical cohorts in hospitalized with COVID-19 were not at increased risk for thromboembolism when compared to historical cohorts in hospitalized COVID-19 patients (p=0.004), but not ICU patients (p=0.71). There was no significant difference in major bleeding between the treatment arms, regardless of setting (p=0.12).15

### Table 2. Modified IMPROVE Score24-25

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>VTE Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior VTE</td>
<td>3</td>
</tr>
<tr>
<td>Diagnosed thrombophilia†</td>
<td>2</td>
</tr>
<tr>
<td>Current lower limb paralysis or paresis**</td>
<td>2</td>
</tr>
<tr>
<td>History of cancer†</td>
<td>2</td>
</tr>
<tr>
<td>D-dimer &gt; 2 times upper limit of normal</td>
<td>2</td>
</tr>
<tr>
<td>ICU or coronary care unit stay</td>
<td>1</td>
</tr>
<tr>
<td>Complete immobilization† ≥ 1 day</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>1</td>
</tr>
</tbody>
</table>

High Risk Score > 4 corresponding with a nearly three-fold higher VTE risk at discharge and warrants consideration for extended-duration VTE prophylaxis;

*Congenital or acquired condition leading to increased risk of thrombosis; **Leg falls to bed by 5 seconds but has some effort against gravity (taken from National Institute of Health Stroke Scale); †Cancer present at any time in past five years; †Defined as confined to bed or chair with or without bathroom privileges

Of note, 54% and 50% of the treatment and control arms, respectively, were admitted to the ICU. Furthermore, all patients received only standard-dose thromboprophylaxis during their hospitalization. Patients were then randomized to receive rivaroxaban 10mg daily for 35 days or placebo. At 35 days, the use of rivaroxaban led to a decrease in thrombotic events [p=0.0293], mainly in the form of decreased pulmonary embolism when compared to the control arm. Of note, no major bleeding events occurred in either arm.28

These results suggest that patients hospitalized with COVID-19 with a modified IMPROVE score ≥ 4 or 2–3 with a D-dimer > 500 derive benefit with the use of extended-duration thromboprophylaxis.

CHEST states that extended-duration thromboprophylaxis should be considered for patients at low risk of bleeding. Meanwhile, ASH advises against its routine use for post-discharged patients but does state that patients can be assessed using the modified IMPROVE score to determine if extended-duration thromboprophylaxis is warranted. ISTH states that extended-duration VTE prophylaxis should be considered for patients who are low risk for bleeding who meet high-risk criteria based upon the modified IMPROVE score.18,20

### CONCLUSION

Over the past two years, the management and treatment of COVID-19 has continued to evolve and change at a dizzying pace – initially guided by limited retrospective data but now guided by high quality evidence garnered from multiple RCTs. The literature surrounding the practice of intermediate-intensity thromboprophylaxis continues to be mostly limited to retrospective data with one RCT [i.e., INSPIRATION] demonstrating no efficacy in ICU patients.14 The use of empiric therapeutic anticoagulation has received more clarity from multiple RCTs though with some conflicting results. Despite this, several themes have emerged: 1) there...
appears to be benefit in patients hospitalized due to COVID-19 who do not require ICU level of care; 2) the largest benefit appears to occur within the first 14 days; and 3) patients with elevated D-dimer levels garner the most benefit (though the exact degree of elevation remains unclear). As far as the use of extended-duration thromboprophylaxis, the MICHELLE trial demonstrated a decreased incidence of post-hospitalization thrombosis in patients hospitalized with COVID-19 after stratification with the modified IMPROVE score of ≥ 4 or score of ≥ 2–3 with a D-dimer level > 500).24

References

Disclosures
Conflicts of Interest: The authors declare no conflicts of interest.

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Describing IgA Myeloma:
An Immunophenotypic and Molecular Approach

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ABSTRACT
Plasma cell myeloma (PCM) is defined as a clonal disease of terminally differentiated plasma cells that secrete immunoglobulin. The biologic underpinnings of IgA-type multiple myeloma’s (IgAMM) aggressive nature, including its increased morbidity and mortality, have not been elucidated. We describe the clinical, phenotypic, and cytogenetic characteristics of IgA-MM. Flow-cytometry analysis was performed to phenotype clonal plasma cell populations, and interface with fluorescent in situ hybridization (iFISH) to exploit cytogenetics to determine risk stratification; 68.1% of cases were of intermediate or high risk. On flow cytometry, samples from our IgA-PCM cohort revealed less frequent CD56 expression when compared to samples with other PCM subtypes. Our study demonstrated lower frequency of CD56 expression (52.8%). We hypothesize that loss of CD56 may play a significant role in the aggressive behavior of IgA-PCM due to the loss of cell-to-cell adhesion resulting in a higher propensity for extramedullary presentation.

KEYWORDS: Multiple Myeloma, IgA Paraprotein, Cytogenetic, Flow Cytometry, CD56, Lytic Bone Lesion

INTRODUCTION
Plasma cell myeloma (PCM) is defined as clonal proliferation of immunoglobulin producing plasma cells within the bone marrow, comprising overall greater than 10% of marrow cellularity. PCM is typically associated with a detectable serum or urine paraprotein with or without secondary organ involvement. The incidence in the United States is over 15,000 annually with a steady increase since the 1990s.1,2 PCM accounts for approximately 20% of hematological cancer deaths and 2% of all cancer deaths.3,4

PCM has been described as an incurable disease, with an overall median survival under 5 years.5 In the United States, PCM affects males more frequently than females [3:2 male to female ratio]. Most affected patients are diagnosed with PCM between the ages of 40 and 84 years with a median age of 65. Although monoclonal gammopathy of undetermined significance (MGUS) can be precursor of PCM, there are no other causal associations.6 Family history of PCM is an established risk factor, as is African American descent. Factors such as lower socioeconomic status, alcohol usage, smoking, poor diet, obesity, and pesticide exposure are weakly associated with PCM.7,8

The etiology of the disease remains unknown. Common clinical and laboratory findings include hypercalcemia, renal insufficiency, anemia, and lytic bone lesions.9,10 These are colloquially described as CRAB symptoms. However, occasional patients may be asymptomatic. PCM presentation, response to treatment, and prognosis are related to chromosomal abnormalities but currently, molecular classifications are not applied as PCM is largely recognized as a single disease entity. In addition to variation in cytogenetic abnormalities, PCM can be categorized by protein production subtype. The most common M-protein in myeloma is IgG, accounting for approximately 55% of cases, followed by IgA which accounts for roughly 22%.11,12 Although less common than IgG myeloma, IgA multiple myeloma [IgA-MM] has a more aggressive clinical course and overall poorer prognosis.13,14

Treatment remains an area of debate as attempts to attain complete remission have been largely unsuccessful, while other approaches focusing on control and containment of disease have shown some success.15 Disease attributes such as cytogenetic alterations and heavy/light chain ratios, among other parameters, have not been fully investigated as predictive markers for IgA-MM.14,16-18 Presently no specific factor has been shown to account for the aggressive behavior of IgA-MM.19

Herein, we aim to elucidate the aggressive nature of IgA-MM through analysis of the clinical, morphologic, and phenotypic features in our study cohort.

MATERIALS AND METHODS
We retrospectively searched our pathology and clinical database [2011–2021] for patients with IgA-PCM following IRB approval. All available hematoxylin and eosin-stained (H&E) slides, immunohistochemical stains, and in situ hybridization preparations were reviewed for all cases. The diagnostic criteria used for the study were according to the revised 2016 World Health Organization (WHO) classification of hematolymphoid neoplasms.6,20,21

Immunohistochemical and in situ hybridization slides were prepared at our own institution on Leica BOND III...
CONTRIBUTION

automated instruments. Fluorescence in situ hybridization (FISH) studies were performed at our institution using encircled areas of foci of interest gathered from formalin fixed, paraffin-embedded tissue sections. FISH was performed using the protocols recommended by the manufacturers of the FISH probes used. A total of 200 interphase cells were analyzed for each sample with images captured and stored using Applied Imaging/Cytovision system. Final results were reported using the cut-offs established in the laboratory for each of the probes tested.

Flow cytometry studies were also performed at our institution. Bone marrow aspirates were collected in EDTA anticoagulant. Cells were incubated with specific monoclonal antibodies for 20 minutes at room temperature in the dark. Plasma cells were first identified by live gating using CD138, CD38, and CD45 and analyzed for additional antigen expression using CD138 in combination with the other antibodies, specifically CD56, CD117 and CD20. CD56 positivity was defined as expression on CD138+ plasma cells that was greater than or equal to 20% of the above the cutoff. Clonal plasma cells were stratified by fluorescent in situ hybridization. The high-risk group was classified as patients with samples harboring t(4;14)(p16;q32)FGFR3-IGH, t(14;16;)(q32;q23)IGH-MAF, 17p13 (TP53) deletion, or 1q21 gain. The intermediate-risk group was classified as patients whose samples showed 1q deletion, and the low-risk group was classified as patients whose samples showed t(11;14)|q13;q32|CCND1-IGH. All others were classified as normal.

Clonal plasma cells were stratified by fluorescent in situ hybridization. The high-risk group was classified as patients with samples harboring t(4;14)|p16;q32|FGFR3-IGH, t(14;16)|q32;q23|IGH-MAF, 17p13 (TP53) deletion, or 1q21 gain. The intermediate-risk group was classified as patients whose samples showed 1q deletion, and the low-risk group was classified as patients whose samples showed t(11;14)|q13;q32|CCND1-IGH. All others were classified as normal.

The clinical and standard laboratory variables collected for our study included age at diagnosis, gender, race, levels of hemoglobin (in g/dL), serum creatinine, and serum lactate dehydrogenase. Beta-2 microglobulin, M-spike extracted from SPEP, clonality from immunofixation, and immunoglobulin quantification by nephelometry, and free light chain assay were also evaluated. We further reviewed and collected any other data pertaining to cytogenetic and flow cytometry analysis when available. These findings were compared to those of non-IgA PCM, namely IgG-PCM. SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Fisher’s exact test was used in the flow cytometry statistical comparison between our data and the literature data.

RESULTS

Demographics of Patient Population

We identified 61 patients with IgA-MM treated at our institution. These included 34 men [56%] and 27 women [44%] [M:F ratio 1.26:1.00] with mean age of 64 years [range: 40–90 years]. Self-reported ethnicities included Hispanic patients [n=29, 48%], followed by White [n=22, 36%] and Black [n=10, 16%]. Demographics for all patients appear in Table 1.

Table 1. Demographics and Laboratory Findings

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age at Diagnosis</td>
<td>63.7 +/- -10.2 (Range: 40.0–90.0)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>n=34 (56%)</td>
</tr>
<tr>
<td>Female</td>
<td>n=27 (44%)</td>
</tr>
<tr>
<td>Ethnicity (self-identified)</td>
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<tr>
<td>Hispanic</td>
<td>n=29 (48%)</td>
</tr>
<tr>
<td>White</td>
<td>n=22 (36%)</td>
</tr>
<tr>
<td>Black</td>
<td>n=10 (16%)</td>
</tr>
<tr>
<td>Laboratory Findings</td>
<td></td>
</tr>
<tr>
<td>Lytic Bone Lesions</td>
<td>n=41 (67.2%)</td>
</tr>
<tr>
<td>Anemia (Hb &lt; 10 g/dL)</td>
<td>n=20 (32.8%)</td>
</tr>
<tr>
<td>Renal Involvement</td>
<td>n=18 (29.50%)</td>
</tr>
<tr>
<td>Serum β globulin &lt; 3.5 g/dL</td>
<td>n=14 (23.0%)</td>
</tr>
<tr>
<td>Solitary (extramedullary) Plasmacytoma</td>
<td>n=12 (19.8%)</td>
</tr>
<tr>
<td>Amyloid Deposits</td>
<td>n=5 (8.2%)</td>
</tr>
</tbody>
</table>

Hb = hemoglobin

Clinical and Laboratory Findings

Lytic bone lesions, indicative of osteolytic damage due to plasma cell burden in bone marrow, were the most characteristic finding, occurring in 67.2% of patients [n=41]. Anemia, defined as a hemoglobin under 10.0 g/dL in both males and females, was found in 33% of patients [n=20]. Renal involvement was found in 29% of patients [n=18]. Serum β globulin, a marker of inflammatory diseases, infection, or immune disorders, was low, defined as below 3.5 g/dL in 23% of patients. Less common findings included solitary, or extramedullary plasmacytoma present in 20% of patients [n=12] and amyloid deposits, found in 8% of patients [n=5]. Laboratory and clinical findings are detailed in Table 1.

Table 2. Serum Protein Electrophoresis (SPEP) Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypogammaglobulinemia</td>
<td>56 (92.0%)</td>
</tr>
<tr>
<td>Abnormal free light chain ratio</td>
<td>34 (55.7%)</td>
</tr>
<tr>
<td>M-spike on β1, β2 region or bridge between β and δ confirmed by IFE</td>
<td>49 (80.3%)</td>
</tr>
</tbody>
</table>

IFE = Immunofixation Blood Test
Flow Cytometry

Flow-cytometry data were available for 53 (n=53, 87%) patients in our cohort; CD56 was expressed in the neoplasms from 28 (53%). This is in contrast to similar studies, where flow-cytometry analysis detected higher percentage of CD56 expression (60–75%). CD20 was co-expressed in samples from only 13.2% of the patients. Expression of CD117 was observed in samples from 24.5% (n=13). Co-expression of CD56 and CD117 was identified in samples from 9 (17.0%) patients. Only one lesion showed co-expression of CD56, CD117 and CD20. Samples from 18 patients (34.0%) showed no aberrant expression of CD20, CD56 or CD117. CD20 expression without CD56 and CD117 was not observed. Flow-cytometry results are highlighted in Table 3.

Table 3. Summary of Flow Cytometry Results of IgA Multiple Myeloma

<table>
<thead>
<tr>
<th>High frequency protein expression identified with flow cytometry</th>
<th>IgA MM cases</th>
<th>MM cases</th>
<th>P-Value overall*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD56</td>
<td>28 (52.8%)</td>
<td>70-80%</td>
<td>0.0099</td>
</tr>
<tr>
<td>CD117</td>
<td>13 (24.5%)</td>
<td>30-32%</td>
<td>0.1959</td>
</tr>
<tr>
<td>CD56+CD117</td>
<td>9 (17.0%)</td>
<td>28%</td>
<td>0.0268</td>
</tr>
<tr>
<td>CD56/CD117 +CD20</td>
<td>7 (13.2%)</td>
<td>17-30%</td>
<td>0.0324</td>
</tr>
<tr>
<td>CD56+CD117+CD20</td>
<td>1 (1.9%)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

No aberrant expression of CD56, CD117, and CD20

| 18 (34.0%) |

MM = multiple myeloma; *Obtained from (22, 27, 31, 33)

Interphase Fluorescence In Situ Hybridization (iFISH) Analysis

Interphase fluorescence in situ hybridization (FISH) was performed on specimens from 47 patients and identified: n=5 (10.6%) chromosome 1q21 gain, n=4 (8.5%) 17p deletion, n=5 (10.5%) 4;14[p16;q32] translocation of FGFR3 and IGH, n=18 (38.3%) 13q deletion, and n= 5 (10.6%) 11[11;14] [q13;q32] translocation of CCND1 and IGH. Material from six patients (12.8%) had normal cytogenetics. Specimens from the remaining patients showed other abnormalities classified as low risk by the cytogenetic risk stratification schemes. According to the cytogenetic and molecular risk stratification schemes provided by International Myeloma Working Group IMWG, 22 (46.8%) patients were either classified as intermediate or high risk. A summary of interphase fluorescence in situ hybridization (iFISH) analysis is provided in Table 4.

