VOLUME 14 • 2021

WHAT'S INSIDE: ORIGINAL RESEARCH • CASE REPORT • REVIEW

KANSAS JOURNAL of MEDICINE

TABLE OF CONTENTS

KANSAS JOURNAL of MEDICINE

Attitudes of Suburban Kansan Parents Regarding School-Required Immunizations and the Influences of the Coronavirus Pandemic

Simon D. Beatty, B.S.[1], Jennifer Villwock, M.D.[1,2]
[1]University of Kansas School of Medicine, Kansas City, KS
[2]Department of Otolaryngology

Received Nov. 23, 2020; Accepted for publication Feb. 15, 2021; Published online May 21, 2021
https://doi.org/10.17161/kjm.vol14.14843

ABSTRACT

Introduction. Understanding suburban, Kansas parental attitudes and adherence of recommended childhood vaccination schedules adopts a new level of importance in the era of the SARS-CoV-2019 (COVID-19) pandemic. With hopes for release of a safe and effective COVID-19 vaccine underway, understanding parental perception of vaccines is important to design successful vaccination interventions.

Methods. A web-based, cross-sectional survey was administered to approximately 900 parents in Johnson County, Kansas during the summer of 2020. Pearson chi square and Mann-Whitney U tests were utilized to assess the attitudes of Kansas parents towards a potential addition of the influenza vaccine to the required list for K-12 students and furthermore, their general perception of vaccinations, and the impact of COVID-19 on those beliefs.

Results. A total of 179 parents responded. Fifty-one percent (n = 92) were in favor of adding the influenza vaccine to the mandatory list (Pro-Addition). Anti-Addition parents had significantly higher levels of distrust (2.1, $p < 0.001$) and were significantly more concerned about vaccine adverse effects. When presented with a hypothetical situation in which a "safe and effective" COVID-19 vaccine was available, 24% of Anti-Addition parents indicated they would receive the vaccine or obtain it for their children (21 people, $p < 0.001$).

Conclusions. Kansas suburban parents were split on their attitudes towards the addition of the influenza vaccine to the required list for children and the effects of the pandemic. Follow-up qualitative studies of Anti-Addition parents are critical for successful vaccine distribution and coverage in the communities. ***Kans J Med 2021;14:116-120***

INTRODUCTION

Achieving higher vaccine coverage rates among school-aged children has been a topic of high priority among health professionals for decades. With vaccine exemptions due to personal parental beliefs on the rise,[1] achieving safe levels of vaccine coverage is becoming more difficult. Common areas of hesitation among parents are in relation to necessity, efficacy, and potential adverse effects of the vaccine.[2] One example of the contentious nature of mandatory vaccines was the public backlash following the Kansas State Department's decision to require hepatitis A and meningococcal vaccines in 2020 for grades K-12.[3] This new addition has been met with criticism from anti-vaccine groups, such as Kansans for Health Freedom, protesting publicly and online throughout cities in Kansas.[4]

Influenza vaccination coverage among children serves as an important example of the public health sector shortcomings. The Healthy People 2020 (HP2020) set a national goal of 80% coverage for childhood influenza immunization rates. Forty-nine out of 50 states fell short of this, with Kansas reaching 63.3% coverage.[5,6] Currently, the influenza vaccine is not on the Kansas School Immunization Requirement list.[7] While required vaccine lists have been shown to increase vaccine coverage significantly among their target population,[8] such public health measures may erode public confidence if not carried out in a tactful manner. As such, it is critical to understand parental belief systems and attitudes regarding vaccines, and their mandatory versus elective status, prior to implementing such initiatives.

Recent National Immunization Surveys (NIS) released by the U.S. Centers for Disease Control and Prevention (CDC) showed anti-vaccine parents are often Caucasian, college-educated families that make over $75,000/year.[9,10] To understand an upper socioeconomic population, such as the CDC described, this study assessed, via survey, the attitudes of suburban Kansan parents toward a potential addition of the influenza vaccine to the required list for children. Additionally, given the current novel COVID-19 pandemic and societal hopes for a safe and effective vaccine,[11] data regarding parental attitudes and openness toward such a vaccine are crucial. Even the best vaccine is only effective if people receive it. As such, we also assessed if parents would obtain for themselves and their families a COVID-19 vaccine that was "safe and effective".

Parents deemed to be suburban for this study had children attending schools in a Johnson County school district. Johnson County parents were selected as our sample population to represent a suburban population because they are the wealthiest county in Kansas (Median Household Income = $89,087), while also having a predominant Caucasian (86.6%) and educated population (96% High school graduate or higher).[12] This population was crucial to study as they are less likely to be affected by financial and sociodemographic barriers to vaccine hesitancy,[13] but still were not often adherent to vaccine guideline, per the NIS from the CDC.[9,10]

The most recent data indicated Johnson County had a 58% total population influenza vaccination rate.[14] If breakthroughs in vaccination rates can be achieved among a highly populated, suburban county such as this, Kansas could come closer to reaching the new Healthy People 2030 goal of 70% coverage among children.[15]

This study sought to assess the attitudes of Kansas suburban parents towards: (1) the addition of the influenza vaccine to the required list, and (2) their likelihood to obtain, if it existed, a "safe and effective" COVID-19 vaccination for their children.

METHODS

This study was reviewed by the University of Kansas Medical Center Institutional Review Board.

Recruitment and Survey Distribution. Subjects were recruited via four Parent Teacher Organization (PTO) presidents through e-mail. Our team e-mailed survey invitations to PTO presidents who then distributed them through group e-mails, social media, and member newsletters to parents in the respective district. There were no financial incentives given to PTOs or participants. All respondents

were asked to complete the survey once and in its entirety. Surveys and associated consent forms were provided in both English and Spanish. A one-month window of time was allotted for data collection during the summer of 2020.

Survey Development and Data Analysis. The survey (see Appendix online only at journals.ku.edu/kjm) was adapted from the previously validated Parent Attitudes about Childhood Vaccines survey (PACV).[16,17] PACV items that were not relevant to the present study (e.g., Have you ever taken a non-medical exemption for any or all of your children's shots?) were removed. The survey also incorporated four items from the Brief Health Literacy Screening Tool (known as the BRIEF), a health-literacy self-assessment.[18] Our resultant survey included 14 out of the 27 original PACV items, 4 BRIEF items, and 10 items our team created. The 10 created items were designed to acquire data specific to parental attitudes towards the addition of the influenza vaccine to the required list for children and to obtain information on parental willingness to receive the coronavirus vaccine.

Study data were collected and managed using REDCap® (Research Electronic Data Capture) electronic data capture tools.[18] REDCap® is a secure, web-based software platform designed to support data capture for research studies, providing an interface for validated data capture.[19,20]

Inclusion criteria for the survey was being the parent of a child enrolled in a Johnson County school district. Since Johnson County is the wealthiest county in Kansas,[12] while also having a large population of Caucasian, educated individuals, our team felt they would be a good representation to explore the CDCs NIS results among parents further.

When discussing differences in income among suburban parents, and its effects on parental attitudes towards vaccines, high-income parents are considered to have an annual household income greater than $75,000 to allow for direct comparisons with prior CDC findings.[9,10] Therefore, low-income parents are considered to be less than $75,000.

Categorical variables were analyzed using a Pearson chi square test looking at the differences in proportions; whereas 5-Point Likert scales were treated as ordinal data and analyzed via a Mann-Whitney U test. All analyses were conducted using SPSS Statistics v. 26. In all cases, p values of < 0.05 were considered statistically significant.

Respondents were stratified into one of two subgroups, Pro-Addition parents or Anti-Addition parents. A Pro-Addition parent responded in favor of the addition of the influenza vaccine to the list of required vaccines for children. An Anti-Addition parent was against the addition.

The demographic characteristics were not included if they had less than five respondents under a category. The following categorical characteristics were not included due to lack of respondents: Race: Black/African American, Asian/Pacific Islander, Hispanic or Latino, Other; Marital Status: Widowed; Type of Doctor: D.O., I don't have a doctor, Naturopath; Insurance status: Uninsured. Totals for each category may not sum to total sample size due to non-response. Percentages represent percentages over a total of 179 respondents.

RESULTS

The four PTOs who agreed to take part in the survey were not able to identify an exact number of parents they distributed the survey to since social media and school newsletters were used as methods of distribution. An estimate of approximately 900 parents were invited to take the survey, with a 19.8% response rate (179 parents), comparable to other surveys assessing attitudes of parents regarding the influenza vaccine.[21] Additionally, this provided a 6.56% margin of error at a 95% confidence interval, thus demonstrating that the sample generally represents the population. Most respondents were female (88.3%) and White (92.7%). The majority of the respondents held at least a bachelor's degree or higher (79%), had private insurance (83.8%), and earned an annual salary higher than $74,999 (82.1%; Table 1).

Table 1. Characteristics of survey respondents.

	n = 179	n (%)
Gender		
Female	158	88.3
Male	18	10.1
Mean age [SD]	46.5	[7.9]
Race/ethnicity		
White	166	92.7
Marital status		
Married	145	81
Divorced or separated	22	12.3
Annual household income range		
Less than $74,999	32	17.9
$74,999 - $100,000	29	16.2
$100,000 or greater	92	51.4
Employed		
Yes	142	79.3
No	36	20.1
Highest level of education completed		
Associate degree or less	36	20.1
Bachelor's degree	75	41.9
Graduate or professional degree	66	36.9
Medical insurance		
Private	150	83.8
Public	18	10.1
Children residing with the parent over half the time		
1 child	37	20.7
2 children	79	44.1
3 children	35	19.6
4 children	13	7.3
What type of doctor do you visit		
M.D.	162	90.5

While there was overlap in demographic characteristics among Pro- and Anti-Addition parents, there were several categories with statistically significant differences (Table 2). Respondents with private insurance were more likely to be Pro-Addition than Anti-Addition (91.3% versus 75.9%; p = 0.024). Furthermore, Pro-Addition respondents were more likely to make $100,000 or more annually (62%) than Anti-Addition (40.2%; p = 0.004). Lastly, Pro-Addition respondents were more likely to have fewer children compared to Anti-Addition respondents (30.4% versus 10.3% have 1 child; p = 0.003).

Table 2. Differences in characteristics of Pro-Addition vs. Anti-Addition.

Characteristics	Pro-Addition n = 92 (51%)	Anti-Addition n = 87 (49%)	p value
Gender			0.43
Female	81 [88.0]	77 [88.5]	
Male	11 [12.0]	7 [11.5]	
Race			0.33
White	87 [94.6]	79 [90.8]	
Marital status			0.41
Married	75 [81.5]	70 [80.5]	
Divorced or separated	13 [14.1]	9 [10.3]	
Highest level of education completed			0.061
Associate degree or less	13 [14.1]	23 [26.4]	
Bachelor's degree	39 [42.4]	36 [41.4]	
Graduate or professional degree	40 [43.5]	26 [29.9]	
Insurance status			0.024
Private	84 [91.3]	66 [75.9]	
Public	6 [6.5]	12 [13.8]	
Type of doctor visited			0.18
M.D.	84 [91.3]	78 [89.7]	
Annual household income range			0.004
Less than $74,999	9 [9.8]	23 [26.4]	
$74,999 - $100,000	14 [15.2]	15 [17.2]	
$100,000 or greater	57 [62.0]	35 [40.2]	
Employed			0.88
Yes	73 [79.3]	69 [79.3]	
No	19 [20.7]	17 [19.5]	
Children residing with the parent over half the time			0.003
1 child	28 [30.4]	9 [10.3]	
2 children	44 [47.8]	35 [40.2]	
3 children	13 [14.1]	22 [25.3]	
4 children	4 [4.3]	9 [10.3]	

Table 3 aims to compare the attitudes of Pro-Addition and Anti-Addition respondents using 2 Likert-type scales. One of them ranging from 1 (strongly disagree) to 5 (strongly agree), and the other Likert-type scale ranging from 1 (not at all concerned) to 5 (extremely concerned). Interventions geared toward making vaccinations more accessible, such as scheduled locations and time for children to receive them, only increased the likelihood of Pro-Addition respondents (3.6, SD = 1.39 versus 1.4, SD = 0.8, p < 0.001). Pro-Addition parents also were more likely to trust the information they receive about shots than Anti-Addition parents, with scores of 4.4 (SD = 0.73) and 2.1 (SD = 1.36), respectively (p < 0.001), and also believe that a required shot list is an important health policy, with scores of 4.7 (SD = 0.45) and 2.5 (SD = 1.55), respectively (p < 0.001).

With respect to reasons for opposing the addition of mandatory influenza vaccination, concern for side effects was significantly higher in the Anti-Addition cohort. Anti-Addition parents were more likely to be concerned for side effects from any type of shot in general and also from the influenza vaccine specifically: General Vaccine Side Effects: 4.7 (SD = 0.44) versus 2.4 (SD = 0.98, p < 0.001); Influenza Vaccine Side Effects: 3.93 (SD = 1.31) versus 1.7 (SD = 0.79, p < 0.001).

Respondent attitude towards mandatory influenza vaccination impacted the likelihood of obtaining a "safe and effective" COVID-19 vaccination for their children. Nearly all Pro-Addition respondents would allow their children to obtain such a vaccination versus less than a quarter of Anti-Addition respondents (96% versus 24%, p < 0.001).

DISCUSSION

Forty-nine out of 50 states, including Kansas, have fallen short of the Healthy People 2020 goal of 80% influenza vaccination coverage for school-aged children.[6] Effective and efficient plans are needed to curb the public health risks that come with a lack of vaccination coverage in schools and communities. Attitudes toward vaccination are particularly important during the current COVID-19 pandemic, as hopes are hinged on safe and effective vaccines. Kansan suburban parents of K-12 students were surveyed on their attitudes toward: (1) the addition of the influenza vaccine to the required list, and (2) their likelihood to obtain, if it existed, a "safe and effective" COVID-19 vaccination for their children. Nearly half of respondents were opposed to the addition of the influenza vaccine to the required list. Only 24% of the Anti-Addition parents would allow their children to receive a "safe and effective" COVID-19 vaccination. Anti-Addition parents do not trust the information they receive about shots. They disagree with the importance of a required vaccine list for children, they have significantly greater concerns about vaccination side effects, and were unlikely to allow their children to obtain a coronavirus vaccine, even if it was "safe and effective".

From our study, Pro-Addition parents had higher incomes compared to Anti-Addition parents, which contradicted prior findings regarding vaccine hesitancy by the CDC National Institute Surveys.[9,10] Interestingly, finances, a common hypothesized barrier to vaccinations,[13,22] did not appear to be significant contributors to Anti-Addition parents' intended actions. Therefore, Anti-Addition parents have stronger reasons than just financial barriers, limiting them from adding the influenza vaccine to the required list for children.

Table 3. Differences of perceptions and attitudes regarding vaccinations between Pro-Addition and Anti-Addition respondents.

