TABLE OF CONTENTS

1  A Few Final Words. Stephen Tarnoff, MD

3  Incoming Remarks. G. Richard Holt, MD

4  Voices From The Permanente Journal: Examining the Past While Embracing the Future. Cuong Le, MA, MAT; Paul Bernstein, MD, FACS; Kirk Fernandes, MS

ORIGINAL RESEARCH ARTICLES

11  Clinical Decision Support to Address Racial Disparities in Hypertension Control in an Integrated Delivery System: Evaluation of a Natural Experiment. Cassondra Marshall, DrPH, MPH; Alyce S Adams, PhD; Lin Ma, MA; Andrea Altschuler, PhD; Mark W Lin, MD, MPH; Nailah A Thompson, DO, MPH; Joseph D Young, MD

The authors evaluated the impact of a clinical decision support tool to improve evidence-based thiazide diuretic prescribing among Black patients to address racial disparities in hypertension control. They observed no change in thiazide use or blood pressure control following the implementation of the tool.

21  Evaluating the Implementation of Digital and In-Person Diabetes Prevention Program in a Large, Integrated Health System: Natural Experiment Study Design. Stephanie L Fitzpatrick, PhD; Meghan Mayhew, MPH; Chris L Catlin, BS; Alison Firemark, MA; Inga Gruß, PhD; Denis B Nyongesa, MS; Maureen O’Keeffe-Rosetti, MS; Andrea M Rawlings, PhD, MS; David H Smith, PhD, RPh; Ning Smith, PhD; Victor J Stevens, PhD; William M Vollmer, PhD; Stephen P Fortmann, MD

Kaiser Permanente Northwest patients who were 19 to 75 years old with prediabetes and obesity were invited to participate in the digital and in-person Diabetes Prevention Program during 2016 through 2018. The mixed-methods, natural experiment design the authors used contributes new knowledge related to best practices for implementing and sustaining the Diabetes Prevention Program within large health systems over the long term.
| 32 | Computed Tomography Use in Children With Minor Head Trauma Presenting to 21 Community Emergency Departments Within an Integrated Health-Care System. | Judy Shan, BS; E Margaret Warton, MPH; Mary E Reed, DrPH; David R Vinson, MD; Nathan Kuppermann, MD, MPH; Peter S Dayan, MD; Stuart R Dalziel, MD; Adina S Rauchwerger, MPH; Dustin W Ballard, MD, MBE |

This study evaluated computed tomography use in children with minor blunt head trauma in 21 community emergency departments within an integrated health care system. Use was low and stable across facilities from 2016 through 2018. This may be indicative of the safe stewardship of resources in the system. |

| 38 | Impact of COVID-19 on the Incidence and Severity of Obstetric and Gynecologic Emergency Department Visits in an Integrated Health Care System. | Cassidy E Tierney, MD; Mary Kathryn Abel, AB; Mubarika M Alavi, MS; Miranda Ritterman Weinraub, PhD, MPH; Andrew Avins, MD, MPH; Eve Zaritsky, MD |

The aim of this study was to assess changes in incidence of OB/GYN emergency department visits and disease severity at time of presentation during the COVID-19 pandemic. The incidence of OB/GYN emergency department visits declined substantially between March and August 2020 but then returned to pre-pandemic levels by fall/winter 2020. |

| 47 | Downstream Acute Care Utilization Following Initial Prescription of an Opioid Pain Reliever Among Emergency Department Patients With Low-Severity Conditions. | Nathan Juergens, MD, MPH; Julia Wei, MPH; Esme Cullen, MD, MPH; Moses Graubard, MD; Vibha K Gupta, MD; Miranda Ritterman Weinraub, PhD, MPH; Dana Sax, MD, MPH |

Authors investigated the association between receipt of an opioid pain reliever in the emergency department and downstream acute health care utilization. Patients who received an opioid pain reliever at their index encounter had substantially increased odds of a subsequent emergency department, urgent care, or inpatient visit. |

| 58 | Variation in Positivity Rates of Computed Tomography Pulmonary Angiograms for the Evaluation of Acute Pulmonary Embolism Among Emergency Department Physicians. | Kori Higashiya, MD; James Ford, MD; Hyo-Chun Yoon, MD, PhD |

Computed tomography pulmonary angiography is an imaging study for which there is substantial evidence for its overuse in the evaluation of acute pulmonary embolism. This study was based in a single emergency department that is part of a geographically isolated integrated health care system. |

| 64 | Pragmatic Randomized Study of Targeted Text Message Reminders to Reduce Missed Clinic Visits. | Ernesto Ulloa-Pérez, MS; Paula R Blasi, MPH; Emily O Westbrook, MHA; Paula Lozano, MD, MPH; Katie F Coleman, MSPH; R Yates Coley, PhD |

Missed clinic appointments waste health system resources, decrease physician availability, and may worsen patient outcomes. Study findings indicate that using a prediction model to target reminders may reduce missed appointments and allow for more efficient use of health care resources. |

| 73 | The Effect of Elexacaftor/Tezacaftor/Ivacaftor on Hospitalizations and Intravenous Antibiotic Use. | Eric Walter, MD, MSc; Jennifer L Bass, MD |

Elexacaftor/tezacaftor/ivacaftor is a highly effective cystic fibrosis transmembrane conductance regulator modulator. The authors performed a single-institution, retrospective review comparing hospitalization and intravenous antibiotic rates before and after the initiation of elexacaftor/tezacaftor/ivacaftor. |

| 80 | Psychological Effect of the COVID-19 Pandemic Among Facial Feminization Surgery Patients. | Nikolas R Block-Wheeler, MD, MS; David W Chou, MD; Kathryn Brandstetter, MD; Andrew Kleinberger, MD; Charles Shih, MD |

The COVID-19 pandemic has had a disproportionately negative impact on mental
health among the lesbian, gay, bisexual, transgender, queer community, with the delay of medical services as a factor. This study revealed greater perceived facial femininity and a lower desire for surgery among facial feminization surgery patients during the pandemic.

85 Identifying Suicidal Ideation and Attempt From Clinical Notes Within a Large Integrated Health Care System. Fagen Xie, PhD; Deborah S Ling Grant, PhD, MPH, MBA; John Chang, MPH; Britta I Amundsen, LMFT; Rulin C Hechter, MD, PhD

Suicide can be a devastating outcome of psychiatric illness is a critical public health problem worldwide. The purpose of this study was to develop a natural language processing algorithm to identify suicidal ideation/attempt from free-text clinical notes.

94 Providing Rapid Access to Care for Underserved Patients During the COVID-19 Pandemic. Aleece Caron, PhD; Kim Bauchens, MSN; David Margolius, MD; Kathryn Teng, MD, MBA

COVID-19 is altering the health care delivery landscape at a rapid pace. This commentary describes our hospital system’s response to the COVID-19 pandemic and how we managed to rapidly transition to telehealth and provide seamless access for underserved patients.

REVIEW ARTICLES

99 Assessing the Role of High-Dose β-Agonists Use in Triggering Takotsubo Syndrome During Asthma Exacerbation. Danish Abbasi, MD; Saif Faiek, MD; Waqas J Siddiqui, MD; Angel Lopez-Candales, MD

A surge in catecholamine levels has been postulated as a potential mechanism causing cardiomyopathy, particularly Takotsubo Syndrome. We conducted a PubMed search for published case reports, experimental studies, animal studies, and review articles examining Takotsubo Syndrome documentation among patients with asthma.

CASE REPORTS

106 High-Dose Pulse Steroids for the Treatment of Acute Hypoxemic Respiratory Failure in COVID-19 Pneumonia: A Simple Case Series. Gholmieh Ghassan, MD, PhD

Pulse steroids therapy is widely used to treat flare-ups of autoimmune diseases, such as systemic lupus erythematosus. The author presents a series of 9 cases that explore the use of high-dose pulse steroids in hypoxemic respiratory failure.

119 Case Report of Novel, Automatic Shocking Vector Adjustment Algorithm: A Life-Saving Feature of a Modern Defibrillator. Mark R Heckle, MD; Sunil K Jha, MD, MRCP, FACC, FHRS

Failed delivery of appropriate shocks against fatal dysrhythmias can be the result of low impedance on high-voltage leads. We describe the case of a 66-year-old man with a high-voltage lead short circuit who was successfully rescued with the use of an overcurrent detection and automatic shocking vector adjustment algorithm.

123 Effect of Immunosuppressive Diseases and Rituximab Infusions on Allowing COVID-19 Infection to Relapse. Rohan M Prasad, DO; Shaurya Srivastava, DO; Enhua Wang, MD; Jason Z Liu, DO; Rakesh Gami, MD; Ayat Abdelgadir, MD; Akhil Sharma, DO; Sumudha Rayamajhi, MD; Richa Tikaria, MD

Relapsing COVID-19 infections have been reported, but their etiology and severity are still unknown. This case series illustrates 2 patients who developed a relapsed infection.

132 Rare Case of Mixed Phenotype Acute Leukemia Presenting as a Myeloid Sarcoma Without Leukemic Involvement. Jeffrey Means, DO; David Feldman, MD; Allison Shaw, MD; Khoan Vu, MD

Mixed phenotype acute leukemia is a rare type of acute leukemia with immunophenotypic features of both myeloid-derived and lymphoid-derived lineages. We present an atypical case of a 32-year-old woman presenting with an anterior
mediastinal mass and pericardial/pleural involvement.

137  **Efficacy and Cost of Maxillary Patient-Specific Implants in Orthognathic Surgery: A Review of Three Patient Cases.** Ho-Hyun (Brian) Sun, DMD, MS; Heshaam Fallah, MD, DDS

Patient-specific implants are accurate, efficient alternatives to traditional plate fixation. We explored the departmental protocol for Lefort 1 patient-specific implant orthognathic surgery at a high-volume, tertiary referral center.

143  **Gangrene of the Foot After Coronary Artery Bypass Graft Surgery.** Julia L Boland, MD; Kristine Cueva, MD; Jessica Pawly, MD; Darius Shahbazi; Maximilian Lee, MD; Shahin Shahbazi, MD

Coronary artery bypass grafting is the most common surgery performed by cardiothoracic surgeons worldwide. The aim of this case report is to present a rare complication of coronary artery bypass grafting with perioperative intra-aortic balloon pump use and to highlight the need for prompt diagnosis and treatment of dry gangrene.

**COMMENTARIES**

148  **Personal Protective Equipment for COVID-19 and Beyond: Occupational and Environmental Exposure Considerations in Primary Care.** Onyemaechi Nwanaji-Enwerem, MS, MPP; Jamaji C Nwanaji-Enwerem, MD, PhD, MPP; Brian Antono, MD, MPH

In this reflection piece, the authors describe a hypertension follow-up visit and draw attention to an often overlooked aspect of a patient’s health: their occupational and environmental history. This article specifically addresses the critical question of how primary care physicians and clinicians can think about, and address, occupational and environmental health hazards in their assessment and treatment of chronic disease in patients.

152  **2021 Reviewer Acknowledgment**
SENIOR EDITORS

James J. Annesi, PhD, FAAHB, FTOS, FAPA
Professor, School of Health Professions
University of Alabama at Birmingham, USA

Gus M. Garmel, MD, FACEP, FAAEM
Clinical Professor of EM (Affiliate) Stanford University
Senior Emergency Physician
Kaiser Permanente Santa Clara Medical Center
Santa Clara, CA, USA

Eric Macy, MD, MS, FAAAAI
Department of Allergy
Kaiser Permanente San Diego Medical Center
Southern California Permanente Medical Group
San Diego, CA, USA

David Riley, MD
Director, CARE - health research reporting
guidelines for case reports
Founder, Scientific Writing in Health and
Medicine and CARE-writer
Network Director, HSCaseRepRN case report
preprint server (Elsevier)
Adjunct Professor, Maryland University of
Integrative Health
Portland, OR, USA

H. Nicole Tran, MD, PhD
Internal Medicine Physician,
Department of Adult and Family Medicine Director
for Quality Improvement and
Patient Safety, Internal Medicine Residency
Kaiser Permanente Oakland Medical Center
Oakland, CA, USA

ASSOCIATE EDITORS

Joshua Barzilay, MD
Endocrinologist, The Southeast
Permanente Medical Group Professor
of Medicine, Emory University
School of Medicine
Adjunct Investigator, Center for
Research and Evaluation, KPGA
Atlanta, GA, USA

Somjot (Sam) Brar, MD MPH
Chief/Director, Regional Department
of Cardiac Catheterization Kaiser
Permanente Medical Center,
Los Angeles, CA, USA
Assistant Clinical Professor
of Medicine, UCLA
Los Angeles, CA, USA

Carrie Davino-Ramaya, MD
Practice Leader and Methodologist
of Guidelines and
Evidence-Based Medicine
Department of Quality Management
and Systems
Northwest Permanente, P.C.
Portland, OR, USA

Kimberly L. Ferrante, MD, MAS
Division of Urogynecology
Department of Obstetrics and
Gynecology
Southern California Kaiser
Permanente Medical Group
San Diego, CA, USA

Lisa J. Herrinton, PhD
Research Scientist, Division of
Research Kaiser Permanente
Northern California
Oakland, CA, USA

Tom M. Judd, MS, CPHIMS, CPHQ,
CCE, FACCE, FHIMSS, FAIMBE
Information Technology and Quality
Former National Project Director
Kaiser Permanente Clinical
Technology Marietta, GA, USA
Health Technology Advisor
World Health Organization
Washington, DC, USA
Board Chair, Global Clinical
Engineering Federation

Raina Phillips, MD, FACP, FAAP
Internal Medicine and Pediatrics,
The Southeast Permanente
Medical Group
Adjunct Clinical Professor,
Department of Internal Medicine,
Emory University
Atlanta, GA, USA

Chunyuan Qiu, MD, MS
Director, Perioperative Service
Chief, Department of Anesthesiology
and Perioperative Medicine
Kaiser Permanente
Baldwin Park Medical Center
Baldwin Park, CA, USA

Calvin Weisberger, MD, FACC, FACP
Cardiologist Partner Emeritus
Southern California Permanente
Medical Group Pasadena, CA, USA
Chairman, Southern California
Regional Product Council
Los Angeles, CA, USA

Scott S. Young, MD
Associate Executive Director,
Clinical Care and Innovation
Senior Quality Director
The Permanente Federation
Oakland, CA, USA
Senior Medical Director and
Executive Director, Care Management
Institute Oakland, CA, USA

Pat Zrelak, RN, PhD, FAHA,
NEA-bc, CNRN, SCRN
Clinical Practice Consultant Clinical
Education, Practice, & Informatics
Kaiser Permanente
Sacramento, CA, USA

EDITORIAL & PUBLISHING OFFICE
Carly Marker: Managing Director
Jennifer Kuhn: Publications Director
Harrington Weihl: Managing Editor
Kerri Hughes: Assistant Editor
Technica Editorial Services: Composition services
In early spring of 2020, I was asked to serve as the interim editor-in-chief for *The Permanente Journal (TPJ)* during a time of evaluation of its mission and future direction. My professional life has been devoted to caring for patients within an integrated, organized system of care. Having just stepped down from a series of leadership roles that focused on supporting continuous quality improvement, a better care experience for patients, and the efficient and appropriate use of medical resources, I welcomed the opportunity to continue my professional passion through the pages of this journal.

My charge was straightforward: maintain our valued Medline indexing status and the high reputation of the journal while the reimagining work unfolded. During my tenure, with the assistance of my editorial and managerial colleagues and staff, we worked to lay the groundwork for the forthcoming revitalization.

We reinforced the scientific integrity of *TPJ* through more discerning acceptance criteria; narrowed the concept scope of our manuscripts; reorganized and expanded our editorial board to be more diverse in terms of geography, clinical and scientific background, age, race, and ethnicity; and refined the editorial processes to better reflect best practices in scholarly publishing. Knowing I played a role in supporting the journal and, hopefully, making some incremental improvements during this challenging transitional period is a source of great satisfaction for me.

I had a lot of help. Because I had little background in running a scholarly journal and my transition time was short, my learning curve was extremely steep. I was fortunate to have many talented individuals assist and support me in the work. I give recognition and thanks to Monica Leigh, our former senior managing editor. Her team from KWF Editorial have been superb partners. Monica is a patient teacher, wise counselor, and first-class editor. My senior and associate editors, despite demanding clinical and administrative responsibilities, worked tirelessly to uphold the integrity and the intellectual rigor of *TPJ*. Manuscript submissions to the journal remain strong. In 2021, we published 122 articles and showcased an impressive 35 days’ average time to first editorial decision. I thank them wholeheartedly for their support and encouragement.

We all owe a collective debt of gratitude to our many peer reviewers. Reviewing requires deep expertise, a precious investment of time, and a commitment to the scientific process. Without our peer reviewers, trust in academic publishing would be undermined. The names of our devoted peer reviewers are published in this issue as a recognition and thanks for the important service they provide.
Behind the scenes, a capable and proficient Steering Committee met regularly to help shape TPJ’s path forward. Their work resulted in TPJ’s new aims and scope as well as other exciting new developments, including a new website that will launch later this year. The committee reaffirmed that TPJ will continue to publish open access, at no cost to authors or funding agencies, eliminating what many authors cite as the most challenging obstacle to participation in scholarly activities.

Finally, and most profoundly, during my tenure, 2 separate and wholly unanticipated events impacted the content and direction of this journal. Both served to underscore and further convince me of TPJ’s tremendous potential and why it will be an important and relevant journal in the years ahead.

The month I started, the COVID-19 pandemic fully broke with all its attendant trauma, pain, and disruption to our communities, our economy, and our personal and professional lives. Less than 3 months later, the murder of George Floyd generated an outpouring of grief, anger, and rage over the enduring harm and damage caused by hundreds of years of persistent, unexamined, and unacknowledged systemic racism. Both events will undoubtably continue to impact our national life for years to come.

For those of us involved with health care, the effects of these events will be especially profound. The global pandemic and the acknowledgment of the impact of systemic racism have rightly and necessarily ushered in a new era of reckoning for health care. They have stripped away so many illusions and clearly exposed the terrible inequities imposed upon people and communities by what we used to more benignly refer to as the “social determinants of health.”

The health care community is hungry for answers on how to address these issues and is looking for new ideas, new approaches, and new solutions. This is the “sweet spot” for TPJ. Grounded in the principles and values of Permanente Medicine and other like-minded integrated systems, its contributors have a longstanding commitment to high-quality, equitable, and affordable care for all. The Permanente Journal, moving forward, intends to be a premier publication for content related to health care delivery science; value-based and high-value care; clinical and applied research; and manuscripts on equity, inclusion, diversity, and health care disparities. It will be a journal that well-intentioned leaders, researchers, and clinicians turn to for the latest learnings in these critical areas.

After an extensive national search, Dr. G. Richard Holt has been selected as my successor. As I pass the torch and welcome him as TPJ’s next editor-in-chief, I am truly excited by what lies ahead for the journal. I welcome you to share your thoughts and feedback by writing to tpj@kp.org.
Incoming Remarks

G. Richard Holt, MD
Perm J 2022;26:22.996 • E-pub: 04/05/2022 • https://doi.org/10.7812/TPP/22.996

I am honored to accept the stewardship of The Permanente Journal (TPJ) from Dr. Tarnoff, who has served the journal with distinction and professionalism for 2 years. The role of editor-in-chief of a medical journal requires a keen appreciation of the efforts of the dedicated editorial team, editors and editorial board members, and reviewers, all of whom contribute significantly to the successful publishing of excellent, peer-reviewed applied research and clinical care articles. We especially appreciate the authors who submit their valued manuscripts to the care and disposition of TPJ, recognizing the challenging work required by them to reach publication.

This issue of TPJ marks the transition from publishing a general medical journal to that of a reimagined journal, with new primary content focused on the following topics:

- health care delivery and delivery science
- integrated health delivery systems
- value-based and high-value clinical care
- health services research.

Additionally, TPJ’s new content will emphasize diversity, equity, and inclusion in medicine, health care disparities, outcomes and quality of care, and clinical care standards that exemplify the aims and goals of TPJ.

As we transition to the new content in the next issue (26:2), we will not only be launching a new website, but also introducing new journal topic headings as well as an outreach program to identify and encourage potential authors to contribute manuscripts within the new content headings. The editorial team and I look forward to collaborating with you as we relaunch The Permanente Journal’s contributions to innovations in health care delivery and value-based health care.

Author Affiliations
G. Richard Holt, MD, MSE, MPH, MABE, D Bioethics
Editor-in-Chief
The Permanente Journal
Professor Emeritus, Department of Otolaryngology-Head and Neck Surgery
University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
Associate Professor of Clinical and Applied Science Education
University of the Incarnate Word School of Medicine, San Antonio, TX, USA
GR.Holt@kp.org

Copyright Information
© 2022 The Permanente Federation. All rights reserved.
Voices From The Permanente Journal: Examining the Past While Embracing the Future

Cuong Le, MA, MAT; Paul Bernstein, MD, FACS; Kirk Fernandes, MS

Perm J 2022;26:22.998 • E-pub: 04/05/2022 • https://doi.org/10.7812/TPP/22.998

Background

This history of The Permanente Journal (TPJ) chronicles how preceding newsletters, bulletins, oral histories, and dedicated staff paved the way for the journal’s sustained, decades-long growth.

Introduction

Since 1997, TPJ has published quarterly issues about innovative developments of America’s health care delivery systems, evidence-based research, and best practices in medicine. Additionally, the journal has emphasized human experiences by touching on the sociological and psychological aspects of medicine and delved into covering pioneering therapies and treatments. The journal began as a space for physicians and leaders to share their experiences, practices, and clinical research and is now transforming into a leading destination for content, focusing on value-based and high-value care and health systems research. To recognize TPJ’s 2022 relaunch, this review of past newsletters, bulletins, and newly conducted oral histories reveal how people and events have led to the journal’s development and how they act as a foundation for its future.

THE BEGINNING, 1943–1950

Kaiser Permanente began with the partnership of industrialist Henry J. Kaiser and a young surgeon, Sidney Garfield, MD. Six Companies, Inc, a group of industrialists, including Kaiser, led the construction of California’s Colorado River Aqueduct project near Desert Center, California, in 1933. The project connected the Colorado River to the Los Angeles Basin. To care for the project’s workers, Dr Garfield’s Contractors General Hospital, implemented a prepaid health plan for a nickel per day per worker. Dr Garfield and Kaiser expanded the prepaid program to care for 15,000 workers and their families at Kaiser’s Grand Coulee Dam worksite in Washington. When the United States entered World War II in 1941, approximately 200,000 workers became employed at Kaiser’s shipyards in California, Oregon, and Washington until the end of the war. Kaiser and Dr Garfield joined together and implemented an integrated, prepaid health plan to care for thousands of diverse shipyard workers and their dependents.

TPJ inherited the legacy of the Permanente Foundation Medical Bulletin, which was first published by physicians treating thousands of workers at the busy Kaiser shipyards. During World War II, a concerning increase of pneumonia cases at the Kaiser Richmond shipyards led Dr Garfield’s friend and colleague, Morris Collen, MD, to publish articles about his pneumonia treatments using penicillin in July 1943, thus establishing the Permanente
Foundation Medical Bulletin. The first issue “carried an account of medical research based on case histories from Kaiser’s shipbuilding industry.” The publication served as a medical journal and annual report for the Permanente Medical Care Plan at the Kaiser shipyards.

In the second annual report, Dr Garfield declared that “a medical care system worthy of perpetuation, in addition to being economically sound, must provide teaching, training, and research, all so necessary for the maintenance of high-quality care.”

Between 1943 and 1945, the Permanente Foundation Medical Bulletin produced 67 articles, and an additional 30 were published in other medical journals, earning praise from the New England Journal of Medicine on August 24, 1944, for maintaining the “high standards and dignity of the medical profession” (Figure 1).

Toward the end of the war, Hannah Peters, MD, and Wilson Footer, MD, published one of the first extensive cohort articles on gynecology in the industrial workplace, established cancer detection...
clinics, and provided educational programs for women about venereal diseases. Together, they made evidence-based recommendations for treating menorrhagia with vitamin B complex after following 23,000 women at the Kaiser shipyards.

After World War II ended, Dr Garfield and Kaiser joined together to open the health plan on July 21, 1945, making it available to the public. As the shipyards slowly closed, the Permanente Foundation Medical Bulletin continued publishing research articles. The increasing demand for continuing medical education and best practices in 1949 led to the publication of the Educational Proceedings of the Permanente Hospitals.

The published proceedings consisted of records of staff lectures, educational seminars, and proceedings of weekly grand rounds to provide “reviews and new developments in the field of medicine which may prove useful in the care of patients.” The Staff Education Committee published the Permanente Foundation Medical Bulletin 10 times per year. Ruth Straus became one of the longest-serving editors on the committee after joining Kaiser Permanente in 1949. The committee’s first project reported and abstracted staff education meetings for publication in the Permanente Foundation Medical Bulletin.

Straus spent the next 25 years editing for the Permanente Foundation Medical Bulletin and later became the executive editor for the Kaiser Foundation Medical Bulletin. Straus, now an experienced medical writer, helped publish the Annual Abstract Issue of the Kaiser Foundation Medical Bulletin in January 1961. The first issue included “57 articles, 2 books, a chapter in a third book, and 2 sections in scientific encyclopedias” published by Permanente physicians in national journals from the previous year.

TOWARD A NATIONAL MEDICAL JOURNAL, 1951–1976

In 1951, Alfred Bolomey, MD, a physician with The Permanente Medical Group at Kaiser Permanente’s Oakland Hospital, known as Kaiser Oakland Medical Center today, proposed the distribution of “abstracts from staff education proceedings to staff doctors, residents, and interns” (Figure 2). Dr Bolomey served as the editor in chief, and Straus became the editorial assistant. His proposal brought Irving Lomhoff, MD, Carl Fisher, MD, and Paul Levatin, MD, from the Staff Education Committee as editors for the new publication. Together they produced a modest gray pamphlet known as the Kaiser Foundation Medical Bulletin.

Unlike the previous periodicals and bulletins, the Kaiser Foundation Medical Bulletin became more comprehensive in 1951 by including content from Kaiser Permanente’s 4 hospitals, serving approximately 50,000 members in 3 states. Eventually, doctors worldwide requested to be on the bulletin’s mailing list. By 1954, the bulletin replaced its humble gray color for a “Kaiser-green jacket, with text set in clean ‘hot type’ on glossy paper that permitted illustrations of textbook caliber.”

During the Kaiser Foundation Medical Bulletin’s first decade, editors and staff attended lectures and conferences hosted by each hospital’s staff education program. Straus, now an experienced medical writer, helped publish the Annual Abstract Issue of the Kaiser Foundation Medical Bulletin in January 1961. The first issue included “57 articles, 2 books, a chapter in a third book, and 2 sections in scientific encyclopedias” published by Permanente physicians in national journals from the previous year.

Clifford H. Keene, MD, an ironworker turned surgeon from New York, served as the general manager of the Kaiser Permanente Medical Care Program and chair of the Kaiser Foundation Medical Bulletin’s editorial board in 1961. Dr Keene’s foreword in the first Annual Abstract Issue conveyed his hope that the bulletin would cultivate “the young and expanding hospital staffs’ interest and skill in scientific writing” and a desire that such “curiosity enhanced the professional climate of our hospitals and [could not] help but benefit the community.
After Ruth Straus retired in 1976, references to either the Kaiser Foundation Medical Bulletin or the Annual Abstract Issue stopped appearing in newsletters, hinting at the end of their respective publications (Figure 3). Another internal periodical would not emerge for 18 years, this time in the Kaiser Permanente Northwest region. The book Permanente in the Northwest, by Ian McMillan, MD, mentions a periodical known as the Permanente Practice, but its origins and further details remain missing from other archival sources. When the Permanente Practice stopped publishing, a new journal emerged in its place, originating with the staff of the Northwest Permanente Medical Group’s Department of Continuing Medical Education.

A NEW BEGINNING
The Northwest Permanente Journal of Clinical Practice came together when Tom Janisse, MD, a Northwest Permanente anesthesiologist, became the interim director of Continuing Medical Education while Phillip Brenes, MD, a Northwest Permanente pediatrician, took a sabbatical year in the early 1990s. As interim director, Dr Janisse took note of widely read department newsletters, such as the Department of Pharmacy, NWP Continuing Medical Education, Medical Legal, and Dermatology Update. He proposed that they gather all these newsletters to start a journal with their respective editors. The first several issues were printed in their respective formats to maintain each department’s uniqueness.

The quarterly publication was “directed to the clinicians of Northwest Permanente and intended to be a major forum for the exchange of clinical information relevant to the practice of medicine in Kaiser Permanente’s Northwest region.” Dr Brenes became the editor in chief, and Dr Janisse became the associate editor in chief. Although the periodical served the physicians of a specific geographic region of Kaiser Permanente, its publication picked up the historical baton left by Ruth Straus’ retirement. Like the Kaiser Foundation Medical Bulletin, the Northwest Permanente Journal of Clinical Practice included an “Abstracts” section like the Annual Abstracts Issues by Straus. This section contained reviews by Northwest Permanente physicians of medical and surgical journal articles across multiple disciplines and specialties to provide a forum where current practitioners could connect and exchange new ideas or practices.

The Northwest Permanente Journal of Clinical Practice distinctly included literature beyond scientific research and clinical practice common in medical journals and previous bulletins. Physicians published their “rich talent and clinical skills” while showcasing their “wide range of experiences from a variety of sources that influence clinical practice.” The new journal’s organic expansion beyond clinical research and practice literature reflected the multifaceted characteristics in the practice of medicine.

A new section, “Soul of the Healer,” located toward the end of each issue’s table of contents, provided an opportunity for practitioners to share creative pieces on the social and psychological aspects of medicine, a genre that later came to be called narrative medicine. Other sections in the journal “flavored by the humanities” included the “Practice Highlights” and “Letters” sections. When the Northwest Permanente Journal of Clinical Practice suspended publication at the beginning of 1997, the “Soul of the Healer” section transitioned to TPJ.

Figure 3: Ruth Straus from KP Reporter 1960.
A VOICE OF PERMANENTE, 1997

Although the Northwest Permanente Medical Group’s compendium of newsletters and distinctive formatting had merged into a more standardized style, it was still not an organization-wide journal like the Kaiser Foundation Medical Bulletin. The Permanente Federation’s 1997 formation created the national leadership organization for the independently practicing Permanente Medical Groups to optimize care delivery following the philosophy and practice of Permanente Medicine. The organization’s relationships and networks provided the opportunity for a programwide journal.

Dr Janisse, then acting as Northwest Permanente’s associate medical director in 1997, discussed the creation of TPJ with Francis J. Crosson, MD, The Permanente Federation’s executive director at the time. Dr Crosson welcomed the idea and understood the goal for a journal to have a broader readership. Similarly, Dr Janisse recognized The Permanente Federation’s need to establish a national voice for the Permanente Medical Groups.

Dr Crosson’s support, combined with the continued successful partnership with the Kaiser Foundation Health Plan and Hospitals, served as the foundation for a new medical journal. Dr Janisse became TPJ’s founding editor in chief. The new journal helped the Permanente Medical Groups come together and provide physicians with a space to discuss best practices and learn about programs in their departments.

The first issue of TPJ opened with “The Voice of Permanente,” where Dr Janisse outlined the journal’s goals, creating its identity and purpose for the next decade. First, it was decided that the journal must “promote and support Kaiser Permanente’s goal of bringing increased value to our members and communities.” Furthermore, TPJ set out to inspire “critical thinking in day-to-day clinical practice and encourage the description of clinical experience in a managed care setting.”

Dr Janisse described Kaiser Permanente and TPJ as having “an obligation to promote research into clinical practices and set the standards and communicate” them to improve quality and patient outcomes. Such goals included the well-being of physicians and clinicians who expressed aspects of their work through artistic media, such as drawings, poetry, and even comic strips.

In its past, art and photographs by talented physician contributors adorned the journal’s front cover (Figure 4). Dr Janisse connected with a community of artists, photographers, illustrators, writers, and sculptors when he lived in Volcano, a small town at the foothills of the Sierra Nevada. Together they founded The Volcano Review, a quarterly publication that preserved the town through the perspectives of local artists, inspiring Dr Janisse to include the “Soul of the Healer” section in TPJ. “Physicians even back then, or probably forever, have been artists,” said Dr Janisse. Drawings often conveyed how clinicians felt about current health crises, such as smoking, or included historical artifacts, as was the case in “Stamp: The Doctor” from 1947 in the journal’s Winter 2007 issue (Figure 5). Although discontinued, this rich content is still available in TPJ’s archives online.

In TPJ’s first decade, it faced the need for more contributors from outside of Kaiser Permanente. To achieve this aim, Dr Janisse attended conferences...
where major health partners and organizations were also present. He spoke with the researchers presenting at the conferences and introduced them to TPJ as a space to publish their research. Unlike other national medical journals, TPJ was free to read and had no publication charges for authors, which helped increase contributions.

After a successful first decade, the journal started to look toward its future as a national medical journal, which meant becoming indexed in MEDLINE, an index of biomedical journals managed by the National Library of Medicine. Known as the second-decade strategy by the TPJ editorial team, Dr Collen, then in his late 80s, helped begin the process of obtaining this important indexing milestone in the early 2000s. During the process, Dr Collen’s top advice included suggestions to 1) order original research or feature articles first, 2) place abstracts and editorials to the back, and 3) focus on medical articles. Although Dr Janisse continued to support the uniqueness and warmth of social science articles, there was a notable decline in contributions to the “Soul of the Healer” section. Dr Collen agreed that such pieces were acceptable, recognizing the importance of psychosocial research. Despite reductions in artistic and literary pieces, Dr Janisse remarked that physicians’ artistic expressions intersected with their clinical practices. The current senior editor, Gus Carmel, MD, FACEP, FAAEM, debuted his “Image Diagnosis” section in 2010 and balanced medicine and art by providing teaching moments for readers with X-rays or diagrams. As a physician, academic, writer, and teacher, Dr Carmel has described the section as a space where someone could grasp complex topics in a short amount of time.

Since 2006, TPJ’s layout and contents has followed headings and sections from the National Library of Medicine. In 2012, the journal became officially indexed in MEDLINE, marking a significant milestone. Having achieved this important goal, the journal thrived throughout its second decade, increasing the number of authors inside and outside of Kaiser Permanente. Like the Kaiser Foundation Medical Bulletin’s international reach, the journal’s authors originated from many parts of the world, including Ireland, Italy, Germany, Japan, Turkey, and Singapore.

TPJ’s website, launched in 2007, expanded the journal to an even wider audience. Useful statistics became available for review by editors and historians. In 2016, the journal accumulated 1.5 million article page views in PubMed, and its website received about 250,000 views. International users visited from more than 180 countries and territories. Following the MEDLINE indexing milestone, the journal was also indexed in PubMed Central, EBSCO Academic Search Complete, and CrossRef. Southern California Permanente Medical Group allergist and senior editor for the journal, Eric Macy, MD, attributed the readership numbers and sources to TPJ’s uniqueness in its free access.

In March 2020, Dr Janisse retired as the journal’s founding editor and Stephen Tarnoff, MD, former president and executive medical director of Washington Permanente Medical Group, accepted the call to become interim editor in chief. THE FUTURE OF TPJ Dr Tarnoff, an avid reader of TPJ for more than 20 years, became attracted to the journal “because it was an atypical source for clinical practice, innovations, and ideas.” Nicole Tran, MD, PhD, an internal medicine physician with The Permanente Medical Group, became senior editor during the transition. Dr Tran started reviewing articles for the journal in 2011 and became interested in including residents in the journal’s editorial process. She accepted an invitation to visit the journal’s editorial team in Portland to propose her new ideas. Like Dr Carmel, Dr Tran described the journal as a teaching space, leading her to propose the idea of “making physicians in training aware of the journal and learning the ins and outs of what happens to an article from the point it is submitted to the point it is reviewed” and published.

One of Dr Tran’s memorable projects was TPJ’s special edition about women in medicine in 2020.
Together with the executive director of the American Medical Women’s Association and fellow physician at The Permanente Medical Group, Eliza Lo Chin, MD, MPH, we wanted to share a special collection of articles about and from women in medicine both within and outside of Kaiser Permanente,” said Dr Tran. She explained that this collaboration reflects the nature of TPJ to allow Permanente physicians and authors to build connections with people in the broader community of medicine and practice.

Looking to the future of TPJ, Dr Garmel imagines that the health care community will continuously discover more value in the journal to help with their practices and support their research, and Dr Tarnoff envisions a greater focus on articles about care delivery and care delivery science.

Dr Macy hopes that the next 5 years will move the journal closer to a first-tier journal, Dr Tran foresees that the journal will experience growth in the pillars of “quality improvement, medical education, health care delivery and improvement, and equity, inclusion, and diversity.” TPJ’s historical connections from a shipyard medical bulletin to the Kaiser Foundation Medical Bulletin reflect a rich medical education and research heritage. The journal will continue to publish peer-reviewed articles about clinical practice improvements, care delivery science, and value-based medicine for patients and communities for decades to come. The full archive of TPJ’s content, from 1997 onward, is available with no barriers to access at www.thepermanentejournal.org.

REFERENCES
Clinical Decision Support to Address Racial Disparities in Hypertension Control in an Integrated Delivery System: Evaluation of a Natural Experiment

Cassondra Marshall, DrPH, MPH1; Alyce S Adams, PhD2; Lin Ma, MA2; Andrea Altschuler, PhD2; Mark W Lin, MD, MPH3; Nailah A Thompson, DO, MPH3; Joseph D Young, MD3

Perm J 2021;00:21.024 • E-pub: 10/25/2021 • https://doi.org/10.7812/TPP/21.024

Abstract

INTRODUCTION: Effective, equity-promoting interventions implemented by health care systems are needed to address health care disparities and population-level health disparities. We evaluated the impact of a clinical decision support tool to improve evidence-based thiazide diuretic prescribing among Black patients to address racial disparities in hypertension control.

METHODS: We employed an interrupted time series design and qualitative interviews to evaluate the implementation of the tool. Our primary outcome measure was the monthly rate of thiazide use among eligible patients before and after implementation of the tool (January 2013-December 2016). We modeled month-to-month changes in thiazide use for Black and White patients, overall, and by sex and medical center racial composition. We conducted key informant interviews to identify modifiable facilitators and barriers to implementation of the tool across medical centers.

RESULTS: Of the 318,720 patients, 15.5% were Black. We observed no change in thiazide use or blood pressure control following the implementation of the tool in either racial subgroup. There was a slight but statistically significant reduction (2.32 percentage points, p < 0.01) in thiazide use among Black patients following the removal the tool that was not observed among White patients. Factors affecting the tool’s implementation included physician and pharmacist resistance to thiazide use and a lack of ongoing promotion of the tool.

DISCUSSION: The clinical decision support tool was insufficient to change prescribing practices and improve blood pressure control among Black patients.

CONCLUSIONS: Future interventions should consider physician attitudes about thiazide prescribing and the importance of multilevel approaches to address hypertension disparities.
Introduction

Effective, equity-promoting interventions implemented by health care systems are needed to address health care disparities and population-level health disparities. Pragmatic strategies that can be scaled and integrated into routine care to address health disparities, particularly in large, diverse health care settings, are needed, and health care leaders must identify determinants of disparities that are potentially modifiable through health system intervention. One key challenge for health care systems is the identification of modifiable determinants of suboptimal blood pressure management among Black patients.1,2

Hypertension is a leading cause of preventable disease and death in the United States,3 and racial disparities in hypertension prevalence and control are well-documented and persistent.4 Approximately 40% of non-Hispanic Black adults have hypertension, the highest prevalence among all US racial/ethnic groups, and Black adults have higher rates of uncontrolled hypertension than non-Hispanic White adults.3 While the causes of hypertension-related disparities are multi-factorial and include factors related to individual patients, their support systems, local and policy environments as well as clinicians and systems,5 one key aspect of uncontrolled hypertension is appropriate medication therapy. Guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure indicate that thiazide diuretics are recommended as first-line therapy for uncomplicated hypertension and frequently should be added to treatment regimens to improve blood pressure control.6 Thiazide diuretics may be especially effective in the control of hypertension and in the prevention of strokes among Black patients.6–8

However, evidence suggests suboptimal prescribing among clinicians with respect to the Joint National Committee recommendation,4,9 resulting in an underuse of these medications in clinical practice. Thus, the promotion of the use of thiazide diuretics at clinically effective doses in routine clinical practice is one strategy that health systems can use to address racial disparities in hypertension control. In 2015, Kaiser Permanente Northern California (KPNC) implemented a region-wide clinical decision support tool to identify Black patients with poor blood pressure control who might have benefited from thiazide diuretic initiation or intensification.10 Given that health systems’ quality improvement efforts to address disparities are understudied11 and a need for greater attention to hypertension implementation and dissemination research specifically for African American patients,12 the purpose of present study was to evaluate the tool’s real-world effectiveness in improving thiazide use among Black relative to White patients.

Materials and Methods

SETTING AND DESCRIPTION OF CLINICAL DECISION SUPPORT INTERVENTION
KPNC is a large integrated delivery system consisting of 250 medical offices serving over 4.5 million members in a 13-county area of Northern California. KPNC has a robust population management infrastructure for hypertension,13 a hypertension quality measure linked to financial incentives for each facility, and an equity-specific measure on hypertension control among Black patients that is shared on a monthly basis with senior leadership. In January of 2015, KPNC implemented a decision support tool region-wide designed to aid clinical care teams in the identification of Black patients at risk for suboptimal use of thiazide diuretics and to facilitate clinically appropriate changes in treatment. The tool utilized data from the electronic health record (EHR), including pharmacy data, to identify patients with poor blood pressure control who were potentially eligible for changes in treatment (ie, no known allergy to thiazides or thiazide-like diuretics). The tool was designed to be used by medical assistants to identify patients for targeted outreach. Once identified, patients were contacted by a medical assistant to encourage repeat blood pressure measurement. Patients whose tests indicated persistent poor control were then contacted by a pharmacist to discuss thiazide use. The tool was implemented following a brief pilot test in one medical center to assess feasibility.14 All quality improvement managers received training on the tool at a region-wide meeting in February 2015, which included education about disparities in hypertension among Black patients and training in effective communication strategies. The clinical decision support tool was available to health care teams starting in January 2015. However, due to a change in pharmacy management systems, the tool was phased out across the system over a period of time between September 2015 and April 2016.
STUDY DESIGN
We employed an interrupted time series (ITS) design to test whether the proportion of Black patients using thiazides increased after the implementation of the thiazide tool (tool off/on/off again). We also conducted key informant interviews to identify modifiable facilitators and barriers to the tool’s implementation. This study was approved by the Institutional Review Board of the Kaiser Foundation Research Institute.

Qualitative Data
We conducted interviews with quality and operations leaders to understand the context of decision-making related to thiazide diuretics and knowledge and use of the tool. We used purposive sampling to select the participants, focusing on the medical centers serving a higher and lower proportion of Black patients in the region. We developed a theory-informed, semi-structured interview to assess how the tool was used, who used the tool, and general impressions of its utility. All interviews were recorded and transcribed. Three authors (CM, ASA, AA) coded interview transcripts using a thematic approach to identify salient themes as well as barriers and facilitators to the tool’s implementation. Themes were mapped to a commonly used implementation science framework.

Setting and Study Population
Our sample included Black and White patients aged 18 to 85 with diagnosed hypertension between January 2013 and December 2016. Patients were required to have at least one inpatient diagnosis or two outpatient diagnoses of hypertension (n = 819,300). We excluded patients based on age (269,458), non-Black or White race (n = 17,310), and with known allergies to thiazide or thiazide-like diuretics (n = 28,080). Allergies were ascertained from the EHR. To ensure stable population characteristics over time and complete data on thiazide use, we required that patients be alive for the entire study period and have continuous enrollment for at least 10 months per year. The final analytic cohort consisted of 49,035 Black and 269,415 White patients (Figure 1). Table 1 describes the baseline characteristics of the study cohort by race.

Measures
All data were extracted from the patient EHR. The primary outcome was the monthly proportion of patients with a prescription for a thiazide (thiazide use). Thiazide use referred to any thiazide use during the month (new users or ongoing users). Patients needed to have at least 1 day of drug coverage per month. Thiazides under study were: hydrochlorothiazide, chlorthalidone, metolazone, indapamide, chlorothiazide, and methyclothiazide. Combination therapy was included. Secondary outcomes included the proportion of patients whose blood pressure was controlled and the proportion of patients using an optimal dosage of thiazides. Blood pressure control was defined as blood pressure >139/89 for patients younger than 60, >139/89 for patients 60 or older who had evidence of diabetes, and 149/89 for patients 60 or older who had no evidence of diabetes. Suboptimal dosages were defined as <50 mg/d for hydrochlorothiazide, <25 mg/d for chlorthalidone, <5.0 mg/d for metolazone, <2.5 mg/d for indapamide, <500 mg/d for chlorothiazide, and <2.5 mg/d for methyclothiazide. We created separate dichotomous variables to indicate before the clinical decision support tool was turned on, was available, and was turned off. We also characterized patients into subgroups by race (Black, White), age (18-44/45-64/65-85), sex (male/female), and the racial composition of the home medical facility (≥20% Black, <20% Black) to facilitate stratified modeling approaches. In this setting, race and ethnicity are available in the EHR and primarily self-reported.
Data Analysis
We used contingency tables ($\chi^2$) to examine differences in characteristics between Black and White patients in the sample. To examine the impact of the clinical decision support tool on thiazide use and dosing, we used segmented regression models to evaluate the effect of the introduction and subsequent removal of the tool on the proportion of thiazides prescribed among Black and White patients. Segmented regression analysis of ITS data allowed us to evaluate the immediate discontinuity and longer-term slope change in thiazide use after the introduction of the thiazide tool. For the ITS models, we excluded patients from one medical center (n = 15,995) due to the presence of a co-occurring intervention to address hypertension disparities in that setting. The periods before, during, and after the implementation period constitute the three segments of the regression models. For these models, baseline (January 2013 to December 2014), time the tool was active (January to December 2015), and time the tool was off (January to December 2016) were 24, 12, and 12 months, respectively. To control for a phase-in and phase-out period, we excluded the observations between December 2014 and February 2015 and December 2015 and March 2016, respectively. We chose December 2015 to March 2016 for the phase out period as this represents when approximately 50% of the service areas within KPNC had changed over to the new pharmacy management system that led to the phase out of the tool. We had at least 8 monthly observations before and after the introduction of the thiazide tool to have sufficient power to estimate regression coefficients. Our models controlled for autocorrelation by testing for first-order autoregressive processes and correcting for significant correlations. We also tested for nonlinearity of the models. The effect of the thiazide tool for Black patients and White patients was estimated separately. We also constructed models to examine changes in thiazide use among Black and White patients by age, sex, and facility. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

Results

QUALITATIVE FINDINGS
We interviewed six quality and operations leaders at five medical centers. There was considerable variation among the key informants with respect to their knowledge of the tool and its purpose. Interviews revealed that an existing and ongoing interest in addressing racial disparities in hypertension control facilitated use of the thiazide tool. In addition, the presence of a champion, that is, a staff member who was dedicated to patient outreach for hypertension control, also positively influenced the tool’s implementation. For example, one medical center described having a medical assistant who was especially effective in interacting with and motivating elderly patients to come in for blood pressure retesting.

In terms of barriers and challenges related to the thiazide tool faced by the medical centers, some participants reported limited awareness of the tool and its purpose. This was described as possibly due to the absence of ongoing messages from health system leadership about the thiazide tool. Another identified barrier was the presence of competing priorities, including other ongoing hypertension-related quality improvement initiatives at the medical center. Some key informants described being focused on these initiatives, such as a program for home blood pressure monitoring, as opposed to the tool. Another barrier was that there appeared to be some level of clinician resistance and hesitation regarding prescribing thiazides at higher dosages. Despite the existence of a systemwide guideline relating to the use of thiazides as first line therapy for Black patients in this setting, some key informants described concerns regarding the safety of thiazides at higher dosages.
dosages for patients with hypertension. This belief, which was mentioned as being connected to postgraduate education and training for physicians and pharmacists, contributed to an underutilization of the thiazide tool. Table 2 summarizes the key facilitators and barriers.

**QUANTITATIVE FINDINGS**

**Baseline Characteristics** Of the 298,921 patients included in the ITS models, 13.4% of patients were Black (Table 3). A significantly greater proportion of Black patients were women compared to White patients (58.2% versus 50.2%). At baseline, the proportion of patients with their blood pressure controlled was 83.1% for Black patients compared to 89.7% for White patients, a gap of 6.6 percentage points (Table 4). Thiazide use was higher among Black patients than White patients at baseline (40.8% versus 35.2%) (Table 3); with Black women having the highest rates of thiazide use.

**Changes in Thiazide Use Among Black and White Patients** Overall, throughout KPNC, the proportion of Black patients using thiazides was stable before and after the introduction of the thiazide tool (Table 3). The implementation of the tool was not associated with a statistically significant immediate increase (Black patients: 0.25 percentage point increase; p = 0.58) or increasing trend (Black patients: 0.02 percentage point decrease; p = 0.69) in the proportion of thiazide use. However, following the removal of the tool, we observed an immediate 2 percentage points decrease in the proportion of Black patients using thiazides (p < 0.01). This change was consistent across sex- and age-specific subgroups. The proportion of White patients using thiazides was stable throughout the study period.

Figure 2 depicts time series of changes in the proportion of Black and White patients using thiazides by facility before and after the introduction and removal of the thiazide tool. We observed an increasing trend in the proportion of thiazide use among Black patients in facilities with less than 20% of Black patients following the introduction of the tool, although this did not reach statistical significance (0.1 percentage points; 95% confidence interval [CI]: −0.0, 0.2) (Table 3). Following the removal of the tool, there was a statistically significant reduction in the proportion of Black patients using thiazides in these facilities (2.3 percentage points; 95% CI: −3.9, −0.8). Thiazide use among White patients at both facility types was stable following the introduction and removal of the tool (Table 3).