Table 4. Summary of Interphase Fluorescence In Situ Hybridization (iFISH) Analysis

<table>
<thead>
<tr>
<th>Abnormalities identified with interphase fluorescence in situ hybridization analysis</th>
<th>IgA MM</th>
<th>MM overall*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q21 gain</td>
<td>5 (10.6%)</td>
<td>35-40%</td>
</tr>
<tr>
<td>(17p) deletion</td>
<td>4 (8.5%)</td>
<td>10%</td>
</tr>
<tr>
<td>t(4;14) translocation</td>
<td>5 (10.5%)</td>
<td>15%</td>
</tr>
<tr>
<td>del 13</td>
<td>18 (38.3%)</td>
<td>45-50%</td>
</tr>
<tr>
<td>t(11;14) translocation</td>
<td>5 (10.6%)</td>
<td>15%</td>
</tr>
<tr>
<td>Intermediate or high risk</td>
<td>22 (46.8%)</td>
<td>50-60%</td>
</tr>
<tr>
<td>Normal cytogenetics</td>
<td>10 (21.3%)</td>
<td>—</td>
</tr>
</tbody>
</table>

MM = multiple myeloma; IgA = Immunoglobulin A; *Obtained from (2, 3)

DISCUSSION

Plasma cell myeloma subtypes are identified using serum protein electrophoresis. However, the identification of the IgA subtype is usually complex. While over 90% of the IgG and IgM paraproteins migrate in the γ globulin region of the SPEP gel, allowing easy identification and quantification, IgA paraprotein frequently migrates in the β region, where other β region proteins such as transferrin, β-lipoprotein, and complement components can conceal them. As such, identification and quantification of IgA paraproteins has intrinsic challenges that further complicate monitoring treatment of patients with IgA-MM. For these individuals, the recommended approach by the IMWG is the use of nephelometry for IgA quantification. However, if the IgA concentration by nephelometry is within the reference range, the presence of an IgA paraprotein cannot be assessed and patients cannot be monitored. In this retrospective study of 61 patients in a routine clinical setting, we assessed patients with hypogammaglobulinemia with additional studies that included immunosubtraction and/or immunofixation. Using available cytogenetic risk stratification schemes, 68.1% of our studied patients were classified as either intermediate or high risk. The aggressive clinical behavior described in the literature for IgA-MM may be related to the high frequency of intermediate/high-risk genetic lesions such as 1q21 gain, del 17, and del13. However, our results were not significantly different from those found for other subtypes of myelomas. Consequently, cytogenetic aberrations alone may not explain the aggressive clinical course of IgA myeloma. On the other hand, our IgA-MM cases demonstrated less frequent CD56 expression when compared to that reported for the other subtypes of plasma cell myeloma (52.8% vs 70–80%). CD56 is a homophilic binding glycoprotein that plays a role in cell-to-cell adhesion. It is not expressed in non-neoplastic plasma cells; however, aberrant CD56 expression is a relatively common finding in neoplastic plasma cells, reported in up to 80% of cases. There is growing evidence supporting an association between absent CD56 expression and poor prognosis in multiple myeloma patients with an increase in extramedullary disease. Lack of CD56 expression in myeloma decreases the average patient lifespan by over six months.

As a typical median survival for patients with MM is under two years, this can be an extremely important prognostic indicator. Our study demonstrated a lower frequency of...
CD56 expression (52.8%) in IgA-MM, which, we hypothesize, may play a significant role in the aggressive clinical behavior due to the loss of cell-to-cell adhesion. No statistically significant (p<0.05) link was present between the CD56 expression or lack of expression and specific cytogenetics risk groups. Expression of CD117 and/or CD20 with or without CD56 expression did not significantly correlate with any other data in our limited cohort; however, it should be further investigated in a larger cohort study.

We also analyzed FISH results in samples with no aberrant expression of CD56, CD117, and CD20. Of these, FISH was not performed on samples from three patients. Twelve patients' specimens demonstrated low-risk FISH abnormalities. Myeloma cells from three patients harbored high-risk cytogenetic abnormalities. Thus, our study underscores the utility of multiparameter flow cytometry analysis as it appears to predict aggressive behavior of IgA plasma cell myeloma.

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Compliance with Ethical Standards
Methods were carried out in accordance with all regulations and guidelines.

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ABSTRACT

OBJECTIVES: To compare the characteristics of individual overdose decedents in Rhode Island, 2016–2020 to the neighborhoods where fatal overdoses occurred over the same time period.

METHODS: We conducted a retrospective analysis of fatal overdoses occurring between January 1, 2016 and June 30, 2020. Using individual- and neighborhood-level data, we conducted descriptive analyses to explore the characteristics of individuals and neighborhoods most affected by overdose.

RESULTS: Most overdose decedents during the study period were non-Hispanic White. Across increasingly more White and non-Hispanic neighborhoods, rates of fatal overdose per 100,000 person-years decreased. An opposite pattern was observed across quintiles of average neighborhood poverty.

CONCLUSIONS: Rates of fatal overdose were higher in less White, more Hispanic, and poorer neighborhoods, suggesting modest divergence between the characteristics of individuals and the neighborhoods most severely affected. These impacts may not be uniform across space and may accrue differentially to more disadvantaged and racially/ethnically diverse neighborhoods.

KEYWORDS: overdose, substance use, descriptive epidemiology, neighborhood characteristics, opioids

INTRODUCTION

Preventing fatal overdose has been a critical public health priority for many years, made even more urgent by the unprecedented spike in overdose deaths recorded in 2020. Since 1999, more than 800,000 people in the United States have died due to overdose, with provisional estimates pointing to 93,000 deaths in 2020 alone. The overdose crisis is a major public health event impacting every state in the country and has been compounded by the COVID-19 pandemic. For obvious reasons, overdose prevention efforts tend to prioritize individuals who use drugs. At the same time, the overdose crisis is also a population-level public health emergency, and its impacts on entire communities have been less extensively explored in the public health literature.

Here, we sought to identify the communities most heavily impacted by persistent overdose activity, and explore the divergence between the individuals and communities most affected by fatal overdose in Rhode Island using descriptive epidemiological methods. Rhode Island is a compelling case study for many reasons. Like much of the United States, Rhode Island communities are highly segregated by race/ethnicity. Mirroring national trends, overdose deaths in the state increased nearly 25% from 2019–2020. The majority of overdose decedents in the state are non-Hispanic White, but rates of fatal overdose are higher among Black Rhode Island residents than their White counterparts [53.9 vs. 36.0 per 100,000 person-years].

An ample “neighborhood effects” literature seeks to situate overdose in a community context by isolating and evaluating the effects of, e.g., neighborhood income or socioeconomic disadvantage, income inequality, policing intensity, residential racial segregation, and racial/ethnic composition on individual or neighborhood-level aggregated overdose risk. Fewer analyses have explored the potential divergence between the characteristics of individuals and the communities or neighborhoods most impacted by fatal overdose. Fatal overdoses tend to exhibit persistent spatial clustering, and persistently high rates of overdose at the community level may have variable and adverse effects on members of a neighborhood or a community, including those who are not directly affected by overdose. While we did not investigate the effects of high levels of fatal overdose on community or individual health, identifying the most heavily impacted neighborhoods could help prioritize interventions to mitigate the potential for such adverse effects.

The objective of this descriptive, exploratory analysis was to compare the characteristics of individual overdose decedents in Rhode Island, 2016–2020 (specifically, race/ethnicity and usual occupation) to the racial/ethnic and sociodemographic characteristics of the neighborhoods in which fatal overdoses occurred over the same time period. Such a comparison has the potential to shed light on the neighborhood-level correlates of high levels of overdose, to sketch a more complete picture of the total impact of the overdose crisis on Rhode Island residents and their communities, and ultimately as a first step towards informing population-level intervention strategies that take community impacts into account.
METHODS

We conducted a descriptive, retrospective analysis of fatal overdoses occurring between January 1, 2016 and June 30, 2020 in the state of Rhode Island. The units of analysis for this study were individual overdose decedents as well as census block groups [roughly corresponding to and hereafter referred to interchangeably as neighborhoods] within Rhode Island where fatal overdoses occurred during the study period. Census block groups are contiguous statistical divisions of census tracts containing 600–3000 people.

Data sources

Data were obtained from multiple sources as part of the Preventing Overdose Using Data and Information from the Environment (PROVIDENT) study. As all data analyzed as part of PROVIDENT are collected through ongoing public health surveillance activities and the use of protected health information involves no more than a minimal risk to the privacy of individuals, the institutional review board [IRB] of record approved a waiver of research participants’ authorization for use/disclosure of information about them for research purposes, in accordance with 45 CFR § 164.512(i) [2][iv].

We leveraged two components of the PROVIDENT data for this analysis. First, neighborhood of injury [i.e., neighborhood of fatal overdose], and residence, race/ethnicity, and usual occupation for each unintentional [any drug] overdose decedent were obtained from the State Unintentional Drug Overdose Reporting System [SUDORS]. SUDORS is a component of the Enhanced State Opioid Overdose Surveillance program of the Centers for Disease Control and Prevention [CDC] intended to improve timeliness of fatal overdose reporting. The neighborhoods of injury [i.e., where a given overdose occurred] and decedent residence both are included in SUDORS data; for the purposes of this analysis, we used injury location when available. For the 93 [6.60%] of records for which neighborhood of injury was missing, we used decedent residence. In Rhode Island between 01/01/16 and 07/31/2020, the majority of overdose deaths [70%] occurred in the private locations, likely the home. Race/ethnicity data, abstracted from death certificates, are reported in SUDORS. Usual occupation is abstracted from information on the death certificate and refers to the work a person usually does (not necessarily their occupation at time of death); we coded usual occupation into standard occupational classifications according to the Bureau of Labor Statistics Standard Occupational Classification System.

Second, neighborhood-level characteristics [percent White, not Hispanic/Latino, of civilians employed in construction, natural resources, and management (CNRM) occupations, and of families with income below the federal poverty limit [FPL]] were obtained from the American Community Survey (ACS) 5-year estimates [2012–2016 5-year estimates for 2016, 2013–2017 5-year estimates for 2017, and so on].

Finally, we used 2018 ACS 5-year population estimates to calculate fatal overdose rates by census block group. The 2018 estimates correspond roughly to the midpoint of the study period. We excluded 6 of the 815 census block groups in Rhode Island with zero population for a total of 809 census block groups in the analytic sample. In a secondary analysis, we also restricted the analytic sample to neighborhoods with more than 600 residents. Neighborhoods with fewer than 600 residents tend to correspond to special land use block groups [e.g., the block group containing Rhode Island T.F. Green International Airport] and may have disproportionately high rates of fatal overdose due to low population. We excluded 61 neighborhoods with ≤600 residents and repeated the above analyses on the resulting analytic sample of 748 census block groups.

STATISTICAL ANALYSIS

We first generated descriptive statistics for individual overdose decedents. We similarly generated descriptive statistics for neighborhoods. To do this, we averaged each ACS-derived neighborhood-level variable of interest across the study period, then examined the overall characteristics of each census block group included in the analysis.

Next, we calculated the fatal overdose rate per 100,000 person-years for each census block group over the study period and examined the median and interquartile range [IQR] of this fatal overdose rate across quintiles of each neighborhood-level variable. Calculation of the rate allowed for more direct comparison of fatal overdose burden across census block groups with different populations.

Finally, to examine possible divergence between the characteristics of individual overdose decedents and the neighborhoods where fatal overdoses take place in more detail, we identified a subset of individual overdose decedents with discordant locations of injury and residence – i.e., individuals for whom the neighborhood of injury (overdose) did not match the neighborhood of residence. We compared the neighborhood characteristics corresponding to the neighborhoods of injury and residence for those in this discordant subset whose state of residence was Rhode Island and also estimated the median distance as-the-crow-flies between centroids (geographic centers) of these discordant neighborhoods.

RESULTS

Among the 1408 overdose decedents during the study period, the average age was 43 [standard deviation = 12], with a range of 17 to 88. Comparing the age distribution of overdose decedents to the age distribution across neighborhoods in Rhode Island, nearly 75% of overdose decedents were 25–54 years old at time of death, while the median proportion of residents in this age group across Rhode Island neighborhoods...
is approximately 35% (Table 1). Nearly 75% of overdose decedents were male, compared to a median proportion of male residents across Rhode Island neighborhoods of 43%. The majority of overdose decedents were White (64%) and non-Hispanic (88%). Compared to neighborhood composition, overdose decedents were less White (the median proportion of White residents across all neighborhoods was 79%) and similarly non-Hispanic (the median proportion of non-Hispanic residents all neighborhoods was 84%). Notably, Black residents are overrepresented among overdose decedents relative to the median proportion of Black residents across neighborhoods (5.3% compared to just over 2%, respectively). Nearly 25% of overdose decedents during this period were employed in a CNRM occupation, though the median proportion of civilians employed in CNRM in Rhode Island neighborhoods is just over 5%. Finally, although SUDORS data do not contain individual-level income information, other research has reported a large proportion of overdose decedents (25% in 2019 and 38% in 2020) live below the federal poverty limit compared to a median of just under 5% across Rhode Island neighborhoods.

Examining all neighborhoods in the state, a marked gradient is evident in neighborhood-level rates of fatal overdose (per 100,000 person-years, see Figure 1). Across increasing quintiles of average neighborhood racial/ethnic composition (percent White and percent non-Hispanic), fatal overdose rates decreased – that is, neighborhoods with higher proportions of White and non-Hispanic residents experienced lower rates of fatal overdose during the study period. For

| Table 1. Characteristics of individual decedents and census block groups, Rhode Island, United States, 01/01/2016-06/30/2020. |
|---|---|---|
| Individual decedents (N = 1408) | Census block groups (N = 809) | Populated Census block groups (N = 748) |
| % | Median (IQR) % among census block groups |
| Age | | |
| < 18 | < 1 | 2.73 (3.10) | 2.87 (2.97) |
| 18–24 | 5.50 | 6.99 (5.34) | 7.15 (5.29) |
| 25–34 | 25.20 | 11.61 (8.00) | 11.58 (7.66) |
| 35–44 | 25.00 | 10.17 (5.44) | 10.28 (5.21) |
| 45–54 | 23.70 | 12.68 (5.61) | 12.68 (5.42) |
| ≥ 55 | 20.50 | 27.63 (14.56) | 27.18 (14.22) |
| Sex | | |
| Male | 73.10 | 42.99 (5.55) | 42.92 (5.50) |
| Female | 26.90 | 45.90 (5.55) | 45.97 (5.50) |
| Race | | |
| White | 64.10 | 78.62 (21.03) | 78.65 (20.69) |
| Black | 5.30 | 2.18 (8.46) | 2.12 (8.33) |
| Other | 18.30 | 7.21 (12.83) | 7.23 (12.70) |
| Missing | < 1 | — | — |
| Hispanic/Latino of any race | 11.90 | 4.85 (14.64) | 4.82 (14.00) |
| Ethnicity | | |
| Hispanic | 11.90 | 4.85 (14.64) | 4.82 (14.00) |
| Non-Hispanic | 88.07 | 84.04 (14.64) | 84.07 (14.00) |
| Standard occupational classification | | |
| CNRM | 24.50 | 5.38 (5.75) | 5.50 (5.68) |
| Poverty | | |
| Household income below FPL | — | 4.51 (12.87) | 4.64 (12.83) |

- Populated census block groups are those with ≥ 600 population.
- These columns present the median percentage of each relevant population characteristic, along with its IQR (interquartile range), across all census block groups included in the analysis. For example, the median percentage of male residents across all 809 census block groups is 42.99%. Abbreviations: CNRM: Construction, natural resources, and maintenance (includes construction and extraction, farming, fishing, and forestry and installation, maintenance, and repair occupations); FPL: federal poverty limit.
- Race and ethnicity are reported separately in this table. Hispanic/Latino ethnicity of any race is presented along with race variables to accord with the presentation and proportions available in the individual-level SUDORS (State Unintentional Drug Overdose Reporting System) data.