Survey Question/Statement and Answer Scale	Pro-Addition n = 92 (51%) Mean [SD]	Anti-Addition n = 87 (49%) Mean [SD]	p value % of All Cases
Items 1 - 7 were recorded from 1 (strongly disagree) to 5 (strongly agree).			
1. I am more likely to support the addition if the State provides the flu shot for free for my child.	3.2 [1.33]	1.3 [0.71]	< 0.001
2. I am more likely to support the addition if there is a scheduled location and time for my child to get vaccinated at the school.	3.6 [1.39]	1.4 [0.80]	< 0.001
3. I am more likely to support the addition if the State provides flu shots for the parents as well.	3.2 [1.31]	1.3 [0.52]	< 0.001
4. State funded flu shots would be a wise use of the state's resources and finances.	3.9 [1.08]	1.4 [0.92]	< 0.001
5. Children get more shots than are good for them.	1.5 [0.78]	3.9 [1.49]	< 0.001
6. I trust the information I receive about shots.	4.4 [0.73]	2.1 [1.36]	< 0.001
7. A required shot list for children is an important health policy.	4.7 [0.45]	2.5 [1.55]	< 0.001
Items 8 - 9 were measured from 1 (not at all concerned) to 5 (extremely concerned).			
8. How concerned are you that your child might have a serious side effect from a shot?	2.3 [0.98]	4.7 [0.44]	< 0.001
9. How concerned are you that the flu shot in particular will not be safe?	1.7 [0.79]	3.93 [1.31]	< 0.001
The BRIEF tool measured with 1 = Inadequate Literacy, 2 = Marginal Literacy, and 3 = Adequate Literacy			
10. BRIEF Tool: Confidence in Health Literacy	2.8 [0.44]	2.9 [0.44]	0.567

Table 4. Coronavirus pandemic impact on parental attitudes toward vaccines.

	Pro-Addition* n = 92 (51%)	Anti-Addition* n = 87 (49%)	p value
If there was a safe and effective COVID-19/coronavirus vaccine available, would you allow your child to get it?			< 0.001
Yes	88 (96%)	21 (24%)	10.31
No	0 (0%)	53 (61%)	9.04
Undecided	4 (4%)	13 (15%)	5.83
The coronavirus pandemic has made my attitude more favorable towards my child and I receiving shots.			< 0.001
Scale from 1 (strongly disagree) to 5 (strongly agree)	3.3 [1.3]†	1.6 [0.88]†	

*Percent of respondents per item out of the total sample.
†Mean [SD]

Anti-Addition parents distrusted information received about vaccines. This conflicted with other studies showing that Health Care Providers (HCP) generally are reported as reliable sources of information for parents regarding vaccines.[23,24] These studies, however, did not focus on suburban parents specifically. This reveals distinct factors could exist among our population causing there to be distrust between parents and HCPs. Further investigation is warranted to assess different sources of distrust for HCPs among suburban parents.

A key finding from the survey showed that Anti-Addition parents were significantly less likely to allow their child to get the COVID-19 vaccine even if it was reported safe and effective. This is alarming for HCPs to see as COVID-19 vaccine production is underway in multiple countries. This vaccine is viewed as an integral piece for society to move forward from the pandemic; however, if large proportions of the state, such as suburban parents, have significant numbers of parents unwilling to consent themselves and their children to such a vaccine, then HCPs' efforts will be undermined. The success of creating a safe and effective coronavirus vaccine will be an amazing achievement, but only half the battle will be won. A vaccine is only as effective as the amount of people it reaches. This vaccine will play a crucial role in our communities and schools to return to relative normalcy. However, much work is needed investigating effective manners and strategies into curbing the concerns of suburban parents so the vaccine can achieve its full potential.

To our knowledge, this is the first study that assessed the effects of the COVID-19 pandemic on suburban parental attitudes towards vaccines. Anti-Addition parents' views towards vaccinations have not become more positive since the onset of the coronavirus pandemic. Ninety-six percent of Pro-Addition parents would accept a "safe and effective" COVID-19 vaccination for their children versus only 24% of Anti-Addition parents. It is important to note that data collection took place prior to reports of children experiencing Kawasaki Disease[25] and multiorgan system inflammatory response, when it was believed that children largely were spared from severe COVID-19 sequelae. It is possible that attitudes towards COVID-19 vaccination may have changed.

Primary limitations seen in this study were a potential lack of external validity due to recruitment only taking place in Johnson County.

However, when comparing our sample demographics to Johnson County parents as a whole, there were strong similarities. Therefore, internal validity was intact. An additional limitation to the study could be a bias of respondents having extreme views. Since survey distribution was primarily through parent-teacher organization e-mails and newsletters, it is possible that the parents who chose to respond were parents who had stronger attitudes towards vaccines. This was a cross-sectional, survey-based study which limited our ability to analyze any data over time and establish cause and effect. To gain further insight, follow-up qualitative studies of Anti-Addition parents are planned, particularly as it relates to attitudes and health behaviors during the ongoing COVID-19 pandemic.

CONCLUSIONS

Suburban parents were split markedly on their attitudes towards the addition and the effects of the pandemic. In Johnson County where this study was polled, 30% of the population is under 18 years old (181,925 children).[12] If 29.6% of the parents and their children opt out of the COVID-19 vaccine like our study indicated, Johnson County could be missing out on crucial herd immunity. A lack of trust in information among Anti-Addition parents was seen which appeared to not be swayed by lower annual household income or the onset of the coronavirus pandemic. Poor attitudes towards vaccinations appear to stem from a lack of trust in information received and a concern for adverse side effects. Future qualitative studies to understand the perspectives of parents who distrust and are opposed to vaccinations are critical to inform successful vaccine-related public health interventions.

ACKNOWLEDGEMENT

The authors acknowledge Mark Villwock and Dr. Kevin Sykes for contributions with statistics and overarching themes.

REFERENCES

[1] Greenwood B. The contribution of vaccination to global health: Past, present and future. Philos Trans R Soc B Biol Sci 2014; 369(1645):20130433. PMID: 24821919.
[2] Williams SE. What are the factors that contribute to parental vaccine-hesitancy and what can we do about it? Hum Vaccin Immunother 2014; 10(9):2584-2596. PMID: 25483505.
[3] Pankrats K. Hep A and meningococcal vaccines to be required for 2019-2020 school year. Kansas Department of Health and Environment. 2019. https://khap2.kdhe.state.ks.us/NewsRelease/PDFs/7-18-19%20vaccine%20requirements.pdf. Accessed June 11, 2020.
[4] Ritter S. Kansas anti-vaccine group surges as parents rush to meet new back-to-school regulation. 2019. https://www.kansascity.com/news/business/health-care/article233311892.html. Accessed June 11, 2020.
[5] U.S. Centers for Disease Control and Prevention. Flu Vaccination Coverage, United States, 2018-19 Influenza Season. 2019. https://www.cdc.gov/flu/fluvaxview/coverage-1819estimates.htm. Accessed June 11, 2020.
[6] Gillespie K. Childhood Influenza Vaccination Coverage in Kansas, an Analysis of BRFSS Surveys. October 8, 2018. https://www.kdheks.gov/immunize/download/BRFSS_Flu_Coverage_2016.pdf. Accessed December 18, 2020.
[7] Kansas Department of Health and Environment. Kansas School Immunization Requirement (Kindergarten – 12th Grade) 2018-2019 School Year. 2018. https://www.kdheks.gov/immunize/download/2018_2019_School_Requirement_K-12.pdf. Accessed June 29, 2020.
[8] Awali R, Samuel P, Marwaha B, et al. Understanding health care personnel's attitudes toward mandatory influenza vaccination. Am J Infect Control 2014; 42(6):649-652. PMID: 24837116.
[9] Lubrano A. Anti-vaccine parents are often white, college-educated, 'Whole Foods moms'. 2020. https://www.inquirer.com. https://www.inquirer.com/news/middle-class-working-class-vaccine-anti-vaxxers-measles-cdc-20190410.html. Accessed June 29, 2020.
[10] U.S. Centers for Disease Control and Prevention. National Immunization Surveys (NIS). https://www.cdc.gov/vaccines/imz-managers/nis/index.html. January 23, 2018. Accessed January 30, 2021.
[11] Cohut M. Five new reasons for hope in the fight against COVID-19. 2020. https://www.medicalnewstoday.com/articles/science-vs-covid-19-vaccine-trial-wins-and-other-hopeful-findings. Accessed June 29, 2020.
[12] U.S. Census Bureau QuickFacts: Johnson County, Kansas; Kansas. Census Bureau. QuickFacts.https://www.census.gov/quickfacts/fact/table/johnsoncountykansas,KS/PST045219. Accessed August 23, 2020.
[13] Schmid P, Rauber D, Betsch C, Lidolt G, Denker M. Barriers of influenza vaccination intention and behavior – A systematic review of influenza vaccine hesitancy, 2005 – 2016. PLoS One 2017; 12(1):e0170550. PMID: 28125629.
[14] County Health Rankings & Roadmaps. https://www.countyhealthrankings.org/app/kansas/2020/measure/factors/155/data. Accessed January 30, 2021.
[15] U.S. Office of Disease Prevention and Health Promotion. Increase the proportion of people who get the flu vaccine every year - IID 09 - Healthy People 2030. https://health.gov/healthypeople/objectives-and-data/browse-objectives/vaccination/increase-proportion-people-who-get-flu-vaccine-every-year-iid-09. Accessed January 30, 2021.
[16] Opel D, Taylor J, Zhou C, Catz S, Myaing M, Mangione-Smith R. The relationship between parent attitudes about childhood vaccines survey scores and future child immunization status: A validation study. JAMA Pediatr 2013; 167(11):1065-1071. PMID: 24061681.
[17] Cunningham R, Kerr G, Orobio J, et al. Development of a Spanish version of the parent attitudes about childhood vaccines survey. Hum Vaccin Immunother 2019; 15(5):1106-1110. PMID: 30735475.
[18] Haun J, Luther S, Dodd V, Donaldson P. Measurement variation across health literacy assessments: Implications for assessment selection in research and practice. J Health Commun 2012; 17(Suppl 3):141-159. PMID: 23030567.
[19] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42(2):377-381. PMID: 18929686.
[20] Harris R, Taylor BL, Minor V, et al. The REDCap consortium: Building an international community of software partners. J Biomed Inform 2019; 95:103208. PMID: 31078660.
[21] Hofstetter AM, Simon TD, Lepere K, et al. Parental vaccine hesitancy and declination of influenza vaccination among hospitalized children. Hosp Pediatr 2018; 8(10):628-635. PMID: 30228245.
[22] Toback SL, Carr W, Hackell J, Bhatt P, Ryan A, Ambrose CS. Influenza vaccination of parents and guardians by US pediatricians. Hum Vaccin 2011; 7(4):436-440. PMID: 21445003.
[23] Brunson EK. The impact of social networks on parents' vaccination decisions. Pediatrics 2013; 131(5):e1397-e1404. PMID: 23589813.
[24] Smith PJ, Kennedy AM, Wooten K, Gust DA, Pickering LK. Association between health care providers' influence on parents who have concerns about vaccine safety and vaccination coverage. Pediatrics 2006; 118(5):e1287-e1292. PMID: 17079529.
[25] Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki Disease. J Infect Dis 2005; 191(4):499-502. PMID: 15655771.

Keywords: immunization, vaccine, COVID-19, health knowledge, attitudes, practice, pandemic

KANSAS JOURNAL of MEDICINE

Burnout and Compassion Satisfaction: Survey Findings of Healthcare Employee Wellness During COVID-19 Pandemic using ProQOL

Meagan L. Dwyer, Ph.D.[1,3], Marcus Alt, Ph.D.[1,3], Joanna Veazey Brooks, Ph.D., MBE[2,3], Hannah Katz, Psy.D.[1,3], Albert B. Poje, Ph.D.[1]
University of Kansas School of Medicine, Kansas City, KS
[1]Department of Psychiatry and Behavioral Sciences
[2]Department of Population Health
[3]University of Kansas Cancer Center, Kansas City, KS

Received Feb. 8, 2021; Accepted for publication Feb. 25, 2021; Published online May 21, 2021
https://doi.org/10.17161/kjm.vol1415171

ABSTRACT

Introduction. Healthcare systems are being bombarded during the COVID-19 pandemic. Understanding burnout, compassion fatigue, and potential protective factors, such as compassion satisfaction, will be important in supporting the vital healthcare workforce. The goal of the current study was to understand the key factors of burnout, compassion fatigue, and compassion satisfaction among healthcare employees during the pandemic within the U.S. in April 2020.

Methods. The authors conducted a single-center, cross-sectional online survey using the Professional Quality of Life (ProQOL) Questionnaire and three open-ended questions around stress and responses to stress during COVID-19 at a large Midwestern academic medical center with nearly 16,000 employees.

Results. Healthcare employees (613) representing over 25 professions or roles and 30 different departments within the health system were surveyed. Participants reported low levels of compassion fatigue and burnout, but moderate levels of compassion satisfaction. Compassion satisfaction was notably higher than prior literature. Key areas of stress outside of work included family, finances and housing, childcare and homeschooling, and personal health.

Conclusions. This was a cross-sectional survey, limiting causal analyses. Also, based on the qualitative responses, the ProQOL was somewhat insufficient in assessing the breadth of stressors, particularly outside of work, that healthcare employees faced due to the pandemic. Although compassion satisfaction was elevated during the initial phases of the pandemic, providing some possible protection against burnout, this may change as COVID-19 continues to surge. Healthcare systems are encouraged to assess and address the broad range of work and non-work-related stressors to best serve their vital workforce.

Kans J Med 2021;14:121-127

INTRODUCTION

The COVID-19 pandemic uniquely has stressed the modern healthcare landscape. Systems are being pushed to the edge of their resources, and fast-paced circumstances have required all who work within healthcare settings to make frequent and sometimes drastic changes to their professional and personal lives. For medical providers and other healthcare workers already at risk for burnout and compassion fatigue,[1,2] the importance of understanding the impact of COVID-19 on mental health[3,4] and emotional and mental well-being is paramount.[5]

Early evidence of the impact of COVID-19 for healthcare workers included a recent cross-sectional study of healthcare workers exposed to COVID-19 in China which demonstrated high levels of depression (50.4%), anxiety (44.6%), insomnia (34.0%), and general distress (71.5%) during the COVID-19 pandemic.[6] Another study examining psychological status of medical workers at a single center in China found higher levels of fear, anxiety, and depression for clinical staff compared to non-clinical staff.[7]

Prior research around sentinel events showed a range of typical psychological effects, including impairments in functioning, lost resources, points of resiliency, and use of coping responses to mitigate the impact of the disaster.[8,9] Prior to COVID-19, there had been growing concern about burnout in the medical workforce as a response to chronic and acute stressors.[10,11] Burnout is the "chronic psychological syndrome of perceived demands from work outweighing perceived resources in the work environment".[12] Signs of burnout include negative work-related attitudes, cynicism, dissatisfaction, and some apathy around work-related issues. While related, there has been less attention on compassion fatigue, which occurs "when caregivers have such deep empathy, they develop symptoms of trauma similar to the patient".[13] Signs of compassion fatigue can encompass physical (e.g., fatigue, insomnia, headaches), psychological (e.g., irritability, sadness, despair), relational (e.g., emotional numbness toward others, blaming patients), and cognitive disturbances (e.g., feeling disorganized or scattered, difficulty with focus).[14] Therefore, one might anticipate compassion fatigue and burnout to be especially important factors to monitor in the medical workforce during the COVID-19 pandemic.