There were no clinically or statistically significant changes in blood pressure control for either Black or White patients before or after the intervention. Table 4 presents the proportion of Black and White patients in control at baseline, while the tool was active, and after the tool was inactive. The proportion of patients with a suboptimal thiazide dose was similarly stable across the study period (Table 4).

**Discussion**

The purpose of this study was to evaluate an EHR embedded tool designed to improve thiazide use among Black patients with poor blood pressure control and reduce disparities in hypertension control within an integrated delivery system. Over the 4-year study period, there were no clinically significant changes in blood pressure control for either Black or White patients before or after the intervention.

<table>
<thead>
<tr>
<th>COM-B Category</th>
<th>Barriers</th>
<th>Facilitators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capability</td>
<td>• Little knowledge of thiazide tool and/or tool’s purpose</td>
<td>• High awareness of tool and tool’s purpose</td>
</tr>
<tr>
<td>Opportunity</td>
<td>• Lack of ongoing messages about tool from health system leadership</td>
<td>• The presence of other facility-initiated hypertension projects</td>
</tr>
<tr>
<td></td>
<td>• Tool was not designed to be used for use during a clinical encounter</td>
<td></td>
</tr>
<tr>
<td>Motivation</td>
<td>• Clinician and pharmacist concern about safety of thiazides at certain dosages</td>
<td>• An already-existing interest in and motivation towards addressing racial disparities in hypertension</td>
</tr>
<tr>
<td></td>
<td>• Belief that tool was just ‘one more thing to do’ in the presence of many other tasks and quality improvement initiatives</td>
<td>• Belief that the tool was useful and valuable</td>
</tr>
<tr>
<td></td>
<td>• The presence of a “champion”</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Barriers and facilitators of the use of the thiazide tool mapped to the Capability, Opportunity, and Motivation (COM-B) model. COM-B = Capability, Opportunity, and Motivation model.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>%</th>
<th>Observed thiazide use at baseline (%)</th>
<th>Baseline Trend Estimate (95% CI)</th>
<th>P</th>
<th>Introduction of thiazide query (95% CI)</th>
<th>P</th>
<th>Post-Introduction Trend Change Estimate (95% CI)</th>
<th>P</th>
<th>Removal of thiazide query (95% CI)</th>
<th>P</th>
<th>Post-Removal Trend Change Estimate (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black patients 18-44</td>
<td>5,451</td>
<td>2.02</td>
<td>2798</td>
<td>0.17 (0.16, 0.18)</td>
<td>&lt;0.001</td>
<td>0.46 (0.10, 1.02)</td>
<td>0.1</td>
<td>0.04 (0.04, 0.11)</td>
<td>0.31</td>
<td>-1.27 (-1.96, -0.58)</td>
<td>&lt;0.001</td>
<td>0.001 (0.01, 0.11)</td>
<td>0.98</td>
</tr>
<tr>
<td>White patients 18-44</td>
<td>16,826</td>
<td>5.48</td>
<td>21.38</td>
<td>0.18 (0.15, 0.21)</td>
<td>&lt;0.001</td>
<td>-0.20 (-1.13, 0.74)</td>
<td>0.67</td>
<td>-0.004 (-0.12, 0.11)</td>
<td>0.95</td>
<td>-0.07 (-1.18, 1.03)</td>
<td>0.89</td>
<td>-0.05 (-0.21, 0.10)</td>
<td>0.47</td>
</tr>
<tr>
<td>Black patients 45-64</td>
<td>21,826</td>
<td>8.37</td>
<td>4219</td>
<td>0.05 (0.01, 0.09)</td>
<td>0.01</td>
<td>0.42 (-0.66, 1.50)</td>
<td>0.44</td>
<td>-0.05 (-0.18, 0.08)</td>
<td>0.41</td>
<td>-1.60 (-2.89, -0.32)</td>
<td>0.02</td>
<td>0.16 (-0.02, 0.33)</td>
<td>0.07</td>
</tr>
<tr>
<td>White patients 45-64</td>
<td>112,048</td>
<td>36.55</td>
<td>34.67</td>
<td>0.05 (0.04, 0.07)</td>
<td>&lt;0.001</td>
<td>-0.49 (-1.19, 0.22)</td>
<td>0.17</td>
<td>-0.003 (-0.09, 0.08)</td>
<td>0.94</td>
<td>-0.56 (-1.66, 0.55)</td>
<td>0.31</td>
<td>-0.004 (-0.12, 0.01)</td>
<td>0.94</td>
</tr>
<tr>
<td>Black patients 65+</td>
<td>12,637</td>
<td>5.08</td>
<td>43.86</td>
<td>-0.15 (-0.17, -0.14)</td>
<td>&lt;0.001</td>
<td>0.02 (-0.56, 0.60)</td>
<td>0.95</td>
<td>0.02 (-0.05, 0.10)</td>
<td>0.53</td>
<td>-1.73 (-2.45, -1.00)</td>
<td>&lt;0.001</td>
<td>0.19 (0.08, 0.31)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>White patients 65+</td>
<td>130,133</td>
<td>42.51</td>
<td>37.24</td>
<td>-0.11 (-0.13, -0.10)</td>
<td>&lt;0.001</td>
<td>-0.51 (-1.39, 0.37)</td>
<td>0.24</td>
<td>-0.01 (-0.11, 0.08)</td>
<td>0.86</td>
<td>-0.24 (-1.56, 1.09)</td>
<td>0.71</td>
<td>0.03 (-0.08, 0.14)</td>
<td>0.6</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black females</td>
<td>23,213</td>
<td>58.2</td>
<td>44.66</td>
<td>-0.03 (-0.04, -0.01)</td>
<td>&lt;0.001</td>
<td>0.35 (-0.41, 1.10)</td>
<td>0.36</td>
<td>-0.02 (-0.12, 0.08)</td>
<td>0.7</td>
<td>-1.74 (-3.14, -0.35)</td>
<td>0.02</td>
<td>0.25 (0.12, 0.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White females</td>
<td>129,935</td>
<td>50.2</td>
<td>39.12</td>
<td>-0.04 (-0.07, -0.01)</td>
<td>0.01</td>
<td>-0.16 (-0.97, 0.65)</td>
<td>0.69</td>
<td>-0.04 (-0.13, 0.05)</td>
<td>0.41</td>
<td>-0.22 (-1.11, 0.67)</td>
<td>0.62</td>
<td>0.04 (-0.08, 0.16)</td>
<td>0.52</td>
</tr>
<tr>
<td>Black males</td>
<td>16,699</td>
<td>41.8</td>
<td>35.44</td>
<td>0.02 (-0.00, 0.03)</td>
<td>0.06</td>
<td>0.21 (-0.34, 0.76)</td>
<td>0.45</td>
<td>0.01 (-0.06, 0.08)</td>
<td>0.77</td>
<td>-1.4 (-2.08, -0.72)</td>
<td>&lt;0.001</td>
<td>0.02 (-0.07, 0.02)</td>
<td>0.62</td>
</tr>
<tr>
<td>White males</td>
<td>129,070</td>
<td>49.8</td>
<td>31.30</td>
<td>-0.01 (-0.04, 0.02)</td>
<td>0.62</td>
<td>-0.01 (-0.71, 0.70)</td>
<td>0.99</td>
<td>-0.05 (-0.13, 0.04)</td>
<td>0.27</td>
<td>-0.2 (-0.93, 0.5)</td>
<td>0.59</td>
<td>0.05 (-0.06, 0.16)</td>
<td>0.38</td>
</tr>
<tr>
<td>Facility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black patients, Facility &lt;20% Black</td>
<td>26,967</td>
<td>8.56</td>
<td>41.05</td>
<td>-0.002 (-0.02, 0.01)</td>
<td>0.83</td>
<td>-0.29 (-1.11, 0.55)</td>
<td>0.48</td>
<td>0.08 (-0.02, 0.19)</td>
<td>0.1</td>
<td>-2.32 (-3.86, -0.77)</td>
<td>&lt;0.01</td>
<td>0.01 (-0.02, 0.25)</td>
<td>0.09</td>
</tr>
<tr>
<td>White patients, Facility &lt;20% Black</td>
<td>237,220</td>
<td>75.33</td>
<td>35.20</td>
<td>-0.02 (-0.05, 0.01)</td>
<td>0.17</td>
<td>-0.10 (-0.85, 0.66)</td>
<td>0.79</td>
<td>-0.04 (-0.15, 0.05)</td>
<td>0.34</td>
<td>-0.22 (-1.01, 0.57)</td>
<td>0.57</td>
<td>0.05 (-0.07, 0.16)</td>
<td>0.42</td>
</tr>
<tr>
<td>Black patients, Facility ≥20% Black</td>
<td>12,947</td>
<td>6.88</td>
<td>40.26</td>
<td>-0.01 (-0.03, 0.01)</td>
<td>0.39</td>
<td>0.75 (-0.05, 1.50)</td>
<td>0.06</td>
<td>-0.12 (-0.22, -0.02)</td>
<td>0.02</td>
<td>-0.74 (-1.70, 0.21)</td>
<td>0.12</td>
<td>0.15 (0.02, 0.29)</td>
<td>0.03</td>
</tr>
<tr>
<td>White patients, Facility ≥20% Black</td>
<td>21,787</td>
<td>9.23</td>
<td>35.54</td>
<td>-0.05 (-0.07, -0.04)</td>
<td>&lt;0.001</td>
<td>-0.04 (-0.73, 0.66)</td>
<td>0.92</td>
<td>-0.03 (-0.12, 0.05)</td>
<td>0.43</td>
<td>-0.63 (-1.75, 0.51)</td>
<td>0.27</td>
<td>0.07 (-0.03, 0.17)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Table 3: Baseline characteristics and estimated effects (in percentage points) of the introduction and removal of the thiazide query tool on thiazide use by race, gender, and facility, Kaiser Permanente Northern California, 2013-2016 (N = 298,921). CI = confidence interval. Bold type indicates statistical significance.
or statistically significant increases in thiazide use following the implementation of the tool in either racial subgroup. However, we did observe a slight but statistically significant reduction in thiazide use among Black patients following the removal of the tool that was not observed among White patients. In addition, there was a slight but clinically significant increasing trend in thiazide use among Black patients in facilities with a smaller proportion of Black patients. These findings indicate the tool may have had some limited impact on thiazide use in Black patients, but no changes were found for hypertension control.

Our findings are similar to another study that examined the impact of an educational intervention for primary care clinicians to increase thiazide prescribing overall. In that study, researchers similarly did not find differences in thiazide prescriptions and identified clinician attitudes and beliefs as one reason for the limited impact. However, another study targeting patient rather than clinician behavior reported increases in thiazide prescriptions among patients with poor blood pressure control.

We believe there are several factors that may have contributed to the limited impact of the tool. The qualitative interviews suggested several possibilities including physician attitudes toward thiazides, lack of ongoing promotion of the thiazide tool, and the limited time the thiazide tool was operational. Of note, physician concerns about thiazides and, specifically, the possibility of serious side effects have been found in other studies.

Another possible explanation for our findings is that the timing and placement of the tool may not have been optimal for the behavior required to enact change. Kawamoto and colleagues noted that clinical decision support interventions should ideally...

**Table 4:** Secondary outcomes of blood pressure control and thiazide dosing during the study period, Kaiser Permanente Northern California, 2013-2016

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Tool on</th>
<th>Tool off</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>White patients</td>
<td>Black patients</td>
</tr>
<tr>
<td>Blood Pressure control (%)</td>
<td>88.8</td>
<td>89.7</td>
<td>83.1</td>
</tr>
<tr>
<td>Optimal thiazide dose (%)</td>
<td>11.5</td>
<td>10.8</td>
<td>14.9</td>
</tr>
</tbody>
</table>
be delivered at the time and location of decision-making.22 The optimal timing and placement of the thiazide tool may be in the clinical setting prior to making treatment decisions with a patient. Instead, the tool alerted medical assistants to have patients potentially eligible for thiazides retest their blood pressure. The qualitative findings also suggested that the region-wide implementation plan may not have adequately accounted for differences in priorities across individual medical centers, thereby limiting the impact of the thiazide tool. Finally, as this is a setting with very high rates of hypertension control,23,24 the lack of movement may also reflect a ceiling effect, limiting the impact of any additional interventions.

An important finding from the interviews is that, overall, the key informants believed there were things that the health system could do to address racial disparities in hypertension control. In fact, some of the medical centers were proactively addressing racial disparities in hypertension control via other center-level initiatives. This is encouraging and suggests an openness toward innovative quality improvement interventions to address disparities.25,26 Importantly, reducing racial disparities in hypertension control likely requires addressing the barriers to hypertension control in Black patients that exist at multiple levels, including factors related to individual patients, families, communities, and policy.6,27,28 Thus, health systems should consider multilevel approaches, with clinical decision support as just one piece of the larger picture to address disparities, as it is unlikely that clinical decision support systems alone will improve clinical care.29 In one integrated system, a multilevel approach that incorporated care team redesign, improvements to access to care, programs on culturally tailored communication, as well as physician-led education on treatment guidelines, closed the gap in hypertension control between Black and White patients.26

To our knowledge, our study is one of the first to examine the impact of a clinical decision support intervention to improve thiazide use as a means of narrowing racial disparities in hypertension control by changing physician prescribing related to thiazide diuretics. Strengths of our study include a rigorous quasi-experimental study design and the use of qualitative methods to provide contextual insights. In addition, our use of the well-tested implementation science framework15 provided a structure to reveal barriers and facilitators of the implementation of the tool into the clinical workflow. Despite these strengths there are some limitations that deserve consideration. There is a possibility that patients may have obtained their prescription from outside of the KPNC health system and therefore were not captured in our analyses. However, this is unlikely as most KPNC members use KPNC pharmacies to fill their prescriptions due to the historical disparity in hypertension control between these two groups in this setting. It is possible that there are other racial/ethnic disparities that were not explored in this analysis. Finally, our findings were generated in the context of an integrated delivery system with very high publicly reported hypertension management performance13 and in which disparities have been eliminated for some subsets of the population,24 so the results may not be generalizable to other health systems. Further, a decision support tool of this nature, which involves both medical assistants in the clinical setting as well as pharmacists, may not be feasible in nonintegrated health settings.

Nevertheless, we believe this study offers lessons for health care practices and systems. Both integrated and nonintegrated health systems use population management, including hypertension registries and decision support tools, as part of their hypertension care programs.30 Our study describes one relatively simple way that technology can be leveraged (via the EHR) to address disparities and identify specific patients who may benefit from additional attention. Although we observed the thiazide tool did not improve thiazide use, our findings offer insights into future approaches that may be used to improve the impact of a thiazide decision support tool. This includes better incorporating facility-level variation in quality priorities, accounting for physician concerns about thiazide dosage, and having a clinician use the tool in the clinical setting prior to making treatment decisions with a patient. As mentioned above, decision support tools should be used as part of multilevel approach to improve care and address hypertension disparities.

**Conclusion**

Our findings suggest that, in the absence of additional educational supports, a clinical decision support tool to increase thiazide use among Black patients was insufficient to change
prescribing and did not impact blood pressure control. Future interventions may need to address variation in competing quality improvement priorities and consider strong physician attitudes about thiazide prescribing in the intervention design.\textsuperscript{31} Given challenges in changing physician prescribing behavior and the importance of multilevel approaches to address hypertension disparities, health systems and future studies consider interventions aimed at increasing patient engagement to facilitate self-efficacy and management.\textsuperscript{19}

Supplementary Materials

REFERENCES

Clinical Decision Support to Address Racial Disparities in Hypertension Control in an Integrated Delivery System


29. Sarkar U, Samal L. How effective are clinical decision support systems? BMJ 2020 Sep;370:m3499. DOI: https://doi.org/10.1136/bmj.m3499


Evaluating the Implementation of Digital and In-Person Diabetes Prevention Program in a Large, Integrated Health System: Natural Experiment Study Design

Stephanie L Fitzpatrick, PhD; Meghan Mayhew, MPH; Chris L Catlin, BS; Alison Firemark, MA; Inga Grüß, PhD; Denis B Nyongesa, MS; Maureen O’Keefe-Rosetti, MS; Andreea M Rawlings, PhD, MS; David H Smith, PhD, RPh; Ning Smith, PhD; Victor J Stevens, PhD; William M Vollmer, PhD; Stephen P Fortmann, MD

Perm J 2021;00:21.056 • E-pub: 12/13/2021 • https://doi.org/10.7812/TPP/21.056

Abstract

INTRODUCTION: Implementation of a Diabetes Prevention Program (DPP) in both in-person and digital health-care settings has been increasing. The purpose of this article is to describe the protocol of a mixed-methods, natural experiment study designed to evaluate the implementation of DPP in a large, integrated health system.

METHODS: Kaiser Permanente Northwest patients who were 19 to 75 years with prediabetes (hemoglobin A1c or glycated hemoglobin, 5.7–6.4) and obesity (body mass index ≥ 30 kg/m²) were invited, via the Kaiser Permanente Northwest patient portal, to participate in the digital (n = 4124) and in-person (n = 2669) DPP during 2016 through 2018. Primary (weight) and secondary (hemoglobin A1c or glycated hemoglobin level) outcome data will be obtained from electronic health records. A cost-effectiveness analysis as well as qualitative interviews with patients (enrolled and not enrolled in the DPP) and stakeholders will be conducted to examine further implementation, acceptability, and sustainability.

CONCLUSION: The mixed-methods, natural experiment design we will use to evaluate Kaiser Permanente Northwest’s implementation of the digital and in-person DPP builds on existing evidence related to the effectiveness of these two DPP delivery modes and will contribute new knowledge related to best practices for implementing and sustaining the DPP within large health systems over the long term.

Introduction

The prevalence of prediabetes and obesity among US adults 40 years and older is significant, with more than 30% having prediabetes and more than 40% having obesity.1,2 Prediabetes and obesity increase the risk for diabetes, cardiovascular disease, and poor quality of life, and are responsible for substantial health-care costs.3 In fact, the estimated costs of managing diabetes in the US was $327 billion in 2017, a 26% increase since 2012.3 In response to the multilevel burden of prediabetes and obesity, there have been several efforts to prevent diabetes at the population level and reduce health-care costs.4,5 including...
national implementation and reimbursement of the successful Diabetes Prevention Program (DPP).

The DPP clinical trial demonstrated conclusively that a lifestyle intervention consisting of nutrition, physical activity, and behavioral counseling was more effective in reducing the incidence of type 2 diabetes and producing clinically significant weight loss than were metformin or placebo. These findings inspired numerous translational studies across the US, conducted in different settings (eg, primary care, community, churches). Meta-analyses of these studies found modest but clinically meaningful effects of the intervention in real-world settings on weight, hemoglobin A1c (HbA1c) and other cardiometabolic risk factors. The National Diabetes Prevention Program was created in 2010 to promote DPP dissemination across the US and currently recognizes both in-person and digital (remotely delivered, primarily internet-based) DPPs that meet their standards and operating procedures.

Beginning in April 2018, the Centers for Medicare & Medicaid Services made a landmark decision to reimburse clinical and nonclinical settings for providing a DPP to Medicare beneficiaries (ie, Medicare DPP); this coverage is currently for in-person DPP only and not digital DPP. The Centers for Medicare & Medicaid Services’ decision to cover a DPP among older adults with prediabetes further catapulted efforts within health-care organizations to address the increasing number of individuals with diabetes receiving care in their facilities. The implementation and effectiveness of DPPs within large health systems—primarily the Veterans Health Administration—has been a focus of recent research. However, few studies have examined the sustainability of providing a DPP based on maintenance of the effect (ie, long-term weight change and HbA1c levels), health-care costs, participant experience, and organizational support. In addition, engaging individuals in a DPP and similar lifestyle change interventions remains a challenge, and identifying useful approaches is needed. Last, although the effectiveness of an in-person DPP is well-established, prior studies evaluating the effect of a digital DPP identified positive outcomes but had some methodological limitations, such as a single arm pre-/posttest design and participant-reported outcomes.

In 2017, Kaiser Permanente Northwest (KPNW), a large, integrated health system serving Oregon and southwest Washington, began piloting both digital and in-person versions of a DPP for its adult health plan members who were 19 to 75 years old with prediabetes (HbA1c, 5.7–6.4%) and obesity [body mass index (BMI) ≥ 30 kg/m²]. We describe a mixed-methods, natural experiment study design to evaluate this large health system initiative by assessing the effects of both a digital and in-person DPP on change in weight and HbA1c level, as well as sustainability based on cost-effectiveness and patient and health-care stakeholder perspectives. We present the approaches KPNW used to identify, recruit, and enroll patients with obesity at high risk for diabetes into a digital and in-person DPP. Furthermore, we describe the two DPP modalities and the mixed-methods approach used in this natural experiment.

Methods

SETTING
KPNW provides comprehensive prepaid health care to more than 600,000 members in Oregon and southwest Washington. All patient contacts within the system and all services referred outside are recorded in a single, comprehensive electronic health record (EHR) (KP HealthConnect, based on Epic®). Approximately 30% of KPNW members have prediabetes, 12% have diabetes, and more than 40% are obese. From 2017 through 2020, KPNW piloted both digital and in-person versions of the DPP for adult health plan members who had both prediabetes and obesity. The decision to target health plan members with both prediabetes and obesity was based on recent predictive modeling using data from more than 77,000 health plan members, which established that an HbA1c level of 6.3 to 6.4 and a BMI ≥30 were associated with more than a 15% probability of developing diabetes in 2 years. There were 2 distinct cohorts recruited by the KPNW health system for participation in the diabetes prevention programs. Cohort 1 included KPNW members who were invited by the health-care system to participate in the digital DPP, which was delivered from April 2017 through April 2018. Cohort 2 included KPNW members who were invited by the health-care system to participate in a group-based in-person DPP program across three waves of recruitment and intervention delivery from October 2017 through February 2020. Each cohort is described in further detail later.

STUDY DESIGN
We use a mixed-methods natural experiment study design to assess clinical and cost outcomes among
the two cohorts. Specifically, we will compare DPP enrollees to nonenrollees (digital DPP and in-person DPP cohorts will be analyzed separately) on changes in weight and HbA1c levels. Randomization was not feasible in this real-world implementation of the DPP; therefore, propensity score adjustment will be used to control for potential confounding. All data to be used in the analyses of clinical and cost outcomes are collected as part of standard health-care administration within the KPNW health-care system. Primary qualitative data are collected from a subset of DPP enrollees and nonenrollees in the 2 cohorts, as well as from health-care system clinicians and stakeholders. This study was approved by the KPNW Institutional Review Board (protocol no. STUDY00000693).

**ELIGIBILITY AND INTERVENTIONS**

**Digital DPP (Cohort 1).** Cohort 1 individuals met the following inclusion criteria as noted in the EHR: 1) current KPNW member 65 to 75 years old, 2) BMI ≥ 30, 3) HbA1c level between 5.7 and 6.4, and 4) no prior diagnosis of diabetes. In addition, patients had to use the KPNW electronic patient portal (approximately 80% of all KPNW members meet this criterion).

For Cohort 1, KPNW partnered with Omada Health to offer their program, a Centers for Disease Control and Prevention (CDC)–recognized translation of the DPP lifestyle intervention that is delivered in a digital format. The program consists of (virtual) small-group support, health coaching from Centers for Disease Control and Prevention–trained lifestyle coaches, a National DPP-approved curriculum, and electronic behavioral tracking tools. Participants are grouped with other individuals with similar demographics, geographic proximity, and BMI. Group participants communicate via a private social network and discussions are facilitated by a health coach. The health coach also communicates with participants through private messages or phone calls, and provides feedback on weight loss progress, and food and physical activity logs. Lessons from the DPP curriculum are posted each week, and participants can review these at their own pace. To facilitate self-monitoring, participants also receive a wireless weight scale and pedometer. The 12-month digital DPP program includes a 16-week intensive program and a 36-week maintenance program. Omada Health has several studies demonstrating the effectiveness of the program in producing clinically significant weight loss. The program was only offered once to KPNW members at no cost as part of this implementation pilot.

**In-person DPP (Cohort 2).** Individuals eligible for in-person DPP included a wider age range of 19 to 75 years and a greater diabetes risk level (HbA1c, 6.0–6.4%) to ensure those at highest risk for diabetes were being targeted given limited enrollment slots, but otherwise had the same criteria as cohort 1.

In Fall 2017, KPNW launched their Preventing Diabetes Program, a 12-month group-based, in-person DPP that closely followed the Centers for Disease Control and Prevention National DPP curriculum. The in-person DPP is overseen by the KPNW Health Engagement & Wellness Services, and group sessions were led by KPNW-registered dietitians. Participants attended sessions weekly for the first 6 months and then monthly for the next 6 months free of charge. Group sessions included approximately 20 participants each and were held at two KPNW clinic locations at a variety of times (daytime and evening) on weekdays and weekends so that participants could attend at their preferred time and place. Participants received hard copies of all curriculum materials, including logs to track weight, eating behaviors, and physical activity, and were encouraged to weigh themselves at home weekly. At the weekly meetings, participants recorded their weight, number of food records kept, and minutes of physical activity from the previous week, and shared these with the group facilitator.

**RECRUITMENT**

Beginning in early 2017, KPNW staff identified eligible members based on their most recent BMI and HbA1c level documented in the EHR. Primary care clinicians were sent an email with a list of their eligible patients and were given 14 business days to opt out if they did not want their patients to be recruited for the DPP. The eligible members whose clinicians did not opt out were sent a secure email message within the KPNW patient portal inviting them to enroll in the DPP (Figures 1 and 2). The invitation message was signed as though it came from the patients’ primary care clinician. The patient portal is used by 80% of KPNW members and is a common venue for patients to schedule appointments, refill prescriptions, get visit summaries and lab results, and communicate with care clinicians.

Figure 3 presents the timeline for cohort identification, recruitment, and delivery of the DPP at KPNW. A total of 4132 individuals were identified who met the criteria for cohort 1 and were sent secure messages in April 2017, inviting them to enroll in the digital DPP, which was the only program
Figure 1: Digital Diabetes Prevention Program secure invitation email.

John Smith, MD

To Jane Doe

Dear Jane,

Diabetes is preventable. Your health records show that you may be at risk for diabetes. I’m reaching out today to tell you about Omada, a program that I think can help you lower your risk of getting diabetes. Omada is a cutting-edge online program. It helps you make small changes that can really help your health. The 16-week program includes:

- A professional health coach who will help you customize your program
- A wireless scale that automatically uploads your weight to your own private page
- Weekly lessons about which changes will have the biggest impact
- A food tracker to help you keep tabs on what you eat and drink
- A small group for constant encouragement

The retail value of this program is $400. But as a Kaiser Permanente member, you receive it at no additional charge.

You can sign up for Omada or learn more about the program at omadahealth.com/kpnorthwest

Please make sure to enter the following registration code during sign up so you will not be charged: PATIENT’S UNIQUE_ID.

There are a limited number of spots available. Registration will close once they are filled.

If you have any questions about registration, contact the Omada Support team at 1-XXX-XXX-XXXX (toll free) or support@omadahealth.com.

You can find other diabetes prevention and weight management programs at Kaiser Permanente. For details, call XXX-XXX-XXXX or 1-XXX-XXX-XXXX, option 2, to speak to a health coach and learn more. Or visit kp.org/healthengagement to explore classes and health topics. If you do not wish to receive any further messages about the Omada program, please call, XXX-XXX-XXXX.

In Health,

John Smith, MD
Evaluating the Implementation of Digital and In-Person Diabetes Prevention Program in a Large, Integrated Health System

Figure 2: In-person Diabetes Prevention Program secure invitation email.

Update on Receiving Care from Kaiser Permanente

John Smith, MD

To Jane Doe

Dear Jane,

I’m reaching out today to tell you about a new program offered through Health Engagement and Wellness Services. Your health records show that you may be at risk for developing diabetes, however diabetes is preventable. The Preventing Diabetes Program can help you lower your risk of getting diabetes. We know that making healthy lifestyle changes is hard work and takes time. This program helps you make small changes over time that can really improve your health.

During the first half of the program (weekly for 6 months), you meet in a small group with a health educator (registered dietitian). You will learn to:

• Eat healthy without giving up all the foods you love
• Add physical activity to your life, even if you don't think you have time
• Track your progress and make plans for small changes
• Cope with challenges that can derail your hard work — like how to choose healthy food when eating out
• Get back on track if you stray from your plan — because everyone slips now and then

In the second half of the program (monthly for 6 months), you will enhance the skills you’ve learned. This can help you maintain the changes you've made. These sessions review and solidify key habits like tracking food and physical activity, setting goals, staying motivated, and overcoming barriers. You may learn some new information, too. The health educator and small group will continue to support you.

Weekly sessions are held on Thursdays and Fridays at — and on Saturdays at ——. To learn more, call XXX-XXX-XXXX or 1-XXX-XXX-XXXX (toll free), option 2, and mention this letter. The program—valued at $400—is being offered to you at no cost, and limited spots are available. Please call today.

You can find other prediabetes or weight management programs at Kaiser Permanente. For details, visit kp.org/healthengagement/classes. If you do not wish to receive any further messages about the program, please leave a message at XXX-XXX-XXXX.

In Health,

John Smith, MD
Sent by Clinical Quality and Population Health MA
available at the time because KPNW’s in-person DPP did not launch until Fall 2017. Members were instructed to click on the unique web link embedded in the message to enroll in the digital DPP (Figure 1). Enrollment was tracked via a unique code, and Omada Health provided enrollment data back to KPNW. KPNW planned to offer a digital DPP once as part of the implementation pilot and, because of limited resources, allow only 500 enrollment slots. Individuals included in cohort 2 were identified beginning in July 2017 and were recruited in 3 waves: first in August 2017, again in April 2018, and then in December 2018. There were 2669 invitation messages sent for in-person DPP. For each wave, invitation emails were sent in 2 to 3 batches during the recruitment period (Figure 2). Reminder emails were sent 14 days after the initial invitation. Enrollment slots were limited to 100 participants in each wave (300 total). In the invitation, members were instructed to call a KPNW health coach if interested in enrolling. Health coaches explained the program details and expectations, and assessed (via phone conversations) participant readiness. If determined to be ready, members signed up for their preferred class day and time.

Recruitment for the digital and in-person DPP did not overlap, as shown in Figure 3. To reduce potential contamination, cohort 1 patients enrolled in the digital DPP were not invited to sign-up for the in-person DPP after that program started. However, eligible patients in cohort 1 who did not enroll in the digital DPP were invited to participate in the in-person DPP.

DATA COLLECTION

Clinical and Cost Data. The primary outcome is change in weight at 12 months for both the digital and in-person DPP cohorts. Secondary outcomes include change in HbA1c level at 12 months for both cohorts and, for the digital DPP cohort, change in weight and HbA1c level at 24 months. We will also conduct a cost-effectiveness analysis for each cohort at 12 months and, for the digital DPP cohort, at 24 months. Data used for these analyses come from the EHR and were collected during routine care. Clinical data entered in the EHR (eg, weight and HbA1c level) up to 12 months prior to DPP invitations/recruitment letters being sent out serve as baseline measures. Follow-up data come from the 14-month (for 12-month outcomes) or 26-month (for 24-month outcomes) period following the date the DPP invitation/recruitment letters were sent out; all available follow-up data will be used in analyses. Health-care use events documented in the EHR (ie, visits, pharmacy dispenses) for the 12-month baseline period described will be used to calculate costs per patient using standard costing algorithms and Medicare fee schedules, and will be compared to costs based on use events during the same 2 follow-up periods assessed for 12- and 24-month clinical outcomes. Clinical covariates (described further later) will also be obtained from
the EHR. We obtained a waiver of informed consent for these population-based analyses.

Qualitative Data. Interview guides were developed to ensure consistency in data collection during the semistructured interviews conducted with patients, health-care stakeholders, and clinicians. From September 2017 to July 2018, a subsample of DPP enrollees and nonenrollees from cohorts 1 and 2, were selected randomly and invited to participate in an hour-long, semistructured phone interview. Interview participants were offered a financial incentive for participation. The interview guide focused on patients’ perception of the methods used to invite them to participate in the DPP, patients’ reasons for participating, barriers and facilitators to enrollment and ongoing participation, patients’ perceived sense of usefulness of program components, and recommendations for improving and sustaining the program. In addition, from June 2018 to August 2018, health-care system leaders and clinicians were invited to participate in hour-long semistructured phone interviews to understand barriers and facilitators to sustaining the DPP within the health-care system. Verbal consent was obtained from all interview participants prior to initiation, and all interviews were audio-recorded with participants’ permission and were transcribed professionally.

DATA ANALYSIS

Power Considerations for Primary Outcome Analysis. Power calculations were conducted for pairwise comparisons of each DPP modality (digital and in-person) vs usual care with the following assumptions: 1) Bonferroni-adjusted type 1 error rate of 0.05/2 ≈ 0.025, 2) the observed weight loss or HbA1c level change for DPP enrollees would be the same for both DPP modalities, 3) there would be 2000 KPNW members eligible for each DPP cohort, and 4) DPP enrollment in each cohort would vary from as low as 5% of eligible KPNW members (n = 100) to as high as 20% (n = 400). This range of enrollment is consistent with previous experience offering such programs using similar recruitment methods in smaller, select populations of patients with prediabetes. The observed weight/HbA1c level change is thus a weighted average of the assumed true DPP effect in DPP enrollees and the assumed change for those in usual care.

For weight, we used a true DPP effect of 9.85 lbs and a usual care effect of 0.93 lb as an average of reported effects from the literature. For the standard deviation of weight change, we assumed 1.2 lbs. As indicated in Table 1, we have excellent power to detect significant differences even with enrollment rates as low as 5%. For the HbA1c level, we used a true DPP effect of a reduction of 0.24% as an average of reported results and 0.0% for patients receiving usual care. For the standard deviation of HbA1c level change, we assumed 0.07%. As indicated in Table 1, with these assumptions we again have excellent power if enrollment rates are at least 10%.

Analysis of Clinical Outcomes. We modeled 12- and 24-month weight trajectories using a linear mixed-effects model. Based on visual inspection of a scatterplot of weights, we considered using a piecewise linear spline function with a knot at 6 or 7 months given the “checkmark” phenomenon often seen in behavioral weight loss studies. Random effects for the intercept and slope(s) were included in the model to allow for person-specific trends in weight trajectories, and we determined the correlation structure for the random effects based on best model fit in terms of Akaike information criterion and Bayesian information criterion values. We will evaluate as covariates the following a priori-chosen variables: age (modeled continuously), race/ethnicity, gender, minutes of exercise per week (0 minutes, 10–140

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>UC Observed weight loss</th>
<th>DPP Observed weight loss</th>
<th>Power</th>
<th>UC Observed HbA1c decrease</th>
<th>DPP Observed HbA1c decrease</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>0.93</td>
<td>1.38</td>
<td>&gt; 0.99</td>
<td>0.00</td>
<td>0.01</td>
<td>0.989</td>
</tr>
<tr>
<td>10%</td>
<td>0.93</td>
<td>1.82</td>
<td>&gt; 0.99</td>
<td>0.00</td>
<td>0.02</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>15%</td>
<td>0.93</td>
<td>2.27</td>
<td>&gt; 0.99</td>
<td>0.00</td>
<td>0.04</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>20%</td>
<td>0.93</td>
<td>2.71</td>
<td>&gt; 0.99</td>
<td>0.00</td>
<td>0.05</td>
<td>&gt; 0.99</td>
</tr>
</tbody>
</table>

Table 1: Power for comparison of each Diabetes Prevention Program modality vs usual care

a Assumes 2-sided with Bonferroni-adjusted type 1 error of 0.05/2 and n = 2000 eligible per cohort.
b Assumes proportion of DPP participants who enroll in the program (i.e., 5% = 100 DPP enrollees per cohort).
c Assumes weight loss of 9.85 lbs for DPP enrollees.
d Assumes HbA1c decrease of 0.24% for DPP enrollees.

DPP = Diabetes Prevention Program; HbA1c: hemoglobin A1c or glycated hemoglobin; UC = usual care.
minutes, ≥ 150 minutes), Charlson comorbidity index score (0, 1, 2, 3, or more), baseline tobacco use (current, former, never), census tract-level proportion with college education or higher, census tract-level median household income, baseline weight and HbA1c level, and metformin use (treated as time-varying as always yes after the first dispense of the medication).

To control further for potential confounding, models will be adjusted for propensity score. We will estimate propensity scores for enrolling in the DPP (digital and in-person) by fitting a logistic regression model, with enrollment status as the outcome and all covariates listed earlier as predictors. To test the robustness of our primary findings, we will conduct propensity score matching as a sensitivity analysis. In addition to the covariates and propensity score, we will also include a 2-way interaction term between time and DPP enrollment status (digital and in-person will be modeled separately) to compare the time trend of weight trajectories between enrollees and nonenrollees. Furthermore, we will include 2-way interactions for time by gender and time by weight at enrollment. Model assumptions will be checked by examining residuals and predicted values cross-sectionally and over time. We will estimate marginal means (95% confidence intervals), model-estimated weights averaged over all covariates in the model (ie, all covariates are held constant at their means) at months 1 through 12. The primary contrasts of interest will be the differences in estimated weight change from time of recruitment between enrollees and nonenrollees at 12 months. Similar analyses will be conducted to compare digital DPP enrollees and nonenrollees on 24-month weight trajectories. HbA1c trajectories for 12 months (both cohorts) and 24 months (digital DPP) will be modeled similarly to weight using a linear mixed-effects model. We plan to include the same covariates as the weight model, but exclude the interactions for time by gender and time by weight at enrollment.

Analysis of Cost Outcomes. We will conduct an economic evaluation over the 12-month follow-up period for both the digital and in-person DPP cohorts as well as over the 24-month period for the digital DPP cohort from the perspective of the health plan, following best practices, and guided by previous economic analyses of DPP interventions. We will compare the healthcare cost functions between DPP enrollees and nonenrollees for each cohort, adjusting for baseline differences using a propensity score similar to that used in the clinical evaluation, but including adjustments for baseline costs. Cost data will include medical care and the cost of intervention delivery. Medical care use will be enumerated using the EHR and will include pharmacy, primary and specialty care office visits, inpatient stays, and laboratory tests. Health-care events (eg, visits, medication) will be costed using existing algorithms. Last, we will report differences in medical care costs between DPP enrollees and nonenrollees. We will consider methods appropriate for cost data (eg, right skewness and potentially censored follow-up time), including 2-part models, bootstrapping, and proportional means regression. Last, we will assess the cost-effectiveness of the DPP using net benefit regression methods, and we will estimate the probability of the DPP being cost-effective at various levels of willingness-to-pay per unit of improvement in clinical outcomes.

Analysis of Qualitative Data. A coding dictionary based on review of transcript content and interview questions with patients invited to each DPP format as well as health system stakeholders will be used by 2 trained coders to establish interrater reliability. Any differences in coding will be resolved through discussion, and coders will meet regularly to discuss and refine coding processes. A qualitative database will be compiled, coded, and analyzed using a qualitative software program (NVivo 12). After all transcripts were coded within the software program, we applied text retrieval and grouping functions on specific codes and combinations of codes for a particular topic, and summarized the issues, agreements, and disagreements in the content for each item (eg, barriers to participation compared across both DPP modalities). This type of theme-focused analysis provides qualitative data that can be integrated with our quantitative findings and improve our breadth of understanding of the DPP program, its implementation options, and effectiveness.

Discussion

This study will address 2 of the most pervasive and potentially costly health conditions in the US: obesity and prediabetes. The mixed-methods natural experiment design we will use to evaluate KPNW’s implementation of a digital and in-person DPP builds on existing evidence related to the effectiveness of these two DPP delivery modes and will contribute new knowledge related to best practices for implementing and sustaining
a DPP within large health systems over the long term. Specifically, many translational studies have documented the success of an in-person DPP outside the research setting; however, evidence related to digital DPP effectiveness remains limited as a result of varied design limitations in studies conducted to date\textsuperscript{17,22-27} and low methodological quality.\textsuperscript{28} The digital DPP shows promise in facilitating access to diabetes prevention services for individuals with physical or geographic barriers,\textsuperscript{55} and evidence supporting its clinical benefit could facilitate expanded coverage of this delivery mode for Medicare and Medicaid beneficiaries. We propose a rigorous study design to evaluate the digital DPP, using a longitudinal, usual care comparison cohort and objectively assessed measures to determine longer term (12- and 24-month) clinical and cost outcomes while applying propensity score adjustment.

In addition, the sustainability of both in-person and digital programs is less certain, particularly in the context of a large health system hoping to offer a DPP to potentially tens of thousands of patients.\textsuperscript{21,56} Further vetting of the Centers for Medicare & Medicaid Services payment model for DPP by health-care systems is needed.\textsuperscript{12,55,57,58} Our cost-effectiveness analysis will determine the impact of a digital and in-person DPP on health-care costs and the return on investment for health-care systems, which could have significant implications for the expansion and sustainability of a DPP.

There are some limitations to this study design. Specifically, enrollment slots for both the digital and in-person DPP are capped at 500 and 300 slots, respectively, because of limited resources, which makes it more challenging to assess program reach. The limited number of slots may have implications for generalizability in terms of enrollee characteristics and study outcomes. In addition, the health-care system restricting recruitment to those with a web-based patient portal account may also limit the generalizability of our findings. Although 80% of KPNW members use our patient portal, based on prior studies, patients who underuse the patient portal or other EHR-based tools tend to be from underserved populations with a high burden of diabetes.\textsuperscript{59-62} Furthermore, each DPP modality will be offered at separate times and to cohorts of individuals with slightly different eligibility criteria (ie, ranges for age and HbA1c levels at baseline for inclusion). This prevents the opportunity to do a head-to-head comparison of digital vs in-person on enrollment based on patient preference.

Conclusion

The mixed-methods natural experiment design we will use to evaluate KPNW’s implementation of a digital and in-person DPP will build on existing evidence related to DPP effectiveness across the 2 delivery modes on change in weight and HbA1c level at 12 months, and for digital DPP at 24 months. In addition, the cost-effectiveness analysis will determine the impact of a digital and in-person DPP on return on investment for health-care systems and sustainability of the program. Findings from our evaluation will therefore inform best practices for implementing and sustaining a DPP within large health-care systems.

REFERENCES


Evaluating the Implementation of Digital and In-Person Diabetes Prevention Program in a Large, Integrated Health System


- Prevention CDCa. CDC Diabetes Prevention Recognition Program standards and operating procedures. Atlanta, GA: Centers for Disease Control and Prevention; 2018.


Evaluating the Implementation of Digital and In-Person Diabetes Prevention Program in a Large, Integrated Health System

jncimonomographs/Iqt002, PubMed PMID: 23962514, PubMed Central PMCID: PMCPMC3748000.


58. Ritchie ND, Gritz RM. New Medicare diabetes prevention coverage may limit beneficiary access and widen health disparities. Med Care 2018 Nov;56(11):908–11. DOI: https://doi.org/10.1097/MRLR.0000000000000981


Computed Tomography Use in Children With Minor Head Trauma Presenting to 21 Community Emergency Departments Within an Integrated Health-Care System

Judy Shan, BS; E Margaret Warton, MPH; Mary E Reed, DrPH; David R Vinson, MD; Nathan Kuppermann, MD, MPH; Peter S Dayan, MD; Stuart R Dalziel, MD; Adina S Rauchwerger, MPH; Dustin W Ballard, MD, MBE

Perm J 2021;00:21.096 • E-pub: 11/22/2021 • https://doi.org/10.7812/TPP/21.096

Corresponding Author
Judy Shan, BS
judyshan@berkeley.edu

Author Affiliations
1Kaiser Permanente Division of Research, Oakland, CA, USA
2Kaiser Permanente Roseville, Roseville, CA, USA
3University of California Davis School of Medicine, Sacramento, CA, USA
4Columbia University College of Physicians and Surgeons, New York City, NY, USA
5University of Auckland, Auckland, New Zealand
6Kaiser Permanente San Rafael, San Rafael, CA, USA

Disclosures
Conflicts of Interest: None declared
Funding: This study was supported by the Kaiser Permanente Northern California Community Benefit Program.

Author Contributions: Dustin W Ballard, MD, MBE, and David R Vinson, MD, obtained funding. David R Vinson, MD, Nathan Kuppermann, MD, MPH, Peter S Dayan, MD, E Margaret Warton, MPH, and Dustin W Ballard, MD, MBE, conceptualized and designed the study. E Margaret Warton, MPH, acquired and analyzed the data. E Margaret Warton, MPH, and Mary E Reed, DrPH, provided statistical expertise. Dustin W Ballard, MD, MBE, E Margaret Warton, MPH, and Judy Shan BS interpreted the data. Dustin W Ballard, MD, MBE, and Judy Shan BS drafted the manuscript. All authors reviewed and revised the manuscript for important intellectual content.

Abstract

INTRODUCTION: Decreasing unnecessary cranial computed tomography (CT) use in pediatric head trauma patients remains important for emergency departments (EDs) across the US. Our study evaluated CT use in children with minor blunt head trauma in 21 community EDs within an integrated health-care system.

METHODS: We studied all children younger than 18 years old presenting to 21 community EDs between 2016 through 2018 with acute minor blunt head trauma, defined by an algorithm of ED chief complaints and diagnoses. We excluded patients with traumatic brain injuries diagnosed in the prior year, a CT within 24 hours prior to the ED visit, or an ED Glasgow Coma Scale score of less than 14.

RESULTS: Among 39,792 pediatric minor head trauma ED visits, the aggregate CT use proportion across all EDs was 12.9% [95% confidence interval (CI), 12.6–13.3%; facility-level range, 5.4–21.6%]. The 7 facilities that had previously received a clinical decision support system intervention implementing the Pediatric Emergency Care Applied Research Network rules during 2013 through 2014 had an aggregate mean CT ordering rate of 11.2% (95% CI, 10.7–11.7%; facility-level range, 5.4–14.3%) compared to 14.1% (95% CI, 13.6–14.5%; facility-level range, 7.3–21.6%) for the nonintervention facilities.

CONCLUSION: CT use for children with minor blunt head trauma in the community EDs of an integrated health-care system was low and stable across facilities from 2016 through 2018. This may be indicative of the safe stewardship of resources in the system, including the absence of financial or medicolegal incentives to scan very low-risk patients as well the availability of resources for close patient follow-up.

Introduction

More than 800,000 emergency department (ED) visits related to pediatric blunt head trauma were reported in the US in 2014, with roughly 50% of these children undergoing cranial computed tomography (CT) imaging.\(^1\)\(^-\)\(^3\) To reduce the risk of malignancy associated with ionizing radiation exposure, considerable efforts have been made to decrease unnecessary imaging in children.
In 2009, the Pediatric Emergency Care Applied Research Network (PECARN) developed and published traumatic brain injury (TBI) prediction rules, which identify children who are at very low risk of clinically important TBI and can safely forgo CT imaging. Since then, several studies have demonstrated that the implementation of clinical decision support (CDS) based on the PECARN rules can result in modest and safe decreases in CT use for children presenting to EDs with minor blunt head trauma. However, cranial CT use in North American community ED settings remains highly variable, with reports of use rates ranging anywhere from 15% to 70%.

Our observational study aimed to evaluate CT use within a large integrated health-care system that emphasizes responsible stewardship of medical resources and has distinctive features that make it well poised to achieve a safe floor of CT use in the pediatric head injury population. These features include a largely capitated payment model, an integrated system that allows for close patient follow-up, stable ED physician staffing models, region-wide emphasis on iterative feedback to physicians on imaging practices, and a comprehensive electronic health record (EHR) that supports CDS tools. Seven of the 21 EDs had previously received a CDS system intervention during 2013 and 2014. This CDS tool remained available but was not promoted actively at the 7 sites for the duration of this study.

Methods

We performed a retrospective observational study of pediatric (<18 years old) minor blunt head trauma encounters from January 2016 to December 2018 across 21 community EDs within Kaiser Permanente Northern California (KPNC). KPNC is a private, nonprofit integrated health-care system that covers 4.4 million members, or approximately one-third of the region's population. KPNC members are comparable to the surrounding population with respect to age, gender, race, and ethnicity. All care facilities (emergency, outpatient, inpatient) within KPNC use the same comprehensive integrated EHR (Epic, Verona, WI).

To define our study patient population, we used a novel hierarchical algorithm based on previously validated "groupers" of ED chief complaints and diagnoses (Supplemental Figure S1). The criteria were informed and refined through iterative medical record review. Prior retrospective work in our system had derived a grouper of 13 ED chief complaints with 86% sensitivity and 90% specificity for an ED head trauma diagnosis (unpublished data using previously described methods). In our current study, we refined this grouper to define our head trauma inclusion criteria with the goal of capturing children with minor blunt head trauma who would likely be eligible for application of the PECARN rule. If a patient had a head trauma diagnosis or a chief complaint of head trauma or head laceration, they were included directly in the study cohort. For other encounters, we screened for alternative validated combinations of ED chief complaints and established two main groupers for alternative chief complaints: a mechanism grouper and a symptom grouper with an associated inclusion algorithm (Supplemental Figure S1). Effectively, this algorithm excluded patients without head trauma-related diagnoses from the ED encounter if their only chief complaint was headache (a symptom grouper), but included those with headache who also had a mechanism grouper or additional symptom grouper.

Because our patient population of interest did not include those with severe, prior, or subacute head trauma, we excluded those with a TBI diagnosis in the prior year, a cranial CT for any reason within 24 hours prior to the ED visit, or any documented Glasgow Coma Scale (GCS) scores <14 (from nursing flowsheet data). We also excluded patients transferred in from other facilities. We compared CT use rates between facilities that had previously received a CDS system intervention and those that had not, and tested for statistical significance with a 2-tailed t-test.