Figure 1. Rate of fatal overdose per 100,000 person-years across quintiles of neighborhood characteristics, a Rhode Island census block groups, 01/01/2016-06/30/2020 (N = 809).
example, the least White neighborhoods (first quintile) had a median [IQR] fatal overdose rate per 100,000 person-years of 41.5 (50.3), compared to 14.1 (35.9) in the most White neighborhoods (fifth quintile). Neighborhoods with the lowest proportions of households with incomes below the FPL had lower fatal overdose rates than neighborhoods with the highest proportions of such households: 17.2 (36.8) in the first quintile, compared to 44.3 (49.7) in the fifth quintile. The findings regarding proportion of civilians employed in CNRM occupations are more equivocal; from the first to the fifth quintiles, the rate of fatal overdose increases slightly, but the most marked change is from the third to the fifth quintile. Results after restricting the sample of census block groups to those populated census block groups with more than 600 residents had almost no effect on these estimates and general patterns (data not shown).

An analysis of the 218 overdose decedents with discordant locations of injury and residence [at the census block group level, across all 809 census block groups in Rhode Island] further revealed modest divergence between the characteristics of individuals and neighborhoods most affected by fatal overdose (Table 2). Compared to the neighborhoods of residence in this subset, the neighborhoods of injury (i.e., where the fatal overdose took place) were moderately less White and less non-Hispanic (78.6% vs. 71.5% and 83.7% vs. 78.3%, respectively). Interestingly, neighborhoods of injury had a markedly higher proportion of households with incomes below the FPL (8.2% vs. 5.5%). The median [IQR] distance between centroids of these discordant neighborhoods of residence and injury was 6868 (3069–15219) meters or approximately 4.3 (1.9–9.5) miles (data not shown).

**Table 2. Characteristics of neighborhoods of injury and neighborhoods of residence among the subset of 218 overdose decedents with discordant neighborhoods of residence and injury, Rhode Island, 01/01/2016–06/30/2020.**

<table>
<thead>
<tr>
<th></th>
<th>Neighborhood of injury N = 218</th>
<th>Neighborhood of residence N = 218</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent White</td>
<td>71.5 (33.4)</td>
<td>78.6 (25.4)</td>
</tr>
<tr>
<td>Percent non-Hispanic</td>
<td>78.3 (29.5)</td>
<td>83.7 (18.4)</td>
</tr>
<tr>
<td>Percent of civilians employed in CNRM</td>
<td>6.0 (7.4)</td>
<td>6.5 (4.9)</td>
</tr>
<tr>
<td>Percent of households with incomes &lt; FPL</td>
<td>8.1 (19.0)</td>
<td>5.5 (13.5)</td>
</tr>
</tbody>
</table>

*Abbreviations. IQR: interquartile range CNRM: construction, natural resources, and maintenance; FPL: federal poverty limit.

**DISCUSSION**

This analysis identified features of the neighborhoods most severely affected by persistently high rates of fatal overdose in Rhode Island between 2016 and 2020. Specifically, rates of fatal overdose were higher in less White, more Hispanic, and poorer neighborhoods in across the state. Our work also confirmed previous findings regarding characteristics of individual overdose decedents in Rhode Island. Most overdose decedents over the study period were non-Hispanic White, and CNRM occupations are the most heavily represented among overdose decedents.

Overall, this work points to modest divergence between the characteristics of individuals and neighborhoods most severely affected by overdose in Rhode Island. Most overdose decedents in Rhode Island are non-Hispanic White, but the neighborhoods in Rhode Island most affected by fatal overdose are not those with the highest proportions of non-Hispanic White people; in fact, our findings suggest the opposite. Neighborhoods with the most families in extreme poverty (measured as proportion of households with incomes below the FPL) also have the highest rates of fatal overdose. In many ways, this is an expected finding; poverty is heavily racialized in the US, and both poverty and racism are spatialized (e.g., racial residential segregation, concentrated disadvantage, and environmental injustice), with wide variation in neighborhood infrastructure.

Labor and occupation are also racialized in the United States. However, while there is a pronounced occupational gradient at the individual level, we did not observe large differences in fatal overdose rates by neighborhood occupational composition. There may be several reasons for this. First, White people are overrepresented in CNRM occupations relative to their share of the state’s population, such that neighborhood-level occupational composition may be an indirect and imperfect proxy for neighborhood-level racial composition. Second, there may be occupational dynamics at play that are not fully captured by looking simply at the neighborhood-level proportion of civilians employed in CNRM occupations. Finally, occupation may be less strongly spatially patterned than race/ethnicity or poverty, or may exhibit less pronounced spatial patterning statewide.

Broadly, we found that community-level indices of social disadvantage track higher rates of fatal overdose during the study period. The divergence between the characteristics of the individuals and the characteristics of the neighborhoods most affected by fatal overdose may point to additional community-level interventions to complement existing individually-focused outreach and overdose prevention programs. In addition to reaching people who use drugs directly, optimizing the allocation of harm reduction resources to communities most impacted by fatal overdose could have important public health benefits. Our findings also support the approach to community-level intervention spearheaded by the Rhode Island Department of Health [RIDOH] with
the creation of Health Equity Zones across the state. For example, through the Health Equity Zones, RIDOH provide technical assistance, surveillance information, and evaluation supports as local coalitions develop community-level overdose response plans.23

This study has several important limitations which should inform interpretation of the results. First, we conducted a descriptive cross-sectional [albeit multi-year] study. Therefore, we are limited in the conclusions we can draw. We were not attentive to causal structures and did not attempt to adjust for confounders or apply any statistical methodology to make causal inferences from the data. Second, we examined only fatal overdose as an endpoint. It is possible that examining nonfatal overdose (EMS runs for suspected overdose) would have yielded different patterns of community impact. Third, Rhode Island is a small, primarily urban state; our findings may not generalize beyond this specific context. Finally, and relatedly, Rhode Island has a high proportion of overdose decedents who overdose in their home neighborhood, and those individuals who overdose in a neighborhood different than their neighborhood of residence may be different from others in meaningful ways. While our analysis of the subset of individuals with discordant neighborhoods of residence and injury revealed that the neighborhoods of injury were moderately less White, more Hispanic, and poorer than the neighborhoods of residence, this finding should be interpreted cautiously as this subset is small and potentially unrepresentative of overdose decedents more generally. One recent study conducted in Cook County, Illinois, found evidence that overdose decedents tended to travel to more racially segregated and poorer neighborhoods to procure drugs than their neighborhood of residence.28 A similar phenomenon may explain our findings, though we caution that the observed discrepancies between locations of injury and residence were small, suggesting that this effect [if present] is less pronounced in Rhode Island. The median distance between centroids of these discordant neighborhoods of residence and location was approximately 4.3 miles; this may represent more or less distance depending on context [for example, 4.3 miles may represent adjacent neighborhoods in rural areas but non-adjacent neighborhoods in more dense and compact urban areas].

Our findings suggest that the community-level impacts of fatal overdose may not be uniform across space and in fact may accrue differentially to more disadvantaged and racially/ethnically diverse neighborhoods. Communities with high rates of overdose should have the resources they need to respond to overdoses in an evidence-based way, and additional research is needed to determine the direct and indirect neighborhood-level effects of persistently high overdose rates on community health outcomes. Specifically, future work should engage a diverse body of stakeholders [e.g., community members, policymakers, friends and family members affected by overdose] as well as existing data sources to elucidate these effects.

References


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ABSTRACT

OBJECTIVES: To determine the rates and characteristics of physicians with medical malpractice adverse outcomes in Rhode Island.

METHODS: A descriptive epidemiologic study of medical malpractice claims from 2008–2018 aggregated by the Board of Medical Licensure and Discipline of the Rhode Island Department of Health. To examine the demographic characteristics of physician malpractice cases we reviewed 10 years of data from Rhode Island medical malpractice lawsuits that were resolved, in whole or in part, via payment to the plaintiff.

RESULTS: Over this 10-year period, there were 460 such cases, 88% of which involved a male physician and 48% of which involved surgical category specialists. Few cases, 17.6% of payments, were over one million dollars, and the mean payment value across all cases was $517,104. The rate of paid claims was found to be stable over the period studied.

KEYWORDS: Medical malpractice

INTRODUCTION

The mission of the Rhode Island Board of Medical Licensure and Discipline (BMLD) is to protect the public through enforcement of standards for medical licensure and ongoing clinical competence.1 Malpractice insurance2 is required for every practicing physician in Rhode Island. Physicians must be prepared to produce proof of malpractice coverage upon request, and every insurer is required to send formal notice to the BMLD of all medical malpractice claims as well as the settlement of or judgement awarded on all such claims.3 Medical malpractice lawsuits are a relatively common occurrence in the United States.4 Forty-two percent of US physicians have been sued for malpractice during the course of their careers.5 To prevail on a claim of medical malpractice, the plaintiff must establish four legal elements: (1) the existence of a physician-patient relationship giving rise to a duty; (2) violation of the applicable standard of care; (3) injury or damage; and (4) a causal relationship between the violation of the standard of care and the alleged harm.4 Other factors, unrelated to the legal elements, have been shown to impact the risk to practitioners of malpractice claims, such as the quality of the patient-physician relationship and the practitioner’s specialty, with specialties which perform more procedures being higher risk, as well as the performance of specific procedures.6,7 A 2021 Medscape survey confirms that malpractice claims are more frequently made against surgical specialties, with plastic surgery, general surgery, orthopedics, urology, Ob/gyn making up the top five survey specialties reporting that they have been named in a malpractice suit.8 Malpractice lawsuits are an important legal recourse for patients harmed during medical treatments/diagnostics/interactions. The consequences of malpractice claims are often devastating to physicians, as they have immediate financial implications and can cause harm to their reputations and adversely impact their ability to practice.4 Beyond the professional harm, malpractice suits are independently associated with physicians reporting increased symptoms of burnout and depression, though it is unknown if this association is causal.9 The fear of malpractice suits can also lead to defensive medicine practices, which include the performance of unnecessary and costly diagnostic and non-diagnostic procedures, as well as the omission of indicated, but potentially high-risk non-diagnostic procedures. The total costs have been estimated to contribute billions of dollars per year to total healthcare expenditures in the US.10,11 Despite widespread understanding of the legal elements of a malpractice claim, there is a great deal of uncertainty among physicians regarding their own risks and potential outcomes of malpractice lawsuits.4 This case-control study reviews the characteristics of physicians with medical malpractice adverse outcomes in Rhode Island, to identify physicians with higher risk characteristics of adverse outcomes and, thereby, provide an opportunity to physicians to mitigate or eliminate perceived risks and reduce the likelihood of future lawsuits.

METHODS

Malpractice suits and settlements/awards were extracted from reports submitted to the BMLD by insurance carriers and the National Practitioner Data Bank (NPDB). This data set does not differentiate settlements from court-awarded damages, and only the final amounts of the settlements or court awarded damages were collected. This paper refers to these collectively as “settlements” or “awards.” Licensing information regarding physician age, gender, and specialty
was compiled from the Rhode Island Department of Health (RIDOH) physician licensing database for the period of January 1, 2008, to December 31, 2018. Individual specialties were categorized in two broad specialty groups: medical and surgical. The dollar amounts of settlements/awards were categorized into three ranges – low, medium, and high – based on the dollar amount of the award; low ($<200,000), medium ($>200,000, but <$1,000,000), and high ($>1,000,000). These ranges were previously set by the BMLD. Duplicate settlements/awards in the BMLD and NPDB data were merged, but each settlement for a single physician was treated as a separate item.

Comparison of specialty category, gender, and age of physicians with settlements/awards to the licensed physician population in Rhode Island was done using publicly available and searchable licensee information from (RIDOH).

To analyze the stability of the rate of malpractice adverse outcomes over time we used Statistical Process Control (SPC) charts. SPC charts are a tool used to detect nonrandom variation in rates measured over time. The SPC chart we used is an XmR chart. The analysis used in XmR charts make no assumption regarding the distribution of the data. Our analysis included standard XmR rules to detect any point outside of the control limit, which is set at three standard deviations from the mean. Additionally, we applied The Western Electric (WE) statistical process control chart rules, which also detect two out of three successive points beyond a 2-sigma limit (two-thirds of the distance between the center line and the control line), four out of five successive points beyond a 1-sigma limit, or eight or more successive points on one side of the center line. Using an XmR chart with this set of rules has been shown to perform well at identifying both statistically significant outliers as well as trends. Rates that fall outside these control limits and rules would suggest a special cause variation, meaning a change in the process of malpractice.

RESULTS

Table 1 summarizes our main results, and Table 2 details adverse outcomes by specialty. After removing duplicates, 460 settlements/awards were found between 2008 and 2018.

Table 1. Main Findings

The number of malpractice adverse outcomes by specialty group and gender in Rhode Island, as well as the number of actively licensed physicians in those categories.