Inversely, constructs such as resiliency and compassion satisfaction have been shown to be protective factors for healthcare workers.[15] Compassion satisfaction allows helpers to derive a sense of value, meaning, and purpose from their challenging work. Slocum-Gori et al.[16] explained this as "the emotional reward for caring for others". While increased levels of stress from the rapid changes in healthcare due to the pandemic may impact healthcare workers negatively, the elevation of their status as highly "essential" and their celebration as "heroes" may yield positive implications for them as well. Prior research looking at burnout and compassion satisfaction among healthcare workers has shown that roughly one-quarter of providers may experience high levels of compassion fatigue and burnout, with 50% or more at moderate levels.[17,18] Inversely, only around 20 - 30% of healthcare workers reported a high level of compassion satisfaction from their work.[19]

During the time of our study (April 2020), national headlines contained a regular stream of developments: COVID-19 related hospitalizations and deaths in New York City, widespread deficiencies in access to personal protective equipment (PPE) for frontline healthcare workers,[20] and growing prevalence and incidence rates occurring nationally as well as locally.[21,22] Local institution guidelines were calling for changes to nearly all aspects of daily activities. Like most medical centers across the country, many clinicians, students, and researchers were sent to work remotely as distance service became "the new

normal", and local, regional, and national outlets began to communicate messages emphasizing potential risks and demonstrating efforts to ascertain individuals' needs and promote resiliency.

While recent studies showed that healthcare workers were being stressed and strained in this current crisis,[6,7] less is known about how the COVID-19 pandemic is impacting compassion fatigue and burnout, and whether a sense of purpose or shared mission in response to the crisis can increase compassion satisfaction and possibly protect healthcare workers from lasting distress. To address this question, an online survey was designed and administered using the Professional Quality of Life (ProQOL) Questionnaire to measure these variables among healthcare workers at one Midwestern academic medical center. To our knowledge, this was the largest study conducted in the U.S to measure the professional quality of life and well-being during COVID-19 for the medical workforce.

METHODS

Study Design and Instrument. A 45-item survey was designed which included demographics, basic employee information (i.e., profession/role, department), open-ended questions on resources and stressors, and the ProQOL Questionnaire, ProQOL 5.[19] The ProQOL is a well-established and validated measure[23] and includes three scales: Compassion Satisfaction, Burnout, and Secondary Traumatic Stress (a component of compassion fatigue). Three open-ended questions exploring experiences during the COVID-19 pandemic also were included: 1) What supportive resources are you using?; 2) What additional stressors are you facing?; and 3) Further comments/suggestions. These optional questions yielded open text responses varying from a few words to several sentences.

Study Context and Data Collection. Survey responses were collected from April 15 through April 30, 2020, prior to the anticipated peak of local COVID-19 cases at our academic medical center. Table 1 outlines the global, national, regional, and local COVID-19 context at the time of data collection. The RedCap® survey was sent via email to each academic, clinical, and research department in the health system, and also was published on an internal research message board and internal employee website. Survey completion was voluntary and anonymous. All employees at one large, academic medical center in the Midwest were invited to participate, including the hospital system, university, and physicians' group with a total estimated population of 15,784 healthcare employees.

Data Analysis. Quantitative data were analyzed with SPSS Version 24. Descriptive statistics were completed for variables related to participants' demographics as well as scores on the three scales of the ProQOL. Pearson's correlational matrix was completed to determine relationships between scores on the ProQOL scales. Single sample t-tests were used to compare ProQOL scores between those who had or had not cared directly for COVID positive patients. Exploratory analysis using ANOVA also tested for differences in ProQOL scores between most common professions in the sample.

Table 1. Timeline of national and local COVID-19 events (April 15 through April 30, 2020).

Worldwide
• The U.S. was the leader in worldwide positive COVID-19 cases at 609,516 and ended with 1,040,488 during this period.
• The prevalence of COVID-19 cases in the U.S. (1,040,488) roughly quadrupled the next closest country of Spain which had 236,899 cases on April 30, 2020.
• Johns Hopkins University reported that COVID-19 cases and deaths started at 2,000,984 and 128,001 and reached over 2,880,000 cases with 200,000 deaths globally by the end of this period.[30]
• 1,004,483 patients diagnosed with COVID-19 successfully recovered since the start of the outbreak.
National
• The U.S. had been under a Declaration of National Emergency since March 1, 2020 which was active throughout the course of this survey.[31]
Regional
• Confirmed COVID-19 cases in the State of Kansas started at 1,494 and ended at 3,738.
• Confirmed COVID-19 cases in the State of Missouri Started at 4,895 and ended at 7,562.
Institutional
• Locally at our hospital system, 39 COVID-19 patients were hospitalized and ended with 24 confirmed patients during this period for a total of 328 patients with an average of 22 (21.866) COVID-19 patients per day.
Contextual
• Daily briefings were ongoing as hospital employees, staff, providers, and leaders were notified of recent trends, changes to practice (e.g., requirements to monitor symptoms, use PPE and practice social distancing) and recommendations for support and self-care.
• Notifications regarding policy change and requirements were posted across campus buildings and providers were increasingly involved in telehealth practices where applicable.

Open-ended questions were analyzed using thematic analysis to identify themes within the responses. Thematic analysis allows for the organization of data into patterns and themes that arise.[24] Two team members conducted analysis of the qualitative data. After first completing an initial review of the responses, each research member reviewed and organized the data into individual codes. An individual's response could have multiple codes if they provided unique items. From this, they reviewed codes, discussing similarities and discrepancies until they gained consensus. Themes were established by grouping similar codes and labeled based on the groupings, in some instances using exact descriptions as appropriate (i.e., "childcare"). They conducted an additional review of the data to refine code definitions further and ensure accurate coding.

RESULTS

Respondents (n = 613) completed the survey from April 15 - April 30, 2020, which represents around 3.8% of the total health system employee population. Participants' mean age was 42.72 years (SD = 11.62), A total of 76.6% of participants identified as female, and 82.2% identified as White/Caucasian. The mean years working in healthcare was 15.70 years (SD = 10.89, range of < 1 to 50 years). Participants represented over 25 professions/roles and more than 30 departments/divisions within the medical center (Table 2, Figure 1). Notably, the survey link was sent out to the chairs or directors of 30 departments across the health system, and at least one survey response was received from each of these departments. Descriptive statistics for the types of coping strategies or resources used are summarized in Figure 2.

across the health system, and at least one survey response was received from each of these departments. Descriptive statistics for the types of coping strategies or resources used are summarized in Figure 2.

ProQOL Results. ProQOL results demonstrated that participants reported low levels of compassion fatigue and burnout, but moderate levels of compassion satisfaction (Table 3). No participants scored in the high range (defined by scores of 42+) for compassion fatigue or burnout, 36.04% of respondents scored in the moderate range for compassion fatigue, and 41.80% in the moderate range for burnout. Only five participants scored in the low range for Compassion Satisfaction, and 52.81% reported high compassion satisfaction.

Compassion satisfaction was significantly and negatively correlated with compassion fatigue ($r = -0.217$, $p < 0.01$), and burnout ($r = -0.646$, $p < 0.01$). Burnout and compassion fatigue were found to be significantly and positively correlated ($r = -0.560$, $p < 0.01$). Both clinical (66.4%) and non-clinical (33.6%) healthcare workers participated. At the time of the initial survey, only 15.8% of participants had provided direct care to a COVID-19 positive patient. There were no significant differences in compassion fatigue, burnout, or compassion satisfaction between those who had or had not provided this direct care to COVID-19 positive patients. Additionally, ProQOL scores were not found to be related significantly to participants' ages or years working in healthcare. Compared to prior studies,[25] the current study failed to demonstrate significant differences between nurses and physicians on ProQOL scores. However, clinical healthcare workers reported significantly higher compassion fatigue ($F = 2.04$, $p < 0.05$) compared to participants not involved in direct clinical service.

Open-ended Responses. Most participants (77.3%, n = 474) provided at least one open-ended response. There was no significant demographic or ProQOL score differences between open-ended responders and non-responders. Of the total 613 respondents, 44.8% (n = 275) reported what supportive resources they were using, 70% (n = 429) responded about additional stressors they faced, and 14.7% (n = 90) provided a comment or suggestion.

Thematic analysis identified significant themes for all three questions (Tables 4 - 6). The focus was on themes from the additional stressors questions that received the most responses (n = 429). Analysis identified five "additional stressors" themes that our sample faced during the initial weeks of the COVID-19 pandemic: 1) family; 2) financial sustainability and housing; 3) impact on personal health; 4) childcare; and 5) work. While not directly prompted, many respondents also described how they were negotiating and responding to these stressors.

Family. Roughly 173 (28.2%) participants commented on family-related stressors. Many respondents reported worry for family members who were at increased risk for COVID due to personal health reasons, as well as concern about potentially spreading the virus to family due to their jobs. Many other respondents expressed concerns about how family members were coping with how the pandemic was re-structuring life and daily routines. Family life transitions across the continuum were reported, including stress around infertility treatment disruptions, concerns about childbirth, illnesses, death, and funerals. A desire to ensure health and provide support for family and friends emerged as prominent in the data, illustrated by this response:

"(concern for) wife who is immunosuppressed and son with asthma, I do not want to bring the virus home to them."

Table 2. Departments responding to the survey.

Department Name	Percentile
Oncology/Hematology	16.4
Non-Clinical Other	11.9
Bone Marrow Transplant/Hematologic Malignancies and Cellular Therapeutics	5.8
Psychiatry and Behavioral Services	5.5
Clinical Other	4.8
Emergency	4.1
Radiation/Oncology	3.7
Case Management	3.6
Pharmacy	3.6
Plastic Surgery	3.4
Clinical Trials	3.2
Police/Safety/Parking	3.2
Respiratory Therapy	3.1
Family Medicine	2.9
Internal Medicine	2.9
Pathology	2.7
Patient Navigation	2.7
Neurology	2.6
Neurosurgery	2.2
Obstetrics/Gynecology	2.2
Urology	2.0
Radiology	1.7
Clinical Nutrition	1.5
Cardiology/Cardiac Surgery	1.0
Orthopedics	0.9
Performance Excellence	0.9
Ophthalmology	0.7
Pediatrics	0.7
Population Health	0.7
Rehabilitation Medicine	0.5
Otolaryngology	0.3

Table 3. ProQol results.

Scale	Mean	SD	Descriptor
Compassion fatigue	21.54	5.67	Low
Burnout	22.27	5.43	Low
Compassion satisfaction	40.85	5.70	Moderate

Note: Range of scales is 10 to 44, with descriptors falling at 22 or lower indicating Low, 23 to 41 Moderate, and 42 or above noting High levels of the given construct.

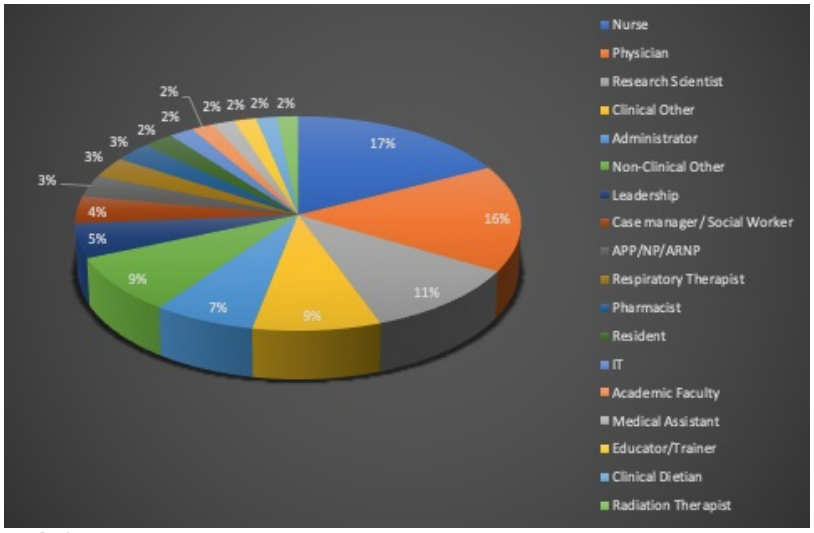


Figure 1. Professions represented in sample.*
*Clinical Other includes: Behavioral Health Tech, Psychologist, Chaplin, Clinical Dietitian, Lab, Physical Therapy, Patient Scheduling; Non-Clinical Other includes: Compliance Auditor, Police/Security, Optimization Analyst

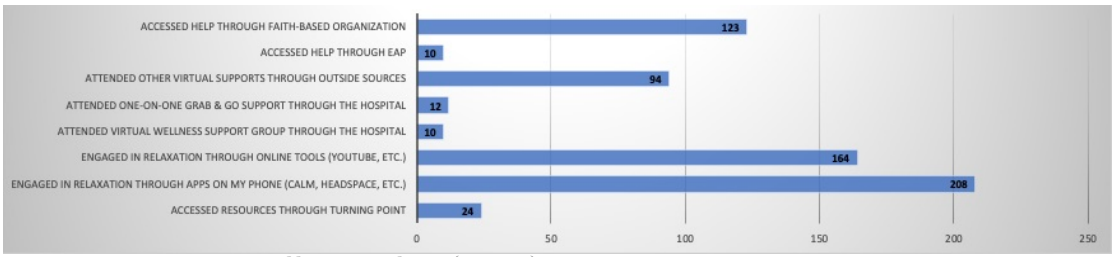


Figure 2. Types of coping strategies or resources used by respondents (n = 305).

Financial Sustainability and Housing. Participants (127, 20.7%) described broad concerns about financial stability due to potential lost wages within their family. Some noted that their partner had lost their job already or that they feared that this could be the case in the future. Additionally, some described facing with the prospect of moving and exploring new residence in the midst of the pandemic. The elements of "unknown" related to how the pandemic impacts their livelihood, was especially notable: "I am the only one in my house working right now, and have become the sole provider for them, and my income alone is not enough."