Results

Our study included 39,792 pediatric head trauma-related ED visits. We excluded 153 patients with TBI diagnoses in the prior year, 128 patients with a CT scan or claim in the prior 24 hours, and 108 patients with ED GCS scores <14 (Figure 1). Our cohort consisted of 156 (0.4%) patient encounters with a GCS score of 14 and 8204 (20.6%) patients who were younger than 2 years of age. By year, aggregate CT ordering rates and facility-level ranges were as follows: 13.2% (range, 6.8–22.7%) in 2016, 12.3% (range, 3.5–21.9%) in 2017, and 13.2% (range, 6.0–23.3%) in 2018. Aggregate CT ordering rate across the 21 EDs throughout the study period was 12.9% [95% confidence interval...
Computed Tomography Use in Children With Minor Head Trauma Presenting to 21 Community Emergency Departments

Facility-level ED CT ordering rates across the entire study period ranged from 5.4% to 21.6%. The 7 facilities that had received the CDS system intervention previously during 2013 and 2014 had an aggregate mean CT ordering rate of 11.2% (95% CI, 10.7–11.7%; facility-level range, 5.4–14.3%) compared to 14.1% (95% CI, 13.6–14.5%; facility-level range, 7.3–21.6%) for the nonintervention facilities (difference, 2.9%; 95% CI, 2.2–3.5%; p < 0.00001). The overall study period CT ordering rates for the 2 trauma sites (sites L and site T) were 14.3% (95% CI, 12.7–15.9%; yearly range, 13.6–14.7%) and 12.4% (95% CI, 11.3–13.5%; yearly range, 11.4–13.0%), respectively (Table 1, Figure 2).

Discussion

Our observational study revealed CT ordering rates to be low across 21 community EDs in an integrated health-care system over 2016 through 2018. Although intrafacility variation in yearly rates of CT use in our study was small (variation range, 0.3–6.5%), study-long variation between facilities was comparatively large, with CT use rates ranging from a low of 3.5% to a high of 23.3%. This was somewhat surprising given that all sites are part of an integrated delivery system, and use the same EHR, standardized documentation templates, order sets, and physician staffing group. Furthermore, the rate of severe pediatric head trauma is extremely low across the entire system (we found and excluded only 108 patients with GCS scores < 14). Although CT use was lower at PECARN CDS sites in this investigation (11.2% vs 14.1%), prior analyses did not reveal a significant pre-/post-implementation change in CT use at intervention sites compared to control sites, so it is unclear whether the observed difference is a result of the prior implementation or other unmeasured facility-level differences.11

Across the US, there is even greater variation in CT use for children presenting to EDs with minor blunt head trauma, with average reported rates hovering around 50%.2,3 The cross-sectional study of Marin et al.3 of 324,435 pediatric head trauma visits to 848 general EDs found a risk-adjusted median CT use rate of 56% (interquartile range, 46.4–64.7%), with nontrauma centers 10% less likely to perform a CT than trauma centers. The 5-year retrospective study of Mannix et al.10 of 161,319 pediatric minor head injury encounters across 40 pediatric EDs revealed a median imaging rate of 36% (interquartile range, 29–42%; range, 19–58%) and found no significant association between institution-specific rates of serious head injury patients and CT use among minor head injury patients (p = 0.44). Lower CT use rates are found more frequently at sites using computerized CDS and/or with ongoing quality improvement initiatives.11,15

Our study used a unique case ascertainment method. Although previous studies have largely used International Classification of Diseases codes, singular chief complaints, and ED disposition diagnoses to derive their cohorts, we used GCS scores as well as combinations of ED diagnoses and chief complaints to derive their cohorts. We used previously validated inclusion criteria of chief complaints and diagnostic groupings in our cohort derivation and, rather than excluding patients with missing GCS scores, as has been done frequently with previous studies, we opted simply to exclude any patient with an explicitly documented GCS score that was less than 14.14 We decided to include patients without documented GCS scores because iterations of chart review revealed that many of these patients were otherwise eligible for our study. Hence, by including these patients, we were able to assemble a more robust cohort that better captured the population of interest.
Although many studies discuss and explore the impact of CDS or quality improvement interventions on rates of CT use, there are few studies on trends of CT use in facilities not actively undergoing these initiatives. Our study captures both populations—demonstrating low CT use in settings with and without CDS interventions with rates that are near the floor (10–15%) of those reported in prior studies.11,15,16 Our findings may be explained by the distinctives of our care delivery model, including comparably lower degrees of financial incentives and medicolegal risk to image very low-risk patients, as well the presence of an integrated system that allows for close patient follow-up. Such dynamics may reassure physicians and parents who choose observation or expectant management rather than immediate CT.17 This use pattern is similar to those seen in New Zealand and Australia, where the retrospective review of Wilson et al.18 of 31 EDs (a mix of tertiary, urban/suburban, and rural EDs) revealed head CT use to be less than 10% on average. Our findings may also be explained by the natural diffusion of the PECARN prediction rules into clinical practice, as the evidence mounts for their effectiveness in reducing CT imaging in children with minor blunt head trauma without compromising safety.4–8 The implementation of these rules into a EHR-based decision support tool in a subset of our study cohort may have spurred more rapid diffusion at other sites in the system.

### Limitations

Our study is limited by its observational nature, and thus we were unable to control for specific factors associated with interfacility variation. In

---

**Table 1:** Cranial computed tomographic scan rate for children presenting with mild traumatic head injury to 21 emergency departments, 2016 through 2018

<table>
<thead>
<tr>
<th>Site</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>Overall study period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No scans, n</td>
<td>CT scans, n</td>
<td>Scan rate, %</td>
<td>No scans, n</td>
</tr>
<tr>
<td>A</td>
<td>584</td>
<td>120</td>
<td>17.0</td>
<td>561</td>
</tr>
<tr>
<td>B</td>
<td>361</td>
<td>56</td>
<td>13.4</td>
<td>348</td>
</tr>
<tr>
<td>C</td>
<td>249</td>
<td>50</td>
<td>16.7</td>
<td>293</td>
</tr>
<tr>
<td>D</td>
<td>595</td>
<td>100</td>
<td>14.4</td>
<td>602</td>
</tr>
<tr>
<td>E</td>
<td>332</td>
<td>75</td>
<td>18.4</td>
<td>392</td>
</tr>
<tr>
<td>F</td>
<td>395</td>
<td>94</td>
<td>19.2</td>
<td>381</td>
</tr>
<tr>
<td>G</td>
<td>346</td>
<td>52</td>
<td>13.1</td>
<td>376</td>
</tr>
<tr>
<td>H</td>
<td>924</td>
<td>89</td>
<td>8.8</td>
<td>917</td>
</tr>
<tr>
<td>I</td>
<td>240</td>
<td>24</td>
<td>9.1</td>
<td>244</td>
</tr>
<tr>
<td>J</td>
<td>568</td>
<td>74</td>
<td>11.5</td>
<td>645</td>
</tr>
<tr>
<td>K</td>
<td>661</td>
<td>79</td>
<td>10.7</td>
<td>768</td>
</tr>
<tr>
<td>L</td>
<td>502</td>
<td>86</td>
<td>14.6</td>
<td>515</td>
</tr>
<tr>
<td>M</td>
<td>485</td>
<td>59</td>
<td>10.8</td>
<td>476</td>
</tr>
<tr>
<td>N</td>
<td>570</td>
<td>167</td>
<td>22.7</td>
<td>583</td>
</tr>
<tr>
<td>O*</td>
<td>501</td>
<td>74</td>
<td>12.9</td>
<td>490</td>
</tr>
<tr>
<td>P*</td>
<td>509</td>
<td>53</td>
<td>9.4</td>
<td>527</td>
</tr>
<tr>
<td>Q*</td>
<td>1176</td>
<td>221</td>
<td>15.8</td>
<td>1331</td>
</tr>
<tr>
<td>R*</td>
<td>812</td>
<td>77</td>
<td>8.7</td>
<td>756</td>
</tr>
<tr>
<td>S*</td>
<td>231</td>
<td>18</td>
<td>7.2</td>
<td>277</td>
</tr>
<tr>
<td>T*</td>
<td>1060</td>
<td>157</td>
<td>12.9</td>
<td>974</td>
</tr>
<tr>
<td>U*</td>
<td>398</td>
<td>29</td>
<td>6.8</td>
<td>418</td>
</tr>
<tr>
<td>Grand total</td>
<td>11,499</td>
<td>1754</td>
<td>13.2</td>
<td>11,675</td>
</tr>
</tbody>
</table>

*These sites received a clinical decision support intervention during 2013 and 2014.

CT = computed tomography.
addition, we did not assess potentially missed TBI, although a review of medicolegal cases for our health system did not suggest this to be an issue. We were also unable to exclude all populations (such as known or suspected abusive head trauma) that might be excluded in a prospective study. However, the volume of such patients in our system is small and we have no reason to believe there was variation in such patients over time or medical facility. Lastly, our study sites are part of an integrated health-care system, and thus our observed CT practice patterns may not be generalizable to other community EDs.

Conclusion

Cranial CT use rates for children with minor blunt head trauma were low and stable at 21 community EDs in this integrated health system between 2016 and 2018. This may be indicative of the safe stewardship of resources in the system, including the absence of financial or medicolegal incentives to image very low-risk patients, as well the availability of resources for close patient follow-up. Because a large proportion of pediatric emergency care is provided by community hospitals, it remains important to generate high-quality imaging use data that can inform future quality improvement studies and interventions.

Supplementary Materials

REFERENCES

Figure 2: Cranial computed tomography (CT) use in children with head trauma in 21 community emergency departments (EDs), 2016 through 2018. * = yearly maximum, minimum, and median facility CT use rates among the 21 EDs.


Impact of COVID-19 on the Incidence and Severity of Obstetric and Gynecologic Emergency Department Visits in an Integrated Health Care System

Cassidy E Tierney, MD; Mary Kathryn Abel, AB; Mubarika M Alavi, MS; Miranda Ritterman Weintraub, PhD, MPH; Andrew Avins, MD, MPH; Eve Zaritsky, MD

Perm J 2022;26:21.136 • E-pub: 04/05/2022 • https://doi.org/10.7812/TPP/21.136

Abstract

OBJECTIVE: COVID-19 has had an unprecedented impact on medical care use and delivery, including stark reductions in emergency department (ED) volume. The aim of this study was to assess changes in incidence of OB/GYN ED visits and disease severity at time of presentation during the COVID-19 pandemic.

STUDY DESIGN: We conducted a multicenter retrospective study of OB/GYN-related ED visits before and during the COVID-19 pandemic. Incidence rates (IRs) and severity measures were compared across time periods and years.

RESULTS: A total of 18,668 OB/GYN ED encounters occurred between January 1 and December 31, 2020, compared to 21,014 encounters between January 1 and December 31, 2019. During shelter-in-place, visits decreased by 41% compared to the pre-pandemic period in 2020 before returning to typical rates (incidence rate ratio (IRR) = 0.98 in fall/winter). We found a similar proportion of patients with hemoglobin < 7 g/dL for diagnoses associated with bleeding and patients with white blood cell count > 12,000 per µL in the setting of infection comparing corresponding time periods in 2019 and 2020. There were fewer formal OB/GYN consults, hospital admissions at time of presentation, and urgent surgical procedures performed across all periods in 2020; however, hospitalization within 7 days substantially increased in the first half of 2020.

CONCLUSION: The incidence of OB/GYN ED visits declined substantially between March and August 2020 but then returned to pre-pandemic levels by fall/winter 2020. The decreased incidence was not accompanied by an increase in severity of presentation.

Introduction

The COVID-19 pandemic has had an unprecedented impact on medical care use and delivery. In addition to navigating the challenges of COVID-19, health care systems were forced to rethink how to deliver non-COVID-19-related health care. In-person visits were replaced with virtual visits, surgical procedures were postponed, and preventive screenings, such as Papanicolaou tests and colonoscopies, were deferred. Previous studies have shown stark reductions

Disclosures

Conflicts of Interest: None declared
Funding: None declared
Consent: Informed consent was received from all case patients.

Copyright Information
© 2022 The Permanente Federation. All rights reserved.
in emergency department (ED) visits for serious conditions, such as myocardial infarction and stroke.\textsuperscript{2–5} Reports of variation in disease severity during the pandemic have been mixed, with some studies suggesting an increase in adverse outcomes in the setting of delayed presentation.\textsuperscript{6–8}

Myriad OB/GYN concerns bring patients to the ED, ranging from miscarriage and ovarian torsion to fibroids. In some cases, such as ectopic pregnancy, delayed treatment can be life threatening. An investigation by this group and others found that ED visits for OB/GYN concerns declined substantially during the early pandemic period\textsuperscript{9,10}; however, to our knowledge, no studies have assessed long-term changes in emergent OB/GYN care. There is also scant literature on the pandemic’s impact on severity of illness at time of presentation specifically for OB/GYN-related concerns.\textsuperscript{11} The objective of this study was to further elucidate trends in OB/GYN ED visits and changes in the severity of presentation during the COVID-19 pandemic, as a proxy for potentially delayed care.

Methods

STUDY POPULATION
Demographic and clinical characteristics among female patients 18 years or older presenting to a Kaiser Permanente Northern California ED for OB/GYN emergencies were examined. Kaiser Permanente Northern California is an integrated health care system that served 1.8 million women in 2020. It includes 21 hospitals and encompasses facilities across the northern and central parts of the state, including the San Francisco Bay Area, Silicon Valley, Sacramento, and much of the Central Valley.

STUDY DESIGN
This study employed a multiple cross-sectional design comparing 2 consecutive years. For each encounter, diagnoses were classified as OB or GYN according to International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) diagnostic codes. OB diagnoses included bleeding < 20 weeks and postpartum, endometritis/pyelonephritis infections, spontaneous/missed abortion, ectopic pregnancy, molar pregnancy, and nausea/vomiting of pregnancy. GYN diagnoses included fibroids/abnormal uterine bleeding (AUB), pelvic inflammatory disease, ovarian torsion/cysts, and pelvic pain. Pelvic pain, molar pregnancy, and nausea/vomiting of pregnancy were excluded from additional analyses after the overall incidence rates (IRs) were calculated because they did not have reliable measures of severity. All medical and demographic data were extracted from the electronic medical record. COVID-19 case and hospitalization data were extracted from the California Open Data Portal through the Government Operations Agency.\textsuperscript{12}

Four time periods in 2020 and corresponding periods in 2019 were compared: pre-pandemic (January 1–March 3), initial California shelter-in-place (March 4–May 31), summer (June 1–August 31), and fall/winter (September 1–December 31). March 4, 2020, marks the first documented COVID-19 death in California and the day California Governor Gavin Newsom declared a state of emergency. A statewide shelter-in-place order was later enacted on March 19, 2020.

Our study was deemed exempt with waiver of consent from Institutional Review Board review by the Kaiser Permanente Northern California Research Determination Office.

STATISTICAL ANALYSES
IRs (per 100,000 person-weeks at risk) during the pandemic period were compared with the pre-pandemic period. Person-weeks were calculated according to the total adult (> 18 years old) membership of Kaiser Permanente Northern California at the middle of each monthly period. Patients who were not Kaiser Permanente Northern California members at the time of ED presentation were included in the overall Kaiser Permanente IR trend analysis (Figure 1) but excluded from all other analyses. Differences among time periods were compared with incidence rate ratios (IRRs), overall and stratified by key patient characteristics and diagnoses (Table 1). Attributable risk percentage changes between the time periods were calculated with 95% confidence intervals (CIs) for demographic characteristics and illness-severity measures, including rates of OB/GYN consult, hospitalization (both at time of encounter and within 7 days), surgery within 7 days, Intensive Care Unit admission within 2 days, and death within 7 days. Mean lengths of hospital stay pre-COVID and during the COVID-19 pandemic were also compared using the two-sample t-test (and validated with nonparametric Mann-Whitney tests).
Impact of COVID-19 on Obstetric and Gynecologic Emergency Department Visits

Only encounters with an OB/GYN primary diagnosis were further analyzed for differences in severity. Relevant vital sign and laboratory measurements by condition, including temperature \( \geq 38^\circ C \) (100.4°F), hemoglobin < 7 g/dL, white blood cell count (WBC) > 12,000 per µL, lactate > 2 mmol/L, and human chorionic gonadotropin > 5000 IU/mL, were compared across time periods using the Pearson Chi-squared test and validated with the Fisher exact test. A two-sided p value < 0.05 was considered significant. All analyses were conducted with SAS (version 9.4; SAS Institute, Inc., Cary, NC).

**Results**

**INCIDENCE**

A total of 35,475 OB/GYN ED encounters occurred between January 1 and December 31, 2020, compared to 42,509 encounters between January 1 and December 31, 2019, a 16.6% reduction in overall visits. Excluding pelvic pain diagnoses and limiting to Kaiser Permanente members, the final cohort consisted of 18,668 encounters in 2020 and 21,014 in 2019. Overall incidence of OB/GYN ED encounters for 2020 decreased dramatically during the start of the COVID pandemic, rising steadily during the summer period corresponding with an increase in COVID-19 cases and hospitalizations before returning to pre-pandemic levels in fall/winter (Figure 1). Among women who had a diagnosis for which a reliable severity measure existed (see above), visits decreased by 41% (IRR = 0.59) during the early pandemic period (March 4–May 31) and by 8% (IRR = 0.92) during the summer (June 1–August 31) compared to the pre-pandemic period (Table 2). Findings were similar when analyzing OB and GYN ED encounters separately. There was a sharp decline in OB and GYN visits during the early pandemic period (IRRs = 0.59 and 0.60, respectively). By Period 3 (summer), GYN ED visits had returned to pre-pandemic levels (IRR = 0.96), while OB
visits remained significantly lower (IRR = 0.82). The incidence of OB and GYN visits were similar to the pre-pandemic period (IRRs = 0.94 and 1.01, respectively) by Period 4 (fall/winter). There were no clinically substantial differences in age or race/ethnicity across the 2 years (Table 1).

**SEVERITY**

An OB/GYN specialty consult was placed less frequently in the ED across all time periods in 2020 compared to 2019, and fewer patients received surgery within 7 days of ED presentation (Table 3 and Figure 2). There were also fewer

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Period 1: January 1–March 3</th>
<th>Period 2: March 4–May 31</th>
<th>Period 3: June 1–August 31</th>
<th>Period 4: September 1–December 31</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>18–39</td>
<td>2355 (68.1)</td>
<td>2395 (65.1)</td>
<td>3257 (63.8)</td>
</tr>
<tr>
<td></td>
<td>40–49</td>
<td>605 (17.5)</td>
<td>702 (19.1)</td>
<td>950 (18.6)</td>
</tr>
<tr>
<td></td>
<td>50–64</td>
<td>260 (8.4)</td>
<td>322 (8.8)</td>
<td>551 (10.8)</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td>65+</td>
<td>207 (6.0)</td>
<td>261 (7.1)</td>
<td>350 (6.9)</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>White</td>
<td>1137 (32.9)</td>
<td>1176 (32.0)</td>
<td>1622 (31.8)</td>
</tr>
<tr>
<td><strong>Conditions</strong></td>
<td>Black</td>
<td>552 (16.0)</td>
<td>585 (15.9)</td>
<td>806 (15.8)</td>
</tr>
<tr>
<td><strong>Fibroids/AUB</strong></td>
<td>Asian American</td>
<td>520 (15.0)</td>
<td>499 (13.6)</td>
<td>829 (16.2)</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>Hispanic</td>
<td>904 (26.1)</td>
<td>1022 (27.8)</td>
<td>1409 (27.6)</td>
</tr>
<tr>
<td><strong>Ovarian torsion</strong></td>
<td>Other/unknown</td>
<td>344 (10.0)</td>
<td>398 (10.8)</td>
<td>442 (8.7)</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>&lt; 24.9</td>
<td>848 (24.5)</td>
<td>868 (23.6)</td>
<td>1277 (25.0)</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>25–29.9</td>
<td>812 (23.5)</td>
<td>811 (22.0)</td>
<td>1230 (24.1)</td>
</tr>
<tr>
<td><strong>Ovarian torsion</strong></td>
<td>30–34.9</td>
<td>580 (16.8)</td>
<td>661 (18.0)</td>
<td>840 (16.4)</td>
</tr>
<tr>
<td><strong>Abortion</strong></td>
<td>35+</td>
<td>658 (19.0)</td>
<td>771 (21.0)</td>
<td>1004 (19.7)</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>559 (16.2)</td>
<td>569 (15.5)</td>
<td>757 (14.8)</td>
<td>629 (19.8)</td>
</tr>
<tr>
<td><strong>Fibroids/AUB</strong></td>
<td>1515 (43.8)</td>
<td>1735 (47.1)</td>
<td>2349 (46.0)</td>
<td>1440 (45.4)</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>277 (8.0)</td>
<td>229 (6.2)</td>
<td>403 (7.9)</td>
<td>254 (8.0)</td>
</tr>
<tr>
<td><strong>Ovarian torsion</strong></td>
<td>989 (28.6)</td>
<td>1148 (31.2)</td>
<td>1537 (30.1)</td>
<td>1000 (31.5)</td>
</tr>
<tr>
<td><strong>Ectopic pregnancy</strong></td>
<td>204 (5.9)</td>
<td>134 (3.6)</td>
<td>247 (4.8)</td>
<td>116 (3.7)</td>
</tr>
<tr>
<td><strong>Abortion</strong></td>
<td>771 (22.3)</td>
<td>794 (21.6)</td>
<td>1081 (21.2)</td>
<td>653 (20.6)</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>252 (7.5)</td>
<td>289 (7.9)</td>
<td>347 (6.8)</td>
<td>244 (7.7)</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of patients presenting to the ED for OB/GYN conditions before and during COVID-19.

- **Bold numbers indicate statistically significant difference in percent change between 2019 and 2020.**
- **AUB = abnormal uterine bleeding; BMI = body mass index in kg/m².**
- **ICD-10-CM codes for conditions are as follows:**
  - Fibroids/AUB (D25.x, N92.4x, N93.9x, N95.0x); infection, including pelvic inflammatory disease, tubo-ovarian abscess, cervicitis, endometritis, or vulvovaginal cellulitis (N76.4x, A18.3x, A54.2x, A56.1x, N70.0x, N70.9x, N71.0x, N71.9x, N72.x, N73.3x, N73.5x, N73.8x, N73.9x, N75.3x, N82.x); ovarian torsion/cysts (N83.5x, N83.2x); ectopic pregnancy (O00.x); spontaneous or missed abortion (O02.1x, O03.x, O20.0x, Z33.2x); and pregnancy-related bleeding prior to 20 weeks or postpartum (O04.x, O20.9x, O26.85x, O44.1x, O44.3x, O45.x).

- **Table 3 and Figure 2.**

- **Less patients received surgery within 7 days of ED presentation.**
Impact of COVID-19 on Obstetric and Gynecologic Emergency Department Visits

<table>
<thead>
<tr>
<th>OB-GYN ED</th>
<th>Person-weeks</th>
<th>ED visits (women)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Period 1:</strong></td>
<td>January 1–March 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16,223,199</td>
<td>114,921</td>
</tr>
<tr>
<td></td>
<td>25,540,527</td>
<td>106,098</td>
</tr>
<tr>
<td></td>
<td>23,579,353</td>
<td>132,961</td>
</tr>
<tr>
<td></td>
<td>30,822,692</td>
<td>181,074</td>
</tr>
<tr>
<td><strong>Period 2:</strong> March 4–May 31</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3680</td>
<td>3174</td>
</tr>
<tr>
<td></td>
<td>13.5 (13.0–14.0)</td>
<td>20.9 (20.3–21.5)</td>
</tr>
<tr>
<td></td>
<td>Reference</td>
<td>0.59 (0.57–0.62)*</td>
</tr>
<tr>
<td></td>
<td>0.92 (0.88–0.96)*</td>
<td></td>
</tr>
<tr>
<td><strong>Period 3:</strong> May 31–August 31</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>228 (10%)</td>
<td>3680</td>
</tr>
<tr>
<td></td>
<td>219 (8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3640</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.5 (13.0–14.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−0.2 (−0.6, 0.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Period 4:</strong> September 1–December 31</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1279 (57%)</td>
<td>936 (42%)</td>
</tr>
<tr>
<td></td>
<td>2025 (56%)</td>
<td>22 (2%)</td>
</tr>
<tr>
<td></td>
<td>16.1 (15.7–16.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.94 (0.87–1.01)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: OB/GYN ED visits during early pandemic and late pandemic periods compared to the pre-pandemic period in 2020

* Denotes p value < 0.001.
* Obstetric ED visit indications were quantified as bleeding (ICD-10-CM codes O20.0, O20.9, O26.8, O44.1, O44.3, O45.x), infection (O23.0), and other (O00.x, O02.x, O03.x, O04.x).

** Gynecologic ED visit indications were quantified as nonobstetric bleeding (N92.4, N93.9, N95.0, D25.x), infection (A18.1, A54.2, A56.1, N70.0, N71.9, N72, N75.1, N76.4, N82), and other (O00.x, O02.x, O03.x, O04.x). Events by indication sum to greater than total events because some patients presented with multiple indications.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Period 1: January 1–March 3</th>
<th>Period 2: March 4–May 31</th>
<th>Period 3: May 31–August 31</th>
<th>Period 4: September 1–December 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>OB/GYN consult in ED</td>
<td>−8.2 (−10.0, −6.4)*</td>
<td>−7.5 (−9.2, −5.8)</td>
<td>−4.8 (−6.2, −3.4)</td>
<td>−3.3 (−4.6, −2.1)</td>
</tr>
<tr>
<td>Surgery within 7 days of ED visit</td>
<td>−2.7 (−3.8, −1.7)</td>
<td>−2.4 (−3.4, −1.4)</td>
<td>−1.8 (−2.7, −1)</td>
<td>−1 (−1.7, −0.2)</td>
</tr>
<tr>
<td>Hospitalization after ED visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hosp. in encounter</td>
<td>−1.8 (−2.5, −1)</td>
<td>−1.2 (−1.9, −0.4)</td>
<td>−0.7 (−1.4, 0)</td>
<td>0 (−0.6, 0.5)</td>
</tr>
<tr>
<td>Hosp. within 7 days</td>
<td>0.5 (−0.1, 1)</td>
<td>0.7 (0.1, 1.3)</td>
<td>0.1 (−0.4, 0.6)</td>
<td>−0.2 (−0.6, 0.3)</td>
</tr>
<tr>
<td>ICU admission within 2 days</td>
<td>−0.1 (−0.3, 0.1)</td>
<td>0 (−0.2, 0.2)</td>
<td>−0.1 (−0.2, 0.1)</td>
<td>0 (−0.1, 0.2)</td>
</tr>
<tr>
<td>Death within 7 days</td>
<td>0 (0, 0.1)</td>
<td>0 (−0.1, 0.1)</td>
<td>0.1 (0, 0.1)</td>
<td>0 (−0.1, 0.1)</td>
</tr>
</tbody>
</table>

Table 3: Changes in presentation and outcome characteristics for OB/GYN ED encounters at Kaiser Permanente Northern California in 2020 compared to 2019

* Results are reported as absolute percent change (% in 2020 − % in 2019) and 95% CIs. ICD-10-CM codes for conditions are as follows: fibroids/AUB (D25.x, N92.4x, N93.9x, N95.0x); infection, including pelvic inflammatory disease, tubo-ovarian abscess, cervicitis, endometritis, or vulvovaginal cellulitis (N76.4x, A18.1x, A54.2x, A56.1x, N70.0x, N70.9x, N71.0x, N71.9x, N72.x, N73.2x, N73.3x, N73.8x, N73.9x, N75.1x, N75.2x, N75.3x, N75.4x, N75.5x, N75.8x, N82.x); ovarian torsion/cysts (N83.5x, N83.2x); ectopic pregnancy (O00.x); spontaneous or missed abortion (O02.x, O03.x, O04.x, O20.0x, O20.9x, O26.8x, O44.1x, O44.3x, O45.x); and pregnancy-related bleeding prior to 20 weeks or postpartum (O04.x, O05.x, O06.x, O07.x, O08.x, O09.x, O09.x, O10.x, O11.x, O12.x, O13.x, O14.x, O15.x, O16.x, O17.x, O18.x, O19.x, O20.0x, O20.9x, O26.8x, O44.1x, O44.3x, O45.x).

Bold numbers indicate statistically significant difference in percent change.

AUB = abnormal uterine bleeding; ED = emergency department; ICU = Intensive Care Unit.

hospitalizations associated with the ED encounter between January 1 and May 31, 2020, compared to the corresponding period in 2019; however, individuals were more likely to be hospitalized within 7 days after the initial ED encounter during the first surge of the pandemic between March 4
and May 31, 2020. Mean length of hospital stay during COVID (March 4, 2020–December 2020) was significantly shorter than during the pre-COVID period (January 2019–March 3, 2020) (76.8 hours [95% CI 70.0, 83.6] vs. 86.4 hours [95% CI 81.3, 91.4], p < 0.03). Intensive Care Unit admission and death were both extremely rare outcomes, with Intensive Care Unit admission occurring in 0.1% to 0.2% of all cases and death occurring in 0% to 0.1% of all cases across all time periods. There were no statistically significant differences in vital sign and laboratory measurements of severity for conditions with primary diagnoses, including temperature, hemoglobin level, WBC, lactate level, and human chorionic gonadotropin level, between the 2 years (Table 4).

**Discussion**

In this integrated health care system, the incidence of OB/GYN ED visits declined precipitously between March and May 2020 but then returned to near-pre-pandemic levels despite the increasing rate of COVID-19 cases across California. The reduction in ED OB visits persisted longer than GYN visits, with IRs remaining substantially below the pre-pandemic period until fall/winter. The underlying reasons for this trend are unclear. One possible explanation is that shelter-in-place mandates as well as concerns regarding safety of medical facilities may have initially shifted thresholds for patients seeking emergent care; however, as government policies changed and “pandemic fatigue” set in, health care utilization patterns returned to baseline, even with COVID-19 cases on the rise.

Several additional factors may have contributed to these findings, such as improved telehealth care decreasing the need for ED visits as well as messaging surrounding the safety of seeking emergency care. The delayed normalization of OB ED visits may be explained by an overall decrease in pregnancies in the early pandemic period and possibly increased virtual prenatal visits initiated with the pandemic. An alternative explanation is that pregnant patients avoided seeking care.
in an ED setting longer than their nonpregnant counterparts due to fear of exposure, a hypothesis supported by evidence of patients choosing to forgo antenatal visits or even considering home birth to avoid entering a medical setting.13–15

We found no evidence that this period of decrease in visits was accompanied by an increase in severity of presentation. There were fewer OB/GYN consults and surgical procedures performed within 7 days of presentation across all periods of 2020 compared to 2019. Notably, however, the lowest chance of hospitalization at time of ED encounter was between January 1 and May 31, 2020 (Periods 1 and 2), but the highest chance of hospitalization within 7 days of the initial ED encounter was between March 4 and May 31, 2020 (Period 2). There was also a substantial decrease in length of hospital stay between the pre-pandemic period and during the COVID-19 pandemic period, with a mean difference of about 10 hours, a difference of uncertain clinical significance. With COVID-19, Kaiser Permanente Northern California rapidly expanded its virtual care visit opportunities for patients, potentially decreasing the overall need to visit the ED. However, there may also have been some hesitation to admit or operate on patients during the pandemic, particularly when COVID-19

### Table 4: Laboratory measurements of illness severity by OB/GYN emergency subtype in 2019 and 2020

<table>
<thead>
<tr>
<th></th>
<th>Period 1: January 1–March 3</th>
<th>Period 2: March 4–May 31</th>
<th>Period 3: June 1–August 31</th>
<th>Period 4: September 1–December 31</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2019 (N = 2026)</td>
<td>2020 (N = 1894)</td>
<td>2019 (N = 2870)</td>
<td>2020 (N = 3064)</td>
</tr>
<tr>
<td></td>
<td>2020 (N = 2026)</td>
<td>2020 (N = 1551)</td>
<td>2019 (N = 2870)</td>
<td>2020 (N = 2331)</td>
</tr>
<tr>
<td>Fibroids/AUB</td>
<td>N = 662</td>
<td>N = 640</td>
<td>N = 992</td>
<td>N = 502</td>
</tr>
<tr>
<td>Hgb, N (%)</td>
<td>627 (94.7)</td>
<td>582 (90.9)</td>
<td>937 (94.5)</td>
<td>476 (94.8)</td>
</tr>
<tr>
<td></td>
<td>1042 (94.3)</td>
<td>761 (94.3)</td>
<td>1254 (93.8)</td>
<td>1084 (95.1)</td>
</tr>
<tr>
<td>&lt; 7 g/dL, % (95% CI)</td>
<td>4.3 (2.7, 5.9)</td>
<td>4.0 (2.4, 5.5)</td>
<td>5.0 (3.6, 6.4)</td>
<td>6.1 (3.9, 8.2)</td>
</tr>
<tr>
<td></td>
<td>5.1 (3.8, 6.4)</td>
<td>5.9 (4.2, 7.6)</td>
<td>4.4 (3.4, 5.7)</td>
<td>6.0 (4.6, 7.4)</td>
</tr>
<tr>
<td>Infectiona</td>
<td>N = 216</td>
<td>N = 164</td>
<td>N = 304</td>
<td>N = 172</td>
</tr>
<tr>
<td>WBC, N (%)</td>
<td>153 (71)</td>
<td>113 (69)</td>
<td>227 (75)</td>
<td>117 (68)</td>
</tr>
<tr>
<td></td>
<td>248 (76)</td>
<td>175 (68)</td>
<td>311 (74)</td>
<td>265 (73)</td>
</tr>
<tr>
<td>&gt; 12,000/µL, % (95% CI)</td>
<td>49.7 (41.8, 57.6)</td>
<td>41.6 (32.5, 50.7)</td>
<td>43.6 (37.2, 50.1)</td>
<td>48.7 (39.7, 57.8)</td>
</tr>
<tr>
<td>Lactate, N (%)</td>
<td>73 (34)</td>
<td>48 (29)</td>
<td>110 (36)</td>
<td>50 (29)</td>
</tr>
<tr>
<td></td>
<td>145 (45)</td>
<td>88 (34)</td>
<td>147 (35)</td>
<td>128 (35)</td>
</tr>
<tr>
<td>&gt;2 mmol/L, % (95% CI)</td>
<td>6.8 (11.1, 12.6)</td>
<td>2.1 (~2, 6.1)</td>
<td>12.7 (6.5, 19)</td>
<td>12 (3.21)</td>
</tr>
<tr>
<td>Temperature, N (%)</td>
<td>213 (99.5)</td>
<td>161 (98)</td>
<td>303 (100)</td>
<td>170 (99)</td>
</tr>
<tr>
<td>≥ 38˚C (100.4˚F), % (95% CI)</td>
<td>0.5 (~0.4, 1.4)</td>
<td>1.8 (~0.2, 3.9)</td>
<td>0 (~0.4, 2.8)</td>
<td>0.6 (~0.2, 1.5)</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>N = 170</td>
<td>N = 116</td>
<td>N = 206</td>
<td>N = 89</td>
</tr>
<tr>
<td>Hgb, N (%)</td>
<td>163 (95.9)</td>
<td>109 (94.0)</td>
<td>199 (96.6)</td>
<td>86 (96.6)</td>
</tr>
<tr>
<td></td>
<td>204 (95.3)</td>
<td>120 (94.5)</td>
<td>222 (95.7)</td>
<td>233 (94.2)</td>
</tr>
<tr>
<td>&lt; 7 g/dL, % (95% CI)</td>
<td>0.6 (~0.6, 1.8)</td>
<td>0.0</td>
<td>0.5 (~0.5, 1.5)</td>
<td>0.0</td>
</tr>
<tr>
<td>hCG, N (%)</td>
<td>166 (97.6)</td>
<td>112 (96.6)</td>
<td>200 (97.1)</td>
<td>84 (94.4)</td>
</tr>
<tr>
<td>&gt;5000 IU/mL, % (95% CI)</td>
<td>38.1 (28.8, 43.5)</td>
<td>37.5 (28.5, 46.5)</td>
<td>33.0 (26.5, 39.5)</td>
<td>32.1 (22.2, 42.1)</td>
</tr>
<tr>
<td>Abortion</td>
<td>N = 663</td>
<td>N = 665</td>
<td>N = 963</td>
<td>N = 551</td>
</tr>
<tr>
<td>Hgb, N (%)</td>
<td>571 (86.1)</td>
<td>599 (90.1)</td>
<td>852 (88.5)</td>
<td>505 (91.7)</td>
</tr>
<tr>
<td>Hgb &lt; 7 g/dL, % (95% CI)</td>
<td>0.9 (0.1, 1.6)</td>
<td>0.3 (~0.1, 0.8)</td>
<td>0.2 (~0.1, 0.6)</td>
<td>0.6 (~0.1, 1.3)</td>
</tr>
<tr>
<td>Bleeding &lt; 20 weeks and postpartum</td>
<td>N = 136</td>
<td>N = 157</td>
<td>N = 157</td>
<td>N = 126</td>
</tr>
<tr>
<td>Hgb, N (%)</td>
<td>127 (93.4)</td>
<td>134 (85.4)</td>
<td>137 (87.3)</td>
<td>112 (88.9)</td>
</tr>
<tr>
<td>Hgb &lt; 7 g/dL, % (95% CI)</td>
<td>0.0</td>
<td>0.7 (~0.7, 2.2)</td>
<td>0.7 (~0.7, 2.2)</td>
<td>0.9 (~0.8, 2.6)</td>
</tr>
</tbody>
</table>

*Test of 2 proportions were performed to assess differences in laboratory values in 2019 versus 2020. No analyses were statistically significant below an alpha level of < 0.05.

**Infection defined as pelvic inflammatory disease, tubo-ovarian abscess, cervicitis, endometritis, or vulvovaginal cellulitis.**

AUB = abnormal uterine bleeding; CI = confidence interval; hCG = human chorionic gonadotropin; Hgb = hemoglobin; WBC = white blood cell.
testing ability was limited and operating room staff had been reassigned, leading physicians to favor outpatient medical management over surgical intervention. This does not explain the initial decline in these parameters, which was noted prior to the first documented case of COVID-19 in California. The increase in hospitalization within 7 days of a patient’s initial ED visit suggests that, in some cases, threshold for admission may have been unusually high to minimize patient exposure to COVID-19 and keep inpatient censuses lower for expected COVID-acquired patients. The shorter mean hospital stay during the pandemic, albeit small and of uncertain clinical significance, is consistent with potential increased focus on shortening inpatient stays for those admitted with non-COVID-19 conditions to both reduce chance of transmission and prepare for potential COVID-19 admissions.

A major strength of our study is the ability to present multicenter data from a wide network of northern California hospitals. To our knowledge, this is the largest study to date specifically assessing trends in OB/GYN emergency care during the pandemic. It is also one of the only studies of its kind, across all disciplines, to present data past the acute phase of COVID-19 (through December 2020 for this study). This gives us the unique ability to observe both the acute impact of the early pandemic as well as changes over time as medical and social norms and care patterns shifted.

This study also has limitations. Given that these data are from an integrated health care system in a single state, conclusions may not be readily generalizable to other health care systems in other parts of the country. We are also limited in our ability to report specifically on OB emergencies. A subset of Kaiser Permanente Northern California facilities have labor and delivery units that address all OB emergencies in pregnant patients ≥ 20 weeks gestation. Because of this, we only included obstetrical conditions that would present to the ED, regardless of the presence of a labor and delivery unit. Therefore, we cannot draw any conclusions about incidence or severity of OB emergencies in the second half of pregnancy.

There were several limitations in our statistical analyses. Calculation of IRs using an estimated time-at-risk inherently assumes the probability of disease during the study period is constant for each individual, which is not true in the case of many OB/GYN emergencies, which are more prevalent (or exclusively seen) in certain age categories. There is, however, consistency in this confounding factor across all calculations. Furthermore, we did not adjust for multiple statistical comparisons, but we were careful not to assert potential differences unless they were consistent across time periods or showed monotonic change over time. Finally, while overall statistical power was usually high, as evidenced by generally narrow CIs, some comparisons had lower power, and findings of no statistically significant differences should be interpreted cautiously.

Finally, limitations also include those inherent to the retrospective nature of the study, including variations in electronic medical record data quality and availability. Mortality data are limited to those deaths that occurred while hospitalized, so we cannot comment on any differences in death occurring outside of the hospital setting. Because our person-time rate calculations only included Kaiser Permanente Northern California members, ED visits of patients without Kaiser Permanente Northern California insurance were excluded from all statistical analyses, limiting our ability to comment on trends for uninsured or otherwise-insured populations.

Our findings suggest that the decrease in ED visits was not accompanied by an increase in acuity; however, it is unclear whether this was because patients were accessing alternative care venues during that time. Current literature suggests that decreases in ED volume were accompanied by increased telehealth usage in several health care systems. Future research is needed to assess whether the initial decline in OB/GYN ED encounters was similarly accompanied by an increase in other care encounter types, such as virtual visits or outpatient office visits.

Conclusion

The incidence of OB/GYN ED visits declined substantially during the early pandemic period but then returned to near-2019 levels by summer 2020, despite a rise in COVID-19 cases and hospitalizations. Illness severity upon presentation to the ED did not appear to change substantially during the pandemic.

REFERENCES


Downstream Acute Care Utilization Following Initial Prescription of an Opioid Pain Reliever Among Emergency Department Patients With Low-Severity Conditions

Nathan Juergens, MD, MPH\(^1,4\); Julia Wei, MPH\(^3\); Esme Cullen, MD, MPH\(^1\); Moses Graubard, MD\(^2\); Vibha K Gupta, MD\(^2\); Miranda Ritterman Weintraub, PhD, MPH\(^4\); Dana Sax, MD, MPH\(^2,3\)

Perm J 2022;26:21.036 • E-pub: 04/05/2022 • https://doi.org/10.7812/TPP/21.036

Abstract

INTRODUCTION: We sought to investigate the association between receipt of an opioid pain reliever (OPR) in the emergency department (ED) and downstream acute health care utilization.

METHODS: Within Kaiser Permanente Northern California, we identified opioid-naïve patients, ages 18–64, who were treated and discharged from the ED for a painful, low-severity condition between January 1, 2017, and December 31, 2017. We also identified patients who received an OPR, either administered in the ED or obtained at a Kaiser Permanente Northern California pharmacy within 7 days of ED arrival, and investigated subsequent acute care utilization in cases with at least 1 ED, urgent care, or inpatient visit within 1 month or 3 months of the index encounter or 2 visits within 12 months.

RESULTS: Of the 39,468 adults included in our study, 50.7% were female, 55.0% were non-White, and 25.2% received an OPR in association with their index ED encounter. After adjustment, we found that patients who received an OPR had greater odds of downstream acute care utilization than those who did not, with odds ratios of 1.68, 1.53, and 1.50 at 1, 3, and 12 months, respectively (all p < 0.05).

CONCLUSION: Patients who received an OPR at their index encounter had substantially increased odds of a subsequent ED, urgent care, or inpatient visit. This effect was most pronounced early in follow-up and persisted for the duration of the study period. Receipt of an OPR among opioid-naïve adults for a painful, low-severity condition is associated with increased downstream acute care utilization.

Introduction

The opioid epidemic in the United States is an ongoing public health emergency. Drug overdoses are the country’s leading cause of injury-related deaths.\(^1\) Deaths from both heroin and opioid pain reliever (OPR) overdoses have quadrupled over the past 2 decades, and overdose deaths continue to rise in many areas despite widespread recognition of the epidemic.\(^2,3\) Health care costs and utilization have increased proportionately with the rise in OPR availability.\(^4\) Drug misuse and abuse led to 2.5 million emergency department (ED) visits in 2011, of which 1.4 million were related to OPRs, and the costs associated
with OPR abuse were estimated at nearly $56 billion in 2007.\textsuperscript{5,6} Prescriptions for OPRs have started to decline; by 2015, more opiate overdoses were caused by heroin and synthetic opioids (fentanyl) than by OPRs, although the first exposure for many patients with opioid use disorder is still through an OPR.\textsuperscript{7–9}

Many patients seek relief from acutely painful conditions in the ED, and it is appropriate that some are treated with an OPR.\textsuperscript{10,11} In the past several years, new regional and national guidelines have been shown to increase the safety of prescribing OPRs and decrease overall prescriptions. OPR prescriptions written during ED encounters are more likely to align with Centers for Disease Control guidelines than are prescriptions written in other care settings.\textsuperscript{12} Unfortunately, there is evidence that some patients develop opioid use disorder after an initial OPR prescription in the ED, even when those prescriptions follow OPR best practices.\textsuperscript{13,14}

The association of an initial OPR prescription to opioid-naïve patients in the ED with downstream acute care utilization is not well understood. Long-term opioid use is associated with an increase in acute care utilization, including a higher frequency of outpatient and ED visits, and this relationship appears to be dose dependent.\textsuperscript{15,16} In addition, OPR prescriptions at hospital discharge have been found to lower the odds of planned, posthospitalization follow-up encounters.\textsuperscript{17} Understanding the relationship between an initial OPR ED prescription and demand for downstream acute care may provide a broader understanding of the potential impacts of OPRs on patient health, beyond the severe consequences of addiction, overdose, and death, as well as on the long-term costs to health systems.

In this study, conducted within a large integrated health care delivery system in Northern California, we analyzed ED encounters among opioid-naïve patients with low-acuity complaints for which pain typically improves rapidly and with whom follow-up acute care utilization was not anticipated. We examined demographic factors associated with receipt of an OPR during or immediately following the ED visit and the association between receipt of an OPR and subsequent acute care utilization.

Using electronic health records (EHRs) and health plan pharmacy databases, we identified adult patients with active Kaiser Permanente membership, ages 18–64 years, who were treated for an acute, painful, low-severity condition and discharged from a Kaiser Permanente Northern California ED between January 1, 2017, and December 31, 2017. We were specifically interested in prescribing practices and downstream utilization among patients not taking OPRs at the time of their ED visit; we therefore excluded patients who were previously prescribed or administered an OPR from a Kaiser Permanente Northern California pharmacy or hospital within the 6 months before the index visit, based on Kaiser Permanente Northern California pharmacy dispensations.

As with prior studies, we focused on common acute, painful, and low-acuity diagnoses for which substantial unplanned follow-up care and recurrent OPRs were not anticipated.\textsuperscript{17} We identified the International Classification of Diseases, 10th revision (ICD-10) diagnostic codes with the top 10 highest frequencies of OPR receipt among Emergency Severity Index level IV and V encounters in our system and used these to develop our study cohort.\textsuperscript{18,19} This list included lumbago (M54.5x), sprains and strains (S43.xx, S46.xx), joint pain (M25.5x), toothaches (K08.8x, K08.9), external abscesses (K12.2, L03.xxx, L02.xx, L98.3), pharyngitis (J02.x), uncomplicated open hand wounds (S61.xxx), corneal abrasions (S05.xx), and herpes zoster (B02.xx). Primary diagnostic codes are assigned by the ED and are identified as the most serious, life-threatening, or resource-intensive diagnosis from the visit. Of note, the list of ICD-10 diagnostic codes among level IV and V charts that most often received an OPR also included forearm fractures. We did not include patients with fractures in this study because of the greater expected need for acute follow-up care for these patients. Table 1 lists the medications considered an OPR in our study.

Only the first eligible encounter for each patient during the study period was included. We limited our cohort to patients with less expected need for OPR prescriptions and therefore excluded those
Downstream Acute Care Utilization Following Opioid Pain Reliever

with active malignancy receiving chemotherapy or hospice, palliative, or comfort care. Patients without health plan pharmacy benefits or with greater than a 45-day gap in membership coverage in the 6 months preceding or the 12 months following the index encounter were also excluded. Prior studies have found that 90% of medications dispensed for Kaiser Permanente Northern California enrollees are captured in Kaiser Permanente Northern California’s pharmacy database, and 100% are captured for the 94% of enrollees with a drug benefit.20

**PREDICTOR VARIABLES AND OUTCOME MEASURE**

Patient age, sex, and self-reported race/ethnicity were obtained from EHRs, whereas neighborhood median household income and neighborhood median level of education were based on 2010 US Census block data and patient address on the date of the index ED visit. Race/ethnicity was classified as non-Hispanic White, Asian (including Pacific Islander and Asian Hispanic), Black (including Black Hispanic), Hispanic, and other or unknown. Patient comorbidities were measured by calculating the Charlson Comorbidity Index (CCI), using comorbidity data from the 12 months preceding the index ED visit.21 The length of stay for each ED encounter was also obtained from the EHRs. Dichotomous acute care utilization in the 6 months before the index ED visit (prior ED, urgent care, or inpatient visit versus no visits) was also obtained as a predictor variable. Patients were categorized as having received an OPR if 1 was administered during their index ED visit or if they filled an OPR prescription within 7 days of the visit at any Kaiser Permanente Northern California pharmacy.

Our primary outcome measure was a dichotomous measure of acute care utilization following the index ED visit, assessed at 3 time points: 1 month, 3 months, and 12 months. Patients met the criteria for acute care utilization if they had at least 1 ED, urgent care, or inpatient visit within 1 month or 3 months of the index ED visit or 2 visits (urgent care, ED, or hospitalization) in the following 12 months. A recent study examining the association of unplanned acute care utilization after hospital discharge among those that did and did not receive an OPR used similar time intervals and a similar definition of unplanned health care utilization.17 Our primary analysis was among all ED patients with an eligible diagnosis; we conducted a sensitivity analysis among patients with a chief complaint of lumbago.