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Licensed Physicians in Rhode Island</th>
<th>N Physicians with Malpractice</th>
<th>Mean Settlement/Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy &amp; Immunology</td>
<td>15</td>
<td>1</td>
<td>low</td>
</tr>
<tr>
<td>Anatomic &amp; Clinical Pathology</td>
<td>148</td>
<td>6</td>
<td>medium</td>
</tr>
<tr>
<td>Anatomic Pathology</td>
<td>54</td>
<td>4</td>
<td>medium</td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>168</td>
<td>11</td>
<td>medium</td>
</tr>
<tr>
<td>Cardiovascular Disease (Internal Med)</td>
<td>43</td>
<td>13</td>
<td>medium</td>
</tr>
<tr>
<td>Child &amp; Adolescent Psychiatry</td>
<td>26</td>
<td>1</td>
<td>medium</td>
</tr>
<tr>
<td>Colon &amp; Rectal Surgery</td>
<td>3</td>
<td>2</td>
<td>medium</td>
</tr>
<tr>
<td>Dermatology</td>
<td>87</td>
<td>5</td>
<td>low</td>
</tr>
<tr>
<td>Diagnostic Radiology</td>
<td>272</td>
<td>18</td>
<td>medium</td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>271</td>
<td>20</td>
<td>medium</td>
</tr>
<tr>
<td>Family Practice</td>
<td>393</td>
<td>28</td>
<td>medium</td>
</tr>
<tr>
<td>Gastroenterology (Internal Med)</td>
<td>31</td>
<td>7</td>
<td>medium</td>
</tr>
<tr>
<td>Hematology (IM:Path)</td>
<td>20</td>
<td>1</td>
<td>high</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>1064</td>
<td>66</td>
<td>medium</td>
</tr>
<tr>
<td>Maternal Fetal Medicine</td>
<td>1</td>
<td>1</td>
<td>high</td>
</tr>
<tr>
<td>Neurological Surgery</td>
<td>27</td>
<td>9</td>
<td>medium</td>
</tr>
<tr>
<td>Neurology</td>
<td>169</td>
<td>7</td>
<td>medium</td>
</tr>
<tr>
<td>Obstetrics &amp; Gynecology</td>
<td>197</td>
<td>51</td>
<td>medium</td>
</tr>
<tr>
<td>Occupational Medicine (Preventive Med)</td>
<td>10</td>
<td>1</td>
<td>low</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>98</td>
<td>8</td>
<td>medium</td>
</tr>
<tr>
<td>Orthopaedic Surgery</td>
<td>102</td>
<td>17</td>
<td>medium</td>
</tr>
<tr>
<td>Otolaryngology</td>
<td>35</td>
<td>6</td>
<td>high</td>
</tr>
<tr>
<td>Pediatric Emergency Medicine</td>
<td>14</td>
<td>1</td>
<td>medium</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>343</td>
<td>7</td>
<td>medium</td>
</tr>
<tr>
<td>Physical Medicine &amp; Rehabilitation</td>
<td>26</td>
<td>1</td>
<td>medium</td>
</tr>
<tr>
<td>Plastic Surgery</td>
<td>24</td>
<td>4</td>
<td>low</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>249</td>
<td>8</td>
<td>medium</td>
</tr>
<tr>
<td>Pulmonary Disease (Internal Med)</td>
<td>57</td>
<td>4</td>
<td>medium</td>
</tr>
<tr>
<td>Radiation Oncology</td>
<td>25</td>
<td>1</td>
<td>low</td>
</tr>
<tr>
<td>Radiology</td>
<td>45</td>
<td>5</td>
<td>medium</td>
</tr>
<tr>
<td>Surgery</td>
<td>156</td>
<td>43</td>
<td>medium</td>
</tr>
<tr>
<td>Thoracic Surgery</td>
<td>9</td>
<td>6</td>
<td>medium</td>
</tr>
<tr>
<td>Urology</td>
<td>37</td>
<td>12</td>
<td>medium</td>
</tr>
</tbody>
</table>

Table 2. Adverse outcomes by specialty

All specialties with malpractice settlements, the number of physicians licensed, and the number with malpractice settlements, as well as the mean settlement range of that specialty.
Actual verdicts were rare, at <5, because of RIDOH’s small numbers policy, the specific number is not reported. There were 402 (88%) adverse outcomes against male physicians; 221 (48%) adverse outcomes were against physicians in surgical specialties. The overall mean settlement/award amount was $517,104. The mean settlement/award amount against men was $519,599, compared to $499,814 against women. Against physicians in surgical specialties, the mean amount was $544,685, compared to $491,601 against physicians in medical specialties. It is not known in this study how many malpractice claims were made, only the final number of adverse outcomes (including both settlements and awards) are available.

Age was categorized by decile, and the mode age for adverse outcomes was the 5th decade of life for all physicians. Figure 1 shows gender distribution by age decile, which shows that the mode for female physicians was the 4th decade of life, and for male physicians was the 5th decade of life.

Figure 2 shows the settlement/award range by specialty category, and Figure 3 breaks down settlement/award range by gender.

Figure 4 shows a SPC X chart\(^4\) of the annual rate of malpractice adverse outcomes. There were no points or trends that fell outside the control limits, or rules, meaning there was no special cause variation, and that this is a process in statistical control. Future rates would be predicted to fall within the control limits, with a lower limit of 22.7 and an upper limit of 61 settlements/awards per year.

In 2017, there were a total of 6,103 actively licensed physicians in Rhode Island, 5,126 of whom self-reported their specialty to the BMLD. Of that number, 794 physicians were categorized in the surgical specialty category (15% of physicians who reported their specialty). Of the 6,103 licensed physicians, 3,883 were male (64%). Using a chi squared test of proportion, there were statistically significant greater proportions of surgeons and males with settlements/awards compared to the general licensee population with a p<0.0001.

**DISCUSSION**

It has been previously noted that medical malpractice claims in the United States are relatively common,\(^4\) with just roughly 4 in 10 US physicians having claims made against them for malpractice during the course of their careers.\(^5\) In

![Figure 1. Malpractice adverse outcomes by age decile and gender.](image1)

![Figure 2. The number of malpractice adverse outcomes by settlement range and specialty group.](image2)

![Figure 3. The number of malpractive adverse outcomes by settlement range and gender.](image3)

![Figure 4. The X chart from an XmR chart, which shows the rate of malpractice adverse outcomes per year. The statistical detection rules applied for this chart are enumerated in the methods section, and are intended to detect significant outliers as well as trends.](image4)
our Rhode Island data set, over a 10-year period, there were 460 malpractice cases with monetary settlements/awards, or approximately 46 per year. The rate of malpractice settlements/awards per licensed physician is approximately 0.9% of actively licensed physicians per year. This rate is comparable to national rates of malpractice from between 2009 to 2014, which was 0.89% of licensed physicians per year during that period [8.9 per 1000 physician-years].

We have previously published data on disciplinary actions in Rhode Island across a similar period [2012–2017]. We showed that the rate of disciplinary actions by the BMLD was 34.5 per year or 0.6% of licensed physicians per year. It should be noted that while there is some overlap between disciplinary cases and malpractice cases, the basis for establishing professional discipline is different from those for establishing malpractice, and external forces, such as cost of litigation and induced settlement of malpractice cases may influence the outcome of a malpractice claim. While similar behaviors might eventually justify both a successful malpractice claim and disciplinary action, it is perhaps surprising that disciplinary actions are less frequent than successful malpractice claims. The framework used by the BMLD for disciplinary actions is currently based on a Just Culture and was codified in 2019.

Annual surveys of physicians suggest that Rhode Island is not among the top 10 states for malpractice lawsuits against physicians. While our study does not compare damages to other states, during the period of our study, there were only 81 payments [17.6%] over one million dollars out of 460 settlements/awards. Settlements/awards over one million dollars were relatively uncommon among surgical specialties – 37 out of 221 [16.7%], among medical specialties, 44 out of 239 [18.4%], among men, 70 out of 402 [17.4%], and among women, 11 out of 58 [19.0%]. These differences were not found to be statistically significant.

A similar number of physicians in each specialty category had malpractice adverse outcomes against them, and the amounts of the settlement/award were also similar. Considering the smaller number of licensed surgeons, however, there was a statistically significant increased proportion of surgeons with settlements/awards against them. This is consistent with previously published data, as surgeons would be expected to perform more procedures, which places them at greater risk for malpractice claims relative to their medical colleagues.

Less intuitively, though consistent with previously published Rhode Island data, male physicians were more likely than their female colleagues to have medical malpractice settlements/awards against them. Our study shows that, across the period of the study, the number of settlements/awards is stable, that there is no special cause variation, and that this is a process that is in statistical control. That said, the annual rate in Figure 4 appears to show a trend towards increasing numbers of malpractice settlements/awards. Prior studies that have looked at a longer time frame have shown an increase in the number of malpractice settlements/awards over time, and it is possible that with a longer period of study the data in Rhode Island would confirm this.

LIMITATIONS
Our study does not directly compare rates of settlements/awards to other states, but Rhode Island's rate is consistent with nationally published data.

While all the BMLD's data relative to successful malpractice claims were treated equally, as only the number of settlements and judge or jury awarded amounts were available, the total number of malpractice claims is unknown. Not knowing how many claims were made, we cannot calculate whether gender or specialty category are more likely to be sued.

In previously published data, Rhode Island has been found to have a higher rate of settlements compared to court-awarded damages than other states. With respect to the data under study, here, because of rules pertaining to data privacy, it is only known that less than 1% of cases went to verdict, with the majority having been settled out of court.

While our study looks at specialty and demographic risk factors for malpractice, other studies have shown that there are elements to the therapeutic relationship and behavioral elements that may increase the risk of malpractice. Our study was not intended to look at those elements of the therapeutic relationship or their independence from the characteristics examined in our study.

For the purposes of our analysis, the number of licensed physicians is assumed to remain stable over the course of the period of analysis. However, based on annual reporting, over the decade, the number of licensed physicians increased by 4%.

CONCLUSION
Our study confirms that the rate of malpractice settlements/awards in Rhode Island is 0.9% of licensed physicians per year. Compared to the general population of licensed physicians, we found certain populations of physicians with higher incidence of settlements/awards who are, therefore, at higher risk for medical malpractice claims. Surgeons and male physicians were found to be more likely to have settlements/awards against them. Prior studies have suggested that performing certain procedures may place surgeons at risk for malpractice, but that does not explain why males are at higher risk. Further study would be helpful to under stand underlying behaviors or elements of the therapeutic relationship that may contribute to these risks.
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21. RI Board of Medical Licensure and Discipline–2019 Annual Report

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No conflicts of interest to report.

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Improving Public Health Surveillance for Neonatal Abstinence Syndrome in Rhode Island

KRISTEN ST. JOHN, MPH; WILLIAM ARIAS, MPH

Neonatal abstinence syndrome (NAS) is the diagnosis given to a newborn who displays signs and symptoms related to withdrawal from prenatal substance use, primarily from opioids. Although a recent trend suggests a decline (114.0 cases per 10,000 newborn hospitalizations in 2017 to 84.8 per 10,000 in 2021), NAS incidence in Rhode Island remains high after steadily increasing from 2010 (58.0 per 10,000 newborn hospitalizations) and continues to be a public health concern affecting newborns and impacting their families. NAS may lead to long-term issues affecting the child’s vision and hearing, as well as developmental problems. However, there exists varying consensus in interpreting NAS among U.S. jurisdictions, hospitals, and healthcare providers. To address this variation, there has been a recent push to standardize the definition of NAS to better understand its incidence.

The Council of State and Territorial Epidemiologists (CSTE) convened a workgroup to gather input from U.S. jurisdictions, state agencies, and subject matter experts, and summarized their findings to create recommendations for public health surveillance for NAS. The workgroup drafted a position statement that recommends a tiered approach to reporting NAS using standardized surveillance case definitions based on clinical case reporting and administrative data. Until 2020, the Rhode Island Department of Health’s (RIDOH) sole source for NAS data was hospital discharge data. NAS reporting was incorporated into the Rhode Island Birth Defects Program’s (RIBDP) reporting regulations in 2020, which allowed RIDOH to explore using an additional data source for obtaining cases. The purpose of this study is to examine the implications of using the HDD and the CSTE NAS case definitions in Rhode Island to understand NAS in the state.

METHODS

Hospital discharge data (HDD) for 2020 and 2021 were obtained for all newborn inpatient hospital admissions (n=20,597) in Rhode Island. A NAS confirmed case was defined as the P96.1 [10th Clinical Modification of the International Classification of Diseases] ICD-10 discharge code in a newborn hospitalization. There is no definition for a probable case using HDD.

As of 2020, all providers and healthcare facilities, including RI birthing hospitals, are required to report newborns diagnosed with an ICD-10 code of P96.1, P04.4, or P04.41 upon discharge from the birth hospital to the RIBDP on a regular basis (§ 216-RICR-10-10-3). The ICD-10 codes in RIBDP regulations were decided on by the NAS/Substance Exposed Newborn (SEN) Data Group, which includes a physician, epidemiologists, and subject matter experts, prior to the release of the CSTE NAS guidance. Per regulations, RIBDP staff can confirm the accuracy of reported diagnoses by conducting subsequent chart review.

CSTE recommends jurisdictions who rely on administrative reporting, which is the classification RIDOH falls under based on its reporting method, use its Tier 2 case definition. The CSTE Tier 2 case definition relies solely on ICD-10 codes, with a confirmed case being a P96.1 ICD-10 code and a probable is a P04.14, P04.17, or P04.1A diagnosis. The Tier 2 probable case ICD-10 codes were not included in the RIBDP reporting regulations, so staff cannot report Tier 2 probable cases counts.

Since the RIBDP has the authority to review medical records of reported cases to confirm accuracy of the diagnosis, it also considered using a hybrid approach: using administrative reporting to identify cases with confirmation via medical record review [aspects of Tier 1]. Using the cases reported through the RIBDP, staff classified newborns reported with the three ICD-10 codes in RIBDP regulations [P96.1, P04.4, P04.41] according to CSTE Tier 1 case definitions [Refer to Table 1 for CSTE Case Definitions]. A CSTE Tier 1 confirmed case had a positive toxicology test for opioids, benzodiazepines, or barbiturates plus any of the following: a diagnosis of NAS, a chief complaint of NAS, or three or more signs of neonatal withdrawal. A Tier 1 probable case had no or unknown newborn laboratory results, maternal history of opioid, benzodiazepine, or barbiturate use or confirmatory maternal laboratory evidence in the four weeks prior to delivery, and any of the following: NAS diagnosis, chief complaint mentioning NAS, or three or more signs of neonatal withdrawal. During medical record review for cases reported from hospitals in 2020 and 2021, information on toxicology testing (infant and maternal), maternal history of drug use, NAS symptoms and scoring, and discharge diagnoses was gathered to classify cases according to the CSTE Tier 1 case definition. Additionally, RIBDP staff verified all cases met the criteria of a diagnosis.
in a newborn under the age of 28 days where the etiology was not explained by another condition. Although Tier 1 classifies cases into confirmed, probable, and suspect, the RIBDP considered only Tier 1 confirmed and probable cases, as CSTE recommends using confirmed and probable cases for NAS reporting. All case information was collected in Microsoft Excel.

After cases were classified using the HDD and CSTE case definitions, the NAS/SEN Data Group reviewed the results of HDD and CSTE Tiers to determine the implications of using each case definition and the need for a Rhode Island-specific NAS case definition. Any cases classified by the CSTE Tier 1 case definitions as ‘not a case’ were discussed by the NAS/SEN Data Group to determine if the case definition should be modified based on findings. Based on these findings, a RIDOH-specific NAS case definition was created (Table 2), which includes newborns with a negative toxicology in its ‘probable’ case category. These newborns had been excluded from the CSTE Tier 1 case definition.

### RESULTS

When examining cases identified as ‘not a case’ for CSTE Tier 1, there were 18 cases from 2020 and 2021 classified as ‘not a case’ due to a negative newborn toxicology test, despite these infants meeting the remainder of the CSTE criteria for a probable case. These infants were all included in the probable case counts for the RIDOH-specific NAS case definition.