Impact on Personal Health. One hundred and four participants (17%) described concern for how the pandemic impacts their own health, with particular concern about sleep. The impact on pre-existing mental health concerns, including anxiety and depression, were also of concern. Additionally, participants described concern for their own increased risk of contracting COVID due to exposure while at work: "I normally have some anxiety but feel my anxiety has hit its maximum. Hardly sleeping, isolation feels terrible, mourning the loss of my normal life, have the ability to work from home but having so much trouble with motivation with EVERYTHING. I'm depressed, worried and feel that life is a complete nightmare right now."

Childcare and Homeschooling. While childcare certainly is related to family stressors, it was coded separately due to its frequency and specificity in the data. One hundred participants mentioned this stressor specifically. As schools and daycares closed, many participants had to manage new work-from-home and homeschooling responsibilities simultaneously, adding another element of stress. Limited resources available to help with childcare made this new reality especially challenging. Even for participants who retained their typical childcare arrangements, there was stress as they worried about whether they should send their children or keep them home due to various safety and cost concerns: "I'm a single parent, so I'm juggling extended days of working at home with homeschooling a kindergartner. I have no family or other resources to assist with her care. Her school is cancelled for the rest of the year and her summer program is not opening in June as planned."

Work. For 83 participants, stress related to work was reported. Some reported stress around learning to work via telehealth or from home, and some expressed concern for the impact of these adjustments and the new threat of COVID-19 on their colleagues: "I feel that sometimes our staff is being cut to the bare minimum and that can make me a little uneasy. I sometimes feel that I do not have the support of extra coworkers to help with my stressful patient load."

A Note on Grief. Respondents' answers about additional stressors conveyed a high level of distress in some instances, and an overall theme of grief, that cut across all five reported themes. Participants articulated that they were grieving the loss of "important things that were planned", grieving the inability to see a new grandchild or be with a sick relative, grieving the inability to grieve death of loved ones and patients, and grieving the obstacles to and an overall loss of "normalcy".

Table 4. Themes from open-ended responses: Other supportive resources used.

Theme	Illustrative Quote
Socializing with others	Virtual interactions with family and friends.
Exercise/diet	Exercising outdoors & taking advantage of online workouts at home.
Recreation/hobbies/ games	Reading, listening to music, watching foreign films, gardening, playing cards, cooking, sitting in the sun, furniture and art re-arranging and deep cleaning.
Faith/belief system	I use my faith and church resources we have available to us online.
Mental healthcare/coun-seling	I have a therapist and a couples therapist that have been extremely helpful during this time.
Meditation/relaxation	Readings on stillness, meditation, writing and reading the work of others.
News	...staying informed in the news and being pro-active.
Other	...relaxing at the end of the day with a glass of wine.

Table 5. Themes from open-ended responses: Additional stressors faced-domains and relevant quotes.

Theme	Illustrative Quote
Family	Mother-in-law passed away and my husband and I were not able to attend the funeral. Elderly father had pacemaker surgery during the crisis, and I was not able to be there to help as I normally would have. Other family members have jobs that put them at high risk of exposure.
Family: COVID-19 specific	Wife who is immunosuppressed and son with asthma, I do not want to bring the virus home to them.
Financial/ sustainability/ housing	I am the only one in my house working right now, and have become the sole provider for them, and my income alone is not enough.
Impact on health and health practice	Loss of sleep, headaches, back and shoulder pain, anxiety.
Childcare	My kids have to be homeschooled, so I divide my time at being a mom, homeschool teacher, and professional.
Work	...work stressors. Coming home and crying because all the changes at work are so hard to keep up with. And I'm afraid to get sick because of my patient numbers and if I don't get patient numbers I can't graduate.
Social impact	Missing face to face human contact. As socializing with friends.
No stressor	Absolutely none. Our lives have not changed at all.
Political stress	...the national government's handling of the situation. Local (county, city and state, and work) government has been much better source of reliable information.
Training/education	I stress that I won't be as good of a surgeon because COVID has robbed me of the majority of my senior surgical training experience, since elective cases have been cancelled. I stress that this will extend into my fellowship, which is only 1 year in length, and further rob me of my training after I have worked 12 years to get to this point in my training. I stress that the job market will be terrible in the coming few years, and that will affect me and my family significantly.
Other	All the unknowns of how this will impact us.

DISCUSSION

The current COVID-19 pandemic has impacted every area of life. Those working in healthcare, in both clinical and non-clinical operations, serve vital roles in managing the welfare of society during this uniquely challenging time. The current study measured rates of compassion fatigue, burnout, and compassion satisfaction[19] among employees at a large academic medical center in the Midwest during the initial wave of COVID-19 cases in April 2020. The inclusion of three open-ended survey questions also allowed participants to describe personal aspects of stress and resilience.

Findings showed that the healthcare employees were experiencing moderate levels of compassion fatigue and burnout, and somewhat elevated levels of compassion satisfaction compared to prior research on nurses, emergency room physicians, primary care, and palliative care professionals.[26-28] Our data suggested that even in the midst of the pandemic, healthcare employees were able to find a sense of value and meaning in the work they do, perhaps bolstered by the public's emphasis of the "essential" or even "heroic" nature of their roles.[29] Further analyses demonstrated that compassion satisfaction was correlated negatively with burnout and compassion fatigue, again indicating that it may serve as a protective factor. Of note, our study was conducted in the early weeks of the pandemic, and it is unclear whether and how this protective effect might shift through time as the pandemic continues.

Table 6. Themes from open-ended responses: Comments and suggestions-domains and relevant quotes.

Theme	Illustrative Quote
Feedback regarding institution system and administration	The health system leadership has done a better job of open, honest, and transparent communication, but their tendency is to conceal information. I hope they have learned the importance of transparency, but I worry they will revert to concealment.
Workflow/adjusting to home	For me, working from home has actually decreased my work-related stress and my productivity has remained stable. I recognize this is in part personal preference and fortunate circumstances, but the fact that the university and my department has encouraged this and been supportive with IT help and weekly updates has been enormously comforting as well.
Need for mental health services and coping strategies	I need a therapist after this. It feels like the stress and anxiety are consuming my life.
Expressed appreciation for the study	This survey made me feel little better by just expressing how I feel!
Feedback on specific survey items	Though it may confound the data you've already collected, I would have appreciated more guidance on what "help" means, unless it was intentionally left that open to interpretation.
Concern for COVID-19 status	It would be nice to have antibody testing to check for immunity. It would be nice to have more tests for COVID-19 that are rapid. It would be nice to have reassurance that we have enough masks and gloves. It seems we have enough.
Other	A vocation to serve is deeply satisfying. The trauma/PTSD of truly caring for all around you from patients, colleagues, staff to family...are all one and the same. Stress of infecting my wife and likely death has made her stressed and I am the vector/risk factor...but will not stop serving others.

Despite reporting somewhat moderate levels of problematic concerns related to their work via burnout and compassion fatigue, the 70% of healthcare employees who responded to our optional open-ended question about additional stressors described increased stress outside of the work setting. This suggested that while the ProQOL may

aid in understanding the impact of work-related stress for those in healthcare and related fields, it may be insufficient at capturing the broader scope of stress that workers have experienced during the pandemic.

Additionally, the current study demonstrated a breadth of responses from employees across the academic health center, including groups that typically have not been reported in the compassion fatigue and burnout literature (i.e., EMR technicians, researchers).[2] Like previous studies finding differences in fear and anxiety between clinical and non-clinical workers during COVID-19,[7] our findings also showed higher levels of compassion fatigue for participants involved in direct patient care compared to non-clinical respondents. However, the fact that 70% of our sample responded to an optional question about additional stressors in their lives showed that the stress of COVID-19 was not limited to clinical workers but extended to the entire healthcare system. This emphasized the need to assess and address the stress impacting our healthcare workforce from a broad perspective, as the pandemic in particular has invaded both professional and personal areas of life. of our sample responded to an optional question about additional stressors in their lives showed that the stress of COVID-19 was not limited to clinical workers but extended to the entire healthcare system. This emphasized the need to assess and address the stress impacting our healthcare workforce from a broad perspective, as the pandemic in particular has invaded both professional and personal areas of life.

Our study had several limitations. Because our survey was available to all employees via our intranet, and additional emails were sent to department chairs to facilitate recruitment, we were unable to calculate an exact response rate, as we cannot know how many employees were aware of the study. However, our sample represented respondents from many different roles in the healthcare system. In addition, the cross-sectional nature of our study limited causal conclusions or the ability to report on how these measures were changing over time. Finally, the ProQOL is focused on aspects related to one's role in work and may not capture the wider array of factors that contribute to stress for healthcare workers. Our data suggested that healthcare systems should assess for outside burdens that may impact employees' well-being external to their daily work tasks.

Our study was the largest to-date examining burnout, compassion fatigue, and compassion satisfaction among the healthcare workforce in the U.S. during COVID-19. Our data showed higher compassion satisfaction scores than prior research on a variety of healthcare professionals,[2,26-28] suggesting that early in the pandemic, respondents may have experienced protective effects from community and national support that encouraged these elevated levels. While encouraging, our study was conducted at an early point in the COVID-19 pandemic when local cases were relatively limited. As cases surge and the pandemic wears on, future research must prioritize and study the emotional well-being of our healthcare workforce.[3,5] We urge healthcare systems to continue to monitor and support both the work and non-work-related stressors of their employees.

ACKNOWLEDGEMENTS

We are thankful to each of the colleagues from our institution who took time to generously respond to this survey and share their experiences.

REFERENCES

[1] Shanafelt TD, Mungo M, Schmitgen J, et al. Longitudinal study evaluating the association between physician burnout and changes in professional work effort. Mayo Clin Proc 2016; 91(4):422-431. PMID: 27046522.
[2] Sinclair S, Raffin-Bouchal S, Venturato L, Mijovic-Kondejewski J, Smith-MacDonald L. Compassion fatigue: A meta-narrative review of the healthcare literature. Int J Nurs Stud 2017; 69:9-24. PMID: 28119163.
[3] Taylor WD, Blackford JU. Mental health treatment for front-line clinicians during and after the coronavirus disease 2019 (COVID-19) pandemic: A plea to the medical community. Ann Intern Med 2020; 173(7):574-575. PMID: 32453637.
[4] Krystal JH. Responding to the hidden pandemic for healthcare workers: Stress. Nat Med 2020; 26(5):639. PMID: 32350461.
[5] Dewey C, Hingle S, Goelz E, Linzer M. Supporting clinicians during the COVID-19 pandemic. Ann Intern Med 2020; 172(11):752-753. PMID: 32196544.
[6] Lai J, Ma S, Wang Y, et al. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. JAMA Netw Open 2020; 3(3):e203976. PMID: 32202646.
[7] Lu W, Wang H, Lin Y, Li L. Psychological status of medical workforce during the COVID-19 pandemic: A cross-sectional study. Psychiatry Res 2020; 288:112936. PMID: 32276196.
[8] Freedy JR, Shaw DL, Jarrell MP, Masters CR. Towards an understanding of the psychological impact of natural disasters: An application of the conservation resources stress model. J Trauma Stress 1992; 5(3):441-454.
[9] Makwana N. Disaster and its impact on mental health: A narrative review. J Family Med Prim Care 2019; 8(10):3090-3095. PMID: 31742125.
[10] Hartzband P, Groopman J. Physician burnout, interrupted. N Engl J Med 2020; 382(26):2485-2487. PMID: 32356624.
[11] Shanafelt TD, Boone S, Tan L, et al. Burnout and satisfaction with work-life balance among US physicians relative to the general US population. Arch Intern Med 2012; 172(18):1377-1385. PMID: 22911330.
[12] Potter P, Deshields T, Divanbeigi J, et al. Compassion fatigue and burnout: Prevalence among oncology nurses. Clin J Oncol Nurs 2010; 14(5):E56-62. PMID: 20880809.
[13] Figley CR. Compassion fatigue: Coping with secondary traumatic stress disorder in those who treat the traumatized. Philadelphia: Brunner/Mazel, 1995. ISBN: 0876307594.
[14] Mendenhall TJ. Trauma response teams: Inherent challenges and practical strategies in interdisciplinary fieldwork. Families, Systems & Health 2006; 24(3):357-362.
[15] Tyson J. Compassion fatigue in the treatment of combat-related trauma during wartime. Clin Soc Work J 2007; 35(3):183-192.
[16] Slocum-Gori S, Hemsworth D, Chan WWY, Carson A, Kazanjian A. Understanding compassion satisfaction, compassion fatigue and burnout: A survey of the hospice palliative care workforce. Palliat Med 2013; 27(2):172-178. PMID: 22179596.
[17] Abendroth M, Flannery J. Predicting the risk of compassion fatigue: A study of hospice nurses. J Hospice Palliati Nurs 2006; 8(6):346-356.
[18] Alkema K, Linton JM, Davies R. A study of the relationship between self-care, compassion satisfaction, compassion fatigue, and burnout among hospice professionals. J Soc Work End Life Palliat Care 2008; 4(2):101-119. PMID: 19042895.
[19] Stamm B. The Concise ProQOL Manual. 2010. http://proqol.org. Accessed October 16, 2020.
[20] Ravelo J, Jerving S. COVID-19 - A timeline of the coronavirus outbreak. https://www.devex.com/news/covid-19-a-timeline-of-the-coronavirus-outbreak-96396. Accessed October 16, 2020.
[21] University of Kansas Health System. Novel Coronavirus Update for Physicians and APPs. Kansas City, KS: University of Kansas Health System, 2020.
[22] Missouri Department of Health and Senior Services. COVID-19 Outbreak. 2020. https://health.mo.gov/living/healthcondiseases/communicable/novel-coronavirus/. Accessed February 24, 2021.
[23] Heritage B, Rees CS, Hegney DG. The ProQOL-21: A revised version of the Professional Quality of Life (ProQOL) scale based on Rasch analysis. PLoS One 2018; 13(2):e0193478. PMID: 29489875.
[24] Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006; 3(2):77-101.

[25] Cocker F, Joss N. Compassion fatigue among healthcare, emergency and community service workers: A systematic review. Int J Environ Res Public Health 2016; 13(6):618. PMID: 27338436.
[26] Duarte J, Pinto-Gouveia J, Cruz B. Relationships between nurses' empathy, self-compassion and dimensions of professional quality of life: A cross-sectional study. Int J Nurs Stud 2016; 60:1-11. PMID: 27297364.
[27] El-Shafei DA, Abdelsalam AE, Hammam RAM, Elgohary H. Professional quality of life, wellness education, and coping strategies among emergency physicians. Environ Sci Pollut Res Int 2018; 25(9):9040-9050. PMID: 29333570.
[28] Samson T, Shvartzman P. Association between level of exposure to death and dying and professional quality of life among palliative care workers. Palliat Support Care 2018; 16(4):442-451. PMID: 28641599.
[29] Felsenthal E. Front Line Workers Tell Their Own Stories. April 9, 2020. https://time.com/collection/coronavirus-heroes/5816805/coronavirus-front-line-workers-issue/. Accessed November 23, 2020.
[30] Johns Hopkins Coronavirus Resource Center. Johns Hopkins Coronavirus Resource Center. April 15, 2020. https://coronavirus.jhu.edu/. Accessed December 4, 2020.
[31] The White House. Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak. April 15, 2020. https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/. Accessed December 4, 2020.