**STATISTICAL ANALYSIS**

We employed Chi-square testing to compare categorical sociodemographic covariates (age, gender, race/ethnicity, neighborhood median household income, neighborhood median education) and clinical covariates (CCI [0, 1–2, 3+], ED length of stay [by quantile], and prior acute care utilization) between those who were and were not dispensed an OPR. Multivariable logistic regression was performed to assess predictors of acute care utilization for each time point. We also conducted a multivariable logistic regression to assess patient-level factors associated with receipt of an OPR. Because missingness in covariates, 549 subjects were not used in the multivariable analyses. A sensitivity analysis included only patients with lumbago as their indexing diagnosis because this was the second largest diagnosis group overall and the group with the highest rate of OPR receipt in our original analysis. Data management and analyses were performed in Statistical Analysis Systems (SAS) 9.4, and a p value of < 0.05 was

<table>
<thead>
<tr>
<th>Type of Opioid</th>
<th>Frequency</th>
<th>Percentage of total OPRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>12,835</td>
<td>47.7%</td>
</tr>
<tr>
<td>Oxycodone (with acetaminophen and aspirin)</td>
<td>3873</td>
<td>14.6%</td>
</tr>
<tr>
<td>Morphine (intravenous and oral)</td>
<td>2356</td>
<td>8.7%</td>
</tr>
<tr>
<td>Tramadol (and with acetaminophen)</td>
<td>1288</td>
<td>4.7%</td>
</tr>
<tr>
<td>Codeine (and with acetaminophen and guaifenesin)</td>
<td>1180</td>
<td>4.4%</td>
</tr>
<tr>
<td>Fentanyl (including intravenous, patch, and oral)</td>
<td>351</td>
<td>1.3%</td>
</tr>
<tr>
<td>Methadone</td>
<td>205</td>
<td>0.8%</td>
</tr>
<tr>
<td>Buprenorphine (including patch, naloxone, nasal spray)</td>
<td>52</td>
<td>0.2%</td>
</tr>
<tr>
<td>Meperidine IV</td>
<td>12</td>
<td>0.0%</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>7</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Table 1: Opioid pain relievers prescribed

*Includes opioid pain relievers administered to the study population in the emergency department and those filled within 7 days of the index emergency department visit. OPRs = opioid pain relievers.
considered statistically significant. This study was approved by the Kaiser Permanente Northern California Institutional Review Board with a waiver of consent.

## Results

There were 39,468 adults who presented to a Kaiser Permanente Northern California ED with 1 of the 9 selected low-acuity diagnoses during the specified 1-year study period from January 1, 2017, to December 31, 2017 (see Figure 1). Of these 39,468 patients, 50.7% were female. Younger adults, ages 18–30 years old, comprised 25.9% of our study population, whereas adults ages 31–50 and 51–64 years comprised 41.7% and 32.5%, respectively (Table 2). The self-reported race/ethnicity of the patients studied included 45.0% White, 23.9% Hispanic, 13.2% Black, 11.7% Asian, and 6.1% multiple or other races/ethnicities. We found that 52.4% of eligible patients lived in neighborhoods with a neighborhood median household income below $80,000, and 16.6% lived in neighborhoods with a median education of high school or below. Most patients (69.2%) had no significant comorbidities (CCI of 0). The 3 most common diagnoses were uncomplicated hand wounds (25.3% of encounters), lumbago (24.5% of encounters), and joint pain (15.6% of encounters).

In our study cohort, 9937 patients (25.2%) had an OPR dispensed in the ED or at a Kaiser Permanente Northern California pharmacy within 7 days of the index visit. The majority of these patients had an OPR dispensed from a pharmacy (80.9%), whereas a smaller proportion (19.1%) had OPRs dispensed only during the ED encounter.

---

**Figure 1:** Cohort assembly of 39,468 adult patients, ages 18–64 years, treated in the emergency department for an acutely painful, low-severity condition between January 1, 2017, and December 31, 2017. ED = emergency department; ICD-10 = International Classification of Diseases, 10th revision; KPNC = Kaiser Permanente Northern California; OPR = opioid pain reliever.
We found differences in OPR prescriptions by patient demographic factors, comorbidity burden, and ED diagnosis in bivariate analysis. The 3 diagnoses with the highest rates of OPR dispensing were lumbago (44.6%), herpes zoster (43.5%), and joint pain (34.3%). Older patients (ages 51–64) were significantly more likely to receive an OPR compared to younger patients ($p < 0.01$), as were female patients compared to male patients ($p < 0.01$) (Table 3). Compared to Black, White, and Hispanic patients, Asian patients were significantly less likely to receive an OPR ($p < 0.01$). Patients living in neighborhoods with lower median income and education levels, patients with higher CCI (compared to lower), and patients with an acute care encounter in the 6 months preceding their index ED visit were significantly more likely to receive an OPR (all $p < 0.01$). In the adjusted analysis, older female patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ED Visits, n (%)</th>
<th>Prescribed OPR, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>39,468 (100%)</td>
<td>9937 (25.18%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–30 y</td>
<td>10,206 (25.86%)</td>
<td>1551 (15.20%)</td>
</tr>
<tr>
<td>31–50 y</td>
<td>16,446 (41.67%)</td>
<td>4359 (26.50%)</td>
</tr>
<tr>
<td>51–64 y</td>
<td>12,816 (32.47%)</td>
<td>4027 (31.42%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4635 (11.74%)</td>
<td>859 (18.53%)</td>
</tr>
<tr>
<td>Black</td>
<td>5224 (13.24%)</td>
<td>1394 (26.68%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9448 (23.94%)</td>
<td>2377 (25.16%)</td>
</tr>
<tr>
<td>Multiple/other</td>
<td>2403 (6.09%)</td>
<td>553 (23.01%)</td>
</tr>
<tr>
<td>White</td>
<td>17,758 (44.99%)</td>
<td>4754 (27.57%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20,020 (50.72%)</td>
<td>5228 (26.11%)</td>
</tr>
<tr>
<td>Male</td>
<td>19,448 (49.28%)</td>
<td>4709 (24.21%)</td>
</tr>
<tr>
<td>Neighborhood median household income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ $80,000</td>
<td>20,407 (52.43%)</td>
<td>5352 (26.23%)</td>
</tr>
<tr>
<td>&gt; $80,000</td>
<td>18,512 (47.57%)</td>
<td>4448 (24.03%)</td>
</tr>
<tr>
<td>Neighborhood median education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or below</td>
<td>6561 (16.62%)</td>
<td>1737 (26.47%)</td>
</tr>
<tr>
<td>Some college or above</td>
<td>32,907 (83.38%)</td>
<td>8200 (24.92%)</td>
</tr>
<tr>
<td>CCI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27,324 (69.23%)</td>
<td>5956 (21.80%)</td>
</tr>
<tr>
<td>1–2</td>
<td>9,722 (24.63%)</td>
<td>2984 (30.69%)</td>
</tr>
<tr>
<td>3+</td>
<td>2,422 (6.14%)</td>
<td>997 (41.16%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal abrasions</td>
<td>1882 (4.77%)</td>
<td>211 (11.21%)</td>
</tr>
<tr>
<td>External abscesses</td>
<td>5217 (13.22%)</td>
<td>1212 (23.23%)</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>524 (1.33%)</td>
<td>228 (43.51%)</td>
</tr>
<tr>
<td>Lumbago</td>
<td>9,665 (24.49%)</td>
<td>4306 (44.55%)</td>
</tr>
<tr>
<td>Pain in joint</td>
<td>6,137 (15.55%)</td>
<td>2103 (34.27%)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>4,585 (11.62%)</td>
<td>590 (12.87%)</td>
</tr>
<tr>
<td>Sprains and strains</td>
<td>1458 (3.70%)</td>
<td>357 (24.47%)</td>
</tr>
<tr>
<td>Toothache</td>
<td>29 (0.07%)</td>
<td>8 (27.59%)</td>
</tr>
<tr>
<td>Uncomplicated hand wounds</td>
<td>9,970 (25.26%)</td>
<td>922 (9.25%)</td>
</tr>
</tbody>
</table>

Table 3: Patient characteristics of those receiving an opioid pain reliever

* Prescribed OPR percentages represent within-row proportions. All p values calculated using Chi-square test.

CCI = Charlson Comorbidity Index; OPR = opioid pain reliever.
patients and those with higher CCI had increased odds of receiving an OPR, whereas Asian patients and patients who identified their race/ethnicity as multiple or other (compared to White) had lower odds of receiving an OPR (Table 4).

We found 5901 patients (15.0%) had at least 1 urgent care, ED, or inpatient encounter within 1 month of their index ED visit. This number increased to 9494 (24.1%) individuals at 3 months; at 12 months, 9736 (24.7%) individuals had at least 2 subsequent acute care encounters. Of the 9937 individuals who had an OPR dispensed in the ED or at a Kaiser Permanente Northern California pharmacy within 7 days, 20.8% had at least 1 acute care encounter at 1 month, 31.3% had at least 1 encounter at 3 months, and 32.1% had at least 2 encounters at 12 months, compared to those who had not received an OPR (13.0%, 21.6%, and 22.2%, respectively, with p < 0.01) (Figure 2). After adjusting for patient demographic and comorbidity data, the odds of acute care utilization among those who received an OPR compared to those who did not was 1.54 (95% confidence interval [CI] = 1.44-1.64) at 1 month, 1.42 (95% CI = 1.34-1.51) at 3 months, and 1.40 (95% CI = 1.32-1.49) at 12 months (Table 5). In addition, the odds of acute care utilization were higher among younger patients, Black patients (compared to White patients at 3 months and 12 months only), female patients (significant only in the models of acute care utilization at 3 and 12 months), those with a higher CCI, those with acute care utilization in the 6 months before their index ED visit, and those living in areas with a lower median education level. The odds of acute care utilization were lower among Asian patients (compared to White patients) (Table 5). In a sensitivity analysis including only patients with lumbago as their indexing diagnosis, the odds of downstream acute care utilization among those who received an OPR were also significantly increased at each of the time points studied: 1.80 (95% CI = 1.58-2.04) at 1 month, 1.47 (95% CI = 1.32-1.63) at 3 months, and 1.23 (95% CI = 1.11-1.37) at 12 months (see Appendix A).

Discussion

In this large sample of adult patients presenting to an ED with an acutely painful, low-severity complaint who had not received an OPR in the prior 6 months, we observed a significant association between OPR prescription and subsequent unplanned acute care utilization after controlling for multiple patient characteristics. The effect was most pronounced in early follow-up among patients who received an OPR, who were found to have 68% greater odds of an acute care encounter in the following month compared to those who did not receive an OPR. Although the effect size decreased slightly over time, patients who received an OPR were also significantly more likely to have higher acute care utilization at 3 and even 12 months. An additional sensitivity analysis was conducted only on the subset of patients with a lumbago diagnosis, which again demonstrated this association.

The exact reason for this observed increase in care-seeking behavior among patients who received an OPR cannot be fully elucidated from our study. We purposely analyzed a cohort of patients with low-acuity diagnoses for which we would expect minimal need for return ED visits, urgent care, or hospital care, and we adjusted for comorbidities and demographic information to try to limit confounding by disease severity. Despite this, we suspect this difference in unplanned acute care use in many cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–30 y</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>31–50 y</td>
<td>1.96</td>
<td>(1.84–2.09)</td>
</tr>
<tr>
<td>51–64 y</td>
<td>2.20</td>
<td>(2.05–2.36)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0.64</td>
<td>(0.59–0.69)</td>
</tr>
<tr>
<td>Black</td>
<td>0.96</td>
<td>(0.91–1.03)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.97</td>
<td>(0.91–1.03)</td>
</tr>
<tr>
<td>Multiple/other</td>
<td>0.83</td>
<td>(0.75–0.92)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.92</td>
<td>(0.86–0.96)</td>
</tr>
<tr>
<td>Neighborhood median household income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ $80,000</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>&gt; $80,000</td>
<td>0.93</td>
<td>(0.89–0.98)</td>
</tr>
<tr>
<td>Neighborhood median education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or below</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Some college or above</td>
<td>0.96</td>
<td>(0.89–1.02)</td>
</tr>
<tr>
<td>CCI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>1.43</td>
<td>(1.35–1.51)</td>
</tr>
<tr>
<td>3+</td>
<td>1.99</td>
<td>(1.81–2.17)</td>
</tr>
</tbody>
</table>

Table 4: Adjusted odds of receiving an opioid pain reliever based on patient characteristics

CI = confidence interval; CCI = Charlson Comorbidity Index.
may be because patients who received an OPR had a more complicated or painful condition and needed to return for worsening symptoms. An additional hypothesis is that this difference in care-seeking behavior may be at least partially explained by initial exposure to OPRs. The return visit may have been secondary to an unintended consequence of OPR use or seeking another prescription.

Prior studies in other settings have suggested that OPR use is associated with increased health care utilization.15-17 An earlier study found that patients undergoing abdominal surgery with preoperative opioid use had higher rates of hospital readmission and higher health care costs for up to 12 months after the procedure.22 Another study found that patients who received an OPR for shoulder or spine pain in an outpatient clinic had higher rates of downstream health care utilization and higher costs in the year following initial OPR use compared to those who did not receive an OPR.23 To our knowledge, this is the first study of the association between OPR prescriptions for low-acuity complaints in an ED and unplanned, acute care-seeking behavior. This study contributes to the growing body of evidence that receipt of an OPR prescription can have unintended consequences on patient health and is associated with an increase in health care expenditures.

Overall, about 1 in 4 patients received an OPR following their index ED visit. This is significantly lower than the nearly 40% reported in similarly designed national studies from the early 2000s, but it is comparable to a more recent study of discharged ED patients.24,25 The differences between this study and those from the early 2000s may reflect the exclusion of patients with more severe and therefore potentially more painful complaints, as well as national trends of decreasing opioid prescriptions.25 During the study period, a region-wide opioid safety initiative with substantial physician training led to a decrease in OPR prescriptions across clinical settings.26

Our findings regarding the patient characteristics associated with dispensing of an OPR both parallel and contrast other studies. Similar to an earlier study, patients of self-identified Asian ethnicity received prescription pain relief at the lowest rates compared to other ethnic groups.27 Other studies have reported that cultural variation in the expression of pain and other aspects of pain reporting may contribute to observed differences in the pain management of people of Asian ethnicity, and this finding does warrant further investigation.25,28 In contrast to several studies that report fewer opioid prescriptions given to Black
patients as compared to White patients, we found that, after controlling for multiple demographic and comorbid conditions, there was no significant difference in the dispensing of OPRs between these groups.

**Limitations**

The conclusions of our study are limited by the possibility that there were differences in pain level or disease severity between patients who did and did not receive an OPR in the ED. Unfortunately, pain scores are not reliably captured from the ED in our EHRs. In an attempt to limit confounding, we adjusted for ED length of stay, included only low-severity, treat and release visits for specific conditions for which unplanned acute care would not be expected, and adjusted for patient characteristics to limit variability between populations.

As with most retrospective studies, there exists the possibility of missing or incomplete data.
In this study, we are limited by our reliance on records of opioids dispensed at Kaiser Permanente pharmacies. Prescriptions filled at non-Kaiser Permanente pharmacies were not included in this analysis, and we therefore likely underestimated the number of opioids prescribed after the index visit. In addition, we used dispensing data, as opposed to actual consumption, employing methodologies used by similar studies.\textsuperscript{32,33} We further defined OPR exposure as either administration of an OPR in the ED or filling a prescription within 7 days of the encounter. There may be small differences between the groups of patients who used OPRs in the ED versus those who filled a prescription immediately afterward. We did not exclude patients for whom non-OPRs were contraindicated because of limitations in accurate electronic capture. We relied on coded diagnoses to abstract our cohort; it is possible that we missed patients who did not receive an appropriate diagnosis code and may therefore have undercounted the true population.

Based on study methods, we are unable to assess a causal link between what occurred during the index ED visit and downstream acute care use. We did not obtain diagnoses from the recurrent visits and therefore have no way of knowing if these subsequent encounters were for opioid-related complications, the same painful complaint present at the patients’ initial ED visit, or other reasons entirely. We also did not separate urgent care, ED, and inpatient visits, and the reasons for visits to these venues may have differed. Lastly, our findings may not be generalizable to settings with less access to outpatient (non-ED or nonurgent care) follow-up or with different patient cost sharing for ED or inpatient visits.

Conclusion

We present data from a large, diverse population across 21 EDs in an integrated health care delivery system with a comprehensive EHR and pharmacy database that allowed for the capture of health care utilization and OPR dispensing across settings. We found that dispensing an OPR to opioid-naïve ED patients with certain low-acuity diagnoses was associated with a significant increase in unplanned acute care at 1 month, 3 months, and 12 months following their index visit. Our findings provide a nuanced perspective regarding how OPRs may have substantial and durable effects on patients’ subsequent care-seeking behavior. More research is needed to evaluate the cause and medical appropriateness of this observed increase in acute care utilization.

REFERENCES


Appendix

Appendix A: Sensitivity analysis with adjusted odds of higher acute care utilization among only patients with an indexing diagnosis of lumbago who received an OPR compared to those who did not, as well as adjusted odds of higher acute care utilization by patient characteristic:

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>1 month OR (95% CI)</th>
<th>3 months OR (95% CI)</th>
<th>12 months OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribed OPR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>1.80 (1.58-2.04)</td>
<td>1.47 (1.32-1.63)</td>
<td>1.23 (1.11-1.37)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-30 y</td>
<td>Reference</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>31-50 y</td>
<td>0.84 (0.70-1.01)</td>
<td>0.82 (0.71-0.95)</td>
<td>0.73 (0.64-0.84)</td>
</tr>
<tr>
<td>51-64 y</td>
<td>0.88 (0.73-1.07)</td>
<td>0.84 (0.72-0.98)</td>
<td>0.68 (0.58-0.79)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>Reference</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Asian</td>
<td>0.62 (0.49-0.80)</td>
<td>0.63 (0.52-0.76)</td>
<td>0.59 (0.49-0.71)</td>
</tr>
<tr>
<td>Black</td>
<td>1.10 (0.92-1.30)</td>
<td>1.10 (0.95-1.28)</td>
<td>1.31 (1.14-1.51)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.93 (0.79-1.09)</td>
<td>0.89 (0.78-1.02)</td>
<td>0.96 (0.84-1.09)</td>
</tr>
<tr>
<td>Multiple/other</td>
<td>0.95 (0.72-1.24)</td>
<td>0.91 (0.73-1.14)</td>
<td>1.01 (0.81-1.25)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Reference</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Male</td>
<td>1.00 (0.88-1.13)</td>
<td>0.86 (0.78-0.96)</td>
<td>0.71 (0.64-0.79)</td>
</tr>
<tr>
<td>Neighborhood median income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ $80,000</td>
<td>Reference</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&gt; $80,000</td>
<td>0.99 (0.86-1.13)</td>
<td>0.91 (0.81-1.02)</td>
<td>0.93 (0.83-1.04)</td>
</tr>
<tr>
<td>Neighborhood median education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or below</td>
<td>Reference</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Some college or above</td>
<td>0.95 (0.79-1.13)</td>
<td>0.92 (0.80-1.06)</td>
<td>0.78 (0.68-0.90)</td>
</tr>
<tr>
<td>CCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Reference</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1-2</td>
<td>1.33 (1.16-1.54)</td>
<td>1.44 (1.28-1.61)</td>
<td>1.80 (1.61-2.01)</td>
</tr>
<tr>
<td>3+</td>
<td>1.76 (1.41-2.18)</td>
<td>2.21 (1.84-2.66)</td>
<td>3.30 (2.75-4.00)</td>
</tr>
<tr>
<td>Prior acute care utilization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>2.39 (2.01-2.72)</td>
<td>2.73 (2.46-3.03)</td>
<td>3.40 (3.07-3.76)</td>
</tr>
<tr>
<td>ED length of stay</td>
<td>1.00 (1.00-1.01)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (0.99-1.00)</td>
</tr>
</tbody>
</table>

Separate models were run for the 1-month, 3-month, and 12-month intervals, with higher acute care utilization defined at 1 and 3 months as ≥ 1 urgent care, emergency department, or inpatient encounter and at 12 months as ≥ 2 such encounters. The primary predictor for each time point was opioid prescription at or within 7 days of the index emergency department visit, and all analyses were adjusted for the listed covariates. Primary acute care utilization is defined as ≥ 1 urgent care, emergency department, or inpatient encounter in the 6 months prior to the indexing encounter. Emergency department length of stay is included as a continuous variable with 10-minute units.

CCI = Charlson Comorbidity Index; CI = confidence interval; ED = emergency department; OR = odds ratio; OPR = opioid pain reliever.
Variation in Positivity Rates of Computed Tomography Pulmonary Angiograms for the Evaluation of Acute Pulmonary Embolism Among Emergency Department Physicians

Kori Higashiya, MD1; James Ford, MD2; Hyo-Chun Yoon, MD, PhD3
Perm J 2022:26:21.019 • E-pub: 04/05/2022 • https://doi.org/10.7812/TPP/21.019

Abstract

Computed tomography pulmonary angiography (CTPA) is an imaging study for which there is substantial evidence for its overuse in the evaluation of acute pulmonary embolism (PE). Prior literature has reported low positive PE rates, but the variability in positive rates among the ordering physicians has not been as well studied. The purpose of this study was to evaluate variation in ordering and positive rates among physicians in an emergency department (ED) within an integrated health care system.

This study was based in a single ED that is part of a geographically isolated integrated health care system. We reviewed the patient records for all patients who underwent a CTPA for the evaluation for acute PE in the ED between January 1, 2018, and December 31, 2019. For each CTPA examination, we recorded the ordering ED physician, serum d-dimer value (mcg/mL), if any, and the results of the CTPA.

Review of CTPAs over the 2-year period revealed 1380 CTPAs ordered by 23 ED physicians with a range of 25–141 studies per physician (mean of 60 ± 31 CTPAs). The overall positive rate for PE was 6.9%. Individual ED physician positivity rates showed wide variability ranging from 0% to 18.4% (mean positive rate 7.6 ± 4.4%). The results of this study confirm the need for greater adherence to existing guidelines using clinical decision rules and d-dimer testing when appropriate among all ED physicians but especially those who order a greater number of studies and have low rates for positive PE.

Introduction

Computed tomography pulmonary angiography (CTPA) is an imaging study in evaluating acute pulmonary embolism (PE). Especially in the US, however, there is considerable evidence for its overuse. In a recently published 4-Level Pulmonary Embolism Clinical Probability Score (4PEPS) study,1 the authors used the existing data from 3 prospective studies on PE to evaluate the use of a 4-level clinical pretest probability score to potentially decrease imaging. The positive PE rates in the 2 European cohorts were 28% and 18%,2,3 while the positive rate in the US cohort was 5.9%.4 Three retrospective studies published in a variety of settings in the US reported a CTPA positive rate of acute PE of 1.8% in 716 CTPA studies performed in an urban community hospital,5 7.4% in 2031 CTPA studies performed in a large hospital system,6 and 5.4% in

Corresponding Author
Kori Higashiya, MD
Kori.higashiya@wsu.edu

Author Affiliations
1. John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA
2. Hawaii Permanente Medical Group, Emergency Medicine, Honolulu, HI, USA
3. Hawaii Permanente Medical Group, Diagnostic Imaging, Honolulu, HI, USA

Author Contributions:
Kori Higashiya, MD, participated in the acquisition of data, analysis and interpretation of the data, drafting, review, and submission of the final manuscript. Hyo-Chun Yoon, MD, PhD, participated in the study concept and design, acquired and analyzed the data, and assisted with the drafting and review of the final manuscript. James Ford, MD, participated in the study concept and design, acquired the data, and assisted with the review of the final manuscript.

Disclosures
Conflicts of Interest: None declared
Funding: None declared

Copyright Information
© 2022 The Permanente Federation. All rights reserved.
295 CTPA studies performed at a university hospital. While the overall positive PE rate is consistently low in all studies from the US, the variability in positive rates among the ordering physicians has not been as well studied. In our hospital, the overwhelming majority of CTPAs is ordered by physicians in the emergency department (ED).

The purpose of this study was to evaluate variation in ordering of CTPAs and the positive PE rates among physicians in a single ED within an integrated health care system, as well as to see how the application of a clinical decision rule might affect these results.

Methods

STUDY DESIGN
The Institutional Review Board approved this study.

STUDY SETTING AND POPULATION
This study was based in a single ED within a geographically isolated integrated health care system that serves approximately 250,000 members. The ED sees 48,000 patients per year, and all patient encounters are included in a comprehensive electronic medical record. We reviewed the patient records for all patients who underwent a CTPA for the evaluation for acute PE in the emergency department between January 1, 2018, and December 31, 2019. Based on internal data from our patient population, our medical group recommended the use of a higher d-dimer threshold (1 mcg/mL FEU) for patients in whom a CTPA study is requested.

Study Protocol: All CTPA studies were performed on one of two 64-slice CT scanners (GE Medical Systems, Milwaukee, WI) with image reconstructions in the axial, coronal, and sagittal planes. All d-dimer tests were performed using the STA-Liatest (Diagnostica Stago, Parsippany, NJ). For each CTPA examination, we recorded the ordering ED physician, serum d-dimer value (mcg/mL), if any, and the results of the CTPA. Results were recorded as either positive, negative, or indeterminate. Indeterminate was used if the report of the CTPA specifically mentioned that patient or technical factors precluded accurate assessment of segmental or more distal branches or if the report questioned if there was a possible embolism. For these indeterminate studies, we assessed what further imaging studies were performed, if any, during the same patient encounter or hospitalization. For positive PE studies, we recorded if the thrombus was limited to the segmental or subsegmental branches (peripheral PE) or in the lobar or more proximal pulmonary arteries (central PE). We excluded any CTPA ordered by an ED physician who only ordered studies from the ED during only one of the 2 years of this study.

To determine if greater adherence to accepted clinical criteria such as the Wells score and appropriate utilization of the serum d-dimer could be used to discriminate between ED physicians with lower PE positive rates from those with higher PE positive rates, we ranked the remaining ED physicians by their positive PE rates. We estimated that we would need to review approximately 120–170 charts to detect a 15% difference in adherence rates between groups of physicians with .05 significance and .80 power. Therefore, we combined the 4 physicians with the highest positive PE rates and who ordered a minimum of 30 PCTAs into one group (High group) and the 4 physicians with the lowest positive PE rates and who ordered a minimum of 30 PCTAs into a comparator group (Low group). We then reviewed the electronic medical record of each ED encounter leading to a CTPA for the patients who had been seen by a physician of the High group. One ED physician in the High group had ordered more than 50 CTPA studies during the study period, and we only reviewed 50 randomly selected patients for that physician in order to minimize any bias from having too many patients from any one ED physician. We also reviewed the electronic medical record of only 50 randomly selected ED encounters leading to a CTPA for each of the 4 ED physicians in the LOW group, except for one physician who ordered only 45 studies during the study period. All 45 of these encounters were included in the review.

For each patient encounter that was reviewed, we calculated the Wells score. We used the following algorithm to determine whether PE was as likely or more likely than any alternative diagnosis: If the patient’s chief complaint on ED physician record was shortness of breath or dyspnea, then we assumed PE was the most likely diagnosis unless 1) the patient had a history of congestive heart failure and chest x-ray was suggestive of edema, 2) the patient had signs and symptoms of a respiratory infection and an abnormal chest x-ray, or 3) the patient had a history of asthma or chronic obstructive pulmonary disease and clinical symptoms of an asthma or chronic obstructive pulmonary disease exacerbation. If the patient’s chief complaint was chest pain, then we assumed...
Variation in Positivity Rates of CT Pulmonary Angiograms

PE was the most likely diagnosis unless the patient had a history of coronary artery disease, prior myocardial infarction, or cardiomyopathy.

However, if the chest pain was further described as substernal, crushing, or radiating to the back or left arm, PE was not assumed to be the most likely diagnosis. For a chief complaint of unilateral leg pain or swelling, PE was assumed the most likely diagnosis unless there was a specific finding in the reported history to suggest a more likely alternative diagnosis. We assumed that the patient did not have signs or symptoms of deep venous thrombosis (DVT) unless the ED physician reported tachycardia. In addition to the standard definition of immobilization (3 consecutive days of bed rest or major surgery within 4 weeks), we also considered this positive if the ED physician noted a recent transpacific flight in their report because this was a frequently mentioned factor. No previous history of DVT or PE was presumed unless it was mentioned in the ED physician report or it was already coded into the patient’s problem list at the time of the ED encounter. Hemoptysis was also considered absent unless specifically mentioned in the ED physician report. Finally, active malignancy was considered absent unless specifically mentioned in the ED physician report or the patient had a diagnosis of malignancy for which they were receiving treatment or in palliative care at the time of the ED encounter based on the electronic medical record. The patients were then stratified into low (Wells criteria score 0–4), moderate (4.5–6), or high (> 6) probability, as was performed in the recent prospective Canadian trial. 11

We then compared the distribution of the Wells scores between the High and Low groups. We compared the utilization of d-dimer tests between these 2 groups of physicians. Finally, we compared appropriate utilization between the groups, where appropriate utilization was defined as a CTPA that was ordered for a patient with a low or moderate Wells score and d-dimer > 1.0 ug/mL or high Wells score irrespective of a d-dimer value, if any.

Results

TOTAL CTPA EXAMS AND POSITIVITY RATES
Between January 1, 2018, and December 31, 2019, 1507 CT pulmonary angiograms were performed. Of them, 127 CTPA studies ordered by 9 physicians were omitted because these physicians worked during only one of the 2 years of this study. The final data set included 1380 CT pulmonary angiograms ordered by 23 ED physicians. Out of all of them, 95 were positive for a PE, 1219 were negative, and 66 were indeterminate. Review of the medical records of the patients with indeterminate findings demonstrated that none were treated for acute PE. Nine of the 66 patients had a US evaluation for DVT that was negative. One patient with a questionable filling defect in a single segmental artery had a follow-up CTPA, which was negative. The remaining 56 patients had no further imaging evaluation for PE. Over this 2-year period, the overall positive rate for PE was 6.9%.

Table 1 lists the number of CTPAs ordered by ED physicians, positive PE rate, number of serum d-dimers ordered, those > 1 ug/mL, and the number of CTPAs performed without a corresponding serum d-dimer. The median number of CT pulmonary angiogram exams ordered by individual ED physicians was 49 (mean 60 ± 31 CTPAs with a

<table>
<thead>
<tr>
<th>Physician</th>
<th>Total CTPAs</th>
<th>Positive rate</th>
<th>D-dimer ordered</th>
<th>D-dimer &gt;1</th>
<th>No D-dimer ordered</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>12.5%</td>
<td>32</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>3.12%</td>
<td>35</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>12.9%</td>
<td>14</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>5.0%</td>
<td>62</td>
<td>50</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>121</td>
<td>2.5%</td>
<td>75</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>10.8%</td>
<td>25</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>3.8%</td>
<td>3</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>102</td>
<td>6.9%</td>
<td>46</td>
<td>23</td>
<td>56</td>
</tr>
<tr>
<td>9</td>
<td>75</td>
<td>13.3%</td>
<td>40</td>
<td>37</td>
<td>35</td>
</tr>
<tr>
<td>10</td>
<td>62</td>
<td>11.3%</td>
<td>27</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>11</td>
<td>36</td>
<td>11.1%</td>
<td>22</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>47</td>
<td>4.3%</td>
<td>20</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td>13</td>
<td>37</td>
<td>8.1%</td>
<td>16</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>14</td>
<td>70</td>
<td>4.3%</td>
<td>52</td>
<td>44</td>
<td>18</td>
</tr>
<tr>
<td>15</td>
<td>75</td>
<td>4.0%</td>
<td>18</td>
<td>14</td>
<td>57</td>
</tr>
<tr>
<td>16</td>
<td>45</td>
<td>0.0%</td>
<td>20</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>17</td>
<td>76</td>
<td>9.2%</td>
<td>54</td>
<td>46</td>
<td>22</td>
</tr>
<tr>
<td>18</td>
<td>49</td>
<td>18.4%</td>
<td>29</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>19</td>
<td>39</td>
<td>7.7%</td>
<td>16</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>20</td>
<td>49</td>
<td>6.1%</td>
<td>28</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>21</td>
<td>34</td>
<td>8.8%</td>
<td>18</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>22</td>
<td>141</td>
<td>3.6%</td>
<td>87</td>
<td>49</td>
<td>54</td>
</tr>
<tr>
<td>23</td>
<td>25</td>
<td>8.0%</td>
<td>24</td>
<td>23</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1: Individual ED physician data
range of 25–141, interquartile range 38). The median positivity rate among ED physicians was 7.7% (range of 0%–18.4%, interquartile range 7.0%).

The 4 physicians who ordered a minimum of 30 CTPA studies over the 2-year study period and had the highest positive CTPA rates (physicians 1, 3, 9, and 18 in Table 1, referred to as the High group) and had individual CTPA positive rates that ranged from 12.5% to 18.4%. These 4 physicians ordered a total of 195 studies with a range from 31 to 75 CTPAs. The 4 physicians who had the lowest positive CTPA rates (physicians 2, 5, 16, and 27 in Table 1, referred to as the Low group) had individual CTPA positive rates that ranged from 0.0% to 3.6%. These physicians ordered a total of 310 studies with a range from 45 to 141 studies.

Among all the reviewed ED encounters for both the High and Low physician groups, the Wells score was mentioned only twice, and no specific value was given in either record. Both mentions of the Wells score were by the same physician in the Low group. In one encounter, the ED physician noted “low risk by Wells.” We imputed a Wells score of 1.5 for this 74-year-old woman who did not have acute PE on her CTPA. In the other encounter, a “high risk by Wells” was mentioned. We imputed a Wells score of 6 for this 86-year-old man, who did not have acute PE on his CTPA.

The calculated Wells scores are presented in Table 2 for the representative sample of randomly selected patients, which was limited to 50 patients for each physician to minimize the bias associated with the different number of studies ordered by each physician. There was no significant difference in the distribution of the Wells scores between High and Low groups of physicians, $\chi^2(2, 370, 4.84, p = 0.09)$. There was no significant difference between the groups for the distribution of patients with or without a d-dimer test, $\chi^2(1, 370, 0.49, p = 0.48)$.

Among the patients who underwent CTPA ordered by the High group physicians with the highest positive PE rates, there were 103 patients who had a d-dimer level drawn. Twenty-six of these patients had a serum d-dimer < 1.0 mcg/mL and did not have an estimated Wells score > 6. These 26 patients would be considered to have inappropriately undergone CTPA. The remaining 77 patients would be considered to have appropriately undergone CT. Among the 4 ED physicians with the lowest positive PE rates, there were 112 patients who had a d-dimer level drawn, and 44 of them had a serum d-dimer < 1.0 mcg/mL and did not have an estimated Wells score > 6. These patients would be considered to have inappropriately undergone CTPA, which shows that a lower percentage of patients in the Low group (25.2%) inappropriately underwent CTPA compared to the High group (39.2%), $\chi^2(1, 215, 4.82, p = .03)$. There were no patients in the High group who had an imputed Wells score > 6 who had a d-dimer value less than 1. There was only one patient in the Low group with an imputed Wells score of 7.5, who would be considered to have appropriately undergone CTPA despite a d-dimer value 0.75 mcg/mL.

There were 3 patients who underwent CTPA ordered by the High group who had estimated Wells score ≤ 6 but had d-dimer values greater than their age-adjusted threshold, but less than the 1 mcg/mL threshold recommended by our medical group. All 3 CTPA studies were negative for PE. There were 2 patients who underwent CTPA ordered by the Low group who had estimated Wells score ≤ 6 but had d-dimer values greater than their age-adjusted threshold but less than the 1 mcg/mL threshold recommended by our medical group. Both CTPA studies were negative for PE. If we include these patients as having appropriately undergone CTPA, there is still a significant difference in the percentage of appropriate patients who underwent CTPA between these 2 groups of physicians (Low 62.5% vs. High 77.6%), $\chi^2(1, 215, 5.85, p = .02)$.

Discussion

This study confirms that there is substantial variability between ED physicians in the number of CTPAs ordered, as well as the positivity rates of PE in their patients. The difference between the ED physician who ordered the greatest number of CTPA studies and the ED physician who ordered the least number of studies was 5.6 times. The median
possession rate of 7.7%, with a range of 0% to 18.4% in these 23 ED physicians, is similar to that reported by Salehi et al, whose study examined 77 ED physicians who had a median possession rate of 9.1% with a range of 0% to 33%.12 In that study, there was up to 22-fold difference in the number of CTPAs ordered per ED encounter between physicians.3

The use of a clinical decision rule, such as Wells criteria, was rarely recorded in the ED encounter within the electronic medical record. Therefore, in order to compare the patients seen by the 2 groups of ED physicians, we retrospectively scored the patients based on the ED encounter reports. However, the distribution of the imputed Wells scores was not significantly different between the High and Low physician groups. There have been mixed results reported in the literature on the mandated use of a clinical decision rule in ordering CTPAs. In a study by Geeting et al, inputting a modified Wells score as part of the ordering process did not significantly increase the possession rate from 6.9% to 7.5%.13 These authors found that while the percentage of appropriately ordered CTPAs increased after ED physicians were required to input the Wells score, the overall utilization of CTPA and positive PE rates did not significantly change. They attribute the observed increased appropriate utilization to the increased use of the subjective component of the Wells score by the ordering physicians. In another study at a quaternary academic center, the implementation of the Wells criteria into the ordering process increased the overall positive PE rate from 9.2% to 12.6%, but there was large variability among the 25 physicians included in the study with a preintervention range of 2.6% to 20.5% and a postintervention range of 0% to 38%. There was only an increase in the positive rates of PE among the patients of 3 physicians.14

There was no significant difference between the High and Low physician groups in the rates at which they ordered d-dimer levels on their patients with possible PE. However, there was a significantly greater proportion of patients in the LOW physician group who underwent CTPA despite a d-dimer < 1 mcg/mL and an estimated Wells score ≤ 6 compared to those patients seen by physicians in the High group. The reason for ordering a CTPA despite a d-dimer < 1 mcg/mL was usually not mentioned in the reviewed reports. There were 2 physicians in the Low group who occasionally noted an “elevated dimer” in their ED reports on patients with d-dimer values <1.0 mcg/mL. However, this was not seen in all their reports. For the other 2 physicians in the Low group and all 4 physicians in the High group, there were no specific mentions of why a CTPA was ordered despite a d-dimer < 1 mcg/mL. Our study would suggest that while it is important to stress that all ED physicians should use clinical decision rules supplemented by d-dimer values when appropriate, those with the lowest positive PE rates may benefit the most from education on the importance of both in determining appropriate utilization of CTPA.

Our acute PE possession rate of 6.9% is consistent with other reported US studies.5-7 Possibility rates in the US have decreased since the 1990s and appear to be an ongoing issue for most centers in the US. As noted by Prologo et al, positivity rates for acute PE in the US decreased from 27.1% in 1997-1998 to 5.7% in 2002-2003.15 A key concern resulting from the low prevalence of acute PE in patients undergoing CTPA is that this can result in more false positives than true positives. Cronin and Kelly demonstrated that if the prevalence of acute pulmonary embolism in a study population is between 5% and 10%, the PPV of CTPA would only be 48.9-66.7%.16 Since our PE positive rate is 6.9%, some 50% of the reported positive PE studies may in fact be falsely positive. In a study by Hutchinson et al, the authors reported that out of 174 CTPA examinations (performed on 64-slice CT scanners, similar to those used in the current study) that were initially reported as positive for PE, 45 (25.9%) cases were subsequently reported as negative when reviewed by expert chest radiologists. Approximately 84.4% (38 out of 45) of the discordant cases were caused by pulmonary embolisms in segmental or subsegmental arteries.17 Given that 57.9% of the positive PEs were reported in the segmental and subsegmental arteries in this study, there is concern that a number of these studies may have been falsely positive and resulted in the unnecessary treatment of patients.

Limitations

In this retrospective review, it is difficult to determine the exact reasoning each physician used for ordering a CTPA. Our integrated health care system does not mandate the use of a clinical decision rule such as the Wells or revised Geneva score prior to ordering a CTPA. Therefore, we used the best available information in the electronic medical record to estimate each patient’s Wells score. We did not capture the total number of encounters seen by each ED physician during the
REFERENCES


Pragmatic Randomized Study of Targeted Text Message Reminders to Reduce Missed Clinic Visits

Ernesto Ulloa-Pérez, MS; Paula R Blasi, MPH; Emily O Westbrook, MHA; Paula Lozano, MD, MPH; Katie F Coleman, MSPH; R Yates Coley, PhD

Perm J 2022;00:21.078 • E-pub: 04/05/2022 • https://doi.org/10.7812/TPP/21.078

Abstract

INTRODUCTION: Missed clinic appointments (“no-shows”) waste health system resources, decrease physician availability, and may worsen patient outcomes. Appointment reminders reduce no-shows, though evidence on the optimal number of reminders is limited and sending multiple reminders for every visit is costly. Risk prediction models can be used to target reminders for visits that are likely to be missed.

METHODS: We conducted a randomized quality improvement project at Kaiser Permanente Washington among patients with primary care and mental health visits with a high no-show risk comparing the effect of one text message reminder (sent 2 business days prior to the appointment) with 2 text message reminders (sent 2 and 3 days prior) on no-shows and same-day cancellations. We estimated the relative risk (RR) of an additional reminder using G-computation with logistic regression adjusted for no-show risk.

RESULTS: Between February 27, 2019 and September 23, 2019, a total of 125,076 primary care visits and 33,593 mental health visits were randomized to either 1 or 2 text message reminders. For primary care visits, an additional text message reduced the chance of no-show by 7% (RR = 0.93, 95% CI: 0.89–0.96) and same-day cancellations by 6% (RR = 0.94, 95% CI: 0.90–0.98). In mental health visits, an additional text message reduced the chance of no-show by 11% (RR = 0.89, 95% CI: 0.86–0.93) but did not impact same-day cancellations (RR = 1.02, 95% CI: 0.96–1.11). We did not find effect modification among subgroups defined by visit or patient characteristics.

CONCLUSION: Study findings indicate that using a prediction model to target reminders may reduce no-shows and spend health care resources more efficiently.

Introduction

Missed clinic appointments result in a waste of health system resources as well as a missed opportunity for patients to receive care. Missed visits also decrease the availability of health care physicians to see other patients, especially in settings where there are a limited number of available appointments. Thus, use of health system resources, as well as patient care, can be improved by reducing the number of missed clinic
appointments (also frequently referred to as “no-shows”).1–5

Health system interventions may reduce missed appointments. Recent meta-analyses found evidence that reminders reduce no-shows for primary care visits.6,7 More specifically, text messages and phone calls (including live calls, automated messages, and interactive voice response calls) have been shown to reduce no-shows for primary care visits.6, 8–11 There is also limited evidence that 2 or more reminders are more effective than a single reminder in reducing missed visits.6, 12

Rather than provide additional phone or text reminders for all visits, risk prediction models can be used to target interventions for visits that are most likely to be missed and, in so doing, reduce the total cost of reminder systems.6, 9, 11–13 For example, Steiner et al developed a 10-variable no-show prediction model that had high discrimination (area under the curve = 0.9) for visits at Kaiser Permanente Colorado.9 In a subsequent trial comparing 2 reminders (delivered via interactive voice response call or text message, per patient preference) to a single reminder, Steiner et al found that the additional reminder reduced missed appointments among visits with the highest no-show risk.12 Shah et al also conducted a randomized trial to reduce no-show rates at the Massachusetts General Hospital primary care clinics among visits predicted to be at high chance of no-show by a prediction model estimated with earlier visits at the same practices.13 They found that reminder phone calls from patient service representatives reduced no-shows compared to automated reminder phone calls.

Epic, the developer of a widely-used electronic health record system, has developed a proprietary algorithm for predicting no-shows that health systems can use to guide interventions to reduce the chance of no-shows or to assist in overbooking and maximize the use of clinical resources.14 We conducted a randomized quality improvement project at Kaiser Permanente Washington (KPWA) to compare the effect of sending 1 versus 2 text message reminders to patients with visits predicted to be at high chance of no-show by the Epic algorithm. Outcomes were no-shows (defined as appointments that the patient did not attend and did not cancel prior to the visit) and same-day cancellations (defined as when the patient canceled the visit on the day it was scheduled to occur.) We examined the effect of an additional text message reminder on missed appointments and same-day cancellations in both primary care and mental health visits.

Methods

STUDY SETTING
The quality improvement study took place at KPWA, a health care system with more than 700,000 members in the state of Washington. About two-thirds of members receive comprehensive care at Kaiser Permanente medical facilities. KPWA has 33 care locations across the state which offer primary and/or specialty care, plus 4 additional facilities that offer specialty care such as eye care and mental health. Members can schedule visits over the phone with assistance from member access representatives or online through KPWA’s patient portal.

At the time of the study, KPWA members received a single text reminder for all scheduled clinic visits 2 business days before the appointment. Members may opt out of receiving text messages at any time. This study examined whether sending an additional text message 3 business days before the appointment for visits that are estimated to have a higher risk for no-show would reduce the rate of same-day cancellations and no-shows for outpatient primary care and mental health visits. No-show risk was estimated using a prediction model provided by Epic, the electronic health record software used by KPWA. No-show predictions are generated every night within Epic for all visits scheduled for the following week, and predictions are generated using the Epic proprietary model which takes as input the members’ demographic characteristics, the number of previous no-shows in the prior year, and visit characteristics (including how many days in advance the visit was scheduled and whether the visit is with the patient’s designated primary care practitioner). The study was conducted in partnership with health system leaders in the hopes of identifying effective ways to decrease unused primary care and mental health appointments.

INTERVENTION DESIGN
We conducted a 1:1 pragmatic randomized study for visits scheduled between February 27, 2019, and September 23, 2019, to assess whether an additional text message improved same-day cancellation and no-show rates for mental health and primary care appointments. Visits met the inclusion criteria if they were scheduled 4 business days or more in advance
and were classified as “high-risk” for no-show, defined as an Epic no-show risk in the top 40% of risk predictions for that type of visit (because the distribution of no-show risk was different between primary care and mental health visits).

Operational partners at KPWA chose to focus the study on visits in the top 40% of risk based on budgetary considerations and satisfactory prediction model performance. At the 40th percentile, sensitivity was 64% and positive predictive value was 9% in 364,940 primary care visits from May 1, 2018 to October 20, 2018. In 76,577 mental health visits from the same time, sensitivity was 62% and positive prediction was 20% at the 40th percentile. The 40th percentile thresholds were defined in this retrospective sample of visits. Visits with no-show risk above 5.1% for primary care visits and 21.1% for mental health visits were classified as high risk.

High-risk visits were randomized to either receive a text message 2 business days before the appointment (standard of care) or receive a text message 3 business days before the visit, in addition to the usual text message reminder 2 business days before the visit (intervention). All text messages were sent in English. For both groups, patients who had opted out of the reminder system did not receive any text messages; the study team did not have access to data on which members opted out of text message reminders. Upon receipt of the text message, members were asked to confirm the visit, or if they were unable to attend, to cancel by phone or online. Members with visits in the intervention arm who confirmed following the first text message reminder (3 business days before the appointment) but prior to the standard text message reminder (2 business days before the appointment) did not receive the standard text message reminder. Because randomization took place at the visit level, members with multiple eligible visits during the study period may have had visits randomized to both study arms. The KPWA Institutional Review Board determined that this project was a quality improvement (not research) project and, therefore, did not require Institutional Review Board oversight.

**STATISTICAL METHODS**

The primary and secondary outcomes of interest were the rate of no-shows and same-day cancellations, respectively. We estimated the intervention’s effect on each outcome as follows. First, we estimated the conditional effect of the intervention using a logistic regression model. To increase precision, logistic regression models were also adjusted for each visit's predicted no-show risk, as estimated by the Epic prediction model. We used generalized estimating equations with a working independent correlation structure to account for the clustering of visits within individuals in our study. To obtain an unconditional estimate of the intervention’s effect (rather than effect conditional on predicted no-show risk), we used G-computation to obtain a marginal relative risk estimate of the intervention’s effect on each outcome (averaged over the distribution of the no-show risk predictions for all visits in the study).

The advantage of the marginal estimate is that the interpretation of the parameter of interest is unconditional with respect to the no-show risk and has more precision than an unconditional estimated relative risk. Finally, we obtained the corresponding 95% confidence intervals of the marginal effects via bootstrapping the observations at the visit level to reflect the expected variability in the population of visits if implementing the prediction model in a clinical setting.

Additionally, we conducted exploratory analyses to assess whether the intervention had different effects within subgroups, also known as heterogeneity of treatment effects, defined by patient or visit characteristics. For these analyses, we examined patient and visit characteristics that prior research suggests might be associated with missed appointments such as the day and time of the scheduled visit, how far in advance the visit was scheduled, and patient characteristics, such as patient age. Subgroups that had a prevalence of less than 1% were removed from this analysis. To estimate the subgroup effect on each outcome, we adjusted for the intervention arm, the Epic risk prediction, the subgroup variable, and the interaction of the intervention with the subgroup in a generalized estimating equation model with logistic link. We tested for effect modification at the 0.05 type I error level using an analysis of variance test. Using G-computation we estimated the marginal effect of the intervention within subgroups and obtained their 95% confidence intervals via the bootstrap.