The findings comparing various case definitions used are shown in Table 3. For HDD, there were 82 cases reported in 2020 and 88 in 2021. For the CSTE and RIDOH-specific case definitions, 83 possible NAS cases were reported to and reviewed by the RIBDP epidemiologist in 2020 and 87 in 2021. Case counts were highest when using HDD and lowest when using the CSTE Tier 1 approach. Comparing the CSTE case definitions, Tier 1 counts were lower than Tier 2. HDD counts were higher than those of the CSTE Tier 2 despite using similar sources [hospital administrative reporting].

### Table 1. Council of State and Territorial Epidemiologists (CSTE) Neonatal Abstinence Syndrome (NAS) Case Definition

<table>
<thead>
<tr>
<th>CSTE Tier 1 Classification: A hospitalized newborn less than 28 days of age with symptoms not explained by another diagnosis meeting the following criteria:</th>
<th>Neonatal Exposure Evidence</th>
<th>Maternal substance use (4 weeks prior to delivery)</th>
<th>Neonatal Symptoms/ Clinical Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
<td>Positive lab for opioid, benzodiazepine, or barbiturate</td>
<td>n/a</td>
<td>3 or more withdrawal symptoms or a diagnosis/ chief complaint mentioning NAS</td>
</tr>
<tr>
<td>Probable</td>
<td>No or unknown lab results (negative results are ‘not a case’)</td>
<td>Positive maternal lab for or chronic maternal history of opioid, benzodiazepine, or barbiturate use</td>
<td>3 or more withdrawal symptoms or a diagnosis/ chief complaint mentioning NAS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CSTE Tier 2 Classification</th>
<th>ICD-10 Diagnosis Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
<td>P96.1</td>
</tr>
<tr>
<td>Probable</td>
<td>P04.14, P04.17, or P04.1A*</td>
</tr>
</tbody>
</table>

* These codes were not added to RIBDP regulations and cannot be used to report NAS probable cases.

### Table 2. Rhode Island Department of Health (RIDOH)'s Neonatal Abstinence Syndrome (NAS) Case Definition

<table>
<thead>
<tr>
<th>RIDOH NAS Case Definition: A hospitalized newborn less than 28 days of age with symptoms not explained by another diagnosis meeting the following criteria:</th>
<th>Neonatal Exposure Evidence</th>
<th>Maternal substance use (4 weeks prior to delivery)</th>
<th>Neonatal Symptoms/ Clinical Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
<td>Positive lab result for opioid, benzodiazepine, or barbiturate</td>
<td>n/a</td>
<td>3 or more withdrawal symptoms or a diagnosis/ chief complaint mentioning NAS</td>
</tr>
<tr>
<td>Probable</td>
<td>Negative, no, or unknown lab results</td>
<td>Positive maternal lab for or chronic maternal history of opioid, benzodiazepine, or barbiturate use</td>
<td>3 or more withdrawal symptoms or a diagnosis/ chief complaint mentioning NAS</td>
</tr>
</tbody>
</table>

### Table 3. Neonatal Abstinence Syndrome Case Counts by Case Type and Definition, Rhode Island, 2020 and 2021

<table>
<thead>
<tr>
<th>Case Definition</th>
<th>2020</th>
<th>2021</th>
<th>2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Discharge Data</td>
<td>82</td>
<td>n/a</td>
<td>82</td>
<td>88</td>
</tr>
<tr>
<td>CSTE Tier 1 Hybrid Approach</td>
<td>52</td>
<td>10</td>
<td>62</td>
<td>56</td>
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<tr>
<td>CSTE Tier 2</td>
<td>73</td>
<td>n/a</td>
<td>73</td>
<td>74</td>
</tr>
<tr>
<td>RIDOH Case Definition</td>
<td>52</td>
<td>18</td>
<td>70</td>
<td>56</td>
</tr>
</tbody>
</table>

* These codes were not added to RIBDP regulations and cannot be used to report NAS probable cases.
DISCUSSION

Before 2020, the only data source available to RIDOH for reporting NAS cases was HDD. This is the first time Rhode Island has compared HDD to other case definitions. Although both case definitions use hospital administrative reporting to define cases, HDD counts were higher than CSTE Tier 2 counts. This may be because RIDOH cannot deduplicate HDD cases due to the lack of identifying information other than medical record number and date of birth. Newborns experiencing NAS are often moved from one hospital to another to receive higher level care, which may result in a newborn counted twice if both hospitals report the case through HDD. These issues do not appear to exist in the RIBDP’s NAS reporting.

Similar to findings in other states, using ICD-10 diagnosis codes alone, as is done in HDD and the CSTE Tier 2 case definitions, may overestimate the true burden of NAS in Rhode Island. After reviewing medical records, some ‘confirmed’ cases per CSTE Tier 2 administrative reporting were classified as ‘not a case’ in Tier 1 when considering the additional information gathered from toxicology testing, history of maternal drug use, and symptomology. Given the caveats of the CSTE Tier 1 case definition, using only administrative reporting [Tier 2 definition and HDD] appears to be overestimating the burden of NAS in Rhode Island. Reliance on hospital ICD-10 coding for identification of cases also may under- or over-ascertain cases due to errors in coding procedures.

Moving forward, RIDOH will use the CSTE recommended approach of reporting confirmed and probable cases, along with its modified case definition. The only difference between these two case definitions involved RIDOH counting newborns with negative toxicology results [CSTE Tier 1 only includes those with no or unknown results]. An additional 18 cases were included as ‘probable’ using the RIDOH case definition. Excluding newborns with a negative toxicology test, as recommended by CSTE, would likely underestimate NAS incidence in the state. Newborn toxicology testing did not always confirm exposure to drugs in these infants, which is dependent on factors including the type of sample collected [urine or meconium], as urine samples have a higher rate of false-negative results due to a short timeframe for drug detection [few days before delivery] and issues collecting enough sample for testing.

Using the RIDOH-specific approach to case classification will allow staff to gather additional information on cases not obtained from strictly using HDD or the CSTE Tier 2 case definitions [ICD-10 codes alone], such as substances found in both toxicology screening and maternal history, while acknowledging the limitations of using the CSTE Tier 1 case definition in relying on newborn toxicology testing. Despite being more time intensive, this additional information will further define the NAS problem in the state, including type of drug exposure [illicit or medication-assisted treatment (MAT)]. As more pregnant women with substance use disorder receive MAT, NAS rates may appear to remain stable or increase, but the percentage of infants exposed to illicit drugs would be expected to decrease over time. This information would not be obtained if RIDOH used only an administrative reporting approach. To better understand NAS in Rhode Island, future analyses will focus on substances of exposure in newborn and maternal toxicology results, along with maternal history, all of which is gathered through medical record reviews. As more CSTE guidance becomes available, RIDOH will consider updating its NAS case definition.

RIDOH will also explore linking NAS cases to other data sources that may help increase the understanding of NAS in the state. Annually, NAS cases will be linked to RIDOH’s Center for Vital Records’ birth file to provide insight into newborn and maternal demographics in the NAS-affected population. Additionally, as a quality check to verify the accuracy and completeness of medical records, RIDOH will also link NAS data to the Prescription Drug Monitoring Program [PDMP] database to verify accuracy of reported prescription drugs and determine any unreported drug exposures. Moving forward, RIDOH will use its case definition to better define the NAS problem in Rhode Island to assist in targeting prevention and outreach efforts.

References
1. Hospital discharge data, Rhode Island Department of Health.

Authors
Kristen St. John, MPH, is a Senior Public Health Epidemiologist in the Center for Health Data and Analysis [CHDA], Rhode Island Department of Health (RIDOH).

William Arias, MPH, is the Maternal and Child Health Epidemiologist in CHDA, RIDOH.
Rhode Island Monthly Vital Statistics Report
Provisional Occurrence Data from the Division of Vital Records

<table>
<thead>
<tr>
<th>VITAL EVENTS</th>
<th>REPORTING PERIOD</th>
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<tr>
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<td>DECEMBER 2021</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>Number</td>
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<tr>
<td>Live Births</td>
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<td>Divorces</td>
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* Rates per 1,000 estimated population
# Rates per 1,000 live births

<table>
<thead>
<tr>
<th>Underlying Cause of Death Category</th>
<th>REPORTING PERIOD</th>
<th>12 MONTHS ENDING WITH JUNE 2021</th>
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<td>JUNE 2021</td>
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<tr>
<td></td>
<td>Number (a)</td>
<td>Number (a)</td>
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<tr>
<td>Diseases of the Heart</td>
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<td>Malignant Neoplasms</td>
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<tr>
<td>Cerebrovascular Disease</td>
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<tr>
<td>Injuries (Accident/Suicide/Homicide)</td>
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<td>1,019</td>
</tr>
<tr>
<td>COPD</td>
<td>29</td>
<td>373</td>
</tr>
</tbody>
</table>

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.
(b) Rates per 100,000 estimated population of 1,097,379 for 2020 (www.census.gov)
(c) Years of Potential Life Lost (YPLL).

NOTE: Totals represent vital events, which occurred in Rhode Island for the reporting periods listed above.
Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.
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Stanley M. Aronson, MD, arrived in Rhode Island in 1970, relocating from New Rochelle, NY, with his wife, the late Betty E. Aronson, MD, and their two young daughters. The Miriam Hospital in Providence, the city where Betty had spent her childhood, was seeking a pathologist-in-chief.

Dr. Aronson, a Professor of Pathology at Downstate Medical Center in Brooklyn, and Assistant Dean of its College of Medicine, contacted the East Side hospital and was invited for an interview in 1969. The Miriam’s leadership impressed him as decisive, pragmatic and visionary. It was refreshing to be in a hospital that “didn’t have its own police force with guns in the halls,” Dr. Aronson said in a series of interviews with this writer, unlike the sprawling Kings County Hospital Center, where he had been Director of Laboratories. “Coming to Rhode Island was such a joy. It was quiet and peaceful. We bought a farm in Rehoboth.”

His arrival coincided with Brown University’s plans to extend its six-year master of medical science program to form a four-year program leading to the MD degree within its Division of Biology and Medicine. The prior year Brown had opened a biomedical center on campus and affiliated with a network of regional hospitals.

It wasn’t long after Dr. Aronson arrived that Brown invited him to discuss leading the medical school effort. The university was impressed with his credentials and Dr. Aronson was intrigued with the challenge of starting a medical school. In 1970, Brown appointed Dr. Aronson a Professor of Medical Science and Chairman of its formative Department of Pathology and Laboratory Medicine.

“There was a small faculty of dedicated and enthusiastic pioneers and exceptional students who helped in the design of the program,” he recalled. The tasks were daunting: to develop the network of affiliated teaching hospitals, design a curriculum, organize and recruit faculty/physicians, oversee operating committees and myriad other challenges, not the least of which was securing State funding.

Neighboring states had allocated millions in opening state medical schools that same year. Then Rhode Island’s Gov. Frank Licht was able to secure a small grant of $245,000 from the State Legislature for the fledgling medical program at Brown and the Rhode Island Medical Society offered strong support as well, by recruiting physicians for the program.

At times, it seemed to Dr. Aronson, the medical school was made of “second-hand clothing and held together by scotch tape. The Dean’s Office was a cubbyhole in the Biomed building which I shared with my secretary, and the classroom was a former laboratory holding room in the basement of the same building.” He juggled multiple leadership positions at the hospital and university, where he also assumed a heavy teaching load. He set up a cot in his Miriam office to catch catnaps when working late – sometimes long past the midnight hour.

In August 1972, Dr. Aronson and his small staff set about preparing for a visit from the National Accrediting Liaison...
Committee of Medical Education, which included preparing the voluminous documentation required for this week-long process. Lacking host-related funds, “I recruited the students to act as chauffeurs,” he recalled. It would turn out to be an effective strategy. The students were such enthusiastic ambassadors, the Committee made note of them in their report.

By October 1972 the school had been granted provisional accreditation. Brown then appointed Dr. Aronson its first Dean of Medicine.

The first clinical rotations were in surgery at the Rhode Island and Miriam hospitals. Due to the contributions of volunteer physicians in the Rhode Island network of hospitals, which also included Memorial Hospital in Pawtucket, and the Lying-In and Roger Williams hospitals in Providence, the program offered more than a hundred clinical electives. There were also opportunities to participate in medical programs in rural America, at a Native American health center in Arizona, and in Afghanistan and Brazil.

In 1975, the program in medicine received its full accreditation and Brown awarded 58 students the MD degree that spring. Dr. Aronson shepherded Brown’s program in medicine for 11 years, until 1981.

Through the years, the name of the school has changed; it is now the Warren Alpert Medical School of Brown University, named for its benefactor. The location moved off-campus in August 2011 to the jewelry district in Providence.

In December 1998, after serving 10 years as Editor-in-Chief of the Rhode Island Medical Journal (RIMJ), Dr. Aronson retired from that position. The staff, without his knowledge, contacted several of Dr. Aronson’s early students and asked them to share their recollections.

Anthony Caldamone, MD,’75, remembered a meeting in the Biomed building when the dean wrote his home phone number on the blackboard, and said: “ ‘Call me anytime, day or night, if you have a problem or if you just need to talk.’ ”

Mitchell H. Driesman, MD,’77, described Dr. Aronson as “our father figure; with his thoughtful eloquence, his work ethic, his boundless love of all learning.”

“Dean Aronson gave us the strength of faith in ourselves,” Julianne Ip, MD,’78, wrote.

“This Message from the Dean appeared in the March 1973 edition of the Rhode Island Medical Journal.”
108 Years Ago: The Arnold Laboratory at Brown Breaks Ground

Dr. Oliver H. Arnold funded lab, the precursor to today’s medical school

MARY KORR
RIMJ MANAGING EDITOR

PROVIDENCE – James Walter Wilson (1896–1969) was a freshman at Brown University in 1914 when the Arnold Biological Laboratory began construction, with funds donated by DR. OLIVER H. ARNOLD, class of 1865.

A biographical sketch of Dr. Arnold in the 1891 History of Providence County, RI, by Richard M. Bayles states that Dr. Arnold received his medical degree from Harvard in 1867, whereupon he “began the practice of medicine at Pawtucket, with Doctor Charles F. Manchester, with whom he remained about four years, having also been a student of Doctor A. H. Okie, of Providence. He continued the practice of his profession from that time to 1883 alone.

“In the summer of 1883 he went to Europe, and remained there two years, traveling, and studying in the hospitals of London, Glasgow, Paris and Vienna, most of the time in the last mentioned place. On his return in 1885 he located in Providence, where he still continues. He was married in 1868, to Emma Josephine Ayer, of Providence. He has had a large and successful practice as a physician.”

Dr. Arnold died in 1911. The terms of Dr. Arnold’s will left $60,000 for the laboratory, $10,000 for a biological fellowship, $10,000 for an archaeological fellowship, dedicated to the memory of his wife, in the Women’s College, and $5,000 for three Women’s College scholarships.