Keywords: psychological burnout, professional burnout, compassion fatigue, COVID-19

KANSAS JOURNAL of MEDICINE

Detection of 2:1 Atrioventricular Block by Echocardiographic Doppler Mitral Inflow Study

Robert T. Tung, M.D., FACC
Department of Veterans Affairs, Eastern Kansas HealthCare System, Cardiology Section, Topeka, KS

Received Nov. 28, 2020; Accepted for publication Feb. 9, 2021; Published online May 21, 2021
https://doi.org/10.17161/kjm.vol1414894

INTRODUCTION

Echocardiography is a commonly used diagnostic tool in diagnosing structural heart disease.[1] In this case report, usefulness of echocardiography in detecting and confirming 2:1 atrioventricular (AV) block is described.

CASE REPORT

Echocardiography was performed on an 86-year-old patient for evaluation of his low extremity swelling in the absence of any other clinical symptoms or signs. The echocardiographic image of pulsed Doppler mitral inflow showing early (E) and late (A) diastolic filling waves is displayed in Figure 1 (top image). The E wave (early mitral inflow wave) reflects the pressure gradient from the left atrium (LA)-left ventricle (LV) generated by the active LV relaxation, while the A wave (late mitral inflow wave) reflects the pressure gradient generated by LA contraction during LV diastole. A single lead electrocardiographic (ECG) tracing showed bradycardia at 39 beats/minute. There was a pattern of alternating E-A and A waves on Doppler mitral inflow and probably 2:1 atrioventricular (AV) block on ECG tracing (Figure 1; bottom image). Further analysis of Doppler mitral inflow A, E waves, and P, QRS waves on the ECG revealed that there is constant relationship of P-A waves (solid, white arrows) to suggest a normal sinus rhythm, while alternating 2:1 P-A to QRS-E (broken arrows) waves confirm 2:1 AV block as his underlying rhythm. A subsequent 12-lead ECG showed normal sinus rhythm and complete AV block with ventricular escape rhythm of right-bundle branch block morphology (Figure 2). With his advanced age and ECG findings, a pacemaker was implanted successfully.

DISCUSSION

The AV block is diagnosed by ECG and can be physiological or indicative of underlying cardiac conduction disease. The AV block is classified as 1st-degree, 2nd-degree, 3rd-degree, or complete block.[2,3] The 1st-degree AV block is defined as PR interval greater than 0.20 second on ECG. The 2nd-degree AV block is present when non-conducted P waves are observed at regular or irregular intervals; it is further sub-classified as Mobitz type I (Wenckebach) and type II block. The Mobitz type I AV block is characterized by progressive PR prolongation culminating in a non-conducted P wave, while in Mobitz type II, the PR interval remains constant prior to the blocked P wave. The block where only 2:1 AV conduction is present cannot be classified as either Mobitz I or II type. This 2:1 AV block can sometimes be misinterpreted as sinus bradycardia when the blocked P waves fall in or at the end of T waves that might be mistaken as U waves. The 3rd-degree or complete AV block is defined when P waves and QRS complexes bear no relationship to one another; clinically, these patients usually have slow pulses and likely symptoms of dizziness or even syncope.

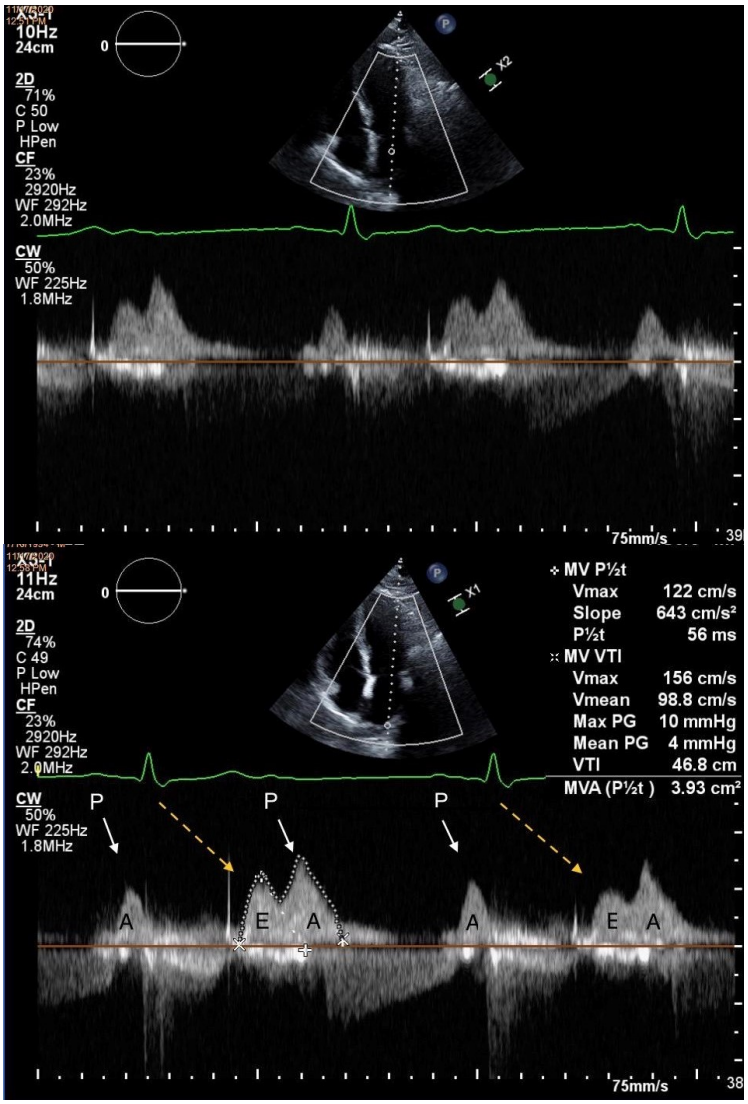


Figure 1. (Top) Echocardiographic image showed pulsed wave Doppler of mitral inflow of E and A waves and A waves with QRS and P waves on ECG are demonstrated here. There is constant relationship of P-A (solid, white arrows) and QRS-E (broken, yellow arrows) waves, but a 2:1 ratio of A-E waves on mitral inflow and P-QRS waves on ECG confirms the 2:1 AV block.

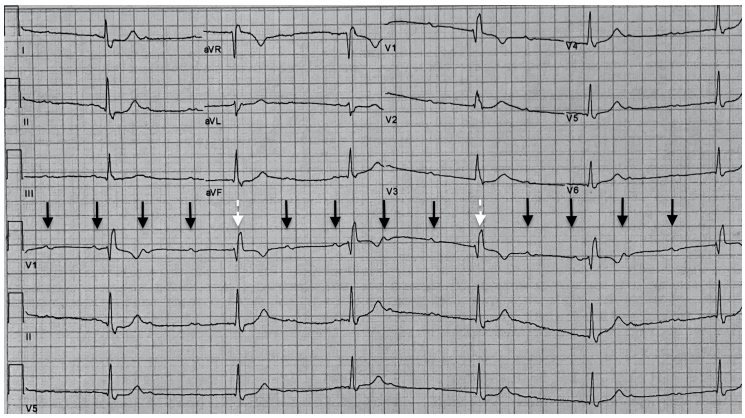


Figure 2. A 12-lead ECG obtained later in the same patient showed normal sinus rhythm and complete AV block with a slow ventricular escape rhythm of right bundle branch block morphology. In lead V1, solid black arrows pointed to P waves; broken white arrows indicated buried P waves within QRS complex.

Literature on echocardiographic findings of AV block included M-mode findings of A wave following P wave during AV block,[4] M-mode of mitral leaflets showing multiple A waves corresponding to atrial tachycardia rate during complete heart block,[5] and diastolic mitral or tricuspid regurgitation during AV block in animal and human models.[6,7] The effects on LV diastolic function reflected by E-A wave changes were only described during 1st-degree AV block, bundle branch block, and cardiac pacing.[8] This report showed a case of 2:1 AV block identified by observing the relationship of mitral inflow E-A waves on echocardiography to P-QRS waves on ECG. This simple observation confirmed 2:1 AV block even before an ECG was obtained.

REFERENCES

[1] Doherty GJ, Kort S, Mehran R, et al. ACC/AATS/AHA/ASE/ASNC/ HRS/SCAI/ SCCT/SCMR/STS 2019 Appropriate Use Criteria for Multimodality Imaging in the Assessment of Cardiac Structure and Function in Nonvalvular Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and the Society of Thoracic Surgeons. J Am Soc Echocardiogr 2019; 32(5):553-579. PMID: 30744922.

[2] WHO/ISC Task Force. Definition of terms related to cardiac rhythm. Am Heart J 1978; 95(6):796-806. PMID: 655094.

[3] Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS Guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines, and the Heart Rhythm Society. J Am Coll Cardiol 2019; 74(7):932-987. PMID: 31416523.

[4] D'Cruz LA, Prabhu R, Cohen HC, Glick G. Echocardiographic features of second degree atrio-ventricular block. Chest 1977; 72(4):459-463. PMID: 908213.

[5] Sajeer K, Raju D, Kanjirakadavath B, Ranjith MP, Krishnan MN. Mitral valve m-mode echo in complete heart block with atrial tachycardia. Heart India 2013; 1(3):83-84.

[6] Appleton CP, Basnight MA, Gonzales MS. Diastolic mitral regurgitation with atrioventricular conduction abnormalities: Relation of mitral flow velocity to transmitral pressure gradients in conscious dogs. J Am Coll Cardiol 1991; 18(3):843-849. PMID: 1869748.

[7] Schnittger IA, Appleton CP, Halte LK, Popp RL. Diastolic mitral and tricuspid regurgitation by Doppler echocardiography in patients with atrioventricular block: New insight into the mechanism of AV valve closure. J Am Coll Cardio 1988; 11(1):83-88. PMID: 3335709.

[8] Nagueh S, Smieseth O, Appleton C, et el. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016; 29(4):277-314. PMID: 27037982.

Keywords: atrioventricular block, mitral valve, echocardiography, Doppler pulsed echocardiography

KANSAS JOURNAL of MEDICINE

Neonatal Appendicitis Presenting as Bilious Emesis and Septic Shock

Jacob H. Umscheid, M.D.[1], Khai M. Nguyen, P4[2], Rhythm Vasudeva, M.D.[1], Nisha Agasthya, M.D.[1]
[1]University of Kansas School of Medicine-Wichita, Wichita, KS Department of Pediatrics
[2]University of Kansas School of Pharmacy, Wichita, KS

Received Dec. 10, 2020; Accepted for publication Feb. 22, 2021; Published online May 21, 2021
https://doi.org/10.17161/kjm.vol1414990

INTRODUCTION

The incidence of neonatal intestinal obstruction is estimated to be approximately 1 in 2,000 live births, often presenting with symptoms of bilious emesis.[1] A surgical indication can be found in up to 38% of infants when presenting with bilious emesis.[2] Plain radiography, contrast radiologic studies, and ultrasonography are imaging studies commonly used in the evaluation of patients presenting with bilious emesis, with upper gastrointestinal series being the preferred modality.[3] The causes of bilious emesis in a neonate are broad and include, but are not limited to, Hirschsprung's disease, bowel atresia, malrotation, and volvulus; the differential rarely includes appendicitis.

Neonatal appendicitis is a rare condition with a reported incidence rate of 0.04 - 0.2%.[4] Classical findings of appendicitis, such as decreased appetite, fever, abdominal pain, and leukocytosis, are often absent, resulting in a delay in diagnosis and management.[4-5] This nebulous presentation rarely results in a preoperative diagnosis and often is discovered on exploratory laparotomy or postmortem examination.[4] Accurate mortality rates are difficult to establish, however, they have improved. Rates in the early 2000s were 23 - 28%, while one retrospective review of 31 cases from 2001 to 2018 showed 0% mortality rate.[6-8] Perforation plays a significant role in predicting the prognosis of neonatal patients with appendicitis.[4-5] Because of the underdeveloped omentum found in neonates, it is thought that any form of purulent material cannot be processed and leads to diffuse peritonitis.[9] Clinical deterioration often prompts surgical intervention leading to the diagnosis. We present a unique case of a neonate with bilious emesis caused by appendicitis that ultimately lead to multi-organ system failure.

CASE REPORT

A 38-week gestational age female with a perinatal history complicated by polyhydramnios was admitted to the special care nursery due to hypoglycemia. After initial requirement for dextrose containing fluids, she was able to maintain euglycemia by infant formula at four days of life (DOL). She was discharged home without any signs of feeding intolerance or bowel irregularity. At DOL five, she was brought to the emergency department by the parents with concerns for fussiness and poor feeding. An abdominal radiograph was unremarkable, and her formula was changed, and she was able to tolerate 33 ml by mouth with resolution of perceived fussiness. Her vital signs were temperature of 99.8°F, heart rate of 129 bpm, respiratory rate of 32 breaths/min, and an oxygen saturation of 100% in ambient air. She was discharged home with anticipatory guidance the same night.

On DOL eight, she was brought back to the emergency department with continued fussiness, poor oral intake, and bilious emesis. An abdominal ultrasound showed small to moderate ascites, but no other abnormalities. An upper gastrointestinal radiograph under fluoroscopy showed no evidence of malrotation or volvulus. However, it revealed episodes of severe reflux to the upper esophagus and multiple dilated loops of small bowel concerning for distal bowel obstruction. The decision was made for emergent exploratory laparotomy after surgical consultation. Intra-operative findings included a contaminated peritoneal cavity with purulent drainage, turbid ascites, and inflammatory small bowel obstruction of the ileum in the right lower quadrant with a perforated necrotic appendix. Appendectomy was performed, peritoneal cultures were obtained, and the abdomen was closed.

She was admitted post-operatively to the Pediatric Intensive Care Unit (PICU) for monitoring. Her initial vital signs at admission were temperature of 97.5°F, heart rate of 172 bpm, respiratory rate of 65 breaths/min, blood pressure of 89/66 mmHg, and an oxygen saturation of 96%. Admission labs are shown in Table 1. Physical exam revealed an ill appearing infant with subcostal retractions and grunting, decreased peripheral pulses with a capillary refill of three seconds, absent bowel sounds, a distended abdomen that was firm to palpation in the lower quadrant, and was responsive to noxious stimuli with moaning.

Table 1. Labs obtained prior to initial exploratory laparotomy.