**Results**

A total of 390,064 visits were scheduled over the 7-month study period, including 302,689 primary care visits and 87,375 mental health visits.
A total of 125,076 primary care visits (41.3%) had a predicted no-show risk at or above 5.1% (40th percentile cut-off) and were randomly assigned 1 text message (n = 62,519) or 2 reminder text messages (n = 62,557). A total of 33,593 mental health visits (38.4%) had a predicted no-show risk at or above 21.1% and were assigned for randomization during the study period; 16,830 mental health visits were sent only one text message reminder and 16,763 were sent an additional text message. The percentage of visits of each type included in the study deviated slightly from 40% due to variation in the distribution of risk predictions between visits in the retrospective sample used to select cut-offs and those during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Primary Care Visits</th>
<th>Mental Health Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62,557 (50%)</td>
<td>62,519 (50%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt; 18</td>
<td>15,133 (24%)</td>
<td>15,318 (25%)</td>
</tr>
<tr>
<td></td>
<td>18 – 29</td>
<td>11,830 (19%)</td>
<td>11,717 (19%)</td>
</tr>
<tr>
<td></td>
<td>30 – 49</td>
<td>17,853 (29%)</td>
<td>17,917 (29%)</td>
</tr>
<tr>
<td></td>
<td>49 – 64</td>
<td>12,637 (20%)</td>
<td>12,678 (20%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 64</td>
<td>5104 (8%)</td>
<td>4889 (8%)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>38,212 (61%)</td>
<td>38,320 (61%)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>24,344 (39%)</td>
<td>24,196 (39%)</td>
</tr>
<tr>
<td></td>
<td>Neither female nor male indicated</td>
<td>1 (0%)</td>
<td>3 (0%)</td>
</tr>
<tr>
<td>Hispanic Ethnicity</td>
<td>Hispanic</td>
<td>7208 (12%)</td>
<td>71,65 (11%)</td>
</tr>
<tr>
<td></td>
<td>Non-Hispanic</td>
<td>51,263 (82%)</td>
<td>51,265 (82%)</td>
</tr>
<tr>
<td></td>
<td>Missing, Declined, or Do Not Know</td>
<td>4086 (7%)</td>
<td>4089 (7%)</td>
</tr>
<tr>
<td>Race</td>
<td>American Indian or Alaskan Native</td>
<td>1168 (2%)</td>
<td>1,217 (2%)</td>
</tr>
<tr>
<td></td>
<td>Asian or Asian American</td>
<td>6222 (10%)</td>
<td>6360 (10%)</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>5537 (9%)</td>
<td>5593 (9%)</td>
</tr>
<tr>
<td></td>
<td>Native Hawaiian or Pacific Islander</td>
<td>831 (1%)</td>
<td>810 (1%)</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>40,435 (65%)</td>
<td>40,141 (64%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>4225 (7%)</td>
<td>4326 (7%)</td>
</tr>
<tr>
<td></td>
<td>Missing, Declined or Do Not Know</td>
<td>4139 (7%)</td>
<td>4072 (7%)</td>
</tr>
<tr>
<td>Copay Due</td>
<td>No copay</td>
<td>42,417 (68%)</td>
<td>42,180 (67%)</td>
</tr>
<tr>
<td></td>
<td>$1 – $15</td>
<td>8018 (13%)</td>
<td>7964 (13%)</td>
</tr>
<tr>
<td></td>
<td>$16 – $60</td>
<td>11,849 (19%)</td>
<td>12,138 (19%)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>273 (0%)</td>
<td>237 (0%)</td>
</tr>
<tr>
<td>Epic No-Show Risk Score</td>
<td>5% – 10%</td>
<td>39,676 (63%)</td>
<td>39,654 (63%)</td>
</tr>
<tr>
<td></td>
<td>11% – 30%</td>
<td>19,875 (32%)</td>
<td>19,797 (32%)</td>
</tr>
<tr>
<td></td>
<td>31% – 51%</td>
<td>2446 (4%)</td>
<td>2447 (4%)</td>
</tr>
<tr>
<td></td>
<td>51% – 96%</td>
<td>560 (1%)</td>
<td>621 (1%)</td>
</tr>
<tr>
<td>Number of No-Shows in Year Prior to Visit</td>
<td>No missed visits</td>
<td>31,205 (50%)</td>
<td>31,312 (50%)</td>
</tr>
<tr>
<td></td>
<td>1 or 2 missed visits</td>
<td>15,070 (24%)</td>
<td>14,849 (24%)</td>
</tr>
<tr>
<td></td>
<td>3–10 missed visits</td>
<td>5100 (8%)</td>
<td>5086 (8%)</td>
</tr>
<tr>
<td></td>
<td>10 or more missed visits</td>
<td>494 (1%)</td>
<td>446 (1%)</td>
</tr>
<tr>
<td></td>
<td>No visits in previous year</td>
<td>10,688 (17%)</td>
<td>10,826 (17%)</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of primary care and mental health visits (Continued)
Table 1 shows the patient and visit characteristics for primary care and mental health visits included in the study. As expected, due to randomization, characteristics were balanced across the study arms in both primary care and mental health visits. Overall, demographic characteristics were similar across mental health and primary care visits, although mental health visits had a higher proportion of patients aged 18–30 and a lower proportion of patients with Asian or Asian American race indicated in their medical record. Visit characteristics such as the time or day of the week the appointment took place were also similar between the two visit types. However, lead time was higher in mental health visits, with 53% of the visits being scheduled more than a month in advance, in contrast to 19% of primary care visits.

Results (shown in Table 2) indicate that the intervention reduced the chance of no-shows in both primary care and mental health visits and reduced the chance of same-day cancellation in primary care visits. The estimated relative risk (RR) of no-show between the control and the intervention arm in primary care visits was 0.93 (95% confidence interval, CI, between 0.89 and 0.96). Thus, we estimate that the no-show risk for that visit will decrease by 7% if an additional text message is sent for any given primary care visit with a high estimated no-show risk. Sending an additional text message reminder also reduced same-day

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Primary Care Visits</th>
<th>Mental Health Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td>Number of Same-Day Cancellations in Year Prior to Visit</td>
<td>No same-day cancellations</td>
<td>32,039 (51%)</td>
<td>32,489 (52%)</td>
</tr>
<tr>
<td></td>
<td>1 same-day cancellation</td>
<td>10,720 (17%)</td>
<td>10,522 (17%)</td>
</tr>
<tr>
<td></td>
<td>2 same-day cancellations</td>
<td>4210 (7%)</td>
<td>4039 (6%)</td>
</tr>
<tr>
<td></td>
<td>3 or more same-day cancellations</td>
<td>4900 (8%)</td>
<td>4643 (7%)</td>
</tr>
<tr>
<td></td>
<td>No visits in previous year</td>
<td>10,688 (17%)</td>
<td>10,826 (17%)</td>
</tr>
<tr>
<td>Appointment Day</td>
<td>Monday</td>
<td>14,092 (23%)</td>
<td>14,047 (22%)</td>
</tr>
<tr>
<td></td>
<td>Tuesday</td>
<td>13,573 (22%)</td>
<td>13,580 (22%)</td>
</tr>
<tr>
<td></td>
<td>Wednesday</td>
<td>11,302 (18%)</td>
<td>11,315 (18%)</td>
</tr>
<tr>
<td></td>
<td>Thursday</td>
<td>10,527 (17%)</td>
<td>10,500 (17%)</td>
</tr>
<tr>
<td></td>
<td>Friday</td>
<td>11,666 (19%)</td>
<td>11,658 (19%)</td>
</tr>
<tr>
<td></td>
<td>Saturday</td>
<td>1397 (2%)</td>
<td>1418 (2%)</td>
</tr>
<tr>
<td></td>
<td>Sunday</td>
<td>0 (0%)</td>
<td>0 (&lt;1%)</td>
</tr>
<tr>
<td>Appointment Hour of Day</td>
<td>Morning (7AM–11:59 AM)</td>
<td>32,934 (53%)</td>
<td>32,877 (53%)</td>
</tr>
<tr>
<td></td>
<td>Midday (12 PM–3:59 PM)</td>
<td>21,184 (34%)</td>
<td>21,310 (34%)</td>
</tr>
<tr>
<td></td>
<td>Evening (4 PM–6:00 PM)</td>
<td>8439 (13%)</td>
<td>8332 (13%)</td>
</tr>
<tr>
<td>Appointment Lead Time in Days</td>
<td>Less than 8</td>
<td>14,339 (23%)</td>
<td>14,280 (23%)</td>
</tr>
<tr>
<td></td>
<td>8 to 14</td>
<td>15,464 (25%)</td>
<td>15,442 (25%)</td>
</tr>
<tr>
<td></td>
<td>15 to 30</td>
<td>20,858 (33%)</td>
<td>20,860 (33%)</td>
</tr>
<tr>
<td></td>
<td>More than 30</td>
<td>11,896 (19%)</td>
<td>11,937 (19%)</td>
</tr>
<tr>
<td>PHQ-9 Score (past year)</td>
<td>No PHQ-9 recorded</td>
<td>34,739 (56%)</td>
<td>35,033 (56%)</td>
</tr>
<tr>
<td></td>
<td>PHQ-9 &lt;10</td>
<td>20,543 (33%)</td>
<td>20,280 (32%)</td>
</tr>
<tr>
<td></td>
<td>PHQ-9 ≥10</td>
<td>7275 (12%)</td>
<td>7206 (12%)</td>
</tr>
<tr>
<td>Had Urgent Care Visit in Past 30 Days</td>
<td>No</td>
<td>59,233 (95%)</td>
<td>59,242 (95%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3324 (5%)</td>
<td>3277 (5%)</td>
</tr>
<tr>
<td>Has MyChart</td>
<td>No</td>
<td>31,269 (50%)</td>
<td>31,410 (50%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>31,288 (50%)</td>
<td>31,109 (50%)</td>
</tr>
</tbody>
</table>

a Number of days in advance that the visit was scheduled.
b Patient Health Questionnaire (PHQ-9) scores of 10, 15, 20 represent moderate, moderately severe, and severe depression, respectively.c

c MyChart is Epic’s online patient portal.
cancellations in primary care; the estimated RR was 0.94 (95% CI: 0.90–0.98). Among mental health visits, the estimated RR between intervention and control was 0.89 (95% CI: 0.86–0.93) for no-shows, indicating that an additional reminder reduced no-shows, and 1.02 (95% CI: 0.96–1.11) for same-day cancellations, indicating that the additional reminder had no impact.

Finally, for each variable listed in Table 1, we found no evidence of heterogeneous treatment effects of the intervention on no-show rates in either primary care or mental health visits, that is, p > 0.05 for all the subgroup effect modification analysis of variance tests. For example, for the time of day of a scheduled visit, the estimated marginal relative chance of the additional text message reminder’s effect on missed visits for primary care were 0.93 (95% CI: 0.89–0.97) for visits in the morning, 0.94 (95% CI: 0.89–1.00) for midday visits, and 0.89 (95% CI: 0.81–0.98) for evening visits. Table 3 shows the marginal relative risk estimates and their corresponding 95% CI for each of the subgroup analyses. We note that, because characteristics associated with no-show risk were selected for subgroup analyses, distribution of these characteristics among visits in the top 40% of risk vary from their distribution in the entire population of primary care and mental health visits at KPWA. Lack of heterogeneous treatment effects among high-risk visits does not imply that there would be no subgroup effect modification if additional text messages were sent to all visits.

Discussion

An additional text message in advance of visits at high chance of being missed was effective in reducing no-shows in primary care and mental health visits, and in reducing same-day cancellations of primary care visits. Our findings suggest that if an additional text message was sent to 18,250 primary care visits with Epic no-show risk predictions in the top 40%—the approximate number of high-risk primary care visits per month at KPWA—about 126 fewer missed visits would occur than if higher risk visits received only a single text message. Similarly, the additional text message is estimated to result in an additional 72 fewer same-day cancellations of primary care visits per month. In mental health, among approximately 4900 monthly visits in the top 40% of risk, we estimate that 106 fewer no-shows would occur per month if an additional text message was sent to high-risk visits.

Results from the randomized study indicate that using a risk prediction model to target reminders may promote efficient use of health care resources. By sending an additional text message reminder to high-risk visits we achieved higher efficiency at lower costs to the health system (compared to sending a message to all visits) and limited unnecessary notifications to patients with a high likelihood of attending their scheduled visit. We note that one smaller study previously found patient satisfaction to be unaffected by sending an additional reminder. One limitation of this study is that we did not monitor for a change in KPWA member requests to opt out of text messages among members with visits in the intervention arm. Although a targeted intervention to reduce no-shows may save resources, this approach involves additional costs of implementing a risk prediction model within the system. Risk-based targeting of additional text message reminders can be further improved by developing a risk model tailored to a particular population. A more precise risk model could improve the effectiveness of the intervention and may also be used to inform more resource-intensive interventions (eg, live reminder phone calls by patient access representatives).

In this study, we used a no-show prediction algorithm provided within Epic and available to health systems with the applicable Epic licenses. The development and implementation of prediction models by electronic health system vendors have the potential to expand access to predictive analytic tools to health care physicians who do not have in-house analytic capabilities. But these algorithms are proprietary, which hinders transparent auditing.
Table 3: Results of subgroup analyses for effect modification in no-show outcome (Continued)
of prediction model performance. We independently evaluated the performance of Epic’s model at KPWA before conducting this quality improvement project. One advantage of Epic’s no-show prediction model is that predictions can be calibrated within a health system to better fit the patient population; this feature is not available in many proprietary prediction models. Being able to independently assess an algorithm is crucial to ensuring that the implementation of prediction models provides accurate and equitable guidance in clinical settings.\textsuperscript{20}

In this study, no-show risk was predicted for all KPWA primary care and mental health visits, and all visits identified as high risk were automatically randomized and included in the study. Because this study did not use additional exclusion criteria, findings in this study reflect the real-life impact of implementing this intervention for all high-risk visits. However, this study was performed in only a single health care system, and effectiveness in other health systems may differ. Nevertheless, we did not find substantial heterogeneity of treatment effects for the no-show outcome, thus, our results may indicate that the effect is generalizable to populations with different visit and patient characteristics. For example, an additional text message was found to decrease no-show risk at Kaiser Permanente Colorado as well as in Denver Health.\textsuperscript{12,21} Thus, our study complements previous results for a different integrated health system and future work should be carried out to examine additional health care systems and models of care.

Finally, it is worth noting that sending an additional text message does not address many of the barriers to health care access that may be driving no-shows and same-day cancellations. Interventions that address social determinants of health need to be further developed and studied. For example, future studies could explore ways to address the lack of transportation to an appointment or the need for backup childcare or eldercare.\textsuperscript{22} Sending an additional text message reminder may help complement more robust interventions to reduce missed visits. Text message reminders are a relatively inexpensive strategy to reduce no-shows; the value of targeting interventions to those at highest risk would be even greater for more resource-intensive interventions.

**Conclusion**

Missed clinic appointments can be reduced through appointment reminders sent via text messages. Our randomized study at KPWA examined whether sending an additional text message reminder could reduce the rate of missed appointments for visits with a high predicted no-show risk. We found that sending an additional reminder, compared to the current practice of a single reminder, reduced the chance of missed appointments among primary care and mental health visits with predicted high no-show risk. This study provides an example of how predictive analytics can be used to target interventions to improve health care delivery and more efficiently allocate health system resources to optimize outcomes.

**REFERENCES**

5. Sharp DJ, Hamilton W. Non-attendance at general practices and outpatient clinics. BMJ 2001; 323(7321):1081–1082. DOI: https://doi.org/10.1136/bmj.323.7321.1081
The Effect of Elexacaftor/Tezacaftor/Ivacaftor on Hospitalizations and Intravenous Antibiotic Use

Eric Walter, MD, MSc; Jennifer L Bass, MD

Perm J 2022;26:21.089 • E-pub: 00/00/0000 • https:/ /doi.org/10.7812/TPP/21.089

Abstract

INTRODUCTION: Elexacaftor/tezacaftor/ivacaftor (ETI) is a highly effective cystic fibrosis transmembrane conductance regulator modulator. It has been shown to improve lung function and decrease pulmonary exacerbations in short-term clinical trials. The effect of ETI on hospitalization and intravenous (IV) antibiotic rates is not known. We performed a single-institution, retrospective review comparing these rates before and after the initiation of ETI.

METHODS: Among patients taking the cystic fibrosis modulator ETI, we compared the cumulative number of days per month hospitalized and cumulative number of days per month on IV antibiotics before and after the initiation of ETI. Electronic medical records from 37 patients were reviewed from 2016 through 2020 to identify demographic data, hospitalizations, and antibiotic use. Results were then stratified by severity of lung disease.

RESULTS: Following the initiation of ETI, there was a decline in days per month hospitalized and on IV antibiotics. The cumulative average number of days per month patients were hospitalized decreased 86% from 27 to 4 after starting ETI. The cumulative average number of days per month on IV antibiotics decreased by 80% (32.5 to 6.4). Most of these reductions occurred among patients with severe lung disease.

DISCUSSION: At our institution, we saw a decline in cystic fibrosis–related hospitalizations and in the use of outpatient IV antibiotics following the initiation of ETI. These reductions were most pronounced among patients with severe lung disease.

CONCLUSION: The initiation of ETI was associated with a decline in days hospitalized and days on IV antibiotics.

Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder caused by a defect in the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. There are more than 2000 known mutations, although most do not cause CF disease. CFTR resides on the epithelial cell surface and regulates sodium, bicarbonate, and fluid transport across the apical cell membrane. Defects in CFTR can lead to multisystem disease. The lungs are most often affected as airway epithelial dysfunction causes mucous to be
dry, thick, and difficult to clear. This, in turn, can lead to bronchiectasis, chronic infection, and progressive respiratory failure.1,2

In 2019, there were more than 31,000 people living with CF in the United States.3 Advances in CF care have made dramatic improvements in quality of life and life expectancy. Predicted median survival in 2004 was 34 years; this increased to 46 years by 2019.3 Prior to 2011, treatments were primarily focused on airway clearance, pancreatic enzyme replacement, and infection control.4 Over the past decade, CFTR modulator therapies have revolutionized the way CF is treated. These small molecule therapies correct the underlying defect in CF, leading to improved CFTR function. In a 2011 landmark trial, the CFTR modulator ivacaftor substantially increased the percent predicted forced expiratory volume in 1 second (ppFEV1), decreased sweat chloride levels, and reduced the rate of pulmonary exacerbations (PEx) in patients with the G551D mutation.5 It was approved by the US Food and Drug Administration (FDA) in 2012 but was only available to the small percentage of CF patients with the G551D mutation. Since 2011, 3 more modulators have been approved (lumacaftor, tezacaftor, and elexacaftor). Current therapies use combinations of these modulators. Combination therapies have shown benefit in many more patients, including those with the most common CF mutation, Phe508del (over 90% of patients have at least 1 copy of Phe508del). The combination therapy elexacaftor/tezacaftor/ivacaftor (ETI) improved ppFEV1 and quality of life and decreased sweat chloride and PEx over 6 months among patients with at least 1 copy of Phe508del.6 Among patients with 2 copies of Phe508del, ETI improved ppFEV1 and quality of life and decreased sweat chloride over a short, 4-week trial.7 On the basis of these 2 trials, ETI was FDA approved in 2019.

Little is known about the long-term safety and efficacy of ETI. An open-label extension study showed that improvements in ppFEV1, sweat chloride, and quality of life were maintained up to 48 weeks without emergence of safety concerns.8 The Real World Clinical Outcomes With Novel Modulator Therapy Combinations in People with CF (RECOVER) study is an ongoing observational study evaluating long-term clinical effectiveness and safety of ETI.9 Results are expected in 2024. Kaiser Permanente Northwest is an integrated health care organization that provides care to more than 600,000 members in Oregon and Washington states. Kaiser Permanente Northwest has both adult and pediatric CF-Foundation-accredited care centers. Shortly after our centers began prescribing ETI, we noticed an abrupt decrease in the frequency of admissions for PEx. We hypothesized that the use of ETI was reducing hospitalizations for PEx. We performed a retrospective review of hospitalizations before and after patients started ETI. Additionally, we compared intravenous (IV) antibiotic use before and after ETI. Some of the results have been previously reported in the form of an abstract.10

## Methods

We conducted a single-center, retrospective cohort study with a waiver of informed consent from the Kaiser Permanente Center for Health Research. Electronic medical records were reviewed from January 2016 through December 2020. Patients who were followed by the Kaiser Permanente Northwest CF Pediatric and Adult Centers on December 31, 2020 with a diagnosis of CF and receiving treatment with ETI were eligible for inclusion. This was a preintervention/postintervention study with the initiation of ETI as the intervention. Demographic data, hospitalization records, and outpatient IV antibiotic usage were reviewed. To control for the year-to-year variability in hospitalizations from years prior to ETI initiation, we used data from 2016 to 2019 as our preintervention period. Most patients had been followed at the Kaiser Permanente Northwest CF Center for the entire study period. Nine patients were new to the Kaiser Permanente Northwest CF Center since 2016, but information on all hospitalizations from 2016 onward were obtained from their electronic medical records.

The cumulative number of days hospitalized per month for CF-related hospitalizations were compared preintervention and postintervention. Non-CF–related hospitalizations were excluded. For patients who had been followed at our center for at least 5 years, complete outpatient IV antibiotic data were available. For this cohort, we compared the cumulative days on outpatient IV antibiotics per month before and after the intervention. If a patient was started on IV antibiotics while in the hospital, IV antibiotic days were calculated by subtracting hospital days from the total number of IV antibiotic days. If an exacerbation was treated without hospitalization, all IV antibiotic days were included. Results were stratified between patients with and without severe lung disease, defined as ppFEV1 less than 40% at any time during the study period. This was a
Results

PATIENT CHARACTERISTICS
Figure 1 depicts a flow chart for selection of eligible patients. Of the 67 patients eligible for ETI, 23 were not taking it. Nearly half (n = 11) had declined the medication. Most patients who declined did so because of typical lung function and a lack of symptoms. Six patients were posttransplant, and 4 did not have routine follow-up at our center. Patients who did not have a full 5 years of hospitalization data available (n = 5) and patients taking ETI for less than 3 months (n = 2) were excluded, leaving 37 patients included in the final analysis.

Patient characteristics of the final cohort are described in Table 1. Just over half of the patients were female (n = 20, 54%). Most patients were adults (n = 31, 83.7%). The median start date for ETI was March 12, 2020 with a range from December 19, 2019 through September 18, 2020. Most patients had commercial insurance (68%). The median ppFEV1 was 56%. Sixteen patients (43%) had severe lung disease.

Figure 1: Flow chart for identification of patient eligibility. KPNW = Kaiser Permanente Northwest; ETI = elixacaftor/tezacaftor/ivacaftor.
There was a decline in the number of days hospitalized following the initiation of ETI. The cumulative average number of days per month patients were hospitalized from 2016 to 2019 was 28.8 (Figure 2). This was relatively stable from 2016 to 2020 until ETI was started. After this, the average number of hospital days dropped to 4 days per month, an 86% reduction. Patients with severe lung disease accounted for most hospital days. Despite having severe lung disease, these patients still had a decrease in hospital days following ETI (Figure 3). In patients with severe lung disease, the average days per month hospitalized decreased to just 1.5 from an average of 22.9, a 93% decrease. The average days per month hospitalized decreased more than 50%, from 6 to 2.5 days per month, among patients without severe lung disease.

**HOSPITALIZATION DATA**

Complete IV antibiotic records back to 2016 were available for the 27 patients (73%) who had been followed by our center since 2016. Following the...
The Effect of Elexacaftor/Tezacaftor/Ivacaftor on Hospitalizations and Intravenous Antibiotic Use

Cumulative number of days per month hospitalized for patients with and without severe lung disease

![Graph showing hospitalization days by year and severity of lung disease](image)

Figure 3: The average number of days hospitalized per month shown by year. The black bars represent patients with severe lung disease, and the gray bars represent patients without severe lung disease. Severe lung disease was defined as an FEV1 < 40% at any time from 2016 to 2020. ETI = elexacaftor/tezacaftor/ivacaftor.

initiation of ETI, outpatient IV antibiotic days decreased (Figure 4). The average number of days per month patients in this group received outpatient IV antibiotics decreased from 32.5 per month preinitiation to 6.4 days per month postinitiation of ETI. This 80% reduction in outpatient IV antibiotic use was similar to the 86% reduction in hospital days. The reduction was most apparent among patients with severe lung disease.

Discussion

We report the results of a single-institution, retrospective study to examine the effect of ETI on hospital admission rates and IV antibiotic use among patients with CF. The original 2 pivotal trials examining ETI were short-term trials of 24 weeks⁶ and 4 weeks⁷. Our study reports longer-term outcomes with patients on ETI for an average of 10 months. Over this period, we saw an 86% reduction in days hospitalized and an 80% reduction in days on outpatient IV antibiotics after ETI was started. Our population was, on average, sicker than those in the randomized controlled trials, suggesting the benefit exists even in patients with severe lung disease. We prescribe ETI in patients with an FEV1 lower than trial enrollment criteria, as others have done.⁴¹¹ Trial patients were required to have an FEV1 of 40% or more at screening. In our study, 6 patients (16%) had an FEV1 < 40% at the time ETI was initiated, and 16 (43%) had an FEV1 < 40% at some time since 2016. Our patients were also hospitalized more often than were trial participants. Middleton et al reported an estimated annualized rate of PEx leading to hospitalization of 0.34 events per patient per year in those on placebo.⁶ Prior to starting ETI, our patients had approximately 1.0 PEx leading to hospitalizations per patient per year. This finding was heavily driven by patients with severe lung disease. Despite our population
being sicker overall, ETI reduced hospitalizations to a level similar to those seen by Middleton. Hospitalization event rates after starting ETI were 0.09 events per year in our study, compared with 0.07 events per year among study drug participants in the trial.

Improvement in CFTR function addresses the underlying problem with CF. However, it is not expected to repair the sequelae of CF such as bronchiectasis. When first approved, there were questions about how well ETI would work in patients with severe lung disease. Among our patients, we saw that the bulk of the reduction in hospital and IV antibiotic days occurred among patients with severe lung disease. Striking examples of improvement include 3 patients with chronic hypoxic respiratory failure and severe lung disease with a ppFEV1 ranging from 21 to 33%. From 2016 to 2019, they averaged a cumulative 18 days per month in the hospital. After starting ETI, none of them were hospitalized in 2020.

While clearly effective, ETI is expensive, with a wholesale acquisition cost of approximately $312,000 per year. Reducing PEx, admissions, and IV antibiotic use may offset some of the cost of ETI. For adults, estimated PEx costs requiring IV antibiotics vary between $57,000 (for patients with ppFEV1 ≥ 70%) to $130,000 (for patient with ppFEV1 < 40%). This estimate does not differentiate between those who were or were not hospitalized. Among the 27 patients in our cohort for whom we have a full 5 years of exacerbation data (both hospitalization and on outpatient IV antibiotics), there were an average of 40 exacerbations per year prior to starting ETI. After accounting for FEV1, this represents an estimated annual cost of exacerbations of $3.4 million dollars. The 2020 estimated cost for ETI for these 27 patients was approximately $8.7 million. Thus, the reduction in PEx following starting ETI potentially offset 40% of ETI costs. Upward of 70% of these savings were attributed to reducing treatment need among patients with severe lung disease.
To our knowledge, this is the largest study looking at real-world use of ETI. O’Shea and colleagues reported the effect of ETI in 14 patients with severe lung disease in Dublin, Ireland. Over an average follow-up period of 5 months, monthly exacerbations decreased approximately 86%. Our results, in a larger population of patients and over an average of 10 months of follow-up, showed a similar reduction. The ongoing RECOVER study will provide additional information when available.9

Our study has several limitations. It is likely that the COVID-19 pandemic affected health care utilization because patients wished to stay out of the hospital. However, we feel that ETI initiation decreased hospitalizations. If pulmonary exacerbations were occurring at the same rate as they were prior to starting therapy and patients were just declining admission, we would have expected to see a rise in home IV antibiotic use. Instead, we saw very similar reductions in both hospitalizations and IV antibiotic use. Comparing hospitalization and IV antibiotic use between those who started ETI and those who did not would help control for the effect of COVID-19. However, these 2 groups were not similar. Those who started ETI were not as healthy as were those who declined (mean FEV1 62% versus 92%). We are a small CF center, and this is a single-institution study; our results may not be applicable to other centers. However, our results are similar to others.11 Our size is also a strength of our study. Kaiser Permanente is an integrated health care organization. Our electronic medical records allowed us to identify all hospitalizations over a 5-year period, and excellent pharmacy support allowed us to track ETI initiation and adherence.

Conclusion

Our study suggests that the initiation of ETI was associated with a reduction in hospital days and days on outpatient IV antibiotics at our institution. This effect was seen among all patients but was most notable among patients with severe lung disease.

REFERENCES

Abstract

BACKGROUND: The COVID-19 pandemic has disproportionately impacted mental health among the lesbian, gay, bisexual, transgender, queer community, with the delay of medical services as a factor. The pandemic’s psychological effect on the transfeminine community pursuing facial feminization surgery remains unstudied.

METHODS: Patients at our institution whose facial feminization surgeries were delayed due to the COVID-19 pandemic were included. A chart review collected validated, self-reported depression and psychological distress measures, as well as perceived facial femininity and desire for feminizing facial surgery prior to the pandemic. The data were compared to repeat measures during the pandemic (March–April 2020).

RESULTS: Thirty patients were included in the study, 11 of whom had repeat data. Respondents during the pandemic (compared to prepandemic) felt their face was more feminine (p = 0.026) and more likely to be perceived as feminine by others (p = 0.026). They indicated a lower desire to alter their appearance with surgery (p = 0.041). Depression and distress indices were greater during the pandemic (p = 0.0018 and p = 0.026, respectively).

CONCLUSION: This study is consistent with increasing depression and psychological distress among transfeminine individuals pursuing facial feminization surgery during the pandemic. The study revealed greater perceived facial femininity and a lower desire for surgery during the pandemic.

Introduction

The severe acute respiratory syndrome coronavirus 2 virus that caused the COVID-19 pandemic has throttled socioeconomic and health-care productivity, as well as affected population health negatively. Along with physical health, mental health has shown a population decline, with greater anxiety and depression measures during the COVID-19 pandemic. The transgender and gender-nonconforming population is affected disproportionately at baseline, with some estimates of suicidal ideation breaching 60%, and is thus at increased risk for mental health burden, particularly among additional pandemic stressors. Urgent work among the surgical community is needed to understand more fully and mitigate additional harm.

The pandemic postponed many nonemergent surgeries, including gender-affirming surgery, which contributes to
greater psychological distress during the pandemic. Yet, facial feminization surgery (FFS) and other gender-affirming surgeries are medically necessary and can prevent suicide and improve safety. Comorbid mood disorder exists at baseline in as many as 42% of patients seeking FFS, with 78% of gender-nonconforming individuals reporting an increase in mental health disease. The pandemic’s negative psychological impact is likely felt by those transfeminine patients pursuing FFS, yet there exists no evidence in the literature.

Our study was designed to characterize the psychological impact of the COVID-19 pandemic on transfeminine patients pursuing FFS. Anxiety and depression measures, as well as perceived facial femininity and desire for facial surgery, were assessed prior to and during the COVID-19 pandemic. We hypothesized anxiety and depression measures among patients pursuing FFS were higher during the pandemic (compared to the prepandemic) period.

### Materials and Methods

#### PARTICIPANTS
Approval was obtained from the Kaiser Permanente Northern California Institutional Review Board for this retrospective study. Participants from our institution whose FFS was postponed as a result of hospital closure of nonurgent surgeries from March through April 2020 were included. Data prior to the pandemic were available for these participants. These participants were resurveyed by US postal mail in an effort maintain communication and provide resources, as postponement of gender-affirming surgery may be distressing.

#### MEASURES
Validated psychological measures from 2018 to 2019 were collected using a chart review of all participants. Responses to the Patient Health Questionnaire (PHQ-9) (α = 0.86–0.89), a self-reported survey measuring depression, and the Global Distress Scale (GDS) (α = 0.86–0.93), a self-reported psychological measure of distress (scale: 0, not at all; 1, several days; 2, more than half the days; 3, nearly every day), were analyzed. Higher scores among these surveys indicate greater depression (PHQ-9) and psychological distress (GDS). All participants completed the Facial Feminization Patient Questionnaire (FFPQ), a self-reported measure of perceived facial femininity and desire for feminizing facial surgery developed by our group (scale: 1, not at all; 2, somewhat; 3, moderately; 4, very much; 5, completely) during their FFS-preoperative appointment. One participant completed the prepandemic FFPQ in 2020 and was excluded from the analysis.

#### ANALYSIS
Prepandemic and pandemic data were compared. Because the FFPQ measures various topics and cannot be collapsed into a composite score, each FFPQ question was analyzed using a 1-tailed, paired sample t-test. The PHQ-9 and GDS data were found to be distributed normally by kurtosis and skew values between −2 and 2, and so were analyzed using independent sample t-tests as a result of a considerable number of missing prepandemic data. Significance was established at p < 0.05. All analyses were carried out using Microsoft Excel (version 2002) with the Analysis ToolPak add-in (Microsoft Corp., Redmond, WA).

#### Results
Thirty participants from our institution whose FFS was postponed because of hospital closure of nonurgent surgeries from March through April 2020 were eligible. One participant was excluded whose prepandemic data was obtained in 2020. Eleven of these participants returned surveys during pandemic delays while surgeries remained postponed indefinitely. One participant did not provide identifying information and was excluded from the paired analysis.

The FFPQ data reveal a significant effect among three of the questions. Pandemic (compared to prepandemic) responses showed greater agreement with “The appearance of my face is feminine” [mean, 2.4; standard deviation (SD), 0.8 vs mean, 1.9; SD, 0.7; t(9) = 2.2; p = 0.026] and “In public, I am confident my facial appearance is perceived as feminine” [mean, 2.2; SD, 1.1 vs mean, 1.8; SD, 0.8; t(9) = 2.2; p = 0.026], and lower agreement with “I would like to alter the appearance of my face (new surgery)” (mean, 4.5; SD, 0.7 vs mean, 4.8; SD, 0.4; t(9) = 1.96; p = 0.041 (Table 1).

PHQ-9 scores were significantly greater among the pandemic (mean, 11.3; SD, 4.4) compared to prepandemic (mean, 5.5; SD, 4.1) responses [t(21) = 3.3, p = 0.0018]. GDS scores were significantly greater among the pandemic (mean, 17.3; SD, 9.2) compared to prepandemic (mean, 10.2; SD, 7.3) responses [t(21) = 2.1, p = 0.026] (Table 1).
Discussion

The negative impact of the COVID-19 pandemic on psychological health is increasingly recognized and has been shown to affect marginalized populations disproportionately.4,12 The lesbian, gay, bisexual, transgender, queer community—and, in particular, the transgender community—is faced with numerous, unique stressors that have been amplified during the pandemic.13 One factor is the delay of medical services, which has been shown to affect patients negatively14; economic distress and loss of medical insurance may also contribute. Our study is consistent with general population studies during the pandemic,1 with greater psychological distress and depression seen among our study population. To our knowledge, our study is the first to investigate the impact of the pandemic (and subsequent FFS delay) on transfeminine individuals’ perception of their facial femininity prior to surgery. Somewhat paradoxically, the data indicate greater perceived facial femininity during the pandemic compared to prepandemic. Imposed social isolation and face coverings while in public may provide insight.

Decreased social contact and imposed face coverings during the pandemic may mitigate some aspects of the negative social response some transfeminine individuals endure in public. While in public, transfeminine individuals may face aggression and humiliation, and the resulting depression and anxiety.15 The psychological distress of this is measurable, and in part contributes to many transfeminine individuals’ pursuit of FFS. Imposed face coverings with a mask to protect others from COVID-19 viral exposure (severe acute respiratory syndrome coronavirus 2) may inadvertently reduce exposure to negative social responses. Facial features perceived as inconsistent with affirmed gender can be obscured easily in a socially acceptable—or, rather, public health-imposed—way. Masks have even been shown to make individuals less likely to be recognized, even when the observer is familiar with the individual.16 Thereby, distress incurred by social interaction may be reduced for these individuals.

Indeed, the psychological distress associated with negative social feedback is well studied. The societal
effect on one’s psychology is evidenced by the social self-preservation theory, which describes distress (shame, lower self-worth) resulting from an attack on the “social self,” with associated cortisol elevation. Conversely, when social interaction is more consistent with one’s felt self, self-perception and self-esteem—which are linked closely with and influenced by social interaction—follow suit.

There exists an important caveat to such a rationale, as work showing the upper facial third, a portion not typically covered by a face mask, is the facial segment with greatest impact on gender perception. In addition, improved perception of facial femininity does not seem congruent with greater depression and distress measures. According to the PHQ-9 results, prepandemic average scores increased from “mild depression” in prepandemic responses to “moderate depression” during pandemic surgery delays. The GDS scores were also elevated significantly, indicating increased social isolation, anxiety, and decreased productivity. In the case of FFS, surgery delays are delays in patients’ transition to their gender-affirmed self, protracting a state of incongruence. The data further bolster the complicated network of factors contributing to mental health in the transgender community during the pandemic.

Our study is limited by several factors. The depression and distress analyses were limited by unpaired data, requiring independent t-testing. The data are nominal, and our rationale for greater perception of facial femininity remains speculative. Thus, additional etiologies should be pursued for clarification. For instance, patients may fear undergoing surgery during the COVID-19 pandemic and, as a coping mechanism, subsequently rationalize their facial appearance while their surgery is delayed. Future work may focus on qualitative measures to understand more fully the underlying mechanism for such shifts in perception.

Conclusion

Our study is consistent with increasing psychological distress among transfeminine individuals pursuing FFS, with significantly greater anxiety and distress measures during the COVID-19 pandemic. To our knowledge, this study is the first to look at the impact of the pandemic on transfeminine individuals’ self-perception of facial femininity. Our study revealed greater perceived facial femininity and a lower desire for surgery during the pandemic. Imposed social isolation and the use of face coverings while in public may provide insight into these findings. The findings inform potential pandemic-related surgery stoppages, and highlight the need for increased mental health and social support for these individuals.

REFERENCES

Identifying Suicidal Ideation and Attempt From Clinical Notes Within a Large Integrated Health Care System

Fagen Xie, PhD; Deborah S Ling Grant, PhD, MPH, MBA; John Chang, MPH; Britta I Amundsen, LMFT; Rulin C Hechter, MD, PhD
Perm J 2022;26:21.102 • E-pub: 04/05/2022 • https:/ /doi.org/10.7812/TPP/21.102

Abstract

PURPOSE: The purpose of this study was to develop a natural language processing algorithm to identify suicidal ideation/attempt from free-text clinical notes.

METHODS: Clinical notes containing prespecified keywords related to suicidal ideation/attempts from 2010 to 2018 were extracted from our organization’s electronic health record system. A random sample of 864 clinical notes was selected and equally divided into 4 subsets. These subsets were reviewed and classified as 1 of the following 3 suicidal ideation/attempt categories (current, historical, and no) by experienced research chart abstractors. The first 3 data sets were used to develop the rule-based computerized algorithm sequentially and the fourth data set was used to evaluate the algorithm’s performance. The validated algorithm was then applied to the entire study sample of clinical notes.

RESULTS: The computerized algorithm correctly identified 23 of the 26 confirmed current suicidal ideation/attempts and all 10 confirmed historical suicidal ideation/attempts in the validation data set. It produced an 88.5% sensitivity and a 100.0% positive predictive value for current suicidal ideation/attempts, and a 100.0% sensitivity and positive predictive value for historical suicidal ideation/attempts. After applying the computerized algorithm to the entire set of study notes, we identified a total of 1,050,287 current ideation/attempt events and 293,037 historical ideation/attempt events documented in clinical notes. Those for which current ideation/attempt events were documented were more likely to be female (59.5%), 25–44 years old (28.3%), and White (43.4%).

CONCLUSION: Our study demonstrated that a computerized algorithm can effectively identify suicidal ideation/attempts from clinical notes. This algorithm can be utilized in support of suicide prevention research programs and patient care quality improvement initiatives.

Introduction

Suicide is a devastating outcome of psychiatric illness and a critical public health problem worldwide.\textsuperscript{1} It is the 10th leading cause of loss of life in the United States\textsuperscript{2} and the second leading cause of death among individuals aged 15–24 years\textsuperscript{3} and members of the US military.\textsuperscript{4} Despite extensive
suicide prevention research efforts, suicide rates in the United States have continued to increase in recent years.5,6 Suicide is a complex process that involves a series of pathways and mechanisms from thoughts of killing oneself, planning, and finally attempt.7 Suicidal behavior differs between genders, age groups, geographic regions, and sociopolitical settings.8 In addition to increasing health care clinician training and restricting access to lethal means, evidence-based screening using validated, population- and setting-specific assessment tools is recommended for patients in all medical settings to detect early suicidal thoughts or preparatory behaviors before an actual attempt.9,10

Previous studies have used survey instruments or clinical diagnoses from health care administrative or claims data to identify suicidal behaviors.11,12 The recent exponential growth in the utilization of electronic health records (EHRs) has provided unprecedented opportunities for researching documented suicidal behaviors using an automated health care database.13 However, a systematic review has reported a low sensitivity (13.8%–65%) for identifying suicide or suicidal ideation using structured administrative or claims data, because suicidal behaviors are often undercoded.14 Utilizing information other than diagnostic codes or questionnaires to identify populations at risk of suicide can mitigate the misclassification bias and facilitate population-based mental health research studies that examine the risk factors for suicide and inform the development of targeted suicide prevention programs.14 To fully utilize the information on suicidal behaviors documented in unstructured free-text clinical notes and improve the efficiency of chart review, natural language processing (NLP) can automate the examination15 and convert information residing in free-text natural language into a more structured format for analysis.16

NLP techniques have been recently utilized to detect suicidality and suicidal behaviors from suicide notes,17 psychiatric clinical databases,18 social media,19 and clinical notes describing US veterans,20,21 adolescents with autism spectrum disorders,22 and pregnant women.23 The combination of advanced machine learning and NLP techniques has also been explored to classify and predict suicidal thoughts and behaviors from both structured24–26 and unstructured data.19–21,27–29 However, studies focused on detecting suicide attempts and suicidal ideation among a large, diverse population in a general medical setting are limited. In this study, we sought to develop and validate a rule-based computerized algorithm and automated process to correctly identify suicidal behaviors (ideation/attempt) from clinical notes in the comprehensive EHR of Kaiser Permanente Southern California, a large integrated health care system.

Methods

STUDY SETTING AND POPULATION

With 15 hospitals and more than 230 affiliated medical offices, Kaiser Permanente Southern California is an integrated health care system that provides complete medical services to over 4.7 million members, including ambulatory primary and specialty care, inpatient care, and emergency care, as well as laboratory, immunization, and pharmacy services. The diverse demographic characteristics of Kaiser Permanente Southern California members are largely representative of the residents in the Southern California region.30 Kaiser Permanente Southern California’s extensive EHR system captures both structured and unstructured data documented by health care clinicians at various care settings, including non-Kaiser Permanente facilities. The structured data contain diagnosis codes, procedure codes, information on pharmacy dispenses, immunizations, laboratory results, pregnancy episodes, and outcomes. The unstructured data include free-text clinical notes, radiology reports, pathology reports, imaging, videos, and more. The protocol for this study was reviewed and approved by the Kaiser Permanente Southern California Institutional Review Board with a waiver of the requirement for informed consent.

SUICIDAL THOUGHTS AND BEHAVIORS KEYWORD SELECTION

The Kaiser Permanente Southern California EHR system captures billions of clinical notes created by clinicians during clinical care. To reduce the sheer volume of notes and process them efficiently, our study only extracted the clinical notes indicating suicidal behavior for analysis. To retrieve relevant clinical notes for processing, keywords and phrases related to suicidal ideation and behaviors were compiled through consultations with mental health clinicians, diagnosis definitions, and ontologies in the Unified Medical Language System.31 A suicidal ideation/attempt term was composed of a compound suicide-related term and thought- or behavior-related term, such as “suicide attempt”, “suicide ideas,” and “suicide plan.” The terms associated with suicide included
Identifying Suicidal Ideation and Attempt From Clinical Notes Within a Large Integrated Health Care System

<table>
<thead>
<tr>
<th>Term category</th>
<th>Keywords and phrases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide</td>
<td>suicide, suicidal, suicidality, parasuicide, parasuicidal, kill self, kill myself, kill yourself, kill herself, kill himself</td>
</tr>
<tr>
<td>Behavior</td>
<td>behavior, action, attempt, idea, ideation, thought, think, tendency, plan, intent, intention, urge, overdose</td>
</tr>
<tr>
<td>Past history section(\textsuperscript{a})</td>
<td>past medical history, previous medical history, patient medical history, past psychiatric history, past psychiatric treatment, past psych history, past psych treatment, past medical, past psychotropics, medical history, pmh, psh, pmhx, phx</td>
</tr>
<tr>
<td>Diagnosis section(\textsuperscript{b})</td>
<td>diagnosis, diagnose, dx, primary diagnosis, primary encounter diagnosis, primary problem, psychiatric problem</td>
</tr>
</tbody>
</table>

\(\textsuperscript{a}\)The algorithm also searched abbreviations, misspellings, and variants (plural form and verb tenses) of these words, where applicable.

\(\textsuperscript{b}\)Used for algorithm development.

The detailed list of variants is summarized in Supplemental Material Table S1.

**CLINICAL NOTE EXTRACTION AND PREPROCESSING**

Clinical notes containing at least 1 of the suicide-related terms listed in Table 1 were extracted from the EHR data for members who received care at Kaiser Permanente Southern California between January 1, 2010, and December 31, 2018, via the SAS PROC SQL. The extracted clinical notes contained the detailed descriptions written by health care clinicians (eg, mental health clinicians, primary care physicians, social workers) regarding the patient’s condition at the time of the visit. The length of the clinical notes varied according to specific medical conditions. Any patient instructional notes were excluded, as these notes usually provide general warnings, instructions, or recommendations regarding medical conditions rather than make diagnoses or describe the patient’s symptoms. A total of 16,642,120 clinical notes with suicide-related terms were retrieved during the study period. These extracted clinical notes were then transferred to a Linux server and preprocessed through sentence separation and tokenization (ie, segmenting text into linguistic units such as words and punctuations) via Python programming,\(^\text{32}\) the Natural Language Toolkit,\(^\text{33}\) and a customized sentence boundary detection algorithm.\(^\text{34,35}\) For example, the special symbols “¶” in the clinical notes indicated the end of sections and sentences in the EHR system. The clinical notes were further standardized using the word tokens listed in Supplemental Material Table S1.\(^\text{a}\)

**TRAINING DATA SET, VALIDATION DATA SET, AND REFERENCE STANDARD**

A representative sample of 864 clinical notes was randomly selected from the entire set of preprocessing clinical notes and equally divided into 4 subsets, each containing 216 notes. These subsets were first sequentially reviewed and each note was classified as 1 of the following 3 suicidal ideation/attempt categories by experienced research chart abstractors: current, historical, and no. If evidence of both current and historical suicidal ideation was presented in the same note, then the note was classified as current to identify the more severe suicide risk situation. The chart review results were then validated and confirmed by another independent, trained chart abstractor. Cases that could not be classified by the abstractors were further reviewed and adjudicated by the study’s principal investigator and project manager with additional consultations from physician experts. Current episodes included notes that mentioned a suicidal ideation/attempt event within 2 weeks of the note date. Historical episodes were defined as documented suicidal ideation/attempt events that occurred more than 2 weeks before the note date. Events were classified as no if there was no evidence of an actual suicidal ideation/attempt event in the note. The manual review results were deemed the reference standard. The results of the first 3 subsets were used for algorithm development, while the rest of the clinical notes were used to evaluate the algorithm performance.

**NLP COMPUTERIZED ALGORITHM**

A rule-based computerized algorithm was developed through an iterative process to ascertain the status of suicidal ideation/attempt for each clinical note using the training datasets. With each iteration, the algorithm was refined to match the results of the reference standards that were derived through manual review and adjudication of the 3 training subsets sequentially. The process first searched suicidal ideation/attempt at the sentence level and then aggregated at the note and date levels. More specifically, the steps were to detect...
suicidal ideation/attempt within each clinical note as shown in Figure 1.

Sentences were excluded for the following:

- No suicide-related term from the list in Table 1
- Someone other than the patient had suicidal ideation/attempt. For example, “patient’s daughter has been acting out and voicing suicidal thoughts.” Terms used for searching nonpatient self-description are summarized in Supplemental Material Table S2.
- Negated or uncertain description of suicidal ideation/attempt. Examples include “patient denies any suicidal ideation,” “negative for suicide ideas,” “no suicidal thinking,” and “may have suicidal ideation.” The list of negated or uncertain terms in the pyConTextNLP was applied and subsequently enhanced by previous studies as well as during the training process. Terms used in searching for negated or uncertain descriptions are summarized in Supplemental Material Table S2.
- Suicidal ideation/attempt description did not refer to an actual situation, such as “discussed risks, benefits, and side effects, including but not limited to suicidal thinking,” and “in case of having any suicidal ideas.” Terms used in searching for general descriptions are summarized in Supplemental Material Table S2.

The status of suicidal ideation/attempt was classified as historical for any of the following situations:

- Sentence contained a question about a “history of suicidal thoughts,” and the corresponding answer was “yes”
- Terms related to suicidal ideation/attempt appeared in the history section of a clinical note, such as “past medical history: suicidal attempt.” A complete list of terms applicable to the history section is presented in Table 1.
- Sentence contained terms indicating historical events (events that occurred more than 2 weeks before clinical note date). Clinical notes typically contained information describing the patient’s history of medical conditions. The temporality terms regarding historical events included the lists in the pyConTextNLP which was enriched based on previous studies and the training data sets. Examples include “one suicide attempt in teen years,” “tried to commit suicide several years ago.” Terms used in searching the history description are summarized in Supplemental Material Table S2.
- Sentence contained a specific time description (ie, date, year, month, weeks, days) associated with a term indicative of suicidal ideation/attempt, and this date was 2 weeks before the clinical note date. This would apply to a note that read “patient mentioned having suicidal thoughts 4 weeks ago,” for example.
A suicidal ideation/attempt was classified as current if 2 conditions were met: 1) a sentence contained phrases or questions asking about “suicidal thoughts within the last 2 weeks” or “thoughts of death/self-harm within the last 2 weeks” with a corresponding answer of “yes,” “some,” “several days,” “more than half of the days,” or “nearly every day” and 2) one of the following situations applied:

- Sentence was part of a suicide risk assessment in which the risk was deemed moderate or above
- Sentence contained a diagnosis code of “V62.84,” “R45.851,” or “E958.9”
- Terms related to suicidal ideation/attempt appeared in the diagnosis, chief complaint, likely self-harm, active problem list, or patient safety sections. Examples include “diagnosis: depression, suicidal ideation, drug overdose,” and “chief complaint: depression, suicidal behavior.” The detailed list of relevant terms in the diagnosis section is presented in Table 1.
- Sentence contained a definitive term before or after a term related to a suicidal ideation/attempt or suicide only. Examples include “positive for depression and suicidal ideas,” “has some suicidal ideation, on and off for about 2 weeks,” and “patient tried to commit suicide 2 days ago.” Terms used in searching for definite descriptions are summarized in Supplemental Material Table S2.