Wilson would later rise to the position of chairman of the Dept. of Biology, which he held from 1945–1960. In the December 1960 issue of the Brown Alumni Monthly, Professor Wilson wrote that Dr. Arnold was a member of the Visiting Committee of the biology department, and related the following anecdote:

The late President Faunce liked to tell how an unannounced visitor arrived at his office one day and had a little trouble getting past his secretary. He had come to tell Prexy that he wanted to give Brown money for a lab. The donation was about $85,000...

In a later Brown annual report, President Faunce described Dr. Oliver this way:

The story of Dr. Arnold’s life, so simple, frugal and obscure, but cherishing a great vision, is fascinating indeed. His rise from poverty to affluence, his devotion to his patients, largely in the rural regions around Providence, his scientific enthusiasm, which led him to drop all practice and spend the years 1883–85 in Vienna, Berlin, London and Glasgow (while Mrs. Arnold was studying Semitic languages with famous German professors), his shy-broaching of his purpose to build the laboratory, his pride and pleasure in working out the details of his gift, all these are the elements in a deeply interesting career, so quiet that our Faculty did not know of his Existence...

This brief article appeared in the New York Times in 1912. The Arnold Laboratory at Brown University on Waterman Street was built in 1915 for $80,000. It provided offices for five professors and later, in 1938, the auditorium on the first floor became a biological sciences library, and three laboratories were installed. Eventually it housed the administrative offices of the medical school.
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3. UK
4. Australia
5. India
6. China
7. Germany
8. Italy
9. Brazil
10. Spain

ATHENS, GREECE
RIMJ Editor-in-Chief
William Binder, MD,
pauses near the Parthenon on the Acropolis, the rocky plateau that rises above central Athens. Built by Pericles in the 5th century BCE, the Parthenon is considered the pinnacle of Doric architecture.

Since 1975, it has been undergoing extensive restoration to repair the damage caused in the 1687 Morean War when a Venetian cannonball exploded gunpowder the Turks were storing inside.

In the early 19th century, many of the Parthenon's sculptures were removed and transported to England where they are on display at the British Museum in London. The Elgin Marbles are the subject of some controversy as there have been efforts to repatriate them.

Wherever you may be, or wherever your travels may take you, check the Journal on your mobile device, and send us a photo: mkorr@rimed.org.
Adventures

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Working for You: RIMS advocacy activities

June 1, Wednesday
Stakeholder conference call regarding Interstate Medical License Compact
Testimony in House Education and House Health & Human Services Committees

June 2, Thursday
RI Department of Health (RIDOH) Diabetes Prevention Program [DPP3]
Stakeholder Network meeting
Testimony in Senate Finance and Senate Judiciary Committees

June 3, Friday
Baby Formula Shortage Update: RIDOH; Neighborhood Health Plan of RI [NHPI]; Rhode Island Health Care Association [RIHCA]; RIMS staff

June 6, Monday
RIMS Council meeting:
Elizabeth Lange, MD, President

June 7, Tuesday
RIMS Physician Health Committee (PHC):
Herbert Rakatansky, MD, Chair
House Corporations Committee heard RIMS’ prior authorization bill, which RIMS leadership and members testified in-person:
Elizabeth Lange, MD, Thomas A. Bledsoe, MD, Michael Migliori, MD; Peter Hollmann, MD

June 8, Wednesday
Rhode Island Department of Health (RIDOH) Board of Medical Licensure and Discipline (BMLD)
Governor’s Overdose Intervention and Prevention Task Force: Sarah Fessler, MD, RIMS Past President

June 9, Thursday
RIMS Virtual Gubernatorial Candidate Forum:
Michael Migliori, MD; Peter Karczmar, MD

June 10–15, Friday–Wednesday
American Medical Association House of Delegates, Chicago:
Peter Hollmann, MD, Delegate; Sarah Fessler, MD, Delegate; Elizabeth Lange, MD, President; Stacy Paterno, CEO

June 14, Tuesday
Testimony in Senate Health & Human Services and House Finance Committees
Rhode Island Foundation Reception for Dean Mukesh Jain, MD, Dean of the Warren Alpert Medical School of Brown University:
Stacy Paterno, CEO

June 15, Wednesday
RIVOH Primary Care Physicians Advisory Committee (PCPAC):
Elizabeth Lange, MD, President

June 16, Thursday
RIMS Climate Change and Healthcare Committee meeting: Co-chairs Alison Hayward, MD, Katelyn Moretti, MD

June 17, Friday
RIMS Physician Health Committee (PHC) meeting:
Herbert Rakatansky, MD, Chair, special guest, Senator Jack Reed, speaking about the passage of the Dr. Lorna Breen Health Care Provider Protection Act; also attended by Governance Committee members and invited RIMS Leadership
July 11, Monday
Governor’s Overdose Task Force (GOTF): Racial Equity Work Group
RIMS Board of Directors meeting: Elizabeth Lange, MD, President

July 13, Wednesday
Rhode Island Department of Health (RIDOH) Board of Medical Licensure and Discipline (BMLD)
Governor’s Overdose Intervention and Prevention Task Force: Sarah Fessler, MD, RIMS Past President

July 18, Monday
Office of the Health Insurance Commissioner (OHIC) Measure Alignment meeting:
Key Considerations for the 2022 Annual Review

July 19, Tuesday
Rhode Island Health Workforce Planning: Health & Human Service Partnerships with Higher Education
OHIC Health Insurance Advisory Committee (HIAC): Catherine A. Cummings, MD, RIMS Past President

July 20, Wednesday
Rhode Island Health Workforce Planning: Health Workforce Data Collection & Analytics Workgroup

July 21, Thursday
Executive Office of Health and Human Services (EOHHS) Health Information Technology (HIT) Steering Committee meeting

July 25, Monday
OHIC Measure Alignment meeting:
Acute Care Hospital & Behavioral Health Hospital

July 27, Wednesday
AMA Medicare Payment Principles: A Vision for Reform
Rhode Island Health Workforce Planning: Health Career Pathways & Pipelines Workgroup

State House honors Steve DeToy, Director of Government Relations
On Thursday, June 2, the Rhode Island Senate and House took time on their respective floors to honor the career of Steve DeToy. Steve’s family, RIMS leadership and staff, and colleagues of Steve joined him in this celebration.

To view the Senate honoring Steve, click here (starts at 25:35 of the video, ends about 34:25)
To view the House honoring Steve, click here (starts at 3:40 of the video, ends about 9:02)

Kathleen Boyd, MSW, Physician Health Program Director, was honored at the 2022 Annual Meeting of the Federation of State Physician Health Programs (FSPHP) held in New Orleans in April for her service to the Federation as the Northeast Regional Director. Since 2013, Ms. Boyd has been a state voting member of FSPHP and served on several committees, including the Performance Enhancement & Effectiveness Review Committee (PEER-C) which has worked for the past four years on developing a process for assessing physician health program alignment with best practices. The pilot program is launching nationally this fall. In 2019, the FSPHP Board of Directors appointed Ms. Boyd to an unexpected vacancy in the Northeast Region and subsequently she was nominated and elected for a two-year term in 2020. She will continue to serve on the PEER-C and the Medical Student & Resident Committee.
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Lifespan's Norman Prince Neurosciences Institute launches brain and spine robotic program

PROVIDENCE – Lifespan’s Norman Prince Neurosciences Institute has expanded its Computer-Assisted Navigation Technology offerings with the addition of two new Globus ExcelsiusGPS robotic surgical systems at Rhode Island Hospital. Surgeons at the Institute recently performed the first ExcelsiusGPS-guided brain and spine surgeries at Rhode Island Hospital. The hospital is the first site in New England to use the ExcelsiusGPS for both cranial and spinal applications.

“Norman Prince Spine Institute is a national leader in specialized multidisciplinary spine care,” said Neurosurgeon-in-Chief ZIYA GOKASLAN, MD. “Now, along with our state-of-the-art Norman Prince Neuroscience Institute, we are among the first centers in New England to offer both these technologies to patients.”

The ExcelsiusGPS is designed to improve the safety and accuracy of surgeries by providing improved visualization of patient anatomy during procedures. Using a surgical plan specific to the patient’s anatomy, the rigid robotic arm is guided to a specific region – like a planned route on a GPS. It can be used for precise pedicle screw placement in spinal fusion procedures and is also utilized in cranial procedures like electrode placement for movement disorders and epilepsy, shunt catheter placement, and brain tumor biopsies.

“These robotic devices add to our already established reputation of providing the most advanced precision technology available to our patients,” said Norman Prince Spine Institute Director and Spinal Surgery Division Director ADETOKUNBO OYELESE, MD, who performed the first spine surgery at Rhode Island Hospital using the ExcelsiusGPS. “For our patients, this means less invasive surgeries that allow for faster recoveries and a more rapid return to their normal lives.”

“This is a new generation of technology,” said Director of Functional Neurosurgery and Epilepsy WAEL ASSAD, MD, who performed the first cranial surgery at Rhode Island Hospital using the ExcelsiusGPS. “These new robotic technologies enable precise targeting of brain circuits and millimeter-scale accuracy in a more streamlined and reliable manner than previous techniques. Patients have been enthusiastic about this new approach when we explain the rationale and benefits to them.”

The new brain and spine robotics program builds on the long history of innovation and early adoption of cutting-edge technology by Brown Neurosurgery, a part of the Warren Alpert Medical School of Brown University and Norman Prince Neuroscience and Spine Institutes at Lifespan who for over a decade has been a national leader in the field of computer-assisted, image-guided navigation-based precision brain and spine surgery.

To see a visual demonstration of the ExcelsiusGPS or learn more about the platform, click on the links below.

ExcelsiusGPS Spine:
https://www.globusmedical.com/musculoskeletal-solutions/excelsiugps/
https://www.youtube.com/watch?v=F3YKhh-DSCgC

ExcelsiusGPS Cranial:
https://www.youtube.com/watch?v=pW2cYXdU8vA&t=212s
CODAC announces mobile medical unit able to dispense methadone as part of full MAT

CODAC’s mobile medical unit is the first in the nation to be approved under the new DEA regulations that went into effect on July 28, 2021.

CODAC’s mild mobile medical unit was made possible by a generous grant from the Champlin Foundation, it features a dispensary examination/treatment room, counseling room, waiting area, restroom, and a fully equipped security system. The mobile medical unit will begin providing MAT services, including counseling, and methadone dispensing (as well as treatment with buprenorphine and naltrexone) to patients residing in Woonsocket. Services will be provided on-site Monday through Saturday from 6:30 to 10 a.m., with the presence of a medical doctor on alternating days of the week. Counseling services will be facilitated via Telehealth in an effort to provide more hands-on support. Other on-site services will include but not be limited to blood pressure screening, glucose reading, and mental health screening.

“Access to care is more important than ever amid our soaring overdose rates,” said LINDA HURLEY, President/CEO of CODAC. “This mobile medical unit will allow us to face that challenge, both geographically and demographically. It will allow us to bring treatment to individuals struggling with addiction and literally meet them where they are – in the places where that treatment is most needed.”

In Rhode Island, deaths from accidental drug overdose (OD) in 2021 were higher than for any other year on record, according to the state Department of Health, and recently passed the benchmark of 100,000 deaths nationally in a twelve-month reporting period.

Reed & Whitehouse, Thundermist announce $1.2M to expand crisis intervention training for police departments across RI

WEST WARWICK – U.S. Senators JACK REED and SHELDON WHITEHOUSE recently joined representatives of Thundermist Health Center and local law enforcement officials to announce $1.2 million in federal funding to support crisis intervention team (CIT) training for police departments across Rhode Island. The event took place at the West Warwick Youth Center, which is run by the West Warwick Police Department.

About 60 percent of local police departments in Rhode Island have already sent an officer to CIT training through Thundermist’s program. As part of the expansion, Thundermist, in partnership with the Rhode Island Police Chief’s Association, will equip local police departments with the tools to divert people in crisis away from the justice system and connect them with the mental and behavioral health resources they need. Thundermist will also help create workflows for 911 and local dispatchers to ensure CIT-trained officers and, if appropriate, an embedded police clinician are sent to calls on an as-needed basis.

“Advocates, in partnership with law enforcement and behavioral health leaders have been working for decades to bring the gold standard in law enforcement crisis response, the Memphis Model Crisis Intervention Team program to Rhode Island. CIT has 30 years of research proving it improves outcomes for people experiencing a behavioral health crisis. CIT increases diversion to treatment and recovery, reduces use of force, and improves officer wellness and safety. We are so grateful to Senator Reed and Senator Whitehouse for their longstanding support of this effort. Thundermist is proud to support this work. We recognize, as a community health center, that health is determined by community outcomes as well as high quality healthcare. CIT will improve the health and mental health outcomes in the communities we serve and beyond,” said SUSAN JACOBSEN, senior director of health equity initiatives, Thundermist Health Center.

“We are at a point in time that we rely on our law enforcement officers to provide services to our communities like never before, and none of those services are more important than when an individual or a family finds themselves in a behavioral health crisis. We know our officers are not trained to make medical evaluations, but they are most often the first responders to provide assistance. We have worked with Thundermist to provide training to not just our officers but also dispatchers in the Memphis Model Crisis Intervention Team program and believe teaming those officers with embedded clinicians helps to provide a safer and more effective outcomes for those in need as well as to those responding. The Rhode Island Police Chiefs’ Association applauds the efforts of Senators Reed and Whitehouse for their continued support in this area. These federal funds will expand our ability to train more officers and supporting personnel,” said SIDNEY WORDELL, Executive Director of the Rhode Island Police Chiefs’ Association.

The initiative will include 24 training academies over four years, including specialized academies on communicating with youth about mental health and dealing with trauma and post-traumatic stress disorder in first responders. The expansion will launch in the fall.
Stephen Salloway, MD, MS, steps down as Director of Butler Hospital’s Memory and Aging Program

PROVIDENCE – Butler Hospital announced in June that STEPHEN SALLOWAY, MD, MS, director of neurology and the Memory and Aging Program at Butler Hospital, who is an internationally recognized leader in clinical trials for the prevention and treatment of Alzheimer’s Disease (AD) has decided to pass along leadership of the program to a new director, though he will continue to work on research studies there. Memory and Aging Program Associate Director Dr. Meghan Riddle will serve as Interim Director until a new director is named, with Dr. Salloway acting as a consult.

In addition to his roles at Butler Hospital, Dr. Salloway is also the Martin M. Zucker Professor of Psychiatry and Human Behavior, and Professor of Neurology at The Warren Alpert Medical School of Brown University and the Associate Director of the Brown University Center for Alzheimer’s Disease Research. He will continue in those roles and will continue to conduct research at the Memory and Aging Program after stepping down as director.

“It has been my honor and privilege to lead the Butler Hospital Memory and Aging Program for the past 25 years. Thanks to the dedication of our staff and contribution of thousands of study volunteers, the Memory and Aging Program has grown into a leading international center for Alzheimer’s research,” Dr. Salloway said. “Working together, we have opened the modern era for the treatment of Alzheimer’s disease and I look forward to continuing to work with the Butler Memory and Aging Program and the Brown Center for Alzheimer’s Disease Research to make exciting new advances in the fight against Alzheimer’s disease.”