Sodium (mmol/L)	136	WBC (k/cumm)	22.6
Potassium (mmol/L)	6.9	Hemoglobin (g/dL)	19.8
Chloride (mmol/L)	102	Hematocrit (%)	55.5
Anion Gap (mmol/L)	22	Platelet (k/cumm)	323
BUN (mg/dL)	29	Creatinine (mg/dL)	0.70
Glucose (mg/dL)	63	Calcium (mg/dL)	6.4
AST (units/L)	117	ALT (units/L)	160
Albumin (g/L)	2.4		

Fluid resuscitation up to 80 mL/kg in aliquots with crystalloids resulted in minimal improvement in perfusion and lactic acid. She soon required tracheal intubation and invasive mechanical ventilation for optimizing oxygen delivery. She was initiated on vasoactive agents norepinephrine and epinephrine for fluid refractory shock and received stress dose hydrocortisone intravenously. The surgical team was reconsulted given her persistent lactatemia, metabolic acidosis, and increasing doses of vasoactive infusions. Her abdomen remained distended, taut, and discolored, and she remained anuric during this time. Given concerns for intra-abdominal hypertension and abdominal compartment syndrome, a repeat exploratory laparotomy was performed 18 hours post-admission and fascial planes were left open with only skin closure for abdominal decompression.

Table 2 shows the progression of labs from before and after second exploratory laparotomy. Eventually, the decision was made to transfer her to a quaternary care center for initiation of veno-arterial extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy for multi-organ failure refractory to conventional therapy. Transfer occurred at around 19 hours postoperatively. The

patient unfortunately had cardiac arrest upon arrival to the outside hospital. Return of spontaneous circulation was achieved after several minutes of resuscitation and decompression of the abdomen with placement of intestinal loops in silo. The bowel appeared ischemic and dusky and the decision was made to not pursue ECMO given poor prognosis. Parents chose discontinuation of life sustaining measures and patient eventually died.

Table 2. Lab trends comparing pre- and post- second exploratory laparotomy.*

	Pre-Op Labs			Post-Op Labs	
	At 10 hours	At 16 hours	At 18 hours	At 21 hours	At 24 hours
Lactate (mmol/L)	7.1	5.0	7.2	9.8	12.1
Sodium (mmol/L)	144	148		151	153
Potassium (mmol/L)	5.1	5.6		5.3	4.4
Chloride (mmol/L)	109	116		116	116
CO2 (mmol/L)	14	13			
Anion Gap (mmol/L)	21	19		23	22
BUN (mg/dL)	28	31		30	32
Creatinine (mg/dL)	1.16	0.71		1.06	1.10
Calcium (mg/dL)	5.4	<5.0		7.1	7.0
Calcium (ionized) (mg/dL)		3.3		4.1	3.9
Magnesium (mg/dL)		2.5			
AST (units/L)				764	611
ALT (units/L)				231	171
Albumin (g/dL)	1.3		0.7	1.4	2.1
Venous blood gas					
pH	7.08	7.04	6.91	7.09	7.12
pCO2 (mmHg)	47	42	40	34	41
HCO3 (mEq/L)	13.6	11.0	7.8	9.9	13
Base Excess (mEq/L)	-16.3	-19.2	-24.9	-19	-15.7
Prothrombin (s)		32.7			
INR		2.8			
aPTT (s)		104			
Fibrinogen (mg/dL)		133			

*Time indicated is in hours from admission. Labs closest to the indicated hour are presented. Her initial laparotomy occurred at seven hours post admission, with her repeat surgery occurring 18 hours post admission.

DISCUSSION

Neonatal appendicitis is a rare but potentially life-threatening condition. This report discussed the unique presentation of a patient that experienced rapid deterioration following admission to the pediatric intensive care unit. Despite the patient's clinical course, this case illustrated the importance of early recognition of neonatal appendicitis and some of the challenges associated with the management of severe shock in the neonatal population.

While appendicitis is seen commonly in children, it rarely causes bilious emesis and rarely affects neonates. This is thought to be due to the wide opening of the appendix in the newborn, infrequent abdominal or respiratory infections, a liquid diet, and recumbent positioning.[10] The wide opening prevents obstruction with fecaliths or other food particles. With lower rates of abdominal and respiratory infections, there is less hyperplasia of lymphoid tissue in the gut, which potentially serves as a protective factor from obstruction of the appendix. Unfortunately, the neonatal appendix tissue is thin-walled and fragile, making it prone to perforation.[6] The neonatal immune system also is inexperienced and responds poorly to overwhelming infections.[11] The omentum is underdeveloped and is unable to absorb purulent material, resulting in widespread dissemination after perforation of the infection to the small neonatal abdominal cavity.[9] Also contributing is the difficulty in making an early diagnosis in this patient population. Most diagnoses occur postoperatively after signs of peritonitis, abdominal distension, or bilious emesis appear.[7,12,13]

Our case followed a similar pattern, whereby an acutely perforated appendix was discovered upon exploratory laparotomy to investigate the source of obstruction. Imaging modalities in neonates provide little assistance in identifying appendicitis, but are helpful in detecting complications, such as pneumoperitoneum on x-ray, free abdominal fluid on ultrasonography, or upper gastrointestinal x-rays with contrast showing bowel obstruction.[11] Signs suggestive of bowel obstruction were identified in our case, which prompted further surgical intervention.

Multiple hypotheses have been made towards the etiology of neonatal appendicitis. One theory is from overdistension of colonic tissue and appendiceal tissue secondary to Hirschsprung disease.[13] There was no evidence of colonic distension in our patient and she lacked the classical findings of delayed meconium passage and had multiple bowel movements in the first day of life. Another suggested theory is a localized necrotizing enterocolitis secondary to necrosis of the appendiceal wall.[14] Even though this is plausible, the patient in our case was not premature, which is a major predisposition to the condition.

Although difficult to assess the presentation of neonatal appendicitis, some clinical features may be indicative of the condition. Early symptoms, as also seen in our case, include irritability and poor feeding while late findings include abdominal distension, abdominal guarding, and bilious emesis.[4-6,15,16] Clinicians should have a high index of suspicion for early diagnosis, management, and prevent sequalae of complications.

CONCLUSIONS

This case illustrated the clinical presentation and course of a term neonate with acute appendicitis. Diagnosis is made by prompt surgical evaluation in addition to clinical and radiographic findings. Complications can include sepsis, abdominal compartment syndrome, multiple organ dysfunction syndrome, and death in rare cases. Albeit a rare cause of bilious emesis, neonatal appendicitis is an important differential for bilious emesis in the neonatal period.

REFERENCES

[1] Juang D, Snyder CL. Neonatal bowel obstruction. Surg Clin North Am 2012; 92(3):685-711. PMID: 22595716.
[2] Godbole P, Stringer M. Bilious vomiting in the newborn: How often is it pathologic? J Pediatr Surg 2002; 37(6):909-911. PMID: 12037761.
[3] Alehossein M, Abdi S, Pourgholami M, Naseri M, Salamati P. Diagnostic accuracy of ultrasound in determining the cause of bilious vomiting in neonates. Iran J Radiol 2012; 9(4):190-194. PMID: 23407700.
[4] Stiefel D, Stallmach T, Sacher P. Acute appendicitis in neonates: Complication or morgues suit generis? Pediatr Surg Int 1998; 14(1-2):122-123. PMID: 9880719.
[5] Khan RA, Menon P, Rao KL. Beware of neonatal appendicitis. J Indian Assoc Pediatr Surg 2010; 15(2):67-69. PMID: 20975787.
[6] Arora NK, Deorari AK, Bhatnagar V, Mitra DK, Singhal PK, Singh M. Neonatal appendicitis: A rare cause of surgical emergency in preterm babies. Indian Pediatr 1991; 28:1330-1333. PMID: 1808059.
[7] Karaman A, Cavuşoğlu YH, Karaman I, Cakmak O. Seven cases of neonatal appendicitis with a review of the English language literature of the last century. Pediatr Surg Int 2003; 19(11):707-709. PMID: 14689209.
[8] Huang X, Huang X, Mbugi J, et al. An experience with 31 cases of neonatal appendicitis: A retrospective study. J Neonatal Surg 2019; (8):21. https://www.jneonatalsurg.com/ojs./index.php/jns/article/view/885/728.
[9] Gadiparthi R, Waseem M. Pediatric appendicitis. StatPearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2020 Jan. 2020. PMID: 28722894.
[10] Bundy DG, Byerley JS, Liles EA, Perrin EM, Katznelson J, Rice HE. Does this child have appendicitis? JAMA 2007; 298(4):438-451. PMID: 17652298.
[11] Raveenthiran V. Neonatal appendicitis (Part 1): A review of 52 cases with abdominal manifestation. J Neonatal Surg 2015; 4(1):4. PMID: 26023528.
[12] Schorlemmer GR, Herbst CA. Perforated neonatal appendicitis. South Med J 1983; 76(4):536-537. PMID: 6340217.
[13] Martin LW, Perrin EV. Neonatal perforation of the appendix in association with Hirschsprung's disease. Ann Surg 1967; 166(5):799-802. PMID: 6057088.
[14] Bax NM, Pearse RG, Dommering N, Molenaar JC. Perforation of the appendix in the neonatal period. J Pediatr Surg 1980; 15(2):200-202. PMID: 7373503.
[15] Drapala B, Trognon B, Canarelli JP, et al. Appendicite neonatal. Arch Pediatr 2000; 7(8):896-897. PMID: 10985195.
[16] Jancelewicz T, Kim G, Miniati D. Neonatal appendicitis: A new look at an old zebra. J Pediatr Surg 2008; 43(10):e1-5. PMID: 18926195.

Keywords: neonate, appendicitis, emesis, multiple organ dysfunction syndrome, case report

KANSAS JOURNAL of MEDICINE

Acute Myeloid Leukemia Masquerading as Idiopathic Intracranial Hypertension: A Rare Initial Presentation

Abdul Wasay Khan, M.D.[1,2], Garrison Olds, MS-3[1], Farheen Malik, MS-4[4], Paul Teran, M.D.[1,2], Nathan Hall, D.O.[1,2,3], Mazahir Ali, M.D.[1,2]

[1]University of Kansas School of Medicine-Wichita, Wichita, KS

[2]Department of Pediatrics

[3]Division of Hematology/Oncology

[4]Dow University of Health Sciences, Pakistan

Received April 30, 2020; Accepted for publication Feb. 23, 2021; Published online May 21, 2021
https://doi.org/10.17161/kjm.vol1413646

INTRODUCTION

Acute Myeloid Leukemia (AML) is a rare childhood cancer that classically presents with fevers, bruising and bleeding, lymphadenopathy, hepatosplenomegaly, and cytopenias.[1] Intracranial hypertension has been reported as a sign of central nervous system (CNS) relapse or an adverse effect of treatment in pediatric acute promyelocytic leukemia (AML-M3) patients. AML rarely presents initially with increased intracranial pressure as described in this case review.

We report the case of a 12-year-old male who presented with complaints of gradual vision changes consistent with idiopathic intracranial hypertension (IIH) months prior to a diagnosis of AML. IIH is defined as increased intracranial pressure in the absence of a space-occupying lesion, enlargement of ventricles, or loss of consciousness. It classically presents with headaches, vision changes, cognitive impairment, and papilledema. However, this case suggested a further hematological workup for children with IIH may be necessary.

CASE REPORT

A 12-year-old boy without any significant past medical history was referred to an ophthalmologist for further evaluation of worsening headaches and papilledema. Papilledema was first detected during a vision exam for a new prescription of glasses by an optometrist. The ophthalmologic evaluation revealed diffuse increased nerve fiber layer and scattered defects with enlarged scotoma bilaterally. Fundus photos showed blurred margins bilaterally with vascular tortuosity and venous congestion (Figure 1). These signs of increased intracranial pressure led to a referral for admission to the pediatric hospital medicine service for further workup and management.

The patient reported no neck stiffness, photophobia, fever, or altered mental state on admission to the pediatric hospital medicine service. His headaches were described as progressive over the six months before admission and episodic without any known aggravating factors. They were mild in intensity (the patient self-scored a three on a numeric pain rating scale of 0-10). He did not require over-the-counter medications for pain relief. His mother reported no family history of any medical conditions.

Medical history revealed an optometrist had suspected papilledema on physical exam as early as nine months before presentation. The patient had severely decreased visual acuity (3/20) in the left eye since birth and normal visual acuity (20/20) in the right eye. General physical examination was unremarkable. He had no weakness, balance, seizure, or hearing problems. The physical exam also did not reveal lymphadenopathy, hepatosplenomegaly, bruising, bleeding, or petechiae. The patient's mother noted that he had gained 30 pounds since last year. His antenatal and postnatal histories were insignificant.

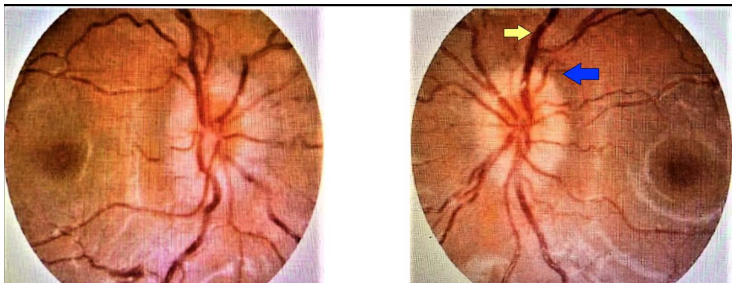


Figure 1. Fundus showed blurred margins bilaterally (blue arrow) with vascular tortuosity (yellow arrow) and venous congestion.

Magnetic resonance imaging (MRI) findings showed distention of optic nerve sheaths with flattening of posterior globes and pituitary gland. The ventricular system appeared slit-like. There were no space-occupying lesions or masses. These findings were highly suggestive of idiopathic intracranial hypertension (Figure 2). Lumbar puncture yielded an opening pressure of 38 cm H_2O. Despite the removal of 12 ml cerebrospinal fluid (CSF), the closing pressure remained high (33 cm H_2O). The patient was started on acetazolamide 250 mg orally twice daily. Incidentally, admission complete blood count (CBC) showed low hemoglobin of 10.7 gm/dL, mean corpuscular volume was 98 fL, platelet count was 93 x 10^3/µL, and an elevated white blood cell (WBC) count of 28 x 10^3/µL. Due to leukocytosis with bicytopenia (anemia and thrombocytopenia), a CBC was repeated and showed increased leukocytosis with a WBC count of 49 x 10^3/µL with 59% blast cells.

In contrast, cytology of CSF showed normal lymphocyte count with scattered monocytes, erythrocytes, a few neutrophils, eosinophils, and small numbers of blast cells (< 5%). Peripheral smear showed numerous blasts, and flow cytometry confirmed acute myeloid leukemia (AML). Bone marrow aspirate demonstrated that the patient had acute myeloid leukemia with minimal differentiation (AML-M0). A double-lumen port was placed in the operating room along with bone marrow biopsy and lumbar puncture with concurrent intrathecal cytarabine administration. He was transferred to the pediatric intensive care unit, where chemotherapy was started as per Children's Oncology Group protocol (AAML0531).