Suicidal ideation/attempts at the note level were prioritized using the following rubric:

1. classify the status of suicidal ideation/attempt as current if at least 1 sentence was deemed current, regardless of the historical status
2. categorize the status of suicidal ideation/attempt as historical if at least 1 of the sentences was considered historical
3. if not 1 or 2, categorize the status of this visit date as no

APPLICATION OF THE COMPUTERIZED ALGORITHM
The developed algorithm was implemented through Python programming on a Linux server to process the entire set of clinical notes. The algorithm created outputs of the suicidal ideation/attempt status at the sentence, note, and visit date levels for further analysis.

DATA ANALYSIS
The computerized algorithm developed from the training data sets was applied to the validation data set to identify suicidal ideation/attempt events at the note level. The results from the computerized algorithm and manual chart review were compared for the validation data set. Sensitivity, positive predictive value (PPV), and F-score were calculated and reported for both the current and historical categories. Sensitivity was defined as the proportion of suicidal ideation/attempt events (current or historical) correctly assigned by the computerized algorithm among all cases confirmed by manual review. PPV was defined as the proportion of correctly determined suicidal ideation/attempt events (current or historical) among all those identified by the computerized algorithm. The F-score was calculated as $2 \times \text{PPV} \times \text{Sensitivity} / (\text{PPV} + \text{Sensitivity})$. The number and percentage of suicidal ideation/attempt events (current or historical) ascertained by the computerized algorithm at the visit date level were summarized by year. The distribution of patients by the total number of current suicidal ideation/attempt cases per patient was reported for the entire study period. Finally, the demographic characteristics of individuals identified with current suicidal ideation/attempt events were examined during the study period.

Results
The classification of suicidal ideation/attempt events by manual review of the training and validation data sets is summarized in Table 2. Among the 216 clinical notes in each data set, about 8.3% to 10.6% were classified as current suicidal ideation/attempt events, and 2.8% to 4.6% were categorized as historical suicidal ideation/attempt events. Among the 216 clinical notes in the validation data set, the computerized algorithm correctly identified 23 of the 26 current suicidal ideation/attempt events and all 10 of the historical suicidal ideation/attempt events.
Identifying Suicidal Ideation and Attempt From Clinical Notes Within a Large Integrated Health Care System

The Permanente Journal

A total of 13,946,374 encounters with clinical notes containing suicide-related terms between 2010 and 2018 were extracted. Of them, 1,050,289 encounters were identified by the validated computerized algorithm as having a current suicidal ideation/attempt event, and 293,038 were identified as having a historical event documented (Table 3). The number and percentage of identified events among the extracted encounters of the study period varied by calendar year, with about 6.0% to 11.8% of the encounter notes containing suicide-related terms categorized as addressing a current suicidal ideation/attempt event and about 1.7% to 3.3% classified as addressing a historical event.

There were 400,436 individuals with 1 or more current suicidal ideation/attempt events identified during the entire study period. Among them, 249,791 (62.4%) individuals had 1 event, 60,511 (15.1%) had 2 events, 27,165 (6.8%) had 3 events, 16,015 (4.0%) had 4 events, and 46,954 (11.8%) had 5 or more events during the study period.

A first current suicidal ideation/attempt event was more likely to be noted for patients who were female (58.7%), aged 15–24 years (28.8%), and Hispanic (41.7%). Taking into account all current events, suicidal ideation/attempt events were still most common among females (59.5%), but they were more likely to be documented for patients who were aged 25–44 years (28.3%) and White (43.4%) (Table 5). In comparison, female patients, White patients, and those 25 years or older were more likely to have a historical event than a current event documented.

### Discussion

In this study, we developed a rule-based computerized algorithm for identifying current and historical suicidal ideation/attempt events from free-text clinical notes, with a high PPV and sensitivity. Our findings suggest it is feasible to apply NLP technology to identify individuals at risk for suicide using automated EHR data, and the use of the NLP algorithm can mitigate misclassification bias in research studies caused by undercoding suicidal ideation/attempts and support accurate evaluation of the association between risk factors and suicide outcomes.

Historical suicidal ideation has been revealed as a risk factor for recurrent/repeated suicidal ideation.37

---

**Table 3:** Classification and accuracy measures of computerized algorithm in identifying suicidal ideation/attempt compared with results confirmed by manual review among the validation data set

<table>
<thead>
<tr>
<th>Classification</th>
<th>Training data set 1 (N = 216)</th>
<th>Training data set 2 (N = 216)</th>
<th>Training data set 3 (N = 216)</th>
<th>Validation data set (N = 216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>23 (10.6%)</td>
<td>18 (8.3%)</td>
<td>20 (9.3%)</td>
<td>23 (10.6%)</td>
</tr>
<tr>
<td>Historical</td>
<td>6 (2.8%)</td>
<td>9 (4.2%)</td>
<td>9 (4.2%)</td>
<td>10 (4.6%)</td>
</tr>
<tr>
<td>No</td>
<td>187 (86.6%)</td>
<td>189 (87.5%)</td>
<td>187 (86.6%)</td>
<td>183 (84.8%)</td>
</tr>
</tbody>
</table>

**Table 4:** Proportion of clinical notes containing predefined keywords identified by the computerized algorithm by calendar year (2010–2018)

<table>
<thead>
<tr>
<th>Year</th>
<th>Status of suicidal ideation/attempt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Current</td>
</tr>
<tr>
<td>2010</td>
<td>129,456 (11.8%)</td>
</tr>
<tr>
<td>2011</td>
<td>75,610 (6.5%)</td>
</tr>
<tr>
<td>2012</td>
<td>77,202 (6.0%)</td>
</tr>
<tr>
<td>2013</td>
<td>97,380 (7.1%)</td>
</tr>
<tr>
<td>2014</td>
<td>104,501 (7.1%)</td>
</tr>
<tr>
<td>2015</td>
<td>112,631 (6.9%)</td>
</tr>
<tr>
<td>2016</td>
<td>119,358 (6.6%)</td>
</tr>
<tr>
<td>2017</td>
<td>139,597 (7.2%)</td>
</tr>
<tr>
<td>2018</td>
<td>194,552 (9.1%)</td>
</tr>
<tr>
<td>Overall</td>
<td>1,050,287 (7.5%)</td>
</tr>
</tbody>
</table>

---

**Table 2:** Classification of suicidal ideation/attempt by manual chart reviews among training and validation data sets

<table>
<thead>
<tr>
<th>Computerized algorithm classification</th>
<th>Manual review classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Current</td>
</tr>
<tr>
<td>Current</td>
<td>23</td>
</tr>
<tr>
<td>Historical</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td>All</td>
<td>26</td>
</tr>
</tbody>
</table>

**Table 3:** Classification and accuracy measures of computerized algorithm in identifying suicidal ideation/attempt compared with results confirmed by manual review among the validation data set

<table>
<thead>
<tr>
<th>Classification</th>
<th>DPV</th>
<th>Sensitivity</th>
<th>F-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>100.0%</td>
<td>88.5%</td>
<td>0.94</td>
</tr>
<tr>
<td>Historical</td>
<td>100.0%</td>
<td>100.0%</td>
<td>1.00</td>
</tr>
</tbody>
</table>

---

**Table 4:** Proportion of clinical notes containing predefined keywords identified by the computerized algorithm by calendar year (2010–2018)

<table>
<thead>
<tr>
<th>Year</th>
<th>Status of suicidal ideation/attempt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Current</td>
</tr>
<tr>
<td>2010</td>
<td>129,456 (11.8%)</td>
</tr>
<tr>
<td>2011</td>
<td>75,610 (6.5%)</td>
</tr>
<tr>
<td>2012</td>
<td>77,202 (6.0%)</td>
</tr>
<tr>
<td>2013</td>
<td>97,380 (7.1%)</td>
</tr>
<tr>
<td>2014</td>
<td>104,501 (7.1%)</td>
</tr>
<tr>
<td>2015</td>
<td>112,631 (6.9%)</td>
</tr>
<tr>
<td>2016</td>
<td>119,358 (6.6%)</td>
</tr>
<tr>
<td>2017</td>
<td>139,597 (7.2%)</td>
</tr>
<tr>
<td>2018</td>
<td>194,552 (9.1%)</td>
</tr>
<tr>
<td>Overall</td>
<td>1,050,287 (7.5%)</td>
</tr>
</tbody>
</table>
Previous studies reported around 30% to 40% of individuals presenting with current suicidal ideation also had a history of suicidal ideation.\textsuperscript{38,39} Our NLP algorithm identified more than 400,000 individuals with 1 or more current suicidal ideation/attempts within our study period, and 37.6% of them had repeated or recurrent events after the first event. This was consistent with the findings from previous studies.\textsuperscript{38,39}

Our computerized algorithm misclassified 3 current suicidal ideation/attempt events in the validation data set. This was because the suicide-related term representing phrases “not be alive” (2 cases) and “wants to jump off bridge” (1 case) did not appear in the training data sets. Refinement to include additional suicide-related linguistics and relevant phrases can be carried out in future work to improve the algorithm’s performance. This could also indicate a need to improve clinical note drafting practices at the organizational level. For example, adding a clinical impression of current suicidal ideation would allow the computerized algorithm to pick up a case even if the clinician also documents the patient’s own idiosyncratic words.

Conducting a full manual chart review is labor intensive and time consuming. Our study included a huge volume of clinical notes that contained predefined suicidal ideation/attempt keywords and phrases. It was not feasible to manually review the entire set of study notes for the algorithm development and validation. To develop an effective algorithm, a small proportional sample (864 notes) was randomly selected from the total set of study notes. This sample was randomly and equally divided into 4 subsets. Such randomization ensures that each subset has similar characteristics and generally represents the study notes. In addition, the iterative training process tuned and produced the robust performance of the computerized algorithm. However, further validation may be considered when the developed algorithm is applied to different study settings.

It is worthwhile to point out that this algorithm is a computerized tool to identify documented suicidal ideation/attempt events from free text automatically, which is markedly different than a clinical screening instrument intended to detect true cases.\textsuperscript{9,10} The performance of this tool relied on the completeness and accuracy of the clinical notes. However, clinicians may sometimes copy text descriptions from previous progress notes and apply them to the current encounter summary. It is challenging to distinguish and omit notes that were

---

Table 5: Demographic characteristics of individuals at the first current, all current, and historical suicide ideation/attempt events during the study period
carried over if there are no specific indicators, such as the encounter date associated with the previous event. Therefore, some historical events might be misclassified as current due to the imprecision of the clinical notes.

In recent years, machine learning techniques used alone or in combination with rule-based NLP have been applied to identify suicidal behaviors for specialized populations.\(^{18-23}\) The performance of these algorithms varies widely, with a PPV ranging from 30% to 92% and a sensitivity ranging from 56% to 98%. The performance of our rule-based computerized algorithm was reasonable and close to the top range of these existing models. However, further research on the combination of rule-based and advanced machine learning approaches, such as random forest and deep neural network learning, may increase the sensitivity of identification of suicidal ideation/attempts in clinical notes among large, diverse populations. In addition, the NLP algorithm can be further enhanced to stratify the level of severity of suicidal ideation. Such enhancements can strengthen the clinical value of this algorithm and facilitate the development and implementation of targeted suicide prevention programs in clinical practice.

This study acknowledges several limitations. First, similar to most existing methods of detecting suicide risk,\(^{17-29}\) our study relies on patient self-reports of suicidal thoughts or behavior to a health care professional, and this discussion must have been accurately documented in the EHR system. Second, our computerized algorithm was limited by the prespecified search terms of interest in screening for potentially relevant clinical notes. We used this approach to increase efficiency and to avoid having to process an enormous number of clinical notes that had no mention of any terms related to suicide. Although classification may occur, as it is impossible to include all possible terms used by clinicians to document such events, the performance of our algorithm was satisfactory with a high sensitivity level. Third, applying this computerized algorithm in other scenarios or health care settings may yield slightly different results, and thus it may need some modification to account for variations in the format and presentation of clinical notes in different health care settings. In this study, our accuracy remained consistent, since the rule-based algorithm was robust and not specifically limited to any fixed or strictly formatted notes. Lastly, our current study algorithm identified suicidal thoughts/ideation and suicide attempt as 2 separate events.\(^{18}\) This distinction could be made with a future algorithm or with manual review by the algorithm’s users if needed. It is worth pointing out the nonlinear relationship between suicidal ideation and completed suicide. Suicidal thoughts can be understood as a symptom and risk factor of completed suicide.\(^{9,10}\) Not everyone presenting with suicidal ideation will carry out suicide. Suicidal thinkers and suicide completers were treated as 2 separate groups but can overlap over time.\(^{40}\)

Despite these limitations, we successfully developed an effective computerized algorithm to identify individuals with documented suicidal ideation/attempts from free-text clinical notes covering a large, diverse population. The algorithm was able to distinguish clinical notes addressing a current event versus a historical event. This computerized algorithm can be automated to regularly process clinical notes to build a near real-time patient database to support suicide prevention research as well as to evaluate the effectiveness of intervention programs intended to reduce suicidal ideation and suicide.

Supplementary Materials

REFERENCES

Identifying Suicidal Ideation and Attempt From Clinical Notes Within a Large Integrated Health Care System


Providing Rapid Access to Care for Underserved Patients During the COVID-19 Pandemic

Aleece Caron, PhD1,2,3; Kim Bauchens, MSN2; David Margolius, MD1,2; Kathryn Teng, MD, MBA1,2

Perm J 2022;26:21.039 • E-pub: 04/05/2022 • https://doi.org/10.7812/TPP/21.039

Introduction

COVID-19 is altering the health care delivery landscape at a dizzying speed. With no widespread vaccine or effective treatment at the early stages of the pandemic, masking, physical distancing, and self-quarantine were the only available interventions. As such, hospitals and health care centers needed to create alternatives to in-person care.1,2 Like others, our institute needed to transition rapidly to telehealth (TH) (video and telephone visits), and like others, we faced many challenges that included structural barriers of the health system, clinical barriers of the physician, and patient-centered barriers. Structural barriers included lack of experience with video platforms and lack of flexibility with video platforms, as well as limited reimbursement for video and telephone visits. Clinical barriers included a lack of appropriate staff and workflows to support the completion of efficient and effective video and telephone visits. This paper will focus on patient-centered barriers associated with TH implementation. With Medicaid patients comprising 39% of our total patient population, patient-centered challenges such as access to technology, reliable broadband, patients’ ability to use the technology, and loss of connectivity3,4 were substantial.

Commentary

Beginning on March 16, 2020, in response to the COVID-19 pandemic, we transitioned 192 primary care nurse practitioners and physicians in the fields of internal medicine, family medicine, medicine-pediatrics, and geriatrics across our health system to predominately TH visits over a 48-hour period. In this paper, we describe this conversion in the primary care practices and how we sustained our TH visits at > 50% in subsequent months.

The MetroHealth System (MHS) is an academic teaching hospital system in Cleveland, Ohio, affiliated with Case Western Reserve University School of Medicine, Cleveland, Ohio, USA. MHS is organized into Service Lines, with the Adult Health & Wellness Service Line managing 192 Adult Primary Care (Family Medicine, Medicine-Pediatrics, and Internal Medicine) and Geriatric clinicians, delivering 353,776 patient visits per year, to more than 21 locations in the Cleveland area. MHS is the only public safety-net hospital in the Cleveland area, with 75% of its patients uninsured or covered by Medicaid patients comprising 39% of our total patient population, patient-centered challenges such as access to technology, reliable broadband, patients’ ability to use the technology, and loss of connectivity3,4 were substantial.

This commentary describes our hospital system’s response to the COVID-19 pandemic and how we managed to rapidly transition to TH and provide seamless access for underserved patients.
Medicare or Medicaid. MHS utilizes the electronic health record system, Epic (version 2020 August) for its medical record documentation and billing. Within Epic, the MyChart program is used as the primary modality of communication between physicians and patients, via MyChart messaging and video platforms.

Prompted by the COVID-19 pandemic, MHS dramatically changed primary care delivery. From March to May 2019, the percentage of TH visits was less than 1%. The shift to TH mid-March 2020 shows an increase in TH to 35.9%. TH visit volumes shifted to 87.4% for the month of April 2020 although leveling to 58.4% in May 2020 when patients were allowed to return to the clinics for in-person care (Table 1). The goal of transitioning to TH was to minimize the number of patients coming into the office (thus reducing risk for virus transmission) although still providing the care and services needed. Concurrently, we reduced the number of physicians and staff physically present in our ambulatory clinics by allowing TH visits to be performed from home or other non-clinical spaces. Both efforts were important to comply with social distancing recommendations.

The key to our rapid conversion to TH was a strategic decision to embrace telephone visits. This was a risky decision for the Institute because at the time, we were unsure about reimbursement for telephone visits, much less telephone visits performed from a non-clinical setting. However, we felt that access to telephone visits was essential for our patients. Being a safety-net hospital system, many of our patients do not have broadband internet or smart phones, and/or are uncomfortable with the technology. Many of these patients rely on local libraries to access the internet, and with COVID-19, access to library resources decreased substantially. According to the Federal Communications Commission, there are approximately 24 million Americans who lack access to broadband. Older adults are particularly disadvantaged, as approximately 51% of Americans 65 and older have broadband at home, only about 42% own a cell phone, and even fewer have a phone capable of streaming video. Additionally, older patients are often less comfortable with video-based TH as they are unfamiliar with the technology needed to access it. Cognitive and sensory impairments, prevalent in the older population, also inhibited our ability to provide seamless care via TH visits. Even for patients who are technologically savvy, our video platform was challenging to use. Although all MHS patients have access to MyChart, overall system utilization was less than 10%, which would substantially limit our ability to successfully ramp up video visits.

We were fortunate that advocacy efforts from many health care systems including our own were successful in changing reimbursement for telephone visits during the pandemic. By April, reimbursement by third-party payers had evolved in 19 states that passed parity legislation to guarantee payment for TH services, and US Department of Health & Human Services waived enforcement of Health Insurance Portability and Accountability Act regulations to permit use of consumer audio and video communication for TH delivery. Video visits were reimbursed at similar levels to in-person visits, with reimbursement based mostly on complexity of medical decision making. Telephone visits were reimbursed based on time spent on the phone with the patient, regardless of medical complexity and decision making.

Although many other systems across the country invested millions of dollars to change their infrastructure for video capability, MHS chose the path of speed and ease of use by focusing on telephone visits in the early transition period. As such, MHS remained consistent to its mission — delivering high quality care, regardless of the ability to pay—and was able to change quickly.

How did we achieve such a successful conversion to telehealth in a short period of time?

**THE RIGHT MULTI-DISCIPLINARY TEAM**

The team that transformed primary care delivery included primary care operational leaders, nursing leaders, the director of our centralized call center, representatives from information technology, billing & compliance, legal, marketing & communications, and patient experience, led by the Vice President
 Providing Care for Underserved Patients During the COVID-19 Pandemic

of Telehealth. This team was responsible for creating solutions and troubleshooting on a daily basis. Important decisions that stemmed from this workgroup included:

- Communication systems and appropriate language to notify patients that their scheduled visits were being automatically converted or flipped to telephone visits
- Process for auto-conversion of in-person visits to telephone visits
- Education and triage by physicians to recommend that patients be flipped to telephone or video visits
- Development of tip sheets and prompts within Epic to train physicians on documentation and billing of telephone and video visits
- Facilitation of information technology needs for telephone visits (headsets for privacy) and video visits (iPads and iPhones)
- Creation of an Information Services (IS) Help Line for physicians to help them trouble-shoot in real time

DEVELOPMENT OF A COVID-19 HOTLINE

Under the leadership of primary care, a COVID-19 hotline was created for patients to call and speak with a doctor about exposure to COVID-19, symptoms, and available testing. The 24-hour hotline was managed by a voluntary pool of doctors via TH. These doctors were trained consistently so they could give the most up-to-date medical advice.

MHS paid the doctors $500 per 12-hour shift, prorated for a 4-hour shift or $8 per call to incentivize doctors to sign up for shifts; however, many doctors picked up a few patients whenever they could in order to help, regardless of pay. The development of such a hotline was important for several reasons. It allowed us to control the flow of information and ensure that the advice being provided about COVID-19 was accurate and up to date, and it enabled us to keep potential COVID-19 patients out of our clinics and at home unless they required more acute care, which reduced spread and transmission of the virus.

COMMUNICATION WITH PRIMARY CARE TEAMS

Keeping the approximately 200 primary care and geriatrics physicians informed, educated, and engaged in the rapid conversion to TH required frequent communication across a variety of modalities.

We utilized 3 primary modes of communication. First, we conducted phone huddles every Monday, Wednesday, and Friday mornings at 7:00 AM before clinics started with clinic leadership. During these huddles, we addressed concerns and heard feedback from our clinical teams. Second, we sent out daily emails with any new decisions or workflows and answers to questions that had arisen at the morning phone huddles. Third, we created tip sheets posted to Epic that we used as the source of the most up-to-date information about workflows, billing, and documentation for TH visits. We implemented a peer-audit system in which every physician was asked to audit 10 charts of a peer physician for accuracy in billing and documentation specifically for TH. A passing score was > 80%. If a physician scored lower than 80%, we provided additional education and then re-audited until they achieved a passing score. We also established an IS Help Line to provide clinicians support with technical issues during the initial transition period. This Help Line was staffed during clinic business hours (Monday through Friday from 7:00 AM to 7:00 PM) and intended to address any clinician-facing questions about Epic functions related to documentation and billing for TH visits.

The goal of our programs was to create rapid and safe access to care for patients during the initial days of the COVID-19 pandemic. During the first 5 weeks of the COVID-19 hotline, the average daily call volume was approximately 150 calls. The remarkable response from our physicians to cover this hotline cannot be over-stated, as this was additional work on top of the physicians’ regular work, caring for their own panels of primary care patients. During the initial 5 weeks of operation, 10,112 patients called the hotline (callers) and were evaluated by a registered nurse using standardized protocols. Of these callers, 4213 (42%) were referred for a physician TH visit (TH patients). The mean age of callers was 42 years; 67% were female, 51% white, and 46% were on Medicaid or uninsured (Table 2). In a previously published manuscript, our colleagues at MHS reported that most TH patients (79%) were advised to self-isolate at home, 14% were determined to be unlikely to have COVID-19, 3% were advised to seek emergency care, and 4% had miscellaneous other dispositions. A total of 287 (7%) patients had a subsequent emergency department visit, and 44 (1%) were hospitalized with a COVID-19 diagnosis. Of the callers, 482 (5%) had a COVID-19 test reported with 69 (14%) testing positive. Among patients advised to stay at home, 83% had no further face-to-face visits.

The IS Help Line was staffed for 12-hour business days, Monday through Friday for 2 weeks. During
these first 2 weeks, only 2 calls were received, and due to low use, the IS Help Line was suspended after week 2. The 2 calls were from physicians who needed help finding the tip sheets in Epic. Although physicians expressed desire to have the Help Line as a back-up resource, the low use of the Help Line was a reflection of the success of our other modes of communication with them. Most physicians seemed to understand the new workflows and how to find the information they needed for proper documentation and billing. For our reassurance, we conducted an audit of all primary care physicians to assess their ability to work from home and successfully perform remote TH. The results of the audit indicated that 80% of physicians were documenting and billing appropriately (100% accuracy), and the remaining 20% reached 100% accuracy by their second audit.

We also examined key patient experience metrics from National Research Corporation regarding perceptions of TH versus in-person visits. The custom survey questions closely resemble CAHPS® Clinician & Group Survey methodology. Patients who had an encounter with a MHS physician for a TH visit were included in the survey sample. If they did not have the encounter with the same physician in the past 9 months, and/or any MHS encounter in the past 2 weeks, they also received a survey.

The percent of surveys completed by visit type are shown in Table 3.

Overall, in-person and video visits resulted in a better perception of experience than telephone visits, as illustrated in Table 4, although overall experience with telephone visits was high and based on patient comments, the availability of telephone visits was appreciated. When we examined more than 1000 patient comments related to telephone visits, we identified a few themes and opportunities for improvement which included perceived ability to describe symptoms and understand instructions given, as well as reduced empathy and connection, especially with new physicians.

Patients preferred in-person visits when meeting a new physician. Patient satisfaction with follow-up visits over the phone and via video improved in April and May, although satisfaction with the in-person follow-up visits decreased slightly during the same time period, as illustrated in Table 5.

### Challenges and Lessons Learned

As our organization moved past the early days of the pandemic and realized that TH would become a mainstay of care delivery going forward, we identified several challenges that needed to be addressed. These included development of support staff workflows for TH visits, environmental and privacy concerns, and gaps in care. We created a workgroup to create ideal workflows for TH visits. The design included pre-visit questionnaires and post-visit discharge follow-up scheduling that would mirror in-person care, but due to the need for our support staff to assist with hospital operations and health screens at our clinical sites, we were unable to implement these workflows. We anticipate that...
Providing Care for Underserved Patients During the COVID-19 Pandemic

as staffing support increases to pre-pandemic levels, we will implement these workflows. With regard to privacy and environmental concerns, our organization preferred that TH visits be conducted on site (rather than in the home environment), but our office and examination room spaces were not properly equipped for TH. Our examination rooms did not have phones or computers with video capability, and in the spirit of team-based care, many of our physician office spaces were shared spaces that did not allow for noise control or privacy during a video visit. We have accordingly provided phones and headsets to physicians who needed them and shared iPad devices for each clinic to use during video visits. We have also provided screens for privacy and created TH hub office space in various locations for those physicians who do not have office space otherwise conducive to TH visits.

As we approach the two-year anniversary of the pandemic, we are most concerned about trends regarding care gaps. Our system referral completion rate dropped from a baseline of 51.3% in 2019 to 38.1% in 2020 and is currently 30.9% thus far in 2021. We also saw a slight decrease in HbA1c completion, but saw the gap close in the last 2 months of 2020 as we made it an organizational priority to close this gap. We feel these trends are related to delays in care (patients wanting to postpone specialty appointments and procedures) related to the pandemic, as well as reduced access for in-person care in specialties and primary care.

Conclusion

In our experience, the successful rapid conversion to TH was made possible by establishing the right multi-disciplinary working team, developing a COVID-19 hotline, and creating frequent & varied communication methods for care teams. Our success has been a result of our ability to bring varied individual experiences and expertise to the team, and our strategic decision to focus our initial efforts on telephone visits. Telephone visits provided the needed access to underserved and elderly patients throughout the early pandemic and enabled us to keep sick patients at home with no negative effect on patient experience. However, the challenges that we needed to work through regarding clinical workflows, technology, and privacy for TH visits were certainly present. In addition, we noted a negative impact on referral completions, reflecting delays and reduced access to care. We anticipate that as more patients feel comfortable resuming in-person care, we will find an equilibrium between supply and demand for TH visits. We still have much to learn about the appropriate use of TH visits and how to enhance the TH experience for both patients and physicians.

REFERENCES

Assessing the Role of High-Dose β-Agonists Use in Triggering Takotsubo Syndrome During Asthma Exacerbation

Danish Abbasi, MD1*; Saif Faiek, MD2*; Waqas J Siddiqui, MD1; Angel Lopez-Candales, MD4
Perm J 2022;26:21.062 • E-pub: 04/05/2022 • https://doi.org/10.7812/TPP/21.062

Introduction

Clinical data have shown that asthma, chronic obstructive pulmonary disease (COPD), and interstitial lung disease are all associated with a higher incidence of cardiovascular diseases through a host of different pathophysiological mechanisms.1-3

Acute, severe asthma is also known to alter cardiovascular function during episodes of exacerbation.6 Most notably, decreased systemic venous return and rapid right ventricular filling shifts the interventricular septum toward the left ventricle (LV), which may lead to left ventricular diastolic dysfunction and incomplete filling. Pulmonary artery pressure may also be increased owing to lung hyperinflation, causing increased right ventricular afterload. In addition, sinus tachycardia can occur as a result of anxiety.
and hypoxemia. The use of β-agonists can further aggravate this tachycardia.

Takotsubo Syndrome (TTS) has been recognized more recently as a reversible form of stress-induced cardiomyopathy that is characterized by an acute and transient wall motion abnormality associated with reduced left ventricular systolic and diastolic dysfunction often related to an emotional or physical stressful event without evidence of obstructive epicardial coronary artery disease.\(^7\)

One of the recognized risk factors for TTS is asthma that is mainly due to β-agonist use, as well as the use of epinephrine, and requires intubation with mechanical assisted ventilation.\(^8,9\)

Even when the etiology of TTS in patients with asthma has not been well characterized, a potential link that has been suggested is the interaction of high levels of neuropeptide Y in these patients.\(^10\) Therefore, this review intends to analyze published literature regarding the documentation of TTS incidence and recurrence during asthma exacerbations.

## Background

TTS (also known as Takotsubo cardiomyopathy, stress-induced cardiomyopathy, broken heart syndrome, or apical ballooning syndrome) is characterized by transient systolic dysfunction of the LV in the absence of obstructive coronary artery disease. The term “Takotsubo” is taken from the Japanese name for an Octopus trap. It was first described in 1990, and since then it has been increasingly recognized. Stress cardiomyopathy occurs in approximately 1% to 2% of patients with suspected coronary artery syndrome and presenting with elevated troponin levels.\(^11\) TTS is more common in elderly populations, especially women. A review of 1750 patients from the International Takotsubo registry by Templin et al showed an overwhelming preponderance of the female sex (89.8%). The patients’ mean age in this study was 66.8 years; however, in Japan TTS mainly affects men following physical stress.\(^12\)

Even when TTS pathophysiology has not been clearly elucidated, acute coronary syndrome presentation preceded by some form of profound predisposing stressors in patients without epicardial luminal stenosis on coronary angiography at the time of initial evaluation has been considered as a typical clinical scenario.

To facilitate diagnosis, the Mayo Clinic has proposed the following elements to be included as findings that suggest TTS: 1) new electrocardiographic abnormalities, 2) modest troponin level elevation, 3) regional wall motion abnormalities beyond a single epicardial vascular distribution, 4) transient dyskinesis of the LV midsegments, 5) no obstructive coronary artery disease or acute plaque rupture, and 6) the absence of pheochromocytoma and myocarditis.\(^12\)

TTS carries a substantial disease burden. Common cardiac complications, especially during the acute phase of the disease, include cardiogenic shock, left ventricular outflow tract obstruction, left ventricular thrombus formation, and left ventricular rupture.\(^13\) A review of the national database of patients with TTS yielded an inpatient mortality rate of 4.2%. Singh et al published a meta-analysis in the *American Journal of Cardiology*, which showed an inpatient mortality rate of 4.5%. Both studies demonstrated an increased rate of mortality in men.\(^14,15\)

Secondary TTS (triggered by physical factors, asthma, surgery, trauma, etc.) has more complications than the primary form. A study by Nunez et al published in the *European Heart Journal* showed that patients affected with the secondary form appear to experience more short- and long-term complications. Such patients required higher doses of inotropic agents and extended periods of mechanical ventilation support, resulting in extended hospitalization. The mortality rate was also higher in this subgroup compared with the control group.\(^16\)

## Role of Catecholamines in TTS

One of the most commonly proposed mechanisms accounting for TTS is catecholamine surge. Clinical observations in humans and recent experimental work on isolated rat ventricular myocytes suggest that an acute catecholamine overload is the dominant mechanism.\(^17\) Rat models support the hypothesis that circulating catecholamines are initiators of stress-induced cardiomyopathy and catecholamine-induced Takotsubo-like cardiac dysfunction in rat cardiac myocytes.\(^18\)

Data from Wittstein et al showed that patients with such profound, reversible left ventricular dysfunction after sudden emotional stress have evidence of excessive sympathetic activation, with plasma catecholamine levels higher than age- and
Assessing the Role of High-Dose β-Agonists Use in Triggering Takotsubo Syndrome During Asthma Exacerbation

sex-matched patients from Killip class III myocardial infarction.19

The β-adrenoceptor is essential in the setting of profound catecholamine overstimulation. A study by Nef et al evaluating serial myocardial biopsies taken during the severe LV dysfunction and after functional recovery showed that during the acute phase, cellular hypertrophy with characteristic morphologic changes were seen in relation to the extreme catecholamine excess.20 Furthermore, Borchert et al studied the β-adrenergic signaling pathway and found an enhanced β-adrenergic signaling and high sensitivity to catecholamine-induced toxicity as mechanisms associated with TTS.21 In addition, in a review of 157 cases of drug-induced TTS, up to 68.2 % of the cases were catecholamine related.22

Finally, Lyon et al hypothesized that high epinephrine levels triggered intracellular signal trafficking involving a change from the Gs to the Gi protein via the b2-adrenoceptor within ventricular cardiomyocytes.23 These receptors’ density appeared more noticeably abundant in the apical myocardium, which might explain the regional apical ballooning.23 A study by Willis et al using a rat model showed that rats developed cardiac apex ischemia when treated with an acute isoproterenol overdose. Cardiac myocytes from these rats showed systolic dysfunction that was reversible at 4 weeks.24

Recurrence of TTS During Asthma Exacerbation

Although there is a substantial amount of literature to support the idea that asthma exacerbations may place a patient at risk for developing TTS, there is a paucity of data to suggest that patients with asthma are more likely to have recurrent episodes of TTS.

According to data from the World Asthma Foundation, not only do an estimated 20 million Americans have asthma (1 in 15 Americans), but asthma prevalence has also continued to increase since the early 1980s across all age, sex, and racial groups.29

Asthma accounts for one-quarter of all emergency room visits in the US each year, with 2 million emergency room visits, more than 10 million outpatient visits, and 500,000 hospitalizations with an average length of stay of 3 days.29 Despite aggressive treatment, the rate of asthma exacerbation has remained constant.30

Despite physicians following guideline-based treatments, patients with asthma continue to experience exacerbations caused by worsening of their underlying intrinsic inflammatory process or loss of disease control. Unfortunately, the prevention of asthma exacerbations remains a crucial unmet need in asthma management.31

Regardless of these patients’ clinical presentation, signs of cardiac decompensation during an asthma
### Table 1: Summary of search results

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Sex</th>
<th>β-Agonist</th>
<th>Diagnosis</th>
<th>Recurrence</th>
<th>Presenting symptom</th>
<th>Fatal</th>
<th>Echo</th>
<th>EKG findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katsa et al[5]</td>
<td>51</td>
<td>F</td>
<td>Y</td>
<td>COPD</td>
<td>Y</td>
<td>Syncope</td>
<td>—</td>
<td>LVEF of 22% and apical ballooning</td>
<td>PR depression in II, III, aVF</td>
</tr>
<tr>
<td>Khwaja et al[7]</td>
<td>UNKN</td>
<td></td>
<td>F</td>
<td>Asthma</td>
<td>—</td>
<td>SOB</td>
<td>—</td>
<td>LVEF 30% with apical akinesia and basal segment hyperkinesia</td>
<td>ST elevation I, aVL, V2-V6,</td>
</tr>
<tr>
<td>Saito et al[8]</td>
<td>63</td>
<td>M</td>
<td>Y</td>
<td>Asthma</td>
<td>—</td>
<td>SOB</td>
<td>—</td>
<td>LVEF 49% apical ballooning</td>
<td>ST elevation in V2-V6</td>
</tr>
<tr>
<td>Sharrett et al[9]</td>
<td>59</td>
<td>F</td>
<td>Y</td>
<td>COPD</td>
<td>Y</td>
<td>APNEA</td>
<td>Y</td>
<td>LVEF 25 antero apical akinesia</td>
<td>PEA</td>
</tr>
<tr>
<td>Landefeld et al[10]</td>
<td>49</td>
<td>F</td>
<td>Y</td>
<td>COPD</td>
<td>—</td>
<td>SOB</td>
<td>—</td>
<td>LVEF 25-30% apical akinesia</td>
<td>ST depression II, III, aVF</td>
</tr>
<tr>
<td>Patet al[12]</td>
<td>78</td>
<td>F</td>
<td>Y</td>
<td>Asthma</td>
<td>—</td>
<td>SOB, chest pain</td>
<td>—</td>
<td>LVEF 40% apical ballooning</td>
<td>ST elevations II, III, aVF, V1 to V4</td>
</tr>
<tr>
<td>Sarkar et al[13]</td>
<td>53</td>
<td>M</td>
<td>Y</td>
<td>Asthma</td>
<td>—</td>
<td>SOB</td>
<td>—</td>
<td>LVEF 25% apical ballooning</td>
<td>No changes</td>
</tr>
<tr>
<td>Salahuddin et al[14]</td>
<td>50</td>
<td>M</td>
<td>Y</td>
<td>Asthma</td>
<td>—</td>
<td>SOB</td>
<td>—</td>
<td>LVEF 25-30% aneurysm anteroapical, apical &amp; infarction walls</td>
<td>ST elevation in V2 3 4</td>
</tr>
<tr>
<td>Venditti et al[15]</td>
<td>81</td>
<td>F</td>
<td>Y</td>
<td>Bronchitis/bronchiecataxis</td>
<td>Y</td>
<td>Cardiac Arrest</td>
<td>Y</td>
<td>LVEF 40% mid apical akinesia</td>
<td>ST elevation lead I, V5-6</td>
</tr>
<tr>
<td>Mendoza et al[16]</td>
<td>76</td>
<td>F</td>
<td>Y</td>
<td>COPD</td>
<td>Y</td>
<td>SOB</td>
<td>—</td>
<td>LVEF 40% apical dyskinesis</td>
<td>Diffuse prominent T wave inversions</td>
</tr>
<tr>
<td>Salemi et al[17]</td>
<td>68</td>
<td>F</td>
<td>Y</td>
<td>Asthma/COPD</td>
<td>—</td>
<td>SOB</td>
<td>—</td>
<td>LVEF 25% hypokinesis of the medial apical segments</td>
<td>Intraventricular conduction disorder, diffuse T wave inversions</td>
</tr>
<tr>
<td>Rennyson et al[18]</td>
<td>68</td>
<td>F</td>
<td>Y</td>
<td>Asthma/COPD</td>
<td>Y</td>
<td>SOB, chest pain</td>
<td>—</td>
<td>LVEF 15% Apical Dyskinesia</td>
<td>ST elevation V1 - V 4</td>
</tr>
<tr>
<td>Osuorji et al[19]</td>
<td>46</td>
<td>F</td>
<td>Y</td>
<td>Asthma</td>
<td>—</td>
<td>SOB</td>
<td>—</td>
<td>LVEF 10% anteroapical akinesia proximal basal hyperkinesia</td>
<td>ST elevation I II V4 5 6</td>
</tr>
<tr>
<td>Satoh et al[20]</td>
<td>51</td>
<td>F</td>
<td>Y</td>
<td>Asthma</td>
<td>—</td>
<td>SOB</td>
<td>—</td>
<td>Apical Akinesia and basal hyperkinesia</td>
<td>ST elevation in II, III, aVF, V2-V6, T-wave inversion in leads V3- V6</td>
</tr>
<tr>
<td>Hernández Lanchas et al[21]</td>
<td>74</td>
<td>F</td>
<td>Y</td>
<td>Asthma</td>
<td>—</td>
<td>SOB, chest pain</td>
<td>—</td>
<td>Apical ballooning</td>
<td>ST elevation precordial leads</td>
</tr>
<tr>
<td>Saeki et al[22]</td>
<td>62</td>
<td>M</td>
<td>Y</td>
<td>A/C</td>
<td>—</td>
<td>SOB</td>
<td>—</td>
<td>Apical dyskinesia and hypersystole in the basal region of the heart</td>
<td>ST elevation, loss of R-wave progression,</td>
</tr>
<tr>
<td>Ripa et al[23]</td>
<td>64</td>
<td>F</td>
<td>Y</td>
<td>Asthma</td>
<td>—</td>
<td>SOB</td>
<td>—</td>
<td>Apical akinesia</td>
<td>—</td>
</tr>
<tr>
<td>Pontillo et al[24]</td>
<td>72</td>
<td>M</td>
<td>Y</td>
<td>Asthma</td>
<td>—</td>
<td>SOB</td>
<td>—</td>
<td>LVEF 37% apical ballooning</td>
<td>ST segment elevation in anterior leads</td>
</tr>
</tbody>
</table>

Abbreviations: aVF = arteriovenous fistula; aVL = artificial ventilation of the lungs; COPD = chronic obstructive pulmonary disease; F = female; LVEF = normal left ventricular ejection fraction; LBBB = left bundle branch block; M = male; N = no; PEA = pulseless electrical activity; SOB = shortness of breath; TSS = toxic shock syndrome; UNKN = unknown; Y = yes.
exacerbation should alert clinicians to have a higher index of suspicion for the possibility of TTS recurrence, especially when we already know from previous literature that among patients with COPD, the amount of energy and oxygen needed for respiration has been associated with a rise in cardiac troponin levels.\textsuperscript{32}

Patients with asthma may be more prone to recurrent TTS episodes and, if so, may be more likely to have life-threatening complications such as cardiac arrhythmias, pulmonary congestion, and hospital death.\textsuperscript{33} Vriz et al prospectively followed 55 patients with TSS and found that 6 patients had recurrences within the first year and that 2 of these patients had recurrences triggered by an asthma exacerbation.\textsuperscript{34}

Based on our review, no guidelines regarding the management of recurrent TTS exists in literature. Furthermore, there are no protocols regarding the monitoring of these patients after an initial episode of TTS. Moreover, the use of β-blockers has not been found protective against recurrent episodes. In fact, a meta-analysis performed by Singh et al showed that there was no correlation between TTS recurrences and the use of β-blockers but, rather, that there was an inverse correlation with the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.\textsuperscript{35} This association was further supported by data published by Brunetti et al from their meta-regression analysis that confirmed that Takotsubo recurrence rates were lower among patients who were treated and compliant with either angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.\textsuperscript{36}

The text of 21 case reports was separately reviewed and evaluated for age, sex, use of β-agonist, underlying diagnosis of asthma vs COPD, and presenting symptoms. Cases were also assessed for an initial or recurrent episode of TTS. We also explicitly evaluated the text for any documented fatality.

### Results

Our review showed that the average age of patients was 62.9 years of age, with a female-to-male ratio of 76%. A total of 15 of the 21 patients had asthma, whereas 4 were diagnosed with COPD, and 1 was listed as having bronchiectasis. All the patients were exposed to repeated doses of β-agonists. Six of these 21 patients were found to have recurrent episodes of TSS. All of the 6 patients with recurrent episodes were female, with an average age of 67.5 years. Three patients had an atypical presentation, 1 patient presented with syncope,\textsuperscript{38} 1 with cardiac arrest,\textsuperscript{39} and 1 with apnea.\textsuperscript{40} Patients with atypical presentation experienced recurrent episodes. Furthermore, 2 of the 19 patients died upon presentation.\textsuperscript{39,40} Finally, all patients with recurrent episodes had been exposed to repeated high doses of β-agonists (Table 1).

### Conclusion

Until more data becomes available it appears that judicious use of β-agonists may prevent recurrent TTS during asthma exacerbation episodes. In addition, the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers have also shown some protective benefit from recurrence.

We suggest that standardized monitoring and treatment protocols should be devised to assist the management of a patient afflicted with recurrent Takotsubo episodes. More importantly, prospective studies are urgently needed to assist us in treating patients with asthma who are more likely to have this cardiac complication.

### References

Assessing the Role of High-Dose β-Agonists Use in Triggering Takotsubo Syndrome During Asthma Exacerbation


Assessing the Role of High-Dose β-Agonists Use in Triggering Takotsubo Syndrome During Asthma Exacerbation


43. Khwaja YH, Tai JM. Takotsubo cardiomyopathy with use of salbutamol nebulisation and aminophylline infusion in a patient with acute asthma exacerbation. BMJ Case Rep 2016;2016:bcr2016217364. DOI: https://doi.org/10.1136/bcr-2016-217364


47. Sarkar S, Arguelles E, de Elia C. Takosubo cardiomyopathy presenting as a non-ST segment elevation myocardial infarction in the setting of cocaine use and asthma exacerbation. Int J Cardiol 2013;168(1):e1–e2. DOI: https://doi.org/10.1016/j.ijcard.2013.04.191


CASE REPORT

High-Dose Pulse Steroids for the Treatment of Acute Hypoxemic Respiratory Failure in COVID-19 Pneumonia: A Simple Case Series

Gholmieh Ghassan, MD, PhD
Perm J 2022;26:21.090 • E-pub: 04/05/2022 • https://doi.org/10.7812/TPP/21.090

Abstract

Pulse steroids therapy is widely used to treat flare-ups of autoimmune diseases, such as systemic lupus erythematosus. The main assumption is that severe inflammation caused by an autoimmune disease must be aggressively quelled before it causes further damage. We present a series of 9 cases that explore the use of high-dose pulse steroids in hypoxemic respiratory failure. We used high-dose steroids to alter the outcome of some patients, using commonly accepted protocols such as 6 mg of dexamethasone via IV, baricitinib, and tocilizumab. The outcome of each case is discussed. The patients were treated with 500 mg of high-dose methylprednisolone via IV for 3 days, followed by 250 mg via IV for 3 days; followed by 12 or 6 mg of dexamethasone was administered daily by mouth or IV. A retrospective review of patients who received a computerized tomography pulmonary angiogram showed that these patients had organizing pneumonia features. Eight out of nine cases had a favorable outcome.

Introduction

The COVID-19 pandemic has had global negative impacts. Millions of people have died with hypoxemia from severe pulmonary inflammation (acute respiratory distress syndrome; ARDS) associated with viral pulmonary infection. Pulse steroids therapy is widely used to treat autoimmune diseases. Examples include rapidly progressive glomerulonephritis; systemic lupus erythematosus; IgA nephropathy; neuromyelitis optica; and many more. The main assumption is that severe inflammation caused by an autoimmune disease must be aggressively quelled before it causes further damage. Pulse steroids are also used in certain intensive care unit (ICU) situations, such as organizing pneumonia (OP) and acute fibrinous OP, a rare type of interstitial lung disease characterized by intra-alveolar fibrin balls and OP with a patchy distribution.

Over the years, use of steroids in ARDS has been controversial. Many educational institutions shy away from high-dose steroids in ARDS because of the associated high risks, including but not limited to opportunistic infections, diabetic ketoacidosis, deep vein thrombosis, and pulmonary embolism. Many publications, however, have found that steroids make a difference in ARDS, including in cases of ARDS associated with viral diseases. With the COVID-19 pandemic and high mortality...
High-Dose Pulse Steroids for the Treatment of Acute Hypoxemic Respiratory Failure in COVID-19 Pneumonia

rate associated with ARDS caused by the virus, questions arose regarding the benefits of steroids in treating COVID-19 pneumonia. Some studies have documented the benefits of steroids in COVID-19 pneumonia, as discussed in the following sections. The consensus adopted at our facility was the one used by the World Health Organization and the RECOVERY study of 6 mg of dexamethasone daily for 10 days. Administering 6 mg of dexamethasone did improve survival; however, the virus progressed in many patients even on the recommended dose of dexamethasone. Many patients were on non-rebreather masks (NRM) for many days and ended up being intubated, resulting in high death rate.

Here we present a series of non-intubated cases where we explored the use of high-dose pulse steroids (HDPS). In most cases, it was used as a salvage therapy. We used high-dose steroids to alter the outcome in patients who were not recovering despite the use of the commonly accepted protocols such 6 mg of dexamethasone via IV, baricitinib, and tocilizumab. Informed consent was obtained from all case patients.

Steroids, ARDS, and COVID-19 in the Literature

It is unclear why some people have a very mild immune response to COVID-19, some have a moderate one, and some have a severe reaction to the pulmonary infection, causing severe ARDS and untimely death. Some recent studies have linked the response to genetic risk factors. What we know, however, is that the COVID-19 virus kills its host by causing severe lung inflammation. If we can control the inflammation, we can improve oxygenation and, hence, survival rates. Many studies have been published on the benefits of steroids and pulse steroids, as we discuss here.

Figure 1: Chest x-ray #1 of case #3 on hospitalization day 1.
Steroids in general ARDS have not been shown to be consistently beneficial. Some positive evidence, however, has emerged over the years. Villar et al have shown positive results. The DEXA-ARDS trial enrolled 277 patients with moderate to severe non-COVID-19 ARDS. Patients in the steroids/dexamethasone group received an IV dose of 20 mg once daily from day 1 to day 5, which was reduced to 10 mg once daily from day 6 to day 10. The study found that patients who received high-dose dexamethasone had lower 60-day, all-cause mortality (21% vs 36%, p = 0.005) and more ventilator-free days (12 vs 7, p < 0.001).

Kolilekas et al reported a case series of 6 consecutive COVID-19 patients with severe pneumonia, ARDS, and laboratory indices of hyperinflammatory syndrome. The authors used 125 mg of methylprednisolone once daily for 3–5 days. All patients were not intubated and were not admitted to the ICU. ARDS resolved within 11.8 days (median). The authors concluded that “early administration of short course corticosteroids improves clinical outcome of patients with severe COVID-19 pneumonia and evidence of immune hyperreactivity.”