“As Director of Neurology and the Memory and Aging Program at Butler Hospital, Dr. Salloway has been a tremendous asset to Butler Hospital and to individuals who suffer from Alzheimer’s Disease. Dr. Salloway is internationally known for his work advancing the diagnosis and treatment of this terrible disease, and we will remain forever grateful that he dedicated his career to this effort. Butler Hospital and Care New England look forward to continuing our work with Brown to advance AD research, including creating a caring environment that encourages people of all backgrounds to participate in research and take advantage of new treatments,” said MARY MARRAN, MS, OT, MBA, president and COO, Butler Hospital.

Dr. Salloway’s program at Care New England’s Butler Hospital has conducted more than 100 clinical trials for Alzheimer’s and related disorders, and he is among the world’s top physicians and researchers on Alzheimer’s disease, the sixth-leading cause of death in America. The program has embarked on a multitude of landmark Alzheimer’s studies focused on the prevention, early diagnosis and treatment of Alzheimer’s.

He has helped to plan the initial protocol for a key trial that showed amyloid PET scans can significantly improve the accurate diagnosis and subsequent medical management of patients with mild dementia. He co-authored a study that found that the brain damage that leads to Alzheimer’s can be detected with a simple blood test up to 16 years before symptoms appear, allowing for earlier intervention and more effective treatment, and he co-authored Appropriate Use Criteria to guide healthcare providers in using another simple and safe tool – a spinal tap – to identify individuals at risk for developing Alzheimer’s years before symptoms appear.

He has chaired the Steering Committees for major AD pivotal trials, such as bapineuzumab and aducanumab, and he has been a key author for key publications in Alzheimer’s research in the New England Journal of Medicine, Nature, and other top-tiered journals that have helped shaped the field of Alzheimer’s research. He also serves on the steering committees for major biomarker and clinical trials and consortia such as ADNI, DIAN, ACTC, GAP-NET, and LEADS.

Dr. Salloway serves as a senior scientific advisor to Prothena and Acumen and has served as a consultant for drug and biomarker development to Biogen, Lilly, Eisai, Amylyx, Alnylam, Novartis, Ono, Amgen, Avid, Axovant, Bolden, GE Healthcare, Gemvax, Janssen, Genentech, Roche, NovoNordisk, Pfizer and Takeda.

He is the Past President of the American Neuropsychiatric Association, a Fellow of the American Academy of Neurology, and a member of the American Neurological Association. He serves as a consultant for drug development to the NIH, the Alzheimer’s Association, the Alzheimer’s Disease Drug Discovery Foundation, and many other groups working on Alzheimer’s therapeutics.

In May 2019 Dr. Salloway was elected to the Rhode Island Heritage Hall of Fame and was selected as the 2019 Rhode Island Man of the Year for his work on Alzheimer’s research. Dr. Salloway received his MD from Stanford Medical School and completed residencies in neurology and psychiatry at Yale University.

Care New England’s Butler Hospital is currently in the process of conducting a national search to replace Dr. Salloway.
Bill to strengthen hospital merger review signed into law

PROVIDENCE – Legislation sponsored by Senate Majority Leader MICHAEL J. MCCAFFREY and House Speaker K. JOSEPH SHEKARCHI to strengthen the hospital merger review process in Rhode Island has been signed into law.

The legislation (2022-S 2349, 2022-H 8343), which passed the General Assembly on June 22, prohibits an expedited review when the combined hospitals after a merger would account for 20 percent or more of the hospitals in the state. It also expands factors that must be taken into consideration.

The legislation was first proposed in 2021, as the Attorney General’s office and health regulators were preparing for consideration of the proposed merger of Rhode Island’s two largest health care systems, Lifespan and Care New England. The merger was denied earlier this year, but almost immediately another potential buyer made an offer to purchase Care New England, and it’s possible that other proposals may come along in the coming months or years.

“This is a transitional time for our state’s health care system. The stakes are too high, and the implications for all Rhode Islanders are too great, for us to settle for anything less than a comprehensive review process when it comes to transactions on the magnitude of the Lifespan-Care New England merger,” said Leader McCaffrey [D-Dist. 29, Warwick]. “This legislation will ensure that experts have the opportunity to analyze every benefit and risk of major deals involving our hospitals.”

Said Speaker Shekarchi [D-Dist. 23, Warwick], “Our local hospitals – particularly Kent Hospital in my own hometown of Warwick, which is part of Care New England – are a vital health resource for the public. Our hospital conversion laws must ensure that the protection of public health is the number one consideration in these decisions. The public must have safe, high-quality hospitals with the capacity to handle our needs, located around the state so they are accessible when people need them. Our conversion laws need to ensure that any consolidation proposal be carefully examined to prevent the reduction of those resources for Rhode Islanders.”

The legislation expands the criteria that must be submitted for review to include plans for services and staffing levels following the merger; retirement plans, including any supplemental executive retirement plans; retirement systems and unfunded pension liabilities; and impact on the community, including community benefits, economic impact, and employment. By specifying these criteria in the statute, the Attorney General and regulators at the Department of Health would be authorized to engage experts to analyze staffing, potential relocation of services, and other aspects pre- and post-conversion.

RI removes barriers to biomarker testing

PROVIDENCE – On July 22, 2022 Gov. DANIEL MCKEE held a ceremonial bill signing for legislation that will increase insurance coverage for biomarker testing – thus making this form of precision medicine available to more Rhode Islanders.

“Cancer patients and those facing a cancer diagnosis owe a debt of gratitude to Gov. McKee and Rhode Island lawmakers. This legislation will help dismantle barriers and bring the promise of precision medicine to cancer patients no matter their income, race or where they live. This will provide many benefits to patients including better outcomes, improved quality of life, and in some cases, reduced costs from bypassing ineffective therapies,” said Cori Chandler, government relations director for the American Cancer Society Cancer Action Network [ACS CAN] in Rhode Island.

“I’m proud to sign this critical piece of legislation today which will provide Rhode Islanders with access to biomarker testing which can help achieve better health outcomes, improve quality of life and reduce overall health care costs,” said Governor Dan McKee. “I thank Senate Majority Whip Goodwin, Deputy Majority Whip Ackerman, the American Cancer Society Cancer Action Network and all those that advocated for and worked to get this bill over the finish line.”

“Biomarker testing can save lives. It can help doctors identify treatment that is faster, more effective and less painful, and can ultimately save treatment dollars. All insurers should embrace this technology,” said Senator Goodwin [D-Dist. 1, Providence].

“Biomarker testing allows doctors to make full use the cancer research and treatment experience that is available. Patients deserve that benefit, and the hope that comes with it.”

“Biomarker technology allows doctors to pinpoint treatment that has the best possibility for success for an individual patient. It saves lives, time and money, and it’s an important advantage in the fight against cancer” said Rep. Ackerman. Covering it just makes good sense for insurers and patients alike.”

For more information on precision medicine, cancer biomarkers, current barriers to biomarker testing and ACS CAN’s policy recommendations, visit: www.fightcancer.org/biomarkers.
RIDOH’s Monkeypox Task Force taking prevention and control measures

PROVIDENCE – As national health experts continue to track the ongoing global outbreak of monkeypox, the Rhode Island Department of Health (RIDOH)’s Monkeypox Task Force is coordinating with healthcare providers, healthcare facilities, and communities on monkeypox prevention and control measures.

As part of this current outbreak, four monkeypox cases have been identified in Rhode Island. More than 1,000 cases have been identified nationally, including 49 cases in Massachusetts, and 159 cases in New York. Current evidence from around the country suggests that the virus is spreading mostly through close, intimate contact with someone who has monkeypox.

“At RIDOH we are working to help the public understand how to prevent monkeypox now, with a focus on communities at higher risk,” said Interim Director of Health UTPALA BAN-DY, MD, MPH. “At the same time, we are laying out future plans to get more prevention tools and resources into the community as they are made available by the federal government.”

There is ample testing capacity for monkeypox, anti-viral treatment (Tecovirimat), and an FDA-approved vaccine (JYNNEOS) available to prevent this infection. However, the vaccine is currently in short supply nationally.

The measures currently being taken by RIDOH’s Monkeypox Task Force include:

- Performing case interviews and contact identification to collect the clinical and epidemiological information needed for isolation, contact monitoring, and post-exposure vaccination.
- In consultation with patients’ healthcare providers and the Centers for Disease Control and Prevention (CDC), assessing cases to determine whether they are appropriate candidates for antiviral treatment (Tecovirimat).
- Coordinating the post-exposure preventive vaccination of close contacts. (All vaccination is being coordinated through RIDOH on a referral basis.)
- Coordinating with select healthcare facilities to serve as vaccination sites. These sites serve communities at the highest risk of exposure.
- Regularly communicating with healthcare providers on clinical recognition, specimen collection, and case reporting 24/7.
- Coordinating specimen collection, transport, and analysis at RIDOH’s State Health Laboratories for clinically compatible cases 24/7.
- Partnering with community organizations and businesses that serve higher risk populations on prevention education.

RIDOH’s Monkeypox Task Force includes staff from RIDOH’s Division of Preparedness, Response, Infectious Disease, and Emergency Medical Services; the Office of Immunization; the State Health Laboratories; the Health Equity Institute; and RIDOH’s Center for Public Health Communication.

Monkeypox Prevention

There is a vaccine to help prevent monkeypox virus infection. However, this vaccine is currently in short supply nationally. The CDC is using a very specific formula to allocate monkeypox vaccine to states, considering factors such as population size, current monkeypox case counts, and historical data on sexually transmitted infections. For this reason, Rhode Island has been allocated much less vaccine than other states (for example, Massachusetts). At this time, Rhode Island has only been allocated enough vaccine to vaccinate close contacts of cases. Vaccination of contacts within four days of exposure can prevent illness and if given within 14 days of exposure can significantly reduce severity of illness should the person develop illness.

More information about monkeypox is available at health.ri.gov/monkeypox
RI enacts executive order protecting access to reproductive health care

PROVIDENCE – On July 5th Governor DAN MCKEE today signed an executive order protecting access to reproductive health care in Rhode Island, ensuring that individuals who come to Rhode Island seeking reproductive health services will be safeguarded from legal liability in other states.

In addition to protecting patients, the Governor’s order protects providers in Rhode Island who perform reproductive health care services for individuals from another state, ensuring they do not lose their professional licenses or become subject to discipline on out-of-state charges.

“As other states attack the fundamental right to choose, Rhode Island must do all it can to protect a person’s access to reproductive health care,” said Lt. Governor SABINA MATOS. “This executive order will ensure that anyone seeking this type of care anywhere in the country can do so in Rhode Island without fear of consequence.”

Patient survey shows unresolved tension over health data privacy vulnerabilities

CHICAGO – A new examination of patient perspectives on data privacy illustrates unresolved tension over the eroding security and confidentiality of personal health information in a wired society and economy. More than 92% of patients believe privacy is a right and their health data should not be available for purchase, according to a survey released July 25th by the American Medical Association (AMA).

The survey of 1,000 patients was conducted by Savvy Cooperative, a patient-owned source of health care insights, at the beginning of 2022 and found concern over data privacy protections and confusion regarding who can access personal health information. Nearly 75% of patients expressed concern about protecting the privacy of personal health data, and only 20% of patients indicated they knew the scope of companies and individuals with access to their data. This concern is magnified with the U.S. Supreme Court ruling in Dobbs v. Jackson Women’s Health Organization as the lack of data privacy could place patients and physicians in legal peril in states that restrict reproductive health services.

“Patients trust that physicians are committed to protecting patient privacy – a crucial element for honest health discussions,” said AMA President JACK RESNECK JR., MD. “Many digital health technologies, however, lack even basic privacy safeguards. More must be done by policymakers and developers to protect patients’ health information. Most health apps are either unregulated or underregulated, requiring near and long-term policy initiatives and robust enforcement by federal and state regulators. Patient confidence in data privacy is undermined as technology companies and data brokers gain access to indelible health data without patient knowledge or consent and share this information with third parties, including law enforcement.”

The survey found an overwhelming percentage of patients demand accountability, transparency, and control as it relates to health data privacy. To prevent unwanted access and use of personal health data, patients want control over what companies collected about them and how it is used:

- Almost 80% of patients want to be able to opt-out of sharing some or all their health data with companies.
- More than 75% of patients want to opt-in before a company uses any of their health data.
- More than 75% of patients want to receive requests prior to a company using their health data for a new purpose.

Patients worry about the repercussions of little or no control over the use and sharing of personal health data that companies have collected. About three out of five patients (59%) expressed concern with personal health data being used against them or their loved ones. Most patients stated they are “very” or “extremely” concerned about discriminatory uses of personal health data to exclude them from insurance coverage (64%), employment (56%), or opportunities for health care (59%). More than half of Hispanic/Latinx and American Indian or Alaskan Natives stated they are “highly” concerned about discriminatory uses of personal health data and two-thirds (66%) of transgender individuals stated they are “extremely” concerned.

Patients also want physicians and their hospitals to have the technology and capability to review apps for privacy and security protections. Nearly nine out of ten (88%) patients believe that their doctor or hospital should have the ability to review and verify the security of health apps before those apps gain access to their health data. Unfortunately, federal regulations prevent providers and even electronic health record (EHR) systems from conducting necessary privacy and security reviews of apps.

The AMA continues to advocate for near-term app transparency requirements, including app privacy attestations collected by EHRs, that will increase transparency and bolster individuals’ choice in which apps to use.
PROVIDENCE – In June, Governor Dan McKee announced the appointment of **Utpala Bandy, MD, MPH**, as Interim Director of the Rhode Island Department of Health (RIDOH).

Dr. Bandy currently serves as the Director of RIDOH’s Division of Preparedness, Response, Infectious Disease, and Emergency Medical Services. She has led RIDOH’s infectious disease division since 2012. In that time, she has helped steer the State’s response to the COVID-19 and H1N1 global pandemics, and she has led efforts to prevent or control outbreaks of diseases of significant concern, including tuberculosis, measles, rabies, and meningococcal disease. She has helped guide efforts to dramatically reduce rates of new HIV infections over the last 30 years in Rhode Island, and manages the federal grants received by RIDOH to do routine infectious disease surveillance and response work.

Dr. Bandy completed a pediatric residency at the University of Texas Medical Branch at Galveston. She holds a Master of Public Health degree from the Harvard University School of Public Health. She joined RIDOH in 1993 as Rhode Island’s State Epidemiologist and the Medical Director for the division that oversaw RIDOH’s infectious disease prevention and control work. She became the Director of RIDOH’s Division of Infectious Disease Epidemiology in 2012.

Dr. Bandy assumed the role of Interim Director on Sunday, June 26. Dr. James McDonald’s last day of state service was July 29.

NEW HAVEN – Planned Parenthood of Southern New England (PPSNE) announced that **Nancy L. Stanwood, MD, MPH**, joined the organization as the inaugural full-time Chief Medical Officer.

Dr. Stanwood is a board-certified obstetrician-gynecologist with over 20 years of experience in clinical practice, medical education, and reproductive health and rights advocacy—with a long-standing relationship with Planned Parenthood. In her new role, she will lead, oversee, and participate in PPSNE’s clinical care services, ensuring high-quality, safe, and patient-centered health care across the 15 health centers in Connecticut and Rhode Island. Dr. Stanwood will lead the organization’s strategic efforts to advance health equity, focusing on improving health outcomes and reducing disparities in PPSNE patient communities.