DISCUSSION

Idiopathic intracranial hypertension (IIH) characterizes increased intracranial pressure in the absence of a space-occupying lesion, enlargement of ventricles, or loss of consciousness.[2,3] IIH presents with nonspecific symptoms, including headache, visual loss, and papilledema. If not diagnosed and managed timely, it may result in permanent loss of vision, chronic headaches, and other neurological impairment. IIH is a diagnosis of exclusion and follows these Modified Dandy Criteria for IIH (Table 1).[4] Criteria include CSF pressure greater than 25 cm H_2O, the standard composition of cerebrospinal fluid, and the absence of any structural, anatomic, or vascular lesions that may cause increased intracranial pressure.[5]

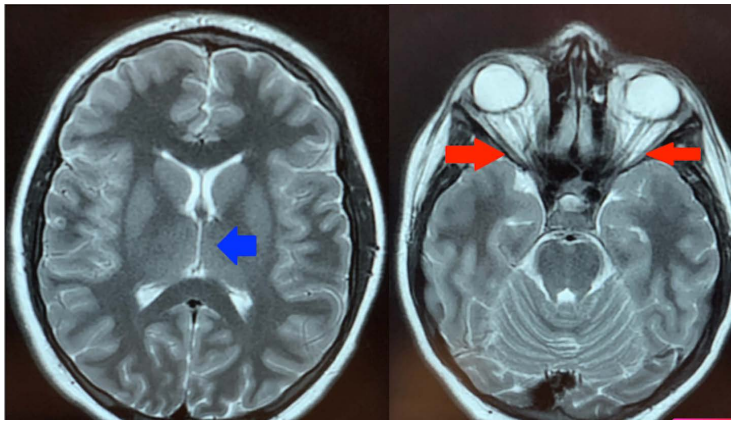


Figure 2. MRI found distention of optic nerve sheaths (Right figure; red arrow) with flattening of posterior globes and pituitary gland. The blue arrow on the left figure indicates slit like ventricles of IIH.

Table 1. Modified Dandy Criteria for IIH.[4]

1. Signs and symptoms of increased intracranial pressure.
2. Absence of localizing findings on neurologic examination.
3. Absence of deformity, displacement, or obstruction of the ventricular system and otherwise normal neurodiagnostic studies, except for evidence of increased cerebrospinal fluid pressure (> 250 mm H_20). Abnormal neuroimaging except for empty sella turcica, optic nerve sheath with filled out CSF spaces, and smooth-walled non-flow-related venous sinus stenosis or collapse should lead to another diagnosis.
4. Awake and alert patient.
5. No other cause of increased intracranial pressure present.

The pathophysiology of IIH remains uncertain. Hypotheses suggest etiologies related to CSF's overproduction, under-absorption of CSF, resistance to the outflow of CSF, or vascular congestion.[6-8] Risk factors for IIH include obesity, certain medications, excess vitamin A, severe anemia, coagulopathies, and Addison's disease.

AML is a malignancy that causes an increase in the number of myeloid cells of the bone marrow, their maturation arrest, and resulting hematopoietic insufficiency (granulocytopenia, thrombocytopenia, or anemia).[9] It may be accompanied by leukocytosis. AML often presents with signs of bone marrow abnormalities such as anemia, thrombocytopenia, and low or elevated white blood cells. Common symptoms include fatigue, bruising, bleeding, petechiae, and weight loss. Leukemia also can present initially with ocular manifestation attributed to neoplastic cells directly infiltrating the CNS.

AML presenting with isolated intracranial hypertension is extremely rare. Intracranial hypertension has been reported with CNS relapse of AML and a side effect of treatment of AML variants with all-trans retinoic acid. No case has been reported with AML initially presenting as IIH with papilledema.[2,10] Awareness of these ophthalmic manifestations should prompt further laboratory evaluation if no other causes are found and the working diagnosis is IIH.

The exact mechanism behind AML induced IIH has not been well established. To understand the relationship better, it is useful to know the varying mechanisms of IIH. One hypothesis to understand IIH is that increased viscosity resulting from lymphocytosis can lead to reduced CSF absorption.[11,12] This could be a likely cause in our patient as he had an elevated systemic WBC count. It also has been speculated that blasts cells can infiltrate the arachnoid granulations directly and alter CSF absorption.[13] Still, no such findings were seen on MRI in our case. Overcirculation of blood through the choroid plexus in cases of isolated anemia (due to high cardiac output secondary to anemia) can cause cerebrospinal fluid (CSF) overproduction. Anemia also may cause relative cerebral hypoxia activating autoregulatory mechanisms causing cerebral over circulation that may elevate intracranial pressure. Raised intracranial pressure causes increased optic nerve sheath pressure, leading to elevated ophthalmic venous pressure and reduced central retinal venous outflow and capillary perfusion.[14,15]

CONCLUSIONS

AML presenting with intracranial hypertension is rare, but this case demonstrated the possibility. This critical case was presented to broaden clinicians' differential when a child presents with intracranial hypertension and gradual vision changes. Early detection of papilledema/IIH without a reasonable explanation warrants further workup with a complete blood count with differential, MRI followed by CSF studies including a cell count, pathology review, and flow cytometry to evaluate for leukemic infiltration. Due to the paucity of information regarding pediatric AML and the association of IIH, further investigation is warranted. A retrospective analysis from large clinical trials in the Children's Oncology Group may be warranted to evaluate the incidence of intracranial hypertension in children that present with newly diagnosed AML. Both scientific and clinical studies are imperative to define the underlying mechanisms and enhance our ability to evaluate and treat similar patients effectively in the future.

REFERENCES

[1] Gibson BES, Wheatley K, Hann IM, et al. Treatment strategy and long-term results in paediatric patients treated in consecutive UK AML trials. Leukemia 2005; 19(12):2130-2138. PMID: 16304572.
[2] Lipton J, Joffe S, Ullrich NJ. CNS relapse of acute myelogenous leukemia masquerading as pseudotumor cerebri. Pediatr Neurol 2008; 39(5):355-357. PMID: 18940560.
[3] Mercille G, Ospina LH. Pediatric idiopathic intracranial hypertension: A review. Pediatr Rev 2007; 28(11):77-86. PMID: 17974701.
[4] Smith JL. Whence pseudotumor cerebri? J Clin Neuroophthalmol 1985; 5(1):55-56. PMID: 3156890.
[5] Friedman DI, Jacobson DM. Diagnostic criteria for idiopathic intracranial hypertension. Neurology 2002; 59(10):1492-1495. PMID: 12455560.
[6] Kesler A, Goldhammer Y, Hadayer A, Pianka P. The outcome of pseudotumor cerebri induced by tetracycline therapy. Acta Neurol Scand 2004; 110(6):408-411. PMID: 15527455.
[7] Warner JE, Larson AJ, Bhosale P, et al. Retinol-binding protein and retinol analysis in cerebrospinal fluid and serum of patients with and without idiopathic intracranial hypertension. J Neuroophthal 2007; 27(4):258-262. PMID: 18090557.
[8] Deonna T, Guignard JP. Acute intracranial hypertension after nalidixic acid administration. Arch Dis Child 1974; 49(9):743. PMID: 4419059.
[9] De Kouchkovsky I, Abdul-Hay M. Acute myeloid leukemia: A comprehensive review and 2016 update. Blood Cancer J 2016; 6(7):e441. PMID: 27367478.
[10] Holmes D, Vishnu P, Dorer RK, Aboulafia DM. All-trans retinoic acid-induced pseudotumor cerebri during induction therapy for acute promyelocytic leukemia: A case report and literature review. Case Rep Oncol Med 2012; 2012:313057. PMID: 22701192.
[11] Guymer RH, Cairns JD, O'Day J. Benign intracranial hypertension in chronic myeloid leukemia. Aust N Z J Ophthalmol 1993; 21(3):181-185. PMID: 8260157.
[12] Nguyen HS, Haider KM, Ackerman LL. Unusual causes of papilledema: Two illustrative cases. Surg Neurol Int 2013; 4:60. PMID: 23646270.

[13] Carr F, Tan K, Stevenson W, Ahmad K. A case of acute myeloid leukemia presenting as subacute intracranial hypertension in a young adult. Neuroophthalmology 2018; 43(5):313:317. PMID: 31741676.
[14] Berk J, Hall D, Stroh I, et al. A child with pancytopenia and optic disc swelling. Pediatrics 2019; 144(5):pii:e20182887. PMID: 31594907.
[15] Hayreh SS, Edwards J. Ophthalmic arterial and venous pressures. Effects of acute intracranial hypertension. Br J Ophthalmol 1971; 55(10):649-663. PMID: 5124843.

Keywords: acute myeloid leukemia, idiopathic intracranial hypertension

KANSAS JOURNAL of MEDICINE

The Relationship Between Functional Dyspepsia, PPI Therapy, and the Gastric Microbiome

Balaji R. Jagdish, B.S.[1],
William R. Kilgore III, M.D., FACP, AGAF[2,3]
[1]Kansas City University of Medicine and Biosciences, Kansas City, MO
[2]Ascension Via Christi, Wichita, KS
[3]University of Kansas School of Medicine-Wichita, Wichita, KS
Department of Internal Medicine

Received Nov. 13, 2020; Accepted for publication Feb. 17, 2021; Published online May 21, 2021
https://doi.org/10.17161/kjm.vol1414831

INTRODUCTION

Dyspepsia refers to symptoms originating from the gastroduodenal region and includes etiologies such as gastroesophageal reflux, hiatal hernias, peptic ulcers, *H. pylori* infections, erosive gastritis, and gastroesophageal malignancy.[1,2] Symptomology often varies, but may include nausea, vomiting, heartburn, dysphagia, and chest pain. Dyspepsia affects about 40% of the general population and etiologies often can be diagnosed with the use of esophagogastro-duodenoscopy (EGD).[3] Despite the use of EGDs, 70% of patients diagnosed with dyspepsia are negative for any structural or infectious (i.e., *H. pylori*) etiology.[4] In such patients, the diagnosis of functional dyspepsia (FD) often is made.

FD can be defined as frequent or continuous uncomfortable postprandial fullness, epigastric pain and/or epigastric burning, early satiation in the absence of an organic etiology.[4-6] The prevalence of these symptoms varies amongst patients with about 90% of patients with FD experiencing epigastric pain, 75 - 88% experiencing postprandial fullness, and 50 - 82% experiencing early satiety.[7] Due to the absence of organic disease, FD can be debilitating to patients as it is difficult to identify and eradicate the inciting factor. Despite this, the use of proton pump inhibitors (PPIs) are used widely as first-line treatment in patients with FD.[1,7,8] Although PPIs do not necessarily eradicate FD amongst patients, they moderately may subdue upper gastroduodenal symptoms and subsequently are used widely in outpatient clinics as a treatment modality. For instance, a meta-analysis demonstrated that PPIs were statistically more effective in treating patients with FD than compared to the placebo.[9] However, the effectiveness of PPI therapy in such patients was minimal. For example, the relative risk reduction in the PPI group was only 13% when compared to the placebo group. Additionally, another meta-analysis analyzing various treatment modalities for FD demonstrated that the therapeutic efficacy of PPIs in patients was only 7 – 10%.[7] Consequently, many patients with FD on PPIs are refractory to therapy and continue to experience symptoms.

Given that PPIs are known to increase the pH of the human stomach and that *H. pylori* negative gastritis is relatively common (1.5% - 21% of all gastritis), this review discusses the role of PPIs on the stomach microbiome.[10] More specifically, this review explores the role of non-*H. pylori* bacteria, such as *Streptococcus* genus, as a highly suggestive potential cause for FD in patients, the influence of PPIs on the growth of this type of bacteria, and the implications for treatment of patients with FD.

Microbiome and PPI Use

The human gut microbiome is a diverse community of microorganisms that often can be considered a separate human organ.[11] Weighing up to two kilograms, the gut microbiome plays a critical role in helping maintain homeostasis within the human body. With the stomach's natural harsher acidic environment, the stomach's microbial load is much smaller than that of the remaining gastrointestinal tract. In the stomach, the microbial load is often between 10^2-10^4 colony-forming units/mL of bacteria while in the colon, the bacterial load is between 10^{10}-10^{12} colony-forming units/mL.[12] Despite this substantial decrease in microbial load within the stomach, the existing bacterial diversity of the organ plays a crucial role in its daily function.

While the bacterial community of the stomach is diverse, certain phyla of bacteria dominate the composition in healthy patients at baseline. For instance, a study using 16S rDNA sequencing to classify gastric bacterial phyla found that in *H. pylori* negative patients, five phyla dominated the gastric microbiome.[13] In decreasing order of density, these were non-*H. pylori* Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria, and Fusobacteria. Similarly, another study using barcoded pyrosequencing found that amongst healthy *H. pylori* negative patients, the same five phyla dominated the gastric microbiome.[14] Additionally, a study using 16S rDNA sequencing to compare the gastric microbiome between normal and gastritis patients found similar results with the average composition being Proteobacteria (37%), Firmicutes (22%), Bacteroidetes (28%), Actinobacteria (8%), and Fusobacteria (4%) in healthy patients.[15] The interrelationship that exists between these five phyla and their respective relative compositional ratios between one another seem to maintain gastric homeostasis. Consequently, it is when this gastric microbial compositional ratio is altered favoring Firmicutes growth, specifically the *Streptococcus* genus, that patients become prone to dyspepsia.[10]

A study analyzing gastric microbiota amongst *H. pylori* negative gastritis patients, *H. pylori* positive gastritis patients, and *H. pylori* negative non-gastritis patients (control group) without prior PPI therapy for at least six months found that compared to the healthy control group, *H. pylori* negative gastritis patients had an increased abundance of *Streptococcus* species and *Hemophilus parainfluenza*.[10] *Streptococcus* species and *Hemophilus parainfluenza* were at a significantly increased risk for *H. pylori* negative gastritis with an odds ratio of 18.9 (95% CI 2.1 - 172.8, $p < 0.009$) and 12.3 (95% CI 1.4 - 109.6, $p < 0.025$), respectively. Also, in the *H. pylori* positive gastritis group, *H. pylori* was instead the most abundant group. Consequently, *Streptococcus* was indicated as a candidate pathogenic bacterial species for *H. pylori* negative gastritis. Additionally, patients with *H. pylori* negative gastritis without any history of prior non-steroidal anti-inflammatory drug use had a significantly greater abundance of Firmicutes in antral biopsies compared to control patients where proteobacteria was dominant.[15] More specifically, it was *Streptococcus* species within the Firmicutes phyla that was increased significantly amongst gastritis patients. *Streptococcus* species was 72% higher in the antral biopsies and 66% higher in the gastric body biopsies of gastritis patients when compared to control patients.