Another study by Chen et al concluded that in a retrospective study of COVID-19 patients in China treated with different doses of steroids, there was a decrease in mortality rate by 40% (HR = 0.592, [95% CI 0.406–0.862], p = 0.006). However, the study had multiple shortcomings, including the use of different types of steroids, different initiation times, and different dosages.

Tomazini et al used 20 mg of dexamethasone via IV daily for 5 days or until ICU discharge in patients with COVID-19. The primary outcome was ventilator-free days during the first 28 days. Patients randomized to the dexamethasone group had a mean 6.6 ventilator-free days (95% CI, 5.0–8.2) during the first 28 days vs 4.0 ventilator-free days (95% CI, 2.9–5.4) in the standard-care group (difference, 2.26; 95% CI, 0.2–4.38; p = 0.04).

**Figure 2:** Chest x-ray #2 of case #3. Patient was started on high-dose pulse steroids on hospitalization day 10.
Fadel et al used short-course methylprednisolone 0.5 to 1 mg/kg/d divided into 2 IV doses for 3 days in 213 COVID-19 patients. They measured the avoidance of ICU escalation; patients benefited from avoiding ICU escalation (34.9% vs 54.3%, p = 0.005).

Finally, the RECOVERY study concluded that “in patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.”

Pulse Steroids, ARDS, and COVID-19 in the Literature

Recent histopathological and imaging studies have pointed out that many cases of COVID-19 ARDS progress into OP. One study questioned if the missed diagnosis of OP was widespread. It also raised the question: “Although RECOVERY along with other cohort studies report positive effects with corticosteroids on morbidity and mortality of COVID-19, treatment approaches could be made more effective given that secondary OP often requires prolonged duration and/or careful and monitored tapering of corticosteroid dose, with ‘pulse’ doses needed for the well-described fulminant subtype.”

We reviewed the literature for use of HDPS. Sauñe et al used high-dose steroids to treat 2 desperate cases in Peru. The 2 cases were rejected by medical institutions likely due to lack of resources. The patients were treated at home with high-dose methylprednisolone, 500 mg via IV for 3 days. This resulted in a favorable outcome and resolution of most symptoms.

Mareev et al used an even higher dose. They used 1000 mg of methylprednisolone for 3 days followed by 8 mg of dexamethasone for another 3–5 days in 17 patients with severe COVID-19 pneumonia. Results

Figure 3: Chest x-ray #3 of case #3 on hospitalization day 14.
showed marked decrease in inflammatory markers. The group who received pulse steroids 1) was much sicker than the control group, 2) developed pulmonary embolism/deep vein thrombosis at a higher rate, and 3) remained hospitalized for a longer period of time. The results of the outcome must be carefully weighted given that the population of the 2 groups were different at baseline.

Edalatifard et al conducted a study in Iran where they used 250 mg of methylprednisolone via IV for 3 days in COVID-19 pneumonia cases. The authors noted marked improvement in patients who received pulse steroids, compared to the patients who did not. Sixty-eight eligible patients underwent randomization (34 patients in each group). The authors stated that: “The percentage of improved patients was higher in the methylprednisolone group than in the standard care group (94.1% versus 57.1%) and the mortality rate was significantly lower in the methylprednisolone group (5.9% versus 42.9%; p<0.001).”

Ruiz-Irastorza et al administered 250 mg of methylprednisolone via IV for 3 days in patients who remained hospitalized for a second week. Receiving methylprednisolone in the second week improved prognosis in patients with severe COVID-19 pneumonia. Of the 242 patients with COVID-19 pneumonia and elevated inflammatory markers at admission, 61 (25%) received week-2 methylprednisolone. The adjusted hazard ratios for death and death or intubation for patients in the week-2 methylprednisolone group were 0.35 (95% CI 0.11–1.06, p = 0.064) and 0.33 (95% CI 0.13–0.84, p = 0.020), respectively.

High-Dose Pulse Steroids Protocol for Acute Hypoxemic Failure

The HDPS protocol we used was based on commonly used rheumatological protocols. We used 500 mg of methylprednisolone via IV daily for 3 days, followed by 250 mg of methylprednisolone via IV daily for 3 days, then 6 mg of dexamethasone via IV or mouth daily. Patients received prophylactic IV antibiotics (ceftriaxone, azithromycin or, or doxycycline) while on HDPS for 6 days. The following were tentatively measured daily for 5 days: white blood cell count, Chem-7, blood urea nitrogen, creatinine, ferritin, C-reactive protein (CRP), lactate dehydrogenase, liver function test, and D-dimer. Chest x-rays were taken on day 1 and day 5. The protocol was unaltered for the first 3 days but then modified to match the needs and changes in the medical status of the patients. We tried to wean steroids as fast as possible if improvements rapidly occurred.

Optimal management of ARDS is based on the Berlin classification that uses PaO\(_2\)/FiO\(_2\). Furthermore, PaCO\(_2\) and acid–base balance are also important in the management of critically ill patients. Although most of our patients were suspected to have ARDS, arterial blood gas was not ordered during the pandemic to decrease the personnel exposure and due to limited resources. Arterial blood gas was reserved for intubated patients and ICU patients. Our patients were on the telemetry or the stepdown ICU units. Hence a better term to use for this series is acute hypoxemic respiratory failure.

Case #1: Simple Case, Good Outcome

The patient was a 48-year-old man with a history of hypothyroidism, who was seen 4 days prior to admission for shortness of breath. He was diagnosed with COVID-19 and sent home with O\(_2\), 6 mg of dexamethasone, and albuterol. Patient’s home O\(_2\) saturation worsened, and he needed 6 L of O\(_2\) at home. Patient’s symptoms included cough, loss of taste, and loss of smell. The patient came back to the emergency room (ER) with worsening shortness of breath and was admitted on January 25, 2021. The patient needed high-flow nasal cannula (HFNC) in the ER.

The patient was started on remdesivir, baricitinib, and IV antibiotics. He was started on HDPS of 500 mg of methylprednisolone via IV for 3 days on the day of admittance (day 1) and then switched back to 6 mg of dexamethasone. The patient was admitted on HFNC 30 L, FiO\(_2\) 100% on day 1, weaned to venturi mask (VM) 15 L, FiO\(_2\) 50% on day 3, and then discharged on nasal cannula (NC) on 4 L on day 7. He was not discharged on steroids. At 30 days follow-up, the patient was off oxygen but had a lingering cough treated with inhaled steroids.

Case #2: Accelerated Improvement

The patient was a 53-year-old woman with a history of hypertension, cholelithiasis, and medication-
induced hepatitis in 2004. She tested positive for COVID-19 6 days prior to admission, where she presented with fever and cough for 2 days. The patient was admitted on February 21, 2021 (day 1) with worsening symptoms associated with myalgias and shortness of breath.

The patient was started on dexamethasone on day 1, remdesivir on day 1, and baricitinib on day 3 along with 2 units of convalescent plasma. She started on HDPS of 500 mg of methylprednisolone via IV daily for 3 days on day 7 but only received 2 doses due to rapid improvement.

The patient was admitted on NRM and slowly improved on day 7 to HFNC 15 L, FiO₂ 50%. She received a computerized tomography pulmonary angiogram (CTPA) because her oxygen saturation decreased easily to low-mid 90s. CTPA was negative for pulmonary embolism. When reviewed with the radiology department, the CTPA presented as consistent with OP. The patient was started on HDPS on day 7. O₂ requirements improved to 3 L at rest on day 10. We are unsure if the HDPS accelerated the recovery or the patient was already on her way to recovery. The drop in oxygen requirement is not, however, easily explained by the recovery process in our subjective experience.

The patient was discharged on steroids taper. Her saturation level on 30-day follow-up visit showed oxygen saturation of 98% on room air, but she was still using oxygen at 1 L/min on exertion.

Case #3: What is There to Lose after 10 days of Failed Treatments?

The patient was a 54-year-old woman with a history of hyperlipidemia, hypothyroid, and obesity. She was diagnosed with COVID-19 2 days prior to admission and presented to the ER on February 19, 2021 (day 1) with shortness of breath for 3 days associated with cough, fever and headache. The patient was diagnosed with COVID-19 pneumonia and was admitted to the hospital.

She was started on remdesivir via IV (days 1–5), baricitinib (for a total of 14 days), 6 mg of dexamethasone via IV (for a total of 9 days before pulse steroids), and IV ceftriaxone and IV doxycycline pending procalcitonin level (stopped 3 days later). The patient received convalescent plasma on day 2. On February 27, 2021 (day 9) CTPA pulmonary was done to rule out pulmonary embolism; it showed viral infiltrates and OP (read in retrospect). She was started on pulse steroids, ceftriaxone, and azithromycin. Her oxygen improvement is listed in Table 1.

The patient was discharged on steroids taper and required steroids inhalers on her follow-up visits. On her 30-day follow-up visit, she was still using 3 L/min of oxygen therapy.

Case #4: Good Result in a Young Person

The patient was a 32-year-old woman with a history of obesity, diagnosed 9 days prior to admission with COVID-19. She presented on April 14, 2021 (day 1) with shortness of breath and cough without a high grade fever. In the ER, patient oxygen saturation was 70% on room air. The patient received 6 mg of dexamethasone via IV; remdesivir on days 1–5; IV dexamethasone via IV (days 1–5); baricitinib for a total of 14 days; 6 mg of dexamethasone via IV (for a total of 9 days before pulse steroids); and IV ceftriaxone and IV doxycycline pending procalcitonin level (stopped 3 days later). The patient received convalescent plasma on day 2. On February 27, 2021 (day 9) CTPA pulmonary was done to rule out pulmonary embolism; it showed viral infiltrates and OP (read in retrospect). She was started on pulse steroids, ceftriaxone, and azithromycin. Her oxygen improvement is listed in Table 1.

The patient was discharged on steroids taper and required steroids inhalers on her follow-up visits. On her 30-day follow-up visit, she was still using 3 L/min of oxygen therapy.

Table 1: Daily oxygen requirements for case #3

| Day 1 | HFNC = 40 L, FiO₂ = 100% |
| Day 2 | HFNC = 40 L, FiO₂ = 100% |
| Day 3 | HFNC = 40 L, FiO₂ = 100% |
| Day 4 | Use of BiPAP, FiO₂ = 90% |
| Day 5 | Use of BiPAP, FiO₂ = 90% |
| Day 6 | Use of NRM, HFNC = 40 L, FiO₂ = 100% |
| Day 7 | Use of NRM, HFNC = 40 L, FiO₂ = 100% |
| Day 8 | Use of NRM, HFNC = 40 L, FiO₂ = 100% |
| Day 9 | Use of NRM, HFNC = 40 L, FiO₂ = 100% |
| Day 10 | Day 1 of 500 mg of methylprednisolone via IV. O₂: Use of NRM, HFNC = 40 L, FiO₂ = 100% |
| Day 11 | Day 2 of 500 mg of methylprednisolone via IV. Use of NRM, HFNC = 40 L, FiO₂ = 100% |
| Day 12 | Day 3 of 500 mg of methylprednisolone via IV. HFNC = 40 L, FiO₂ = 80% |
| Day 13 | Day 1 of 250 mg of methylprednisolone via IV. HFNC = 35 L, FiO₂ = 60% |
| Day 14 | Day 2 of 250 mg of methylprednisolone via IV. HFNC = 30 L, FiO₂ = 45% |
| Day 15 | Day 3 of 250 mg of methylprednisolone via IV. HFNC = 25 L, FiO₂ = 35% |
| Day 16 | Day 1 of 12 mg of dexamethasone via IV. NC = 5 L. Patient progressively weaned from steroids and remained stable |
| Day 19 | Patient required 3 L of NC at rest and 5 L of NC when ambulating |

BiPAP = bilevel positive airway pressure; FiO₂ = fraction of inspired oxygen; HFNC = high-flow nasal cannula; NC = nasal cannula; NRM = non-rebreather mask.
The patient was discharged on steroids taper. On the 30-day follow-up visit, the patient was off oxygen. She still had fatigue and chest tightness that was treated with inhaled steroids.

**Case #5: Rapid Improvement in Milder Cases**

The patient was a 42-year-old man with obesity and history of asthma. He presented with shortness of breath. The patient first developed COVID-19 symptoms on January 9, 2021, associated with fevers, cough, and shortness of breath that were progressively worsening. He checked his pulse oximeter at home, and it was 88%. The patient came to the ER and was subsequently admitted on January 22, 2021 (day 1). He needed 6 L of NC and would desaturate with minimal exertion, including eating. His CRP was higher than 380 (more than 7x normal). On day 1, the patient was started on HDPS 500 mg of methylprednisolone via IV for 3 days, in addition to remdesivir, and antibiotics (ceftriaxone and doxycycline). The patient improved markedly and was discharged on 2 L of NC on day 7. The patient was not discharged on steroids, and on his 30-day follow-up, he was off oxygen.

**Case #6: Modified Protocol for Diabetic Patient with Labile Blood Sugar**

The patient was a 46-year-old man with a history of type 2 diabetes, hyperlipidemia, and an ex-smoker. He presented to the ER with shortness of breath and cough; he received his first COVID-19 vaccine 12 days prior to admission. He then developed fevers and headache, which he attributed to the vaccine side effects. Nine days prior to admission, he developed a progressive worsening of cough and shortness of breath. He presented to the ER on April 19, 2021 (day 1). The patient was admitted and started on dexamethasone, remdesivir, and antibiotics. The patient received tocilizumab on day 2 while on NRM.

The patient was started on HDPS on day 8 but, given that his sugar level was very labile,
admitted on April 20, 2021 (day 1) at an outside-network hospital with COVID-19 pneumonia. His presenting O2 saturation was 81% on room air. His CRP and procalcitonin were moderately elevated, with an elevated white count of 18,000. Chest x-rays showed bilateral infiltrates. He required an NRM shortly after admission. The patient was diagnosed with acute respiratory hypoxemic respiratory failure due to COVID-19.

He was treated with 12 mg of ivermectin by mouth on day 1 and day 3; 600 mg of tocilizumab via IV on day 2; and remdesivir days 1–5. Six mg of dexamethasone was started on day 1, which was increased to 10 mg per day on day 2; doxycycline days 2–7; and piperacillin/tazobactam days 2–7. He also received zinc and vitamin D. His COVID-19 antibody was positive on day 1; therefore, the patient was not given convalescent plasma. Right peripherally inserted central catheter line was placed, and the patient was given total parenteral nutrition due to his poor nutritional status. His respiratory status deteriorated, requiring HFNC. He never required intubation. The patient signed against medical advice and came to our hospital by private transportation on day 12. His peripherally inserted central catheter line was removed prior to discharge.

Chest x-rays on admission to our facility showed bilateral infiltrates (see Figure 7). No pneumothorax or effusion was observed. He was tachypneic on arrival. He required NRM, which was changed to HFNC 40 L, FiO2 100%. He was given piperacillin/tazobactam on admission. On day 13, his white blood cell count improved, and the procalcitonin was found to be low; therefore,
Figure 5: Chest x-ray #2 of case #4. Patient was started on high-dose pulse steroids on hospitalization day 5.

Figure 6: Chest x-ray #3 of case #4 on hospitalization day 9.
the antibiotics were stopped. He also had right-upper extremity swelling at the previous site of the peripherally inserted central catheter line. An ultrasound confirmed deep vein thrombosis. The patient was started on a full dose of subcutaneous enoxaparin 1 mg/kg twice a day. The CTPA was negative for pulmonary embolism but showed bilateral extensive ground glass opacities. The CTPA was reviewed with the radiology department in retrospect and found to be consistent with OP. The patient remained on HFNC 40 L, FiO₂ 100%.

The patient was started on HDPS on day 16 with 500 mg of methylprednisolone via IV daily for 3 days, then 250 mg via IV daily for 3 days, then 6 mg of dexamethasone via IV daily. However, he was noted to have unexplained elevation of his alanine transaminase (6x normal levels) while on HDPS, despite the troponin, CK, and hepatitis panels being negative. In light of this unexplained transaminitis, the patient was rapidly weaned from steroids. His oxygen requirement is described in Table 3.

The patient was discharged on steroids taper. On his 30-day follow-up, he was saturating 97% on room air but was complaining of protracted dizziness.

Case #8: Stuck on 15 L Venturi Mask

The patient was a 55-year-old man with a history of hypertension and stroke. He presented with fever and shortness of breath after testing positive for COVID-19, which he was tested for 14 days prior to admission. His symptoms began worsening a few days later. He developed body aches, weakness, and then a fever that got progressively worse. He became tired and short of breath with ambulation.

The patient was admitted on May 6, 2021 (day 1) with COVID-19 pneumonia, on NRM that improved to VM the next day. The patient, however, remained on 15 L 50% VM. He was started on a high-dose steroids protocol on day 5. Patient oxygen improved to 5 L NC by day 9, then he was slowly weaned to 2 L NC on day 12, the day of discharge.

The patient was not discharged on steroids taper. On his 30-day follow-up, he was still using 2.5 L/min of oxygen on exertion and during the night.
Case #9: Crash and Burn

The patient was a 64-year-old man with a history of hypertension, hyperlipidemia, and tobacco use. He was diagnosed with COVID-19 one week prior to admission on March 5, 2021 (day 1), where he presented with COVID-19 pneumonia. The patient was treated with remdesivir, dexamethasone, convalescent plasma, tocilizumab, and empiric antibiotics. He required increasing amounts of oxygen support since admission. He was treated with high-dose IV steroids on day 15. The patient desaturated while on bilevel positive airway pressure and was transferred to ICU for intubation on day 18. Standard hospital course was complicated by left-hand fifth digit ischemia felt to be due to microemboli from COVID-19, treated with therapeutic anticoagulation. He remained intubated in respiratory failure and underwent tracheostomy and percutaneous endoscopic gastrostomy placement. The patient was discharged after protracted hospitalization (more than 2 months with hospital-acquired pneumonia) to a long-term care facility, but he was readmitted shortly after for fever of unknown origin, presumed to be due to aspiration pneumonitis.

Discussion

We have presented a case series where COVID-19 pneumonias causing hypoxemia and respiratory failure were treated with HDPS. These case series are not proof that pulse steroids are the ultimate treatment for COVID-19 pneumonia. However, these cases, along with the literature review, are presented in order to raise awareness of the possibility of newer treatment protocols for COVID-19 pneumonia-related hypoxic failure. Some patients had confirmed secondary OP from COVID-19-related infection.

It was noted in the presented case series that an improvement in oxygen requirement usually started around 72–96 hours post-HDPS, and the best improvement in oxygenation was observed 5 to 7 days later. On average, we started HDPS on the seventh day of admission. Although there was a protocol set, modification of the protocol was done to accommodate each patient. We have also subjectively observed, as did Yao et al., that D-dimer correlated with the patient’s clinical improvement but ferritin, lactate dehydrogenase, and CRP did not. Some CRP was in the typical range when HDPS was started. None of the first 8 patients had superimposed opportunistic infection.

Corticosteroid therapy is the cornerstone in treating both OP and acute fibrinous OP in dosing similar to cryptogenic OP, including methylprednisolone pulse therapy for severe cases, followed by maintaining prednisone dose (0.75 to 1.0 mg/kg daily) for 4–8 weeks. In this case, we are unsure if HDPS should be modified to include higher doses of steroids because the 6 mg of dexamethasone daily after the pulse steroids may be insufficient.

We suspect that our protocol was effective because it treated patients with OP, where steroids are the cornerstone of therapy. These findings should be used in conjunction with current protocol to control cytokine storms. Since OP develops over time, we propose that cytokine storm medications, such as tocilizumab, should be given at the time of admission, followed by CTPA a few days later if the hypoxemia is not improving (we propose 5–7 days). If the CTPA shows pulmonary embolism, the patient should be treated accordingly. If the CTPA shows OP, the patient should be treated with...
High-Dose Pulse Steroids for the Treatment of Acute Hypoxemic Respiratory Failure in COVID-19 Pneumonia

Figure 8: Chest x-ray #2 of case #7. Patient was started on high-dose pulse steroids on hospitalization day 16.

Figure 9: Chest x-ray #3 of case #7 on hospitalization day 20.
In addition, future prospective studies should investigate the role of the HDPS on admission as well as 1 week into admission. Each investigative arm should also include a rapid-tapering arm vs a slow-tapering arm for steroids.

REFERENCES


Case Report of Novel, Automatic Shocking Vector Adjustment Algorithm: A Life-Saving Feature of a Modern Defibrillator

Mark R Heckle, MD; Sunil K Jha, MD, MRCP, FACC, FHRS
Perm J 2022;26:21.007  •  E-pub: 04/05/2022  •  https://doi.org/10.7812/TPP/21.007

Abstract

BACKGROUND: Failed delivery of appropriate shocks against fatal dysrhythmias can be the result of low impedance on high-voltage leads. This malfunction might be missed on routine interrogation. We describe the case of a 66-year-old man with a high-voltage lead short circuit who was successfully rescued with the use of an overcurrent detection and automatic shocking vector adjustment algorithm.

CASE REPORT: A 66-year-old man with severe nonischemic cardiomyopathy was admitted after receiving 2 shocks from his cardiac resynchronization therapy cardioverter-defibrillator. Interrogation of his defibrillator confirmed 2 consecutive episodes of ventricular fibrillation. For each episode, the initial shock therapy was aborted due to low impedance (<10 ohms) detected on the default shocking configuration: right ventricle to superior vena cava/implantable cardioverter generator. As a result, the device algorithm excluded the superior vena cava coil and immediately delivered a shock of 40 joules between the right ventricular coil and the cardiac resynchronization therapy cardioverter-defibrillator implantable cardioverter generator. This successfully terminated the ventricular fibrillation. All other lead measurements were normal.

CONCLUSION: High-voltage lead malfunctions can lead to failed therapy of life-threatening dysrhythmias. Malfunctions like a low impedance of high-voltage leads may not be detected on routine interrogation. Fortunately, the overcurrent detection algorithm recognized the low impedance, and another shocking configuration was selected and successfully terminated the ventricular dysrhythmias. With these algorithms, overcurrent detection and automatic shocking vector adjustment, this patient was rescued. We suggest this feature be considered in all modern defibrillators.

Introduction

Failed delivery of appropriate shocks by an implantable defibrillator can be the result of low impedance detected on high-voltage leads. Malfunctions such as these might be missed on routine interrogations, and thus might go unrecognized. Herein we describe a case of the rescue of a patient with a high-voltage lead malfunction with the use of a novel algorithm.

Case Report

The patient was a 66-year-old Black man with a history of severe nonischemic dilated...
cardiomyopathy with a severely reduced left ventricular ejection fraction, ventricular fibrillation (VF), and persistent atrial fibrillation. He presented to the emergency room after receiving 2 shocks from his cardiac resynchronization therapy cardioverter-defibrillator (CRT-D), after a witnessed brief loss of consciousness while at home.

Upon interrogation of his Quadra Assura 3365-40C (Abbott, Plymouth, MN, USA) defibrillator there were two confirmed consecutive episodes of VF (Figure 1A). For each episode, the first attempt to terminate the VF with implantable cardioverter-defibrillator (ICD) shock therapy was unsuccessful from the dual-coil high-voltage right ventricular lead, Durata 7120 (Abbott, Plymouth, MN, USA). For each episode, the initial shock therapy was not delivered due to low impedance (<10 ohms) detected on the superior vena cava (SVC) coil (Figure 1B). The default shocking configuration was right ventricle (RV) to SVC/implantable cardioverter generator (CAN). As a result of the low impedance, the device algorithm (overcurrent detection and DynamicTX™ algorithm) excluded the SVC coil and immediately delivered a rescue shock of 40 joules between the RV coil and the CRT-D generator CAN (Figure 1C). This successfully terminated the VF. In addition, with the first shock therapy from the ICD, his persistent atrial fibrillation was converted back to normal sinus rhythm as well. All other lead measurements were within normal limits, with RV pacing impedance of 400 ohms and left ventricle pacing impedance of 940 ohms with pacing vector of M3–M2. The RV pacing threshold was 0.5 V at 0.5 ms, and the left ventricle pacing threshold was 0.5 V at 1.0 ms (M3–M2). RV sensing was found to be greater than 12.0 mV (bipolar). Afterwards, the SVC coil was turned off due to failure to deliver shock therapy from the low impedance.

Because the patient had recurrent VF and subsequently his SVC coil was turned off, it was decided to perform a defibrillation threshold test. VF was successfully induced with high-voltage, high-frequency right ventricular pacing. Successful termination of VF was achieved with a single 30 joule shock, with RV coil to CRT-D CAN shocking vector. A full timeline of the case report can be found in Table S1.

**Discussion**

The annual rate of ICD lead defects reaches ~20% in a 10-year follow-up. In a prior study, 56% of major causes of lead failure were due to lead insulation breaks. Nearly 2/3 of lead defects can be detected on electrical parameters during routine follow-up, but in 1/3 of the cases, the lead defects are found after failed shock therapy. High-voltage lead malfunctions can lead to failed therapy of life-threatening dysrhythmias. In our case, the high-voltage lead malfunction occurred between the RV coil and

---

**Figure 1:** Intracardiac tracings during spontaneous VF episode is shown. (A) VF was successfully detected. (B) The first shock attempt. The exclamation point at the first shock denotes overcurrent detection, which in turn lead to 0.0 joules being delivered. (C) Subsequently, a maximum shock (40.0 joules) using the “RV-CAN” shocking-vector configuration was delivered with successful termination of VF. CAN = implantable cardioverter generator; RV = right ventricle; VF = ventricular fibrillation.
the SVC/CAN because the impedance was below the detection limits (<10 ohms). Fortunately, the overcurrent detection algorithm recognized the low impedance, and the initial shock was not delivered. The automatic shocking vector adjustment algorithm (DynamicTX™) then excluded the SVC coil, and a 40-joules shock therapy was delivered with RV-CAN shocking vector configuration with successful termination of VF (Figure 2).

The novel overcurrent detection algorithm is exclusive to the Ellipse, Fortify Assura, Quadra Assura, and Unify Assura series (Abbott, Plymouth, MN, USA) systems. The overcurrent detection algorithm is designed for a dual-coil system with an active SVC coil (Figure 3). During shock delivery, when low impedance is detected (<10 ohms) in the initial configuration, the overcurrent detection algorithm will abort the shock therapy. This helps prevent damage to the ICD system. After a low impedance is detected in a given shocking vector, the DynamicTX™ algorithm selects an alternative configuration. The vector-switching sequence varies based on the programmed configuration (Figure 3). In our case, the initial configuration (RV to SVC/CAN) failed, therefore it was changed to RV to CAN with delivery of shock therapy and successful termination of VF (Figure 1). At the end of the rescue, the device defaulted back to the initial programmed shocking vector (RV to SVC/CAN). Activation of the Dynamic Tx™ algorithm results in multiple alerts to indicate the presence of a high-voltage lead failure and initiation of an alternative shock configuration. A vibratory alert, if turned on, will also be delivered to the patient.

A case published by Mizobuchi et al⁴ described a patient with low lead impedance detected on SVC coil on a Riata lead (Abbott, Plymouth, MN, USA) while performing a defibrillation threshold test at the time of ICD generator replacement. In their case, a successful rescue shock was delivered from the RV coil to the CAN using the overcurrent detection and DynamicTX™ algorithm. The Food and Drug Administration classified the Riata family of ICD leads as a Class I recall due to inside-out abrasions underneath the shocking coils.⁵ Chung et al described a patient with recurrent VF in the setting of a high-voltage lead short circuit with successful rescue using the DynamicTX™ algorithm.⁶ In their case, shock therapy was delivered through an SPL SP02 dual-coil RV ICD lead (Ventritex, Sunnyvale, CA, USA). To our knowledge, the present case is the first to show the efficacy of the DynamicTX™ algorithm in a currently implanted ICD lead. In addition, our case further highlights the importance of overcurrent detection and the success of the DynamicTX™ algorithm in a clinical setting.

**Conclusion**

Without the DynamicTX™ algorithm, patients such as ours might not be rescued. In patients who
present after failed delivery of an appropriate shock for a fatal dysrhythmia, we recommend seeking input from an electrophysiologist to help determine the cause of the failed shock. A defibrillation threshold test should be considered if a high-voltage lead short circuit is suspected. Finally, to provide patients with the utmost protection from fatal dysrhythmias, we suggest algorithms, such as the DynamicTX™ algorithm, be considered in all modern defibrillators.

**Supplementary Materials**


**REFERENCES**

Effect of Immunosuppressive Diseases and Rituximab Infusions on Allowing COVID-19 Infection to Relapse

Rohan M Prasad, DO; Shaurya Srivastava, DO; Enhua Wang, MD; Jason Z Liu, DO; Rakesh Gami, MD; Ayat Abdelgadir, MD; Akhil Sharma, DO; Sumugdha Rayamajhi, MD; Richa Tikaria, MD


Abstract

INTRODUCTION: Relapsing COVID-19 infections have been reported, but their etiology and severity are still unknown. In addition, there have been no cases in the literature that associate relapsing infection with immunosuppression, either from a disease course or medications.

CASE PRESENTATION: This case series illustrates two patients who developed a relapsed infection, likely from recent rituximab infusions. In addition, both cases depicted a severe form of infection than the initial one. Laboratory investigations revealed these patients were unable to produce COVID-19 antibodies, even though one of the patients received convalescent plasma.

CONCLUSION: Clinicians should be aware of the possibility of relapsing COVID-19, especially in immunosuppressed patients. Because rituximab induces B-cell depletion, it can also decrease the effectiveness of the COVID-19 vaccine. Therefore, these patients should receive the vaccine before their scheduled rituximab infusion.

Introduction

On January 30, 2020, the World Health Organization declared a global public health emergency involving COVID-19 that was causing a disease named severe acute respiratory syndrome coronavirus 2. This virus is classified under the ß subdivision of the family of coronaviruses. Relapses of COVID-19 infections have been demonstrated; however, its effect and severity in patients with immunosuppressive disorders and medications is unclear. This case series was prepared following the Case Report CARE guidelines.

Case Presentation

The following cases illustrate two patients who developed severe, relapsing COVID-19 infections in the setting of recent rituximab infusions and chronic immunocompromised states. In both patients, the relapsing infection was more severe than the initial infection, and antibodies were not detected. This was seen even though 1 of the patients received convalescent plasma.

The first patient, KT, is a 73-year-old woman with a history of hypothyroidism, diabetes,
and mantle cell lymphoma who presented for worsening shortness of breath, productive cough, and recurrent fevers for 1 week in January 2021. The patient stated that her last dose of rituximab for the lymphoma was in November 2020. She was initially diagnosed with COVID-19 in December 2020 via 2 positive polymerase chain reaction (PCR) nasal swabs. KT was treated with 10 days of Decadron and 5 days of remdesivir, ceftriaxone, and azithromycin. Initially, she required 2 L of oxygen, but was eventually weaned down to room air. On discharge, her D-dimer level was only mildly elevated; thus, she was not started on anticoagulation. She tested negative on 2 consecutive days from the COVID-19 PCR swabs 7 days after her initial positive test. In addition, on day 12 of that hospital stay she was negative for COVID-19 immunoglobulin G (IgG) antibodies.

In January 2021, KT was found to be COVID-19 positive, 38 days after the initial positive test, and her D-dimer level was greatly elevated (Table 1). Chest x-ray showed bilateral infiltrates (Figure 1). In addition, chest computed tomographic angiography demonstrated pulmonary emboli and bilateral ground-glass infiltrates (Figure 2). COVID-19 IgG antibodies were negative on days 1 and 9 of this hospital course (Table 1). Therefore, KT received cefepime for 7 days and convalescent plasma on days 1 and 12. Eventually, she developed a spontaneous right-side pneumothorax on day 5 (Figure 3) and bilateral pneumothoraces on day 9 (Figure 4). She initially tolerated bilevel positive airway pressure, but required intubation and an intensive care unit transfer. She also received a therapeutic dose of enoxaparin, and placement of bilateral chest tubes, which exhibited slow improvement in her respiratory status. However, KT continued to require maximum levels of ventilation and did not tolerate weaning trials. As a result, on day 20, a tracheostomy tube was placed after 2 preprocedural COVID-19 PCR swabs had a negative result. She patient was eventually discharged to a facility for long-term weaning after 2 negative COVID-19 PCR swab results. A poor prognosis was delivered to the family on the possibility of the patient surviving this disease course. Since discharge from the hospital, KT has tolerated weaning from the vent and is now using a speaking valve. With this progress, she was discharged from long-term rehab and now resides at home with her family. A timeline of KT’s pertinent history and hospital course is depicted in Figure 5.

Our second patient, JP, is a 45-year-old man with a history of secondary progressive multiple sclerosis, a chronic Foley for neurogenic bladder, and recurrent urinary tract infections. He presented in January 2021 with 2 days of difficulty breathing, fever, and sepsis. The patient was treated with multiple regimens for multiple sclerosis, including rituximab infusions starting in June 2015. His most recent rituximab infusion was in September 2020. In October 2020, JP was found to be COVID-19 positive via PCR from a urology preprocedural screening evaluation. His only symptom at that time was a mild cough. Twelve days after his initial positive test, JP retested negative for COVID-19 via PCR.

On admission in January 2021, JP had two COVID-19 PCR results that were positive, which occurred 55 days after his initial positive test. In addition, a urine analysis was consistent with a urinary tract infection (Table 2). The chest x-ray on admission showed mild, right-side hilar infiltrates (Figure 6). JP was treated with guideline-based dexamethasone and intravenous remdesivir along with urine culture sensitivity-directed antibiotics. His fevers and oxygen requirements improved until day 13, when he developed fevers, difficulty breathing, and declining mentation. Repeat imaging later that day revealed progressive bilateral and multifocal airspace opacities (Figures 7 and 8). His COVID-19 IgG antibodies were negative on days 5 and 13 of the hospital course. Convalescent plasma was not given to JP per his and his family’s wishes. Ultimately, he required intubation, continuous renal replacement therapy, and an intensive care unit transfer. COVID-19 PCR on day 28 was once again positive. Unfortunately, as a result of a prolonged intensive care unit course with no improvement in multiorgan failure despite medical treatment, JP’s family decided to pursue comfort care measures on day 30 of his hospital stay. JP’s pertinent history and hospital course are illustrated in Figure 9.

Discussion

According to the Centers for Disease Control and Prevention, a relapse or reactivation of COVID-19 is when a repeat PCR test is positive during a 90-day window, which indicates prolonged viral shedding. However, it is currently unknown whether these patients require droplet isolation precautions. In comparison, COVID-19 reinfection is 2 positive PCR tests conducted at least 90 days
Effect of Immunosuppressive Diseases and Rituximab Infusions on Allowing COVID-19 Infection to Relapse

<table>
<thead>
<tr>
<th>Date</th>
<th>Subjective and objective</th>
<th>Diagnostic testing</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/18/21</td>
<td>The patient reports 1 wk of shortness of breath, productive cough, and recurrent fevers.</td>
<td>White blood cells 12 × 103 cells/µL Neutrophils, 94.4% C-reactive protein, 8.9 mg/dL Lactic, 1.9 mmol/L Procalcitonin, 0.16 ng/mL Ferritin, 1078 ng/mL Lactate dehydrogenase, 553 U/L D-dimer, 20.26 mg (FEU)/µL COVID-19 PCR, positive × 2 COVID-19 antibodies, &lt; 3.8 Urine analysis Blood culture, no growth × 2 Chlamydia pneumonia PCR, negative Mycoplasma pneumonia PCR, negative Legionella pneumonia PCR, negative Streptococcus pneumonia urine antigen, negative Legionella urine antigen, negative Methicillin-resistant Staphylococcus aureus PCR, negative Influenza A and B direct antigens, negative Adenovirus PCR, negative Parainfluenza 1–4 PCR, negative Metapneumovirus PCR, negative Respiratory syncytial virus PCR, negative Chest x-ray, bilateral pulmonary infiltrates Computed tomography angiography of the chest, acute pulmonary emboli and bilateral ground glass infiltrates</td>
<td>Convalescent plasma was given. Started heparin drip. Started cefepime for 7 d. Infectious disease was consulted.</td>
</tr>
<tr>
<td>1/20/21</td>
<td>The patient reports shortness of breath with any movement.</td>
<td>None</td>
<td>Oxygen requirements are increasing. Consulted pulmonology. Stopped heparin drip and started daily therapeutic enoxaparin.</td>
</tr>
<tr>
<td>1/23/21</td>
<td>The patient has some one episode of bloody sputum.</td>
<td>Chest x-ray, right-sided pneumothorax and mild vascular congestion</td>
<td>Right chest tube placed.</td>
</tr>
<tr>
<td>1/27/21</td>
<td>None</td>
<td>Chest x-ray, new left-sided pneumothorax and increasing bilateral infiltrates COVID-19 antibodies, &lt; 3.8</td>
<td>Transferred to the intensive care unit. The patient was intubated. Sedated on fentanyl drip. Started on norepinephrine and vasopressin drips. Convalescent plasma was given. Left chest tube placed.</td>
</tr>
<tr>
<td>2/1/21</td>
<td>The patient is agitated and dyssynchronous with the vent.</td>
<td>None</td>
<td>Started cisatracurium drip. Vasoppressors were stopped.</td>
</tr>
<tr>
<td>2/4/21</td>
<td>Code blue is called for cardiac arrest.</td>
<td>Pulseless electrical activity Post code chest x-ray, no new or worsening pneumothoraces</td>
<td>Received 2 rounds of cardiopulmonary resuscitation. Received 2 doses of epinephrine, 1 of bicarbonate, and 1 g of calcium chloride. Return of spontaneous circulation achieved after 6 min.</td>
</tr>
<tr>
<td>2/7/21</td>
<td>The patient is not passing spontaneous breathing trials and persistently requires maximum levels of ventilator support.</td>
<td>COVID-19 PCR, negative × 2</td>
<td>Tracheostomy performed.</td>
</tr>
</tbody>
</table>

Table 1: Timeline of care for patient 1, a 73-year-old woman with a history of hypothyroidism, diabetes, and mantle cell lymphoma on rituximab presented for worsening shortness of breath, productive cough, and recurrent fevers for 1 wk. FEU = Fibrinogen equivalent units; PCR = polymerase chain reaction.
after the initial 2 positive PCR tests, regardless of symptoms, or a repeat positive PCR within 45 to 89 days in a patient with symptoms consistent with COVID-19, other explainable cause for the symptoms, or no recent COVID-19 exposure. However, this timeline requires further delineation in immunocompromised individuals. For example, an 89-year-old woman developed a fatal case of COVID-19 reinfection 2 days after starting chemotherapy for Waldenström macroglobulinemia, which correlated with an onset of 59 days after her initial exposure. Another differential diagnosis is prolonged shedding of the virus, but these patients are typically asymptomatic. Both of the patients in our case series developed symptomatic relapsed COVID-19 infection and more severe forms of the disease than the initial infection. Antibodies were tested multiple times and neither patient was able
to produce an adequate response. Moreover, the second patient’s IgG antibody level had decreased despite developing and recovering from COVID-19 (Table 2). Because of the perceived likelihood of infectivity, isolation droplet precautions were initiated in these patients. However, further studies should evaluate the true viral infectivity in relapsed patients to determine the necessity of isolation. In addition, a viral load from the initial infection should be greater than 35 cycle threshold values, and 1 or 2 negative PCR results between the 2 episodes is required. Unfortunately, viral loads were not obtained; but, because of the temporal relationship of the symptoms and positive COVID-19 tests, a presumptive assumption was made.

Usually, the first infection of the virus activates B-cell maturation and a primed immune system that acts as a robust and rapid response to protect the host from subsequent infections. These antibodies can be detected within 10 to 14 days from the onset of symptoms, but those with a mild form of COVID-19 may have low or undetectable titers. Nonhuman primates with a robust humoral immunity consisting of antireceptor-binding domain antibodies were shown to be protected from reinfection. The effectiveness of these neutralizing antibodies can predict disease severity, mortality rate, and reinfection rate. The primed immune responses could possibly have a similar effectiveness in preventing the onset of both reinfections and relapses. However, some reports have indicated that patients with antibodies can still develop COVID-19 reinfection. Theories and pathogenesis are unclear on the severity of the COVID-19 relapse symptoms and disease course in comparison to the initial infection. Mild reinfections have been explained by the priming of the immune system with a robust and rapid B-cell maturation. On the other hand, a severe disease course may develop through antibody-dependent enhancement, which is when a virus-antibody immunocomplex binds to cells with a complement or Fc receptor that activates viral cell uptake.

In the literature, there are previous cases indicating COVID-19 relapses and reinfections with negative PCR results after the initial infection. However, none of these patients had a history of immunosuppression along with negative COVID-19 antibodies. Furthermore, 1 case illustrated a patient with mantle cell lymphoma who received rituximab and then had a prolonged course of COVID-19 with persistently positive PCR results. Our case series is different; both patients had negative COVID-19 PCR results between the 2 periods of infections. In addition, COVID-19 antibodies were measured at a substantially low level, which indicated a negative immune response. Our 2 cases share similarities; they both have a chronic disease process (mantle cell lymphoma and multiple sclerosis) and recently received rituximab infusions 1 month prior to the initial COVID-19 infection. It is important to note

<table>
<thead>
<tr>
<th>History of Patient</th>
<th>A 73-year-old female with a history of hypothyroidism, diabetes, and mantle cell lymphoma on rituximab.</th>
</tr>
</thead>
<tbody>
<tr>
<td>November 2020</td>
<td>Most recent Rituximab infusion</td>
</tr>
<tr>
<td>December 2020</td>
<td>Tested COVID-19 positive on 2 nasal PCRs. Admitted to the hospital. Infection resolved in 10 days after treatment with Decadron, Remdesivir, Rocephin, and Azithromycin.</td>
</tr>
<tr>
<td>January 18th, 2021</td>
<td>Patient tests negative for COVID-19 on repeat nasal swabs 7 days later and has negative IgG antibodies to COVID-19.</td>
</tr>
<tr>
<td>January 23rd, 2021</td>
<td>Patient tests COVID-19 positive on nasal PCR. Chest imaging shows bilateral infiltrates consistent with COVID-19 and pulmonary emboli. Patient is admitted to the hospital. COVID-19 IgG antibodies are negative.</td>
</tr>
<tr>
<td>January 27th, 2021</td>
<td>Patient developed worsening shortness of breath. CXR shows right sided Pneumothorax and right chest tube placed.</td>
</tr>
<tr>
<td>February 3rd, 2021</td>
<td>New left sided pneumothorax noted and left chest tube placed. The patient is intubated due to worsening oxygenation and infiltrates, and transferred to ICU.</td>
</tr>
<tr>
<td>February 4th, 2021</td>
<td>The patient was agitated on vent requiring a cisatracurium drip. Continually requiring vasopressors.</td>
</tr>
<tr>
<td>February 7th, 2021</td>
<td>Patient had a PEA arrest. ROSC was obtained after 6 minutes of downtime, 2 rounds of CPR, 2 doses of Epinephrine, 1 of Bicarbonate, and 1 of Calcium chloride. The patient did not tolerate breathing trials; thus, a tracheostomy was placed.</td>
</tr>
<tr>
<td>March 5th, 2021</td>
<td>The patient was successfully weaned off and discharged home.</td>
</tr>
</tbody>
</table>

Figure 5: Timeline of events for KT depicting the pertinent history, admission date, and treatment course.
<table>
<thead>
<tr>
<th>Date</th>
<th>Subjective and objective</th>
<th>Diagnostic testing</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/7/21</td>
<td>The patient admitted to 2 d of difficulty in breathing, fever, and chills.</td>
<td>White blood cells, 7.5 × 103 cells/µL&lt;br&gt;C-reactive protein, 12.4 mg/dL&lt;br&gt;Serum Lactic, 1.4 mmol/L&lt;br&gt;Procalcitonin, 0.28 ng/mL&lt;br&gt;Ferritin, 1434 ng/mL&lt;br&gt;Lactate dehydrogenase, 751 U/L&lt;br&gt;D-dimer, 15.81 mg (FEU)/µL&lt;br&gt;COVID-19 PCR, positive × 2&lt;br&gt;Blood culture, no growth × 2&lt;br&gt;<em>Chlamydia</em> pneumonia PCR, negative&lt;br&gt;<em>Mycoplasma</em> pneumonia PCR, negative&lt;br&gt;<em>Legionella</em> pneumonia PCR, negative&lt;br&gt;<em>Streptococcus</em> pneumonia urine antigen, negative&lt;br&gt;<em>Legionella</em> urine antigen, negative&lt;br&gt;Methicillin-resistant <em>Staphylococcus aureus</em> PCR, negative&lt;br&gt;Influenza A and B direct antigens, negative&lt;br&gt;Adenovirus PCR, negative&lt;br&gt;<em>Parainfluenza</em> 1–4 PCR, negative&lt;br&gt;Metapneumovirus PCR, negative&lt;br&gt;Respiratory syncytial virus PCR, negative&lt;br&gt;Chest x-ray, mild right-sided hilar infiltrates</td>
<td>Started dexamethasone for 10 d.&lt;br&gt;Started remdesivir for 5 d.&lt;br&gt;Started cefepime.</td>
</tr>
<tr>
<td>1/12/21</td>
<td>The patient reports symptom- atic improvement, including fevers. Oxygen requirements are also decreasing.</td>
<td>Urine culture: <em>Proteus mirabilis</em> (&gt;100,00 CFU/mL), <em>Pseudomonas aeruginosa</em> (50,000–75,000 CFU/mL), sensitive to meropenem&lt;br&gt;COVID-19 antibodies, 7</td>
<td>Stopped cefepime and started meropenem for 14 d.&lt;br&gt;Patient declined convalescent plasma.</td>
</tr>
<tr>
<td>1/20/21</td>
<td>The patient develops new-onset fevers, shortness of breath, and altered mentation.</td>
<td>Chest x-ray, progressive bilateral and multifocal airspace opacities&lt;br&gt;COVID-19 antibodies, 5.6</td>
<td>Transferred to the intensive care unit.&lt;br&gt;Infectious disease was consulted.&lt;br&gt;Family still declined convalescent plasma.</td>
</tr>
<tr>
<td>1/28/21</td>
<td>The patient still has fevers as well as progression of drowsiness and lethargy.</td>
<td>None</td>
<td>Started bilevel positive airway pressure.</td>
</tr>
<tr>
<td>1/30/21</td>
<td>The patient becomes dyspneic, tachycardic, and somnolent despite bilevel positive airway pressure.</td>
<td>None</td>
<td>The patient was intubated.&lt;br&gt;Sedated on fentanyl and propofol drips.&lt;br&gt;Central venous catheter was placed.&lt;br&gt;Started norepinephrine drip.</td>
</tr>
<tr>
<td>2/3/21</td>
<td>The patient is unresponsive during spontaneous awakening trials.</td>
<td>COVID-19 PCR, positive × 2</td>
<td>Still hypotensive; added vasopressin drip.&lt;br&gt;Nephrology was consulted.&lt;br&gt;Started continuous renal replacement therapy.</td>
</tr>
<tr>
<td>30</td>
<td>The patient remains unresponsive.</td>
<td>None</td>
<td>The family decided to pursue comfort measures.</td>
</tr>
</tbody>
</table>

*Table 2:* Timeline of care for patient 2, a 45-year-old man with a history of secondary progressive multiple sclerosis on rituximab, chronic Foley for a neurogenic bladder, and recurrent urinary tract infections.

FEU = Fibrinogen equivalent units; PCR = polymerase chain reaction.
that the first patient received convalescent plasma, which is used to instigate the formation of COVID-19 antibodies. However, 2 doses of this treatment method did not result in a detectable amount of antibodies.

Rituximab, a chimeric murine/human anti-CD20 monoclonal antibody that remains in the blood for months after administration, is a likely link between these 2 patients not being able to produce an immune response against COVID-19. The proposed pathogenesis of rituximab eliminating B cells includes complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and stimulation of the apoptotic pathway. Therefore, rituximab alters the function of circulating antibodies and memory B lymphocytes. The effect of immunosuppression has been proposed to be a risk factor for reinfection, relapse, and a prolonged disease course of COVID-19. However, it also may be protective against severe disease by stunting an overstimulated immune system. A study on Syrian hamsters showed that the absence of functional B and T cells led to an exaggerated early disease course, decreased viral clearance, and more severe outcomes.
Because our patients did not receive rituximab directly before their relapse, it must be considered whether the underlying immune process is truly the common factor. Genome sequencing was unable to be done in these patients; thus, we cannot indicate definitively whether these are relapsing or reinfections of COVID-19. Current studies are being conducted to determine an effective treatment regimen for COVID-19 patients. Remdesivir has been shown to decrease viral RNA proliferation; thus, it also shortens the needed recovery time, but it was only evaluated in immunocompetent patients.\textsuperscript{13,16} Convalescent plasma may be beneficial in patients who cannot produce antibodies on their own.\textsuperscript{13,16} In addition, the rituximab-induced B-cell depletion may decrease the effectiveness of the vaccine. Therefore, the vaccine’s initial dosages and boosters should be given before receiving rituximab infusions to allow for a successful B-cell response.\textsuperscript{18} The current data indicate that antibodies persist for 6 months after being vaccinated, and 8 months after developing a COVID-19 infection.\textsuperscript{19–22} However, as previously illustrated, immunocompromised patients are at risk for not developing a robust immune response to COVID-19 infections; thus, it must be evaluated whether they are capable of developing an adequate response to the vaccine. Further randomized controlled trials should be conducted to recommend a specific treatment regimen in immunosuppressed patients with an underlying disease or with conditions for which they are taking medication.