Since 1998, she has worked as an abortion provider at Planned Parenthood health centers. And for the past eleven years, she has served dual roles: at Yale School of Medicine as the Section Chief of Family Planning and director of the Complex Family Planning fellowship while also serving part-time as PPSNE’s Associate Medical Director.

In reflecting on this new chapter in her career, Dr. Stanwood says, “I first walked into a Planned Parenthood health center as a patient seeking contraception when I was in medical school. This care allowed me to focus on becoming a physician so that when I next walked into a Planned Parenthood health center, it was as an abortion care provider.” She continues, “In this critical time, with the erosion of almost 50 years of legal protection for reproductive rights and with growing health disparities due to systemic racism, I am committing myself fully to the mission and work of Planned Parenthood of Southern New England. All people deserve access to the care they need to live their lives with dignity and to thrive. I am thrilled to join the vibrant PPSNE team as we work to bring high-quality health care to the communities we serve.”

A Connecticut native, Dr. Stanwood received her undergraduate degree from Brown University, a Master of Public Health from the University of North Carolina at Chapel Hill, and her medical degree from the University of Pennsylvania. She completed her obstetrics and gynecology residency training at the University of Michigan and her fellowship at the University of North Carolina at Chapel Hill. Dr. Stanwood has been awarded notable distinctions for her work in sexual and reproductive health and medical education. She is a fellow of the American College of Obstetrics & Gynecologists and of the Society of Family Planning.
Appointments

Arthur S. Robbins named chair emeritus, HopeHealth Board of Directors

PROVIDENCE – Over the years, Providence business leader ARTHUR S. ROBBINS has earned a shelf’s worth of honors for his leadership, citizenship and philanthropy in the community.

He recently received another, this time from a health organization he helped shape: After 41 years as a board member, Robbins was appointed chair emeritus of the HopeHealth Board of Directors.

In the mid-1970s, when Robbins first got involved with the organization, HopeHealth was one of just two hospice providers in the United States. Today, it’s a regional leader in hospice, palliative and home health care. Robbins looms large in that success story: As the organization helped blaze the trail for hospice in the U.S., Robbins was at the governance table. He was a passionate advocate for creating a center for inpatient hospice care, at a time when very few health systems understood or appreciated the need for such a facility.

“Arthur was steadfast,” says HopeHealth Chief Medical Officer EDWARD MARTIN, MD, MPH. “He was this very strong voice on the board: ‘We have to do this for our patients.’”

Robbins subsequently led the fundraising campaigns that built HopeHealth’s first inpatient unit, the Hulitar Hospice Center, which opened in 1993, followed by the current Hulitar Hospice Center on North Main Street in Providence which opened in 2010 – the only freestanding inpatient hospice facility in Rhode Island. There, patients who need the most acute levels of hospice can receive the care they need.

“Arthur Robbins has been an absolute champion for end-of-life care in this community,” says HopeHealth President & CEO DIANA FRANCHITTO. “Through our inpatient hospice center alone, he has helped bring compassion and dignity to thousands of patients in their final days, and to their loved ones. That legacy will only grow.”

The Board of Directors, led by Chair Keith Kelly, named Robbins chair emeritus at a special ceremony June 29, 2022.

“Without Arthur Robbins, we would not be here today,” Kelly said. “Arthur was and continues to be a driving force at HopeHealth, and we owe him a tremendous debt of gratitude.”

Robbins, who is 89 years old, is the principal of Robbins Properties in Providence. He is renowned for his philanthropy and leadership in the community, among many notable contributions, he helped launch the Providence Holocaust Museum, the Providence Warwick Convention & Visitors Bureau, and the first charter school in Rhode Island. He has served on more than 20 civic and nonprofit boards, including HopeHealth’s.

“It takes dedicated people to move any organization to greater heights,” Robbins said, reflecting on his move to chairman emeritus of the HopeHealth Board of Directors. “Having been a [HopeHealth] board member for all of these years and having seen what has happened in our organization after all these years, is truly amazing.”

Woo Jin Lee, MD, joins pain medicine team at University Orthopedics

EAST PROVIDENCE – University Orthopedics will now offer pain management services in the south-western part of Rhode Island with the addition of DR. WOO JIN LEE, board-certified in anesthesiology and fellowship-trained in pain medicine.

Dr. Lee treats all types of pain, specializing primarily in spinal conditions like degenerative disc disease/spondylolisthesis, spinal canal stenosis, radiculopathy, facet joint arthropathy, sacroiliac joint arthropathy, vertebrogenic/compression fractures, and complex regional pain syndrome (CRPS). He also treats major peripheral joint pain, including hip, shoulder, and knee arthropathy. He offers a variety of interventional treatment options, including epidural steroid injection, radiofrequency nerve ablation, joint steroid injection, peripheral nerve blocks, sympathetic plexus blocks, spinal cord stimulation, and vertebral augmentation.

Dr. Lee completed a fellowship in pain medicine at Massachusetts General Hospital in Boston. Prior to that, he completed his anesthesiology residency at New York-Presbyterian Hospital/Columbia University Irving Medical Center. He earned his medical degree at George Washington School of Medicine and Health Sciences in Washington, DC. In addition to seeing patients at University Orthopedics’ Westerly location, Dr. Lee will also perform procedures and surgeries in various locations including Westerly Hospital, UOI’s East Bay Surgery Center in East Providence, and the practice’s East Greenwich office.

Dr. Lee treats all types of pain, specializing primarily in spinal conditions like degenerative disc disease/spondylolisthesis, spinal canal stenosis, radiculopathy, facet joint arthropathy, sacroiliac joint arthropathy, vertebrogenic/compression fractures, and complex regional pain syndrome (CRPS). He also treats major peripheral joint pain, including hip, shoulder, and knee arthropathy. He offers a variety of interventional treatment options, including epidural steroid injection, radiofrequency nerve ablation, joint steroid injection, peripheral nerve blocks, sympathetic plexus blocks, spinal cord stimulation, and vertebral augmentation.

Griffin Kane Reynolds, MD, joins the Roger Williams Hematology Oncology group

PROVIDENCE – DR. GRIFFIN KANE REYNOLDS has joined the Roger Williams Hematology Oncology group and the skilled team of medical, surgical and radiation oncologists at the Roger Williams Cancer Center.

Dr. Reynolds is a graduate of Bucknell University and St. George’s University School of Medicine. He is triple board-certified in internal medicine, hematology, and oncology, respectively. He joins Roger Williams Cancer Center from Lincoln Medical Center in New York City and was previously affiliated with Westchester Medical Center in Valhalla, New York. Dr. Reynolds has conducted cancer research at the Harvard Stem Cell Institute in Boston and the Wistar Institute in Philadelphia.

He joins the members of the Hematology Oncology group at RWMC of Drs. Ritesh Rathore, Todd Roberts, Bharti Rathore and Gerald Colvin.
Newsweek names Women & Infants one of America’s best maternity hospitals

PROVIDENCE – Newsweek and data firm Statista have recently announced their ranking of America’s Best Maternity Hospitals 2022, and has awarded Women & Infants Hospital with a Four Ribbon Performance.

The list names the top 350 leading hospitals for maternity care in the U.S., divided into two performance categories: five ribbon hospitals (161 institutions) and four ribbon hospitals (189 institutions). The evaluation is based on three data sources: a nationwide online survey in which hospital managers and maternity healthcare professionals (e.g., neonatal care providers and OB/GYNs) were asked to recommend leading maternity hospitals; medical key performance indicator data relevant to maternity care (e.g., a hospital’s rate of cesarean births); and patient satisfaction data (e.g., how patients rated a hospital’s medical staff for responsiveness and communication).

Women & Infants Hospital, a designated Baby-Friendly® USA hospital, is the ninth largest stand-alone obstetrical service in the country and the largest in New England, delivering approximately 8,500 babies annually.

Matthew David Howe, MD, PhD, receives 2022 NIMH Outstanding Resident Award

PROVIDENCE – MATTHEW DAVID HOWE, MD, PhD, Psychiatry Resident [PGY-3], Research Track, at Butler Hospital has been selected to receive the 2022 National Institute of Mental Health [NIMH] Outstanding Resident Award. He is currently working in the Memory and Aging Program at Butler Hospital on blood biomarkers for Alzheimer’s Disease detection.

As an ORAP awardee, he will be invited to participate in the virtual award program, which is tentatively scheduled for Monday, October 3rd through Tuesday, October 4th.

The program will include talks from NIMH investigators and interactive meetings with NIMH leadership, extramural staff, and current clinical fellows.

Thundermist NP Fellowship programs gain national accreditation

WEST WARWICK – Thundermist Health Center achieved national accreditation of its Psychiatric Mental Health Nurse Practitioner Fellowship Program and Primary Care Nurse Practitioner Fellowship Program. The National Nurse Practitioner Residency and Fellowship Training Consortium [NNPRFTP] Accreditation Committee granted the program’s initial programmatic accreditation for the period of three years. Thundermist is the first organization in Rhode Island to earn national accreditation for Nurse Practitioner Fellowship programs.

Thundermist launched its Nurse Practitioner Fellowships in 2015 to help address the growing need of primary care providers and to better prepare providers to provide care in the community health center setting.

“Our organization has always recognized and valued the contributions of Nurse Practitioners as Primary Care and Psychiatric Mental Health Providers,” said JEANNE LACHANCE, President/CEO. “The shortage of Primary Care Providers and Psychiatric Mental Health prescribers urged us to think creatively and strategically about how to build upon workforce development, work life balance, education, and talent. Seeking and achieving national accreditation through the NNPRFTP further strengthens our commitment to creating satisfying and long-term career opportunities for Nurse Practitioners within community health centers.”

“The COVID-19 pandemic has underscored the critical importance of the nursing profession in ensuring the health and well-being of our Rhode Island communities. Our programs two specialization tracks both meet our fellow’s career goals and our health centers’ needs in Primary Care and Psychiatric-Mental Health. The accreditation will further our efforts in developing our program’s ability to support achieving outstanding clinical quality outcomes, address social determinants of health and health inequity amongst the populations we serve.”

“Since 2015, Thundermist Health Center trained 20 primary care Nurse Practitioner Fellows and 10 psychiatric Nurse Practitioner Fellows,” said MILAGROS COLON PILLA, Program Manager, Nurse Practitioner Fellowships. “Sixteen of these graduates continue to provide care at our health center. This is a workforce development strategy that works and improves access to care for our community.”

The one-year fellowship program prepares new nurse practitioners to provide exceptional care to patients with complex medical, behavioral health, and social needs. The intensive training supports fellows in developing the skills to deliver comprehensive health care as leaders of a robust care team. They develop long-lasting skills to achieve outstanding clinical quality outcomes, address social determinants of health, and create health equity amongst the populations they serve. Fellows are required to work at Thundermist for one year following graduation.
CRAIG ALAN HARRIS, MD, passed away peacefully on June 17, 2022. He was the beloved daughter of the late Henry and Mildred MacFarlane Isé of Cranston, Rhode Island. She is survived by her brother, William H. Isé, Esq, and sister-in-law, Nancy Isé of Newport Beach, CA, and Narragansett, RI; her nieces, Sabrina Lovell of MD, Suzanne Isé of CA, and Jennifer Isé of CA; her grandnephew and grandniece, Robert and Erin; cousins Anna Willett of Warwick, RI, Everett Pizzuti of East Greenwich, RI and Kathie Wapenski of Foster, RI, and her long-time friend, Martha Frigoletto of Wellesley, MA. She also leaves numerous other cousins and relatives in Rhode Island, Pennsylvania, Florida, and California.

She was a summa cum laude graduate of Classical High School, Providence, RI; a graduate of Smith College, Northampton, MA; received her master’s degree from Columbia University; and was a graduate of Boston University Medical School. She did her internship at Mt. Auburn Hospital, Cambridge, and completed her residency at McLean Hospital, Belmont, MA. Dr. Isé was affiliated with Mount Auburn Hospital and McLean Hospital as a specialist in geriatric psychiatry. She kept a private practice in Belmont, MA for many years.

Carolyn spent many a happy summer at her family’s farm in Narragansett, RI. Carolyn took great joy in and was devoted to her nieces and her grandniece and grandnephew. She took her nieces on trips to Bermuda, England, Colombia, and many other places in Europe. She visited William and Nancy when they were stationed on active duty in Japan and traveled with her nieces around Japan and China. Carolyn enjoyed the many years she lived at her beautifully decorated apartment in Cambridge, with a view of the Charles River. Carolyn shared her love of art, antiques, interior design, reading, and travel with her family and friends. She was incredibly thoughtful and generous and delighted in picking out the perfect cards and gifts for every special occasion. She especially loved Christmas and sending unique Christmas decorations to friends and family every year. In lieu of flowers, memorial donations are greatly appreciated to McLean Hospital (https://giving.mcLean.org). Please share memories and condolences at www.WoodlawnGattone.com.

CAROLYN E. ISÉ, MD, passed away peacefully on June 17, 2022. He was the beloved daughter of the late Henry and Mildred MacFarlane Isé of Cranston, Rhode Island. She is survived by her brother, William H. Isé, Esq, and sister-in-law, Nancy Isé of Newport Beach, CA, and Narragansett, RI; her nieces, Sabrina Lovell of MD, Suzanne Isé of CA, and Jennifer Isé of CA; her grandnephew and grandniece, Robert and Erin; cousins Anna Willett of Warwick, RI, Everett Pizzuti of East Greenwich, RI and Kathie Wapenski of Foster, RI, and her long-time friend, Martha Frigoletto of Wellesley, MA. She also leaves numerous other cousins and relatives in Rhode Island, Pennsylvania, Florida, and California.

CRAIG ALAN HARRIS, MD, 84, of Portsmouth, RI, formerly of Cumberland, RI, passed away on Wednesday, July 13, 2022. His family at his side, he transitioned in peace, with the dignity and grace that characterized his whole life.

He is survived by his wife of 59 years, Judith (Holden) Harris; his children, Holly A. Harris, of Naperville IL; Jonathan H. Harris, and his wife, Elizabeth, of Portsmouth, RI; and Jeffrey L. Harris, and his wife, Alicia, of Charlotte, NC; and several grandchildren.

Dr. Harris graduated from Providence Country Day School in 1955, Brown University in 1959, and Tufts Medical School in 1963. After a residency at Mountainside Hospital in Montclair, NJ, he served as a captain in the US Air Force at Pope Air Force Base, Fort Bragg, NC.

He enjoyed a successful internal medicine practice in Cumberland, RI, for over 30 years before finishing his career as the medical director at The Rehab Hospital of Rhode Island. He retired in 2011 and relocated to Portsmouth, RI, with his wife Judy.

A celebration of his life will be held at The United Congregational Church, 524 Valley Road, Middletown, RI, on Friday, August 12, 2022, at 11:00 a.m.

In lieu of flowers, donations may be made in his name to:
The United Congregational Church (endowment fund) 524 Valley Road, Middletown, RI 02842
Doctors Without Borders, at https://donate.doctorswithoutborders.org/
The Martin Luther King Center, at https://mlkcccenter.org/donate/