\section*{Conclusion}

Relapsing COVID-19 infections are rare, but could be more likely in immunosuppressed patients and more severe than the initial infection. Our case series, in which both patients had immunosuppressive diseases and medications, indicates that further studies should be performed to determine the pathogenesis behind this disease course. Moreover, these patients should receive the vaccine before their scheduled rituximab infusion. In this way, they can mount an appropriate antibody response to the vaccine as well as receive treatment to keep their immunosuppressive disease in control.

\section*{REFERENCES}


Effect of Immunosuppressive Diseases and Rituximab Infusions on Allowing COVID-19 Infection to Relapse


Rare Case of Mixed Phenotype Acute Leukemia Presenting as a Myeloid Sarcoma Without Leukemic Involvement

Jeffrey Means, DO; David Feldman, MD; Allison Shaw, MD; Khoan Vu, MD

Perm J 2022;26:21.070 • E-pub: 04/05/2022 • https:/ /doi.org/10.7812/TPP/21.070

Abstract

INTRODUCTION: Mixed phenotype acute leukemia (MPAL) is a rare type of acute leukemia with immunophenotypic features of both myeloid-derived and lymphoid-derived lineages.

CASE PRESENTATION: We present an atypical case of a 32-year-old woman presenting with an anterior mediastinal mass and pericardial/pleural involvement that was initially diagnosed as primary mediastinal diffuse large B-cell lymphoma. However, flow cytometry on pleural fluid confirmed the diagnosis of MPAL of B-cell/myeloid lineage without peripheral blood/bone marrow involvement. The patient was treated with an acute lymphoblastic leukemia-type regimen and proceeded with myeloablative allogeneic hematopoietic cell transplantation in first complete remission.

CONCLUSION: MPAL can rarely present with isolated extramedullary disease without leukemic involvement and can often be misdiagnosed as a non-Hodgkin lymphoma. Careful integration of all the clinical data, particularly flow cytometry results, can clarify the diagnosis and change the treatment plan.

Introduction

Accurate diagnosis of leukemia is imperative given that treatment and prognosis rely heavily on the lineage of the proliferative blast. Evaluation typically incorporates blast morphology, flow cytometry, karyotyping, and other genetic analyses to identify the leukemic cells as primarily myeloid or B- or T-lymphoblasts. Assignment of lineage typically relies on flow cytometry and immunohistochemical stains. There exists a rare situation in which the leukemic blasts are of both myeloid- and lymphoid-derived lineages, a condition known as mixed phenotype acute leukemia (MPAL). MPAL may be bilineal, in which there are 2 or more discrete components with lineage-specific markers, or biphenotypic, in which there is 1 population having coexpression of lineage-specific markers. MPAL comprises roughly 1%-4% of all leukemias. Exact data regarding the true incidence and survival of MPAL have been limited owing to the relatively sparse number of cases, but the prognosis is typically poorer compared with other leukemias. Like most leukemias, diagnosis relies on bone marrow biopsy, which will often demonstrate an increased blast population of multiple lineages. However, in rare circumstances, leukemias
Rare Case of Mixed Phenotype Acute Leukemia Presenting as a Myeloid Sarcoma Without Leukemic Involvement

Present as solid extramedullary tumors known as myeloid sarcomas (MS). One study suggested that these tumors occur in about 0.8% of patients with acute myeloid leukemia (AML)\(^4\). Therefore, MPAL without peripheral blood/bone marrow involvement is extremely rare with few documented cases in the literature\(^5,6\). We present a rare case of MPAL of myeloid and B-cell lineage presenting with an anterior mediastinal mass and pericardial/pleural involvement without leukemic involvement.

**Case Presentation**

A 32-year-old woman with no substantial past medical history presented with 1 month of progressive dyspnea, cough, and intermittent fevers. Computed tomography (CT) of the chest demonstrated a 9.6-cm anterior mediastinal mass, moderate right pleural effusion, and large pericardial effusion with mass effect.

She was admitted for expedited workup and underwent pericardiocentesis with drainage of 650 mL of bloody fluid. She then underwent a CT-guided needle biopsy of the mediastinal mass, which showed extensive crush artifact and focal necrosis. In intact areas, there was an atypical lymphoid infiltrate composed of large cells that were positive for CD19, BCL-2, and c-MYC and negative for CD5, CD10, CD20, CD30, CD34, BCL-6, and MUM-1. A TdT stain was equivocal, and the Ki-67 proliferation index was 60%-70%. Fluorescence in situ hybridization tests were negative for MYC, BCL-2, and BCL-6 gene rearrangements. Overall, the findings were felt to be most consistent with CD20-negative diffuse large B-cell lymphoma (DLBCL), non-germinal center B-cell-like subtype.

Positron emission tomography (PET)/CT scan demonstrated a large intensely hypermetabolic 9.8-cm anterior mediastinal mass with pericardial involvement; extensive hypermetabolic bilateral pleural masses; and numerous mediastinal, cervical, axillary, and upper retroperitoneal lymph nodes (Figure 1).

She was discharged but was readmitted soon after with worsening dyspnea. A repeat CT chest showed an interval increase in size of the mediastinal mass now measuring 10.3 cm, with pericardial invasion. There was also an interval increase in her left pleural effusion. Her labs showed a lactate dehydrogenase level of 273 U/L, white blood cell count of 11.7 \(\times 10^3\) /\(\mu\)L, hemoglobin level of 12 g/dL, and platelet count of 370 \(\times 10^3\) /\(\mu\)L. She underwent a left-sided thoracentesis and was immediately started on DA-R-EPOCH (dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) for presumed primary mediastinal DLBCL.

However, flow cytometry from the pleural fluid came back showing a population of cells that were...
positive for CD34, CD19 (dim), CD33, CD15 (partial), CD11b, CD11c, and TdT (dim partial) (Figure 2). The population also expressed partial cytoplasmic CD22 and partial cytoplasmic CD79a. CD64 expression was equivocal but favored to be positive. On the basis of these flow results, her diagnosis was felt to be more consistent with MPAL of B-cell and myeloid lineage.

DA-R-EPOCH was discontinued on day 2, and she underwent bone marrow biopsy and lumbar puncture for staging. Both bone marrow and cerebrospinal fluid were negative for leukemic involvement based on morphology and flow cytometry.

Molecular analysis of her pleural fluid was negative for BCR-ABL rearrangement, FLT3 gene mutation, MLL gene rearrangement, and Philadelphia chromosome-like genetic alterations. She was treated with an acute lymphoblastic leukemia (ALL) pediatric regimen (CALGB 10403 protocol) and achieved complete remission on post-induction PET scan (Figure 1B). She then proceeded to consolidation therapy with hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) for cycles 2 and 3. She then proceeded with a myeloablative matched related donor allogeneic hematopoietic cell transplantation and remains in remission at > 6 months from transplant. The timeline of her diagnostic and therapeutic events is summarized in Table 1.

Discussion

The diagnosis of MPAL was first reported in the 1980s, when leukemias stemming from multiple

![Figure 2](image-url)
lineages were found to proliferate in the bone marrow. Although this disease is much rarer than typical leukemias, the true incidence may be underestimated because the use of restrictive immunophenotypic panels or combinations can lower the sensitivity of detection. Extramedullary disease, also known as MS, without concomitant peripheral blood/bone marrow involvement is a rare phenomenon in acute leukemia. Extramedullary MPAL without leukemic involvement suggests an ultrarare disease presentation, with a limited number of cases reported.

Our review of the literature revealed only 18 documented cases of MPAL without bone marrow infiltration. One report consisted of 11 pediatric cases: 7 B/myeloid, 2 T/myeloid, and 2 B/T-cell. All 11 cases achieved complete remission after standard ALL therapy. Only 1 case of adult B/myeloid MPAL was documented, who remained in remission 19 months after transplant. A common theme among these cases is the difficulty in obtaining an accurate diagnosis, which played a prominent role in our case as well. Pure medullary sarcoma (ie, without leukemic involvement) is often misdiagnosed as other lymphomas, Ewing’s sarcoma, or carcinoma up to 47% of the time. Indeed, after the initial biopsy, our patient was believed to have primary mediastinal DLBCL and treated with DA-R-EPOCH. This was likely confounded by a suboptimal biopsy sample of the mediastinal mass and lack of peripheral blood/bone marrow involvement. Remarkably, flow cytometry of the pleural effusion was able to elucidate and confirm the diagnosis of MPAL and, ultimately, changed her treatment plan.

Based on the 2016 World Health Organization classification, MPAL can be subdivided into the following categories: 1) acute undifferentiated leukemia, 2) MPAL with (9;22)(q34.1;q11.2);BCR-ABL1, 3) MPAL with t(v;11q23.3); KMT2A rearranged, 4) B/myeloid not otherwise specified, and 5) T/myeloid not otherwise specified. Although prognosis has been difficult to track owing to the relative paucity of cases, the presence of BCR-ABL1 (Philadelphia chromosome) gene rearrangement, the presence of MLL gene (KMT2A) rearrangement, and the T/myeloid phenotype have been associated with worse outcomes. Retrospective studies suggest that patients with MPAL do better with an ALL regimen rather than an AML regimen. One study of 100 patients with MPAL showed that an ALL regimen was associated with a higher response rate (85% vs 41%) and higher median overall survival (139 vs 11 months) compared with an AML regimen. As with Ph-positive ALL, addition of a tyrosine kinase inhibitor is recommended for MPAL with the Philadelphia chromosome. Regarding the role of allogeneic hematopoietic cell transplant (allo-HCT) in MPAL, it is generally recommended in first remission for adult MPAL patients based on cohort studies showing favorable outcomes with chemotherapy followed by allo-HCT compared with chemotherapy alone. It is possible that there are select patients (eg, early minimal residual disease negativity, patients < 40 years of age treated with a pediatric ALL regimen) who would do well with chemotherapy alone and be spared the toxicities of allo-HCT. In our patient’s case, she was treated with an ALL regimen followed by allo-HCT and remains in remission.

**Conclusion**

Here, we presented a rare case of MPAL presenting as a pure MS without leukemic involvement that was initially misdiagnosed as primary mediastinal DLBCL. What is also unique about this case is how flow cytometry on pleural fluid was able to confirm the diagnosis of MPAL. This shows that flow cytometry data can be crucial in making the diagnosis when the tissue sample is limited or suboptimal.

**REFERENCES**

Efficacy and Cost of Maxillary Patient-Specific Implants in Orthognathic Surgery: A Review of Three Patient Cases

Ho-Hyun (Brian) Sun, DMD, MS; Heshaam Fallah, MD, DDS

Perm J 2022;26:21.054 • E-pub: 04/05/2022 • https:/ /doi.org/10.7812/TPP/21.054

Abstract

INTRODUCTION: Patient-specific implants (PSIs) are accurate, efficient alternatives to traditional plate fixation. They are well-suited for use in procedures that require the utmost accuracy, stability, and efficiency. Although PSIs have demonstrated such qualities in craniomaxillofacial reconstruction, they have so far found limited utilization elsewhere.

CASE PRESENTATION: We explored the departmental protocol for Lefort 1 PSI orthognathic surgery at a high-volume, tertiary referral center. Three cases were selected that matched predetermined criteria, which included treatment by the same surgical team, concurrent Lefort 1 osteotomy and bilateral sagittal split osteotomy, Angle’s type 3 malocclusion, lack of interdental osteotomies, and American Society of Anesthesiologists classification 2 or less without metabolic or osseous diseases. The operative outcomes from these patients were then compared to similar cases also meeting the same criteria and conducted within the same time period.

CONCLUSION: The use of PSI in Lefort 1 osteotomy is associated with anatomically sound designs that could contribute to postoperative stability of the jaws. They also have not shown increased rates of complications such as infection, dehiscence, or relapse at 6 weeks postoperatively but may in fact decrease the operative duration. These findings are consistent with the results gleaned from literature on the use of PSI in craniomaxillofacial reconstruction.

Introduction

Orthognathic surgery is a well-accepted and safe modality for the treatment of a variety of maxillomandibular discrepancies. In the past, planning for orthognathic surgery required complex and time-consuming surgical simulations on handmade stone models; these simulations were also prone to error and operator fatigue.1 Today, much of the planning is conducted virtually, which renders the treatment process more affordable, accurate, and simple.2,3

Similarly, patient-specific implants (PSIs) have been associated with accurate, efficient reconstruction of the skull in the aftermath of craniomaxillofacial trauma or pathologic ablation. These implants would often come in the form of titanium plates to allow adequate function, contour, and biocompatibility. Studies have shown that 3-dimensionally designed PSIs demonstrate accuracy equal to, if not greater...
Efficacy and Cost of Maxillary Patient-Specific Implants in Orthognathic Surgery

than, hand-bent titanium plates, with the added benefits of reduced surgery time and possibly shortened recovery period.\(^4,5\)

Recent studies have indicated that PSIs may also be a viable option in orthognathic surgery, especially in surgeries of the maxilla. PSIs were associated with improvements in fidelity of hardware shapes to preexisting patient anatomy during Le Fort 1 osteotomy.\(^6,7\) When used in nonsyndromic patients, PSI fixation also demonstrated similar stability and complication rates, in terms of infection and dehiscence, to traditional mini-plate fixation.\(^9,10\)

Here, we describe a departmental PSI protocol at a high-volume, regional orthognathic referral center. We present a streamlined treatment approach and outline postoperative comparisons of the PSI modality to traditional orthognathic surgery. For a timeline of the key events, see Table 1.

Case Narrative

Three PSI patient cases from 2020 were included in this study. Inclusion criteria included 1) age range of 18 to 35 years; 2) treatment by the same surgical team (the authors); 3) concurrent LeFort 1 osteotomy and bilateral sagittal split osteotomy; 4) Angle’s type 3 malocclusion; 5) lack of interdental osteotomies; 6) American Society of Anesthesiologists classification 2 or less without metabolic or osseous diseases; and 7) male gender. None of the patients presented with obesity or obstructive sleep apnea.

Virtual surgical planning (VSP) and PSI production were done according to cone beam computed tomography (CBCT) and intraoral scan of each maxillomandibular complex. VSP determined the osteotomy sites, degree of maxillary advancements and mandibular setbacks, as well as the number and location of maxillary plate screws according to cortical thickness. Mandibular setbacks were planned at 5 mm or less to minimize the chance of sleep-disordered breathing.\(^11,12\) Two side-specific titanium Facial ID® PSIs were designed (Stryker Corp, Kalamzoo, MI) for the fixation of the maxilla in a thickness of 1.0 mm. Each PSI consisted of 3 relatively straight titanium struts in a roughly U-shaped formation, which avoids the thin areas of the anterior maxillary sinus walls, with 3 or

---

**Table 1:** Timeline

ADA = American Society of Anesthesiologists; BSSO = bilateral sagittal split osteotomy.
more screw fixation points each on the medial vertical strut along the nasomaxillary buttress, the horizontal strut along the alveolar buttress, and the lateral vertical strut along the zygomaticomaxillary buttress (Figure 1). This design was intended to distribute the forces of occlusion and muscular traction along the main weight-bearing portions of the skull. An anatomical, bone-borne titanium surgical guide (3D Systems Inc, Rock Hill, SC) was also produced that spanned the anterior walls of both maxillary sinuses and temporarily secured with 2 screws. It incorporated two 1.5-mm-wide horizontal osteotomy slots, each spanning from the piriform rim approximately 1 cm superior to the nasal floor to the lateral maxilla approximately 1 cm inferior to the zygomatic arch. Bone hooks were devised around the edges of the guide to engage the inferior piriform rim and the anterior zygomatic arch (Figure 2). This guide serves as a cutting and marking guide to predict the placement of the predetermined screw osteotomies.

The patients underwent surgery with PSI in the maxilla only. After application of the titanium surgical guide, the Lefort 1 osteotomy was conducted in standard fashion, and all predicted bony interferences were reduced. The mobilized and reduced Lefort 1 segment was fixated to the rest of the midface using a PSI on each side. Maxillary fixation was performed based on predrilled screw osteotomies without maxillomandibular fixation (MMF) or seating of the temporomandibular joint complex. The bilateral sagittal split osteotomies were completed and the mandibular segment secured via MMF for application of the mandibular plates. Upon completion, the MMF was released and the patient placed in guiding elastics.

Patients were admitted for overnight surveillance and then followed biweekly for a minimum of 6 weeks with CBCT imaging conducted at 2 weeks postoperation. Patients were instructed to undertake a non-chewing diet for 6 weeks. Any complications, including dehiscence, infection, and relapse, were noted.
Results

The preoperative overjet for the 3 patients (A, B, and C) were −10 mm, −2 mm, and −9 mm, respectively, with an average of −7 mm. The operating times from the first incision to the conclusion of the final suture were 172, 152, and 125 minutes, also respectively, with a mean of 149 minutes (Table 2). All demonstrated no complications at 6 weeks, and postoperative imaging demonstrated appropriate placement of the hardware and bony segments. No relapses were noted at 6 weeks, and each patient remained satisfied with their postoperative presentation.

The records of the 3 individuals who underwent treatment with occlusal splints and hand-bent plates were also accessed. These individuals met the same inclusion criteria, as well as additional stipulations, so that, when compared to their paired PSI patients, their surgeries were conducted within approximately 2 weeks. The mean operative time for the traditional surgery group (TG) was longer, at more than 177 minutes (p = 0.0115). The average age of the TG group was 21 years, compared to 24 years for the PSI surgery group (PG). The average overjet of the TG group was comparable to the PG group at −9 mm (p = 0.69). For all patients, the open bite and maxillary/mandibular midline discrepancies were minimal at 2 mm or less with no discernable maxillary cant. All were also fully dentate with at least 6 teeth in each quadrant. A general consent was received from each patient to utilize anonymized clinical data for academic and educational purposes.
Discussion

PSIs are well-established treatment modalities for the reconstruction of the facial skeleton, and their use in orthognathic surgery has begun to gain acceptance. Although data on orthognathic patients are somewhat limited by the recent implementation of PSIs, several studies have attested to the reproducibility, ease, and low complication rates of PSIs in nonsyndromic craniofacial patients.\textsuperscript{6–9,13,14} PSIs allow placement of screws along predetermined stable bony landmarks of the midface, reducing operator error and dependence on ideal seating of the bilateral condyles.\textsuperscript{8} Our surgical guide design sought to further increase this accuracy by incorporating hooks for the piriform aperture and zygomatic buttress for a more secure fit and verification. PSI postsurgical stability is enhanced by the cross-stabilization of a uni-design that spans the nasomaxillary and zygomaticomaxillary pillars.

A search of the MEDLINE English literature for keywords “custom” OR “customized” OR “specific” AND “implants” AND “orthognathic” did not yield data regarding the time efficacy of PSIs as of late 2020. The PSI modality may confer benefits to orthognathic surgery and, in our experience, does not lead to an increased rate of complications, including relapse. Trained VSP engineers can increase integrity of the osseous movements by incorporating thicker plates akin to those of reconstruction plates. These engineers can also help avoid the thinner areas of the maxillary sinus wall, which could compromise the engagement and stability of the screws. Surgeons can avoid plate fatigue, which is associated with traditional plate bending. In addition, PSIs could reduce reliance on single-use acrylic occlusal splints, which may deform, are difficult to decontaminate, and do not degrade well in the environment.

Unsurprisingly, our PSI protocol may also confer operative time benefits over traditional plates. Comparison of the TG and PG via paired \emph{t}-testing showed a 28-minute benefit (\(p = 0.0115\)), which translates to approximately $2500 savings in operating room personnel costs alone (in 2020 US dollars).\textsuperscript{15,16} A comparison of all our TG and PG orthognathic patients, without accounting for similarities in age and gender, also showed an 11-minute benefit to PSI surgery, even though PSIs were more frequently utilized in complex segmental maxillary osteotomies. These benefits are likely much greater when considering the additional, non-personnel costs associated with operating room usage. In fact, a 2018 meta-analysis showed that complication rates increased by approximately 14\% for every 30 additional minutes under anesthesia.\textsuperscript{17}

Conclusion

The added CBCT-based planning and customization of maxillary PSIs may be conducive to successes in orthognathic surgery. Comparisons in well-paired large cohorts may further demonstrate the value of this new technology and the proposed alternative way of executing this type of surgery.

Table 2: Patient demographics. Capitalized letters denote patients who underwent surgery with PSI, and lowercase letters denote patients who underwent traditional surgery.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Occlusion Class</th>
<th>Op Time</th>
<th>Overjet</th>
<th>Overbite</th>
<th>Max Midline</th>
<th>Mand Midline</th>
<th>Incisal Show</th>
<th>Max Cant</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>21</td>
<td>3</td>
<td>172</td>
<td>−10 mm</td>
<td>−1 mm</td>
<td>Coincident</td>
<td>Coincident</td>
<td>3 mm</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>20</td>
<td>3</td>
<td>152</td>
<td>−2 mm</td>
<td>0 mm</td>
<td>Coincident</td>
<td>Coincident</td>
<td>1 mm</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>31</td>
<td>3</td>
<td>125</td>
<td>−9 mm</td>
<td>−1 mm</td>
<td>Coincident</td>
<td>1 mm left</td>
<td>3 mm</td>
<td>None</td>
</tr>
<tr>
<td>a</td>
<td>20</td>
<td>3</td>
<td>197</td>
<td>−5 mm</td>
<td>1 mm</td>
<td>Coincident</td>
<td>Coincident</td>
<td>0 mm</td>
<td>None</td>
</tr>
<tr>
<td>b</td>
<td>18</td>
<td>3</td>
<td>187</td>
<td>−12 mm</td>
<td>−2 mm</td>
<td>Coincident</td>
<td>1 mm right</td>
<td>2 mm</td>
<td>None</td>
</tr>
<tr>
<td>c</td>
<td>25</td>
<td>3</td>
<td>148</td>
<td>−10 mm</td>
<td>2 mm</td>
<td>Coincident</td>
<td>2 mm right</td>
<td>3 mm</td>
<td>None</td>
</tr>
</tbody>
</table>

References

Efficacy and Cost of Maxillary Patient-Specific Implants in Orthognathic Surgery


Gangrene of the Foot After Coronary Artery Bypass Graft Surgery

Julia L Boland, MD1,2; Kristine Cueva, MD2; Jessica Pawly, MD2; Darius Shahbazi2,3; Maximillian Lee, MD1; Shahin Shahbazi, MD2
Perm J 2022;26:21.176 • E-pub: 04/05/2022 • https://doi.org/10.7812/TPP/21.176

Abstract

Coronary artery bypass grafting (CABG) is the most common surgery performed by cardiothoracic surgeons worldwide. Risks of CABG include neurological outcomes, deep vein thrombosis, renal or gastrointestinal injury, and death. Perioperatively, some patients may need intra-aortic balloon pump (IABP) use to help assist with cardiac function. In this case, a 75-year-old man presented with multivessel myocardial infarction requiring IABP for cardiac assistance prior to undergoing CABG. Eighteen days after his CABG, his toes turned black at home. A CT angiogram showed aortic atherosclerosis, right tibioperoneal trunk stenosis, mild atherosclerotic right proximal anterior tibial artery stenosis, and multifocal occlusive lesions in the right and left infrapopliteal vessels. Vascular surgery performed balloonangioplasty of the right anterior tibial artery and podiatry performed a transmetatarsal amputation of the dry gangrene. The aim of this case report is to present a rare complication of CABG with peri-operative IABP use and to highlight the need for prompt diagnosis and treatment of dry gangrene.

Introduction

Coronary artery disease is the most common form of heart disease and the leading cause of death worldwide.1 In a myocardial infarction, atherosclerosis inside coronary arteries stenose the vessels, leading to ischemia and rupture of the thrombosis.2 Coronary artery bypass grafting (CABG) is a revascularization procedure that has been shown to lead to reduced mortality, reduced repeat myocardial infarctions compared to percutaneous coronary intervention.3 However, there are serious risks associated with CABG, including adverse neurologic outcomes such as stroke, requirement of mechanical circulation or ventilation support, deep vein thrombosis, renal failure, gastrointestinal injury, infection, and death.4 5 In the perioperative period, intra-aortic balloon pump (IABP) use is sometimes necessary to assist with cardiac output during acute myocardial infarction. Limb ischemia is a possible complication of IABP use with a rate of occurrence ranging from 1% to 31%.6

Case Report

A 75-year-old man with a past medical history of hypertension, type 2 diabetes mellitus, end-stage renal disease on
peritoneal dialysis, paroxysmal atrial fibrillation on warfarin, and mild aortic stenosis presented to the emergency department with left sided chest pain that radiated to his left arm after walking approximately one mile. A review of systems was positive for shortness of breath, diaphoresis, and fatigue. He denied palpitations, nausea, vomiting, or abdominal discomfort. His recent history was significant for 3 days of mild chest pressure and left arm pain that was worse at night. His physical examination showed trace pedal edema but was otherwise unremarkable. His electrocardiogram showed normal sinus rhythm with a rate of 94 and ST depressions in I, avL, V5, and V6, which were new compared to his prior electrocardiogram. His echocardiogram demonstrated moderately decreased left ventricular systolic function with an ejection fraction of 40%, along with apical akinesis with anteroseptal marked hypokinesis.

He underwent cardiac catheterization, which showed critical left main stenosis, heavy calcification of the left main and proximal left-sided vessels, severe ostial left anterior descending artery stenosis, occlusion of the mid-left anterior descending, severe ostial, proximal, and mid-left circumflex artery disease, and moderate right coronary artery disease. Upon arrival at the catheter laboratory, the patient was in atrial fibrillation with rapid ventricular response. He converted to normal sinus rhythm after intravenous amiodarone.

An IABP was placed via the right common femoral artery for coronary perfusion, and he was referred to cardiothoracic surgery for CABG at a different facility, which was done 3 days after initial presentation. The left saphenous vein was harvested for his CABG. While an inpatient for his CABG, he was noted to have an ulcer to the right fourth toe without signs of cellulitis. The inpatient wound department care removed the right third toenail because it was loose and then provided local wound care. The patient applied antibiotics to the right toes postoperatively.

Eighteen days post CABG, the patient woke with new-onset painless color changes of his right toes and presented to the emergency department. Physical examination demonstrated dry gangrene of the right third and fourth toes (Figure 1) and erythema extending into the dorsum of the foot. The onset of these symptoms most likely occurred
at home, given that dry gangrene usually takes several days to present. His femoral, popliteal, and radial pulses were palpated bilaterally and dorsalis pedis and posterior tibial pulses were weakly palpated bilaterally. A Doppler examination of his right foot demonstrated weak biphasic waveform in the dorsalis pedis and posterior tibial artery pulses. His right femoral region showed a healed catheter site and no mass, bruit, or tenderness. An x-ray of the foot was normal. He was started on broad spectrum antibiotics in the emergency room. An echocardiogram was done to rule out left ventricular thrombus. The patient had a CT angiogram (CTA) of the abdominal aorta that showed aortic atherosclerosis, severe ostial soft plaque causing right tibioperoneal trunk stenosis, and mild atherosclerotic right proximal anterior tibial artery stenoses. He had multifocal occlusive lesions in the right and left infrapopliteal vessels. He had a nonocclusive lower extremity arterial ankle-brachial index (Table 1).

The patient was discharged home with home health care and instructed to follow-up with podiatry and vascular surgery as an outpatient. At follow-up, the severity of his toes appeared to be progressively more gangrenous (Figure 2). The vascular surgery department performed balloon angioplasty of the right anterior tibial artery with 2.5–3.0 mm x 210 mm balloon. The podiatry department performed transmetatarsal amputation for definitive treatment of right foot digital gangrene. Findings included

<table>
<thead>
<tr>
<th>Blood pressure (mmHg)</th>
<th>ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Brachial</td>
<td>155</td>
</tr>
<tr>
<td>Ankle PTA</td>
<td>67</td>
</tr>
<tr>
<td>Ankle DPA</td>
<td>150</td>
</tr>
<tr>
<td>Great toe</td>
<td>19</td>
</tr>
<tr>
<td>Left Brachial</td>
<td>160</td>
</tr>
<tr>
<td>Ankle PTA</td>
<td>85</td>
</tr>
<tr>
<td>Ankle DPA</td>
<td>&gt; 254</td>
</tr>
<tr>
<td>Great toe</td>
<td>77</td>
</tr>
</tbody>
</table>

Table 1: Ankle-brachial index

The right toe pressure of 19 mmHg does not predict for wound healing. The right leg demonstrates no substantial arterial occlusive disease with an ABI of 0.94. The left leg demonstrates moderate arterial occlusive disease with an ABI of 0.53.

ABI = ankle-brachial index; DPA = dorsalis pedis artery; PTA = posterior tibial artery.

Figure 2: Presentation of gangrenous toes 8 days after discharge from hospital.
Gangrene of the Foot After Coronary Artery Bypass Graft Surgery

soft-tissue abscess of the dorsal and plantar forefoot at the base of digits, no soft-tissue necrosis at the level of amputation, and bone grossly viable at level of amputation. Intraoperative wound cultures demonstrated *Escherichia coli*, and the patient was treated with piperacillin-tazobactam and daptomycin. A summary of the case is shown in Table 2.

**Discussion**

In this case, the differential diagnosis for this patient's dry gangrene of the toes included aortic atheroma, cholesterol emboli, poor perfusion, deep venous thrombosis, heparin-induced thrombocytopenia (HIT), Buerger's disease, trauma, and infectious process. This patient's CTA showed aortic atherosclerosis, severe plaque in the distal popliteal artery, and multifocal occlusive lesions in the infrapopliteal vessels. These imaging findings suggest that cholesterol emboli or displaced aortic atheroma may have caused the ischemia. However, it is possible that poor perfusion from the IABP may have caused the dry gangrene. IABP use has been associated with serious vascular adverse effects including limb ischemia. Complications from IABP are more common in patients with a history of smoking, diabetes, hypertension, or peripheral vascular disease. Of note, this patient had a history of diabetes and hypertension. His echocardiogram lacked the clear presence of an LA or LV thrombus,

**Table 2: Presentation of case**

<table>
<thead>
<tr>
<th>Date</th>
<th>Relevant history</th>
<th>Summary of visit</th>
<th>Diagnostic tests</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to admission</td>
<td>Hypertension, type 2 diabetes mellitus, end-stage renal disease of peritoneal dialysis, paroxysmal atrial fibrillation on warfarin, mild aortic stenosis</td>
<td>- 3 day history of mild chest pressure and left arm pain, shortness of breath, diarrhesis, fatigue - Trace pedal edema</td>
<td>- EKG: normal sinus rhythm, ST-segment depressions in leads aVL, VS, V6, new from prior</td>
<td>- Admission as NSTEMI - Heparin drip</td>
</tr>
<tr>
<td>ED presentation</td>
<td>- Cardiac catheterization: - Development of afib with RVR - Hypotension post-cath - Transfer to ICU - Referral to tertiary center for CABG</td>
<td>- Cardiac catheterization: critical left main stenosis, heavy calcification of the left main and proximal left-sided vessels, severe ostial LAD stenosis, occlusion of mid LAD, severe ostial, proximal, and mid-left circumflex disease, moderate RCA disease</td>
<td>- Cardiac catheterization for CAD - IV amiodarone for afib with RVR - Placement of IABP for postop hypotension - Transfer to tertiary center for CABG</td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>- Transfer to outside hospital - CABG performed - Ulcer noted on right lower extremity fourth digit</td>
<td>- Low extremity doppler: weak biphasic waveform of DP and PT pulses</td>
<td>- CABG with left saphenous vein graft - Removal of right third digit toenail by wound care - Topical antibiotics to toes</td>
<td></td>
</tr>
<tr>
<td>3 days after initial presentation to ED</td>
<td>- Sudden onset painless color changes of right toes - Presentation to ED</td>
<td>- X-ray R lower extremity: normal - Echocardiogram: negative for LV or LA thrombus - CT angiogram: aortic atherosclerosis, severe ostial soft plaque causing right tibio peroneal trunk stenosis and mild atherosclerotic right proximal anterior tibial artery stenosis, multifocal occlusive lesions in right and left infrapopliteal vessels - ABI right lower extremity: 0.94</td>
<td>- IV antibiotics - Discharged home with home health with outpatient podiatry and</td>
<td></td>
</tr>
<tr>
<td>18 days post-CABG</td>
<td>- Dry gangrene of right third and fourth toes, erythema extending to the dorsum of the foot - Pulses present bilaterally</td>
<td>- Intraoperative wound cultures positive for <em>E. coli</em></td>
<td>- vascular surgery follow-up</td>
<td></td>
</tr>
<tr>
<td>Outpatient follow-up</td>
<td>- Toes appeared more gangrenous - Soft tissue abscess of the dorsal and plantar forefoot at base of digits</td>
<td>- Balloon angioplasty of right anterior tibial artery - Transmetatarsal amputation - Initiation of piperacillin-tazobactam and daptomycin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ABI = ankle-brachial index; CAD = coronary artery disease; CABG = coronary artery bypass grafting; DP = dorsalis pedis; ED = emergency department; EF = ejection fraction; EKG = electrocardiogram; IABP = intra-aortic balloon pump; ICU = Intensive Care Unit; LA = left anterior; LAD = left anterior descending; LV = left ventricular; NSTEMI = non-ST-elevation myocardial infarction; PT = posterior tibial; RCA = right coronary artery; RVR = rapid ventricular response.
making an intracardiac emboli unlikely but still possible. Deep venous thrombosis was unlikely as a cause of this patient’s gangrene because he had positive occlusive findings on CTA. Heparin was used in both the cardiac catheterization and CABG surgery for this patient. However, there was no thrombocytopenia and pretest probability of HIT based on the 4 Ts score was low in this case.† Therefore, HIT is also unlikely to have caused this patient’s dry gangrene.

Acute ischemia is a known but rare complication following IABP and CABG. The objective of this case was to educate about the chance of gangrene requiring amputation after IABP use and CABG surgery. Prompt treatment of any skin color changes after IABP and CABG is warranted, and we advise warning patients of this possible risk to prevent them from delaying seeking care in the postoperative period.

Conclusion

We experienced a case of dry gangrene approximately 2 weeks following CABG with IABP use. Although generally considered safe, the risks of ischemia following CABG and IABP exist. Clinicians are encouraged to look for signs of ischemia in the postoperative patient following CABG and IABP.

REFERENCES
2. Ambrose JA, Singh M. Pathophysiology of coronary artery disease leading to acute coronary syndromes. F1000Prime Rep. 2015;7:08. DOI: https://doi.org/10.12703/P7-08
COMMENTARY

Personal Protective Equipment for COVID-19 and Beyond: Occupational and Environmental Exposure Considerations in Primary Care

Onyemaechi Nwanaji-Enwerem, MS, MPP; Jamaji C Nwanaji-Enwerem, MD, PhD, MPP; Brian Antono, MD, MPH

Perm J 2022;26:21.129 • E-pub: 04/05/2022 • https://doi.org/10.7812/TPP/21.129

Abstract

In this reflection piece, the authors describe a hypertension follow-up visit and draw attention to an often overlooked aspect of a patient’s health: their occupational and environmental history. For years, physicians and clinicians have understood and treated disease secondary to conspicuously harmful environmental exposures; the impacts of everyday exposures on patient health are less understood and appreciated. This article specifically addresses the critical question of how primary care physicians and clinicians can think about, and address, occupational and environmental health hazards in their assessment and treatment of chronic disease in patients. We present 3 strategies that primary care physicians and clinicians can adopt to better account for environmental and occupational risks: good history taking, advising or advocacy, and education.

STEVE, HIS ENVIRONMENT, AND PRIMARY CARE

Steve (name changed to preserve anonymity) is a Black man in his early thirties with no relevant family medical history. He came to our family medicine clinic for a hypertension follow-up visit. He had a history of chronic back pain and was diagnosed with hypertension earlier in the year. At that time, he was started on a single agent and was advised to make lifestyle modifications of which he obliged. He reduced his cigarette consumption from 1 pack per day to an occasional cigarette and began incorporating healthier foods into his diet. During his visit on this particular day, he brought his blood pressure log, which, unfortunately, showed elevated pressures nearly identical to those from his prior visits.

Before diving too deeply into his hypertension, we asked him, much like we do with all of our patients, how he was doing and if he had any other concerns that he wanted to address. After chatting briefly about the most recent sports news, we pivoted to a conversation about his social life. We learned that he had been working at an industrial site as a forklift driver for a couple of years, and his back pain was secondary to a work accident that he experienced not too long ago. During our conversation, we noticed that Steve sounded congested and occasionally coughed. His chart revealed that he was dealing with a long-term cough that, despite multiple evaluations, was still of unknown etiology. Upon further discussion, Steve described that it was not uncommon for boxes filled with industrial agents to explode in his

Corresponding Author
Onyemaechi Nwanaji-Enwerem, MS, MPP
on18@duke.edu

Author Affiliations
1 Duke University School of Medicine, Durham, NC, USA
2 Gangarosa Department of Environmental Health, Emory Rollins School of Public Health, and Department of Emergency Medicine, Emory University School of Medicine, Atlanta, GA, USA
3 Division of Environmental Health Sciences, School of Public Health and Center for Computational Biology, University of California, Berkeley, Berkeley, CA, USA
4 Department of Family Medicine and Community Health, Duke University School of Medicine, Durham, NC, USA

Author Contributions:
Onyemaechi Nwanaji-Enwerem, MS, MPP, participated in the conception of the manuscript idea, drafting, review, and submission of the final manuscript. Jamaji C. Nwanaji-Enwerem, MD, PhD, MPP, participated in the conception of the manuscript idea, drafting, review, and submission of the final manuscript. Brian Antono, MD, MPH, participated in the drafting, review, and submission of the final manuscript.

Disclosures
Conflicts of Interest: None declared
Funding: None declared

Copyright Information
© 2022 The Permanente Federation. All rights reserved.
face during transportation and lifting. He mentioned that 1 week prior to this visit, 1 of the explosions caused discoloration in his fingers that persisted for nearly 12 hours. Steve also shared that he rarely wore goggles, gloves, industrial grade masks, or other personal protective equipment (PPE) at work. Masks were just now being worn every day because of the COVID-19 pandemic.

At this point, we pivoted from a discussion that was based solely on his hypertension to a conversation that also touched on how his work exposures were likely contributing to his chronic cough and sinus symptoms. We discussed the possible harms related to unknown exposures and the potential risk reduction related to wearing PPE, including gloves, goggles, and an occupation-appropriate mask. Although there was an obvious connection between Steve’s back pain and his occupation, a less obvious, but equally important, connection was the potential relationship between Steve’s hypertension and his occupational exposures.

To date, cholesterol, diabetes, hypertension, obesity, and smoking are often cited as modifiable cardiovascular risk factors. Often omitted from this list are environmental risk factors, which are increasingly being shown to play a role in the manifestation of cardiovascular disease and a number of other chronic ailments. Research from Yang et al has shown a positive association between ambient air pollution and hypertension. Bellavia et al showed mechanistic evidence that inhaling several air pollutants induces changes in the autonomic nervous system, resulting in endothelial dysfunction and systemic inflammation related to elevated systolic blood pressure. The question then becomes: how might primary care physicians and clinicians think about, and address, occupational and environmental health hazards in their assessment and treatment of chronic disease in patients?

Although occupational and environmental medicine is a board-certified specialty of its own, patients may present to their primary care physicians and clinicians with complaints relevant to environmental and occupational exposures. For years, we have known that occupational exposure to asbestos increases occupational exposures. For years, we have known that occupational exposure to asbestos increases occupational exposures.

The relation between the percentage of those injuries and illnesses and toxin exposure in the workplace is unknown. In addition to carrying substantial physical harms, the compensation of hand laborers is low compared to other workers. In 2019, the recorded median income for hand laborers and material movers was $14.66 per hour (or $30,490 yearly), which falls drastically below the median hourly earnings of all private industry employees ($30.33). Hence, on top of workplace hazards, by virtue of their income, workers in this sector are more likely to experience economic challenges that further compound health outcomes.

Children, the elderly, and those with existing comorbidities also represent populations particularly vulnerable to the effects of environmental exposures. Consequently, picking up on these connections can be meaningful for a substantial segment of the population. Fortunately, environmental exposure histories can often be done in a matter of minutes. The Agency for Toxic Substances and Disease Registry (ATSDR) offers free online course materials for physicians and clinicians who may need assistance implementing environmental exposure history taking in their practice.

ADVISING AND ADVOCACY FOR HEALTH EQUITY

Primary care physicians and clinicians are ideally positioned to intervene and assist patients in protecting themselves from environmental exposures because we establish longitudinal...
relationships with patients and are tasked with gaining a comprehensive understanding of a patient’s health and their community. If it becomes apparent that patients are regularly experiencing harmful occupational or environmental exposures, physicians and clinicians have an obligation to recommend strategies that mitigate them and prevent associated illness. This may involve working with social work, contacting company occupational health departments, making referrals to occupational and environmental health specialists, and interacting with other stakeholders to get the patients the care that they require.

It is also important to acknowledge that some exposures cannot be individually modified because of logistics, socioeconomic, or political barriers. It may be unrealistic to ask a patient to move or change jobs, even if these recommendations are aimed at improving their health. This is why advocacy for broader health equity changes has become exceedingly necessary. For a Black man like Steve, there are also important racial health equity considerations. For far too long, clinical medicine has prescribed racial differences in health outcomes to biology rather than societal constructs such as racism. Not surprisingly, environmental racism is one among many manifestations of this injustice. Racial segregation has been associated with increased exposure to air pollutants, among other toxins, with minority communities often bearing disparate burdens of these harms. Thus, just as physicians and clinicians have done for a number of other social issues, including gun violence and mental health, they should also continue to use their platforms to advocate for policies that can create the systemic changes necessary to mitigate this egregious problem.

EDUCATION AND MEDICAL CURRICULAS

Although there may be some exceptions, medical students across the country are not being extensively trained to understand the impact of the environment on a patient’s health. In 2016, the Association of American Medical Colleges reported that approximately one-quarter of medical schools did not require any content related to environmental medicine. Furthermore, among medical schools that did require environmental medicine, students received just 7 hours of training. These trends appear to continue into residency education. In order to ensure that future generations of physicians and clinicians are well-equipped with the tools necessary to identify and holistically treat the “Steves” who walk into our clinics, environmental and occupational medicine must become larger areas of focus in general and graduate medical education. The American Academy of Family Physicians offers a publicly available occupational medicine curriculum guidelines for family medicine residents. The previously mentioned online ATSDR course materials can also be useful for programs and department leadership interested in educating their staff and medical trainees. The ATSDR also provides free adult and pediatric case studies for a number of environmental medicine topics, including lead and environmental triggers of asthma, as well as subjects that may be more obscure to general medicine audiences (eg, polychlorinated biphenyls, nitrates, and trichlorethylene).

LOOKING FORWARD

Like with many chronic health issues, managing Steve’s hypertension will be ongoing, requiring regular physical examinations and evaluations of his risk factors and treatment progress. It will be the same for other patients presenting with different symptoms or perfect health. Like people, environments are not static, and phenomena such as climate change only contribute to their volatility. Individuals who are privileged to be exposed to minimal workplace hazards and environmental toxins today can find their position changed tomorrow, and vice versa. For instance, the increased prevalence of wildfires and heat waves, such as those found on the western coast of the United States, have been found to negatively impact health outcomes, including the exacerbation of asthma, declines in respiratory function among those without asthma, and an increase in mortality rate.

The climate crisis means that fewer people will be exempt from exposure to environmental hazards. As arduous as this may sound, there is still a glimmer of hope. Although slow, the passage of domestic health policy has, to an extent, signaled some understanding of the importance of establishing cleaner environments. Take, for example, the paradigm shift that came with public education about the harms of secondhand smoke. A 1995 California law that banned smoking in workplaces (Labor Code 6404.5) initiated a wave of smokefree policy adoption across the country. After 2 decades, it is rare to encounter a public space where smokefree policies have not been adopted.

Through history taking, advising, advocacy, and education, family medicine physicians and other primary care physicians and clinician have a tremendous opportunity to support broader
structural/policy-based protections and make meaningful environmental and occupational health strides for their patients. Concerns of physician burnout and how asking more might make things harder are equally important. Addressing these concerns, although very complex, should not be a barrier to taking steps that we know are important and necessary for optimizing the health of our patients, especially those who are most vulnerable to environmental and occupational harms.

REFERENCES
The Permanente Journal wishes to acknowledge and thank the 247 below-named individuals who contributed at least 1 peer review during the 2021 calendar year. Their expertise across multiple disciplines strengthened TPJ’s caliber by improving the published works and imparting confidence to readers.

In alphabetical order by last name:

Sagiv Aaron
Maher A. Abbas
Al-Ola Abdallah
Natalie Aboubechara
Latha Achanta
Annette Adams
Ana F. Águeda
Mahendran A J
Syed Ajaz Ahmed
Aishah Albakr
Michael Alberts
Ibrahim Al-Busaidi
Mansour Alghamdi
Maria Alkureishi
Brenda Allison
Hilman Amin
Fabio Amorim
Sylvia Anggraeni
Stanley Ashley
Cesar Avila
Francisco R. Avila
David Baer
Dustin Ballard
Nicholas Baltar
Matthew Banegas
Subhendra Banerjee
Priya Bansal
Erica Barbazza
Carole Bartolotto
Joshua Barzilay
David Baer
Jane Benton
Paul Bernstein
Prarthna Bhardwaj
Kimberlee Blyden-Taylor
Shelley Bobb
Balazs Bodai
Thomas Bodenheimer
Julia Boland
Juan Botero-Meneses
Heidi Brown
Carol Cain
Thomas Campbell
Monique Canonicò
Nathan Carlson
Jo Carol Hiatt
Gabrielle Chartier

Stephanie Chen
Homer Chin
Ian Chong
David Clarke
Jeff Convissar
Alan Cortez
Ellen Cosgrove
Peter Cvietusa
Chris D’Adamo
John Damrose
Sean Deane
Richard Della Penna
Vimal Desai
Stacie Deslich
Sara Doster
Shanta Dube
Ashlen Duncan
Barbara Eichhorn
Charles Elder
Rachid Elkoustaf
Mihal Emberton
Vincent Felitti
Stephanie Fitzpatrick
Diane Flynn
Christine Foley
Steven Foy
Carlos Franco-Paredes
Geoff Galbraith
Jennifer Gander
Gus Carmel
Jay (James) Gehrig
Monique George
Lauren Gilbert
Rebecca Gologorsky
Marcela Gómez-Suárez
Alexandra Gordon
Nancy Gordon
Shel Gottlieb
Doug Grey
Peeyush Grover
Michael Gunthermaher
Nitesh Gupta
Gustavo Gusso
Paloma Gutierrez
Jeffrey Hallam
Matt Handley
James T. Hardee

Terry Harrison
Katie Heinrich
Natália Heredia
Daniel Hernandez
Lisa Herrinton
Brandon Hidaka
Donya Hosseini
Anne Ichiuji
Mary Ichiuji
Marc Ikeda
Aubrey Ingraham
Brenda Jackson
Monica Jain
Martina Jelley
Elina Jerschow
Khunsia Junaid
Joseph Kahwaji
M. Kamal Khalid
Michael Kaplan
Jonathan Kei
Mamata Kene
Gunver Kienle
Marianna Kong
Geeta Lal
John Lee
Mingsum Lee
James Lee
Peter Lee
Joel Levis
Sarah Levy
Jay Levy
De-Kun Li
Evelyn Lifsey
Tracy Lippard
Brent Lorenzen
For-Shing Lui
Jonathan Lukoff
Adam Luxenberg
Gregory Maletis
Peter J. Martin
Kin Man Lai
Elizabeth Mannino Avila
David Marlin
Mollie Marr
John Martin
Patrick Mcclesky
Craig Mccormick
2021 Reviewer Acknowledgment

Nima Mehran
Melissa Meighan
Erin N. Miller
Raffy Mirzayan
Pietro Modesti
David Moiel
Lisa Morrise
Timothy Munzing
James Mykytenko
Thomas Nachbaur
Mona Nada
H. Nicole Tran
Virgil Nielsen
Victoria O’Connor
Akihito Okazaki
Anish Pal
Michelangelo Palco
Ted Palen
Jo Paluzzi
Minggui Pan
Santosh Pandey
Michael Parchman
Jason Park
Mina Patel
Cathriya Penny
Denis Prudencio
Maisara Rahman
James Ralston
Lisa Rapoport
Albert Ray
Sarah Reif
Bradley Richie
Kathryn Ridout
Gunter Rieg
Nardine Riegs
David Riley
Melissa Rockefeller
Beverly Rogers
Nareg Roubinian
Andrea Rubinstein
Daniel Saal
Athanasios-Panagiotis Saitis
Musa Sami
Vikas Satyananda
Kimberly Schertzer
Adam Schwartz
Elizabeth Scruth
Kira Seiger
Anand Shah
Adam Sharp
Javed Sheikh
Jiaxiao Shi
Ali Shukor
Gregorio Sicard
Sreevathsan Sidhar
Matthew Silver
Ning Smith
Ellen Song
Joseph Spitzer
V. M. Sreekantan
John Steiner
Maximilian Storz
Joshua Strait
Ho-Hyun Sun
Varun Suryadevara
Malgorzata Szczuko
Jean-Luc Szpakowski
Christopher Tenggardjaja
Steven Thalberg
Mark Thanassi
Micah Thorp
Luis Tierradentro-García
Ian Tofler
Marco Tomassi
Anastasios Toumpanakis
John Trinity
Sachin Vaid
Philip Verhoef
Ankur Verma
Ann VonGehr
Suma Vupputuri
Antariksh Waghmare
Melanie Wall
Elizabeth Walsh
Eric Walter
Kevin Wang
Oliver Wang
Regina Wang
Kenneth Wei
Joshua Weil
Calvin Weisberger
Paul Werthmann
Craig Wetterer
Andrew White
Aaron Wilcox
Tom Williams
Abigail Wilpers
Min Xu
Hui Xue
Naveen Yarlagadda
Leonid Yavorkovsky
Deborah Young
Joseph Yousefian
Sijie Zheng
Lin Zhu
Patricia Zrelak