Furthermore, similar results were found in a study comparing the bacterial composition of gastric mucosa and gastric juices between patients with and without chronic gastritis.[16] In this study, patients suffering from chronic gastritis, who were not undergoing any PPI or nonsteroidal anti-inflammatory drug therapy, had higher rates of *H. pylori, Streptococcus mitis,* and *Neisseria* species colonizing their gastric mucosa compared to control patients. Finally, another study looking at the mucosa-associated microbiota between FD and healthy patients using 16S rRNA sequencing, found that *Streptococcus* species were increased significantly in the FD patients and the relative abundance of the bacterium was correlated positively with the upper gastrointestinal symptoms in the FD patients.[6] Consequently, there exists a relationship between the bacterial overgrowth of *Streptococcus* species in the stomach and dyspepsia in patients.

This finding is congruent with the limited current literature regarding *Streptococcus* species and the bacteria's natural acid producing nature. For instance, a study using a pH-sensitive green fluorescent protein as an in vivo, in situ pH meter to monitor *Streptococcus* acid production demonstrated that when introduced to sucrose, the bacteria lowered the environmental pH via acid production.[17] Additionally, Senadheera et al.[18], studying acid production and acid survival in *Streptococcus* mutans, demonstrated that the bacterial species possessed key proteins involved in acid production. While these studies were designed to understand *Streptococcus* species' role of acid production in the oral cavity better, it is believed that the bacterium retains its acid producing abilities and acts similarly in the stomach.

Finally, a study looking at the differences in bacterial activation of neutrophils demonstrated that streptococcal strains induced significantly higher release of heparin-binding protein (HBP) and the cysteine-rich adipocytokine, resistin.[19] HBP has been associated with immunostimulatory activity while resistin has been characterized as a potent pro-inflammatory molecule associated with inflammatory conditions. Consequently, through the activation of neutrophils and release of these two proteins, *Streptococcus* species allow for a pro-inflammatory state that could contribute to the symptoms of FD. This notion of a pro-inflammatory response playing a role in FD is similar to the findings by Wauters et al.[20] and Liebregts et al.[21] Wauters et al.[20] showed that functional dyspepsia in children was found to be strongly associated with duodenal eosinophilia and suggestive of the role of a pro-inflammatory state secondary to eosinophilic inflammation in FD. Liebregts et al.[21] demonstrated that amongst *H. pylori* negative FD patients and healthy matched controls, the former group had significantly higher levels of TNF alpha, IL-1B, and IL-10 compared to the latter group. Additionally, amongst the *H. pylori* negative FD patients, an increase in cellular immune activation with increased small bowel homing T cells was seen, indicating an overall pro-inflammatory state involvement in FD patients. Furthermore, IL-1B, IL-10, and small bowel homing T cells also were significantly correlated to the intensity of dyspeptic symptoms including epigastric pain, abdominal cramps, nausea, and vomiting in the *H. pylori* negative FD patient group. While TNF alpha, IL-1B, and the increase in recruitment of T cells were congruent in the overall pro-inflammatory setting of FD, the increase in anti-inflammatory IL-10 was not. One possible explanation for the phenomenon was that IL-10 is produced increasingly to subdue the overly inflammatory state and shift the immune response from a Th1 to a Th2 response.[22] However, studies, such as Kindt et al.[22], demonstrated a decrease in IL-10 amongst FD patients, suggesting that levels of IL-10 depend on the onset of FD (acute vs. chronic) and warranting further research on the topic.

Interestingly, this bacterial overgrowth of *Streptococcus* species has been seen in patients undergoing PPI therapy. For instance, Sterbini et al.[1] analyzed gastric mucosal biopsies of 24 dyspeptic patients, 12 of whom were undergoing PPI therapy for at least the past 12 months and 12 of whom were not on PPI therapy or had not been for at least six months prior to the study. The study demonstrated that the Firmicutes phylum, specifically *Streptococcus* species, was increased significantly in relative abundance in patients on PPI therapy when compared to the untreated group of patients. Additionally, *Streptococcus* species were increased significantly in relation to PPI treatment and independent of *H. pylori* infection.

Another study, analyzing fecal microbiota using 16S and 23S rRNA-target quantitative RT-PCR in patients with reflux esophagitis receiving PPI therapy for eight weeks, demonstrated that *Streptococcus* species was increased significantly in patients at the four and eight weeks of PPI therapy compared to before the start of the treatment.[23] Additionally, Parsons et al.[24] demonstrated using 16S rRNA sequencing on RNA extracted from gastric corpus biopsies on *H. pylori* negative gastritis patients on PPI therapy that *Streptococcus* species were increased significantly in these individuals compared to the control patients whom were without any gastritis nor on PPI therapy.

Finally, a study analyzing the bacterial composition of the gastric juice and gastric mucosa of patients with GERD on acid inhibitory therapy vs. dyspeptic patients with no acid inhibitory therapy demonstrated that the prevalence of non-*H. pylori* bacteria was significantly higher in former group.[25] More specifically, patients on PPI therapy had a higher prevalence of particularly oropharyngeal flora (*Neisseria* species, *Streptococcus* species, and *Corynebacterium* species) in the gastric juice compared to dyspeptic patients not receiving acid inhibitory treatment or histamine 2 blocker therapy.

Furthermore, the effects of PPI therapy extend beyond the gastric microbiome and involve similar changes in the gut microbiome. For instance, Jackson et al.[26] analyzed the relationship between PPI use and the effects on the gut microbiome in 1,827 twins. Using 16S rRNA sequencing on stool samples, PPI users had a significantly higher abundance of pharyngeal commensals in the gut compared to those not on PPI therapy, mainly *Streptococcaceae* and *Micrococcaceae*. In addition, the study showed that amongst monozygotic twins with discordant for PPI use that there was a higher abundance of *Streptococcaceae* in those that were on PPI therapy.

Another study comparing the microbial composition of stool samples of patients with greater than or equal to five years of continuous PPI therapy vs. patients on no PPI therapy demonstrated that Firmicutes was in higher abundance in the stools of the PPI therapy group.[27] More

specifically amongst the Firmicutes phylum, *Streptococcus* along with *Lachnospiraceae* family, *Holdemania* and *Blautia* were found to be in higher abundance. Finally, a meta-analysis analyzing the stool samples of 211 patients on PPI therapy showed that compared to those patients not on PPI therapy, patients on PPI therapy had a significant increase in the following bacteria: *Enterococcus*, *Streptococcus*, *Staphylococcus*, and potentially pathogenic species *Escherichia coli*.[28] This change seen in the gut microbiome was more prominent than the changes in the microbiome seen with either antibiotics or other commonly used drugs in the study.

Consequently, a relationship appears to exist between an overgrowth of *Streptococcus* species in the gastric microbiome and dyspepsia in patients. PPI therapy leads to an overgrowth of *Streptococcus* species in the gastric microbiome and subsequently may contribute to dyspepsia in patients. While there is a lack of literature on temporal studies exploring *Streptococcus* species causality in FD, Mishiro et al.[29] recently demonstrated that when healthy non-dyspeptic patients with no probiotic use within the past three months or prior medical treatments were treated with esomeprazole 20 mg for four weeks, they had a statistically significant increase in *Streptococcus* species in their fecal microbiome. Additionally, apart from the increase in *Streptococcus* species, the overall fecal microbial composition remained otherwise stable amongst the study population post-PPI treatment. Finally, while patients did not necessarily have an onset of dyspeptic symptoms after the brief study; due to the various strains of *Streptococcus* species that exist, the lack of symptoms could be due to an overgrowth of a particular non-pathological strain of *Streptococcus* in the study patients. Thus, further research is warranted to identify strains of pathologic acid inducing strains of *Streptococcus* species that could multiply with PPI use and lead to FD.[29]

These findings from the above studies taken together provide a plausible explanation for why patients with dyspepsia often are diagnosed with FD with no known etiology and when put on PPI therapy, have a low rate of therapeutic improvement. With no standard method for streptococcal species detection in gastric biopsies or eradication of the bacteria used in the clinical setting, patients often are undiagnosed after being ruled out for structural causes and *H. pylori* infection of their dyspepsia. With an unknown existing potential overgrowth of streptococcal species, specifically acid producing strains, in patients' gastric microbiome, patients who are prescribed PPIs as part of the standard treatment for FD can exacerbate their pre-existing streptococcal species overgrowth further. Thus, patients enter a vicious cycle in which they can never truly rid themselves of their dyspepsia.

Given the evidence within the literature, especially with studies such as Liu et al.[16] demonstrating a statistically significant relationship between the abundance of *Streptococcus* species and FD symptoms in patients, this review proposes the idea that while *Streptococcus* species clearly is correlated to FD in patients, that it may in fact be a pathological cause for FD that is exacerbated by PPI use (Figure 1). Due to the very limited literature on the topic, further studies should be conducted, specifically temporal studies and animal studies with direct inoculation of the microbiome with *Streptococcus* species to explore the very suggestive possible causality of streptococcal species in FD.

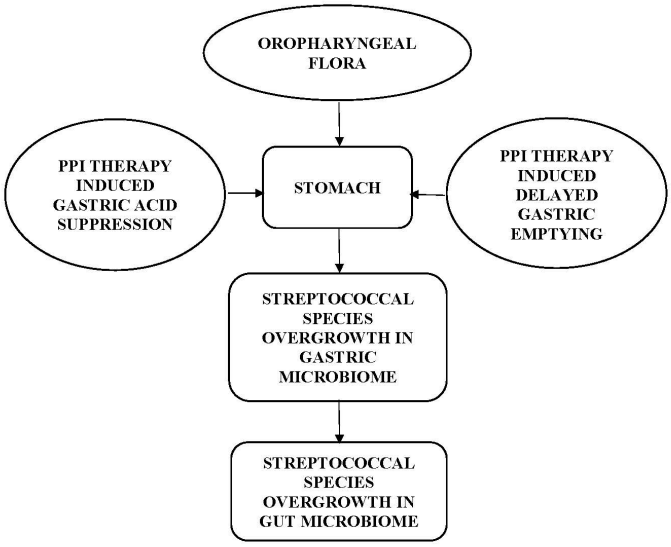


Figure 1. Diagram shows that *Streptococcus* species is correlated to FD in patients, but it may be a pathological cause for FD that is exacerbated by PPI use.

Mechanism of Action of PPI Therapy on Streptococcal Overgrowth

While it is evident that PPI therapy influences the composition of the gastric microbiome, the mechanism by which PPIs alter it is not well known. However, the two main theories that exist are that PPI therapy induces a favorable environment for microbial growth via raising the gastric pH and inducing gastroparesis.[8,23,30]

The stomach's acidic environment often makes it inhospitable to bacterial overgrowth, killing bacteria within 15 minutes when the pH is less than three.[30] However, when placed on PPI therapy, the pH of patients' stomach often is elevated to a pH of four or greater. For instance, Sanduleanu et al.[25] found that in their study population, fasting gastric juice pH values above four were measured more frequently in patients on PPI therapy than in those on histamine 2 blockers or patients on no acid suppressive therapy. Consequently, this creation of an achlorhydric environment removes the protective barrier function of the stomach, allowing translocation of oropharyngeal bacteria to the stomach and further colonization of this bacteria in the stomach.[26] This overgrowth of bacteria in the stomach offers bacteria the opportunity to later extend into and colonize the gut microbiome, and explains the abundance of *Streptococcus* species found in fecal samples of patients on PPI therapy.

Furthermore, Tsuda et al.[31] demonstrated that the salivary microbiota and gastric microbiota were similar in composition in both PPI and non-PPI patients, with a significant increase of *Streptococcus* species in the fecal matter of PPI-users. PPI users had a one thousand times greater bacterial growth in their stomach compared to non-PPI users. Consequently, the study suggested that the suppression of gastric acid secretion in PPI-users allowed the normal oropharyngeal flora that usually passes to the stomach via eating and swallowing to overgrow, subsequently influencing the relative abundance of bacteria as it passed

to the fecal microbiome. Hojo et al. [23] theorized that a reason for their findings was that PPI's effects on gastric suppression allowed for potential bacterial translocation from the oral cavity to the upper GI tract.

Regarding the second theory, PPI therapy inducing gastroparesis in patients, it is important to consider the "acid-pepsin maldigestion hypothesis".[8] Normally, the process of gastric emptying of solids involves peptic hydrolysis. However, with the reduction of gastric acid via PPI use, this hydrolytic process is impaired due to the deactivation of pepsin, subsequently prolonging gastric emptying time.

This hypothesis is supported by several studies in the literature. For instance, Tougas et al.[32] demonstrated that omeprazole increased the time required for gastric half-emptying by 17 minutes. Benini et al.[33] showed that with a four-day pretreatment with 40 mg of omeprazole in patients, gastric emptying time significantly increased from 199.6 minutes at baseline to 230.9 minutes. Rasmussen et al.[34] also demonstrated delayed gastric emptying in patients treated with 40 mg of omeprazole daily for ten days. Lastly, Parkman et al.[35] showed that omeprazole's suppression of gastric acid augmented the amplitude of postprandial antral contractions. This increase in antral contractility paradoxically prolongs gastric emptying due to failed harmonization of antral contraction with pyloric opening.[8,35] These findings compounded with studies demonstrating relationships between delayed gastric emptying times and FD in patients provided a secondary plausible explanation of how PPI therapy can contribute to bacterial overgrowth.[36,37] With delaying gastric emptying time, PPI therapy allows for increased periods of gastric content stasis, allowing bacteria the opportunity to multiply.

With both theories taken together, PPI use may induce a perfect environment for streptococcal species traveling from the oropharynx to take residence in the stomach and predominate the gastric microbiota leading to FD in patients. However, with the current limited research regarding the matter, further research is warranted to explore other possible theories.

Clinical Implications

While the current literature regarding therapeutic modalities for patients with streptococcal species overgrowth is limited, studies focusing on the use of novel prokinetic agents in patients with FD have showed promising results, offering a potential avenue for therapeutic intervention in patients with *Streptococcus* species overgrowth. For instance, studies have focused on the use of acotiamide, a drug that promotes acetylcholine release and inhibits acetylcholinesterase, to improve gastric emptying time in patients with FD and subsequently diminish symptoms in such patients. One such study was a phase III trial in which patients with FD either received a placebo three times a day for four weeks or 100 mg of acotiamide three times a day for four weeks.[38] Matsueda et al.[38] demonstrated that in those patients receiving acotiamide, symptom severity significantly improved, and meal-related symptoms were eliminated. Additionally, they reported that the number needed to treat for a reduction in dyspeptic symptoms was 6, while the number needed to treat for elimination of all dyspeptic symptoms was 16.

Another study analyzing the effectiveness of acotiamide in 34 patients with FD demonstrated that the drug significantly improved gastric accommodation, gastric emptying, and dyspeptic symptoms in patients.[39] Additionally, a review looking at drug DA-9701 (Motilitone), a botanical drug compound derived from the plants Pharbitidis Semen and Corydalis Tuber and approved for treatment for FD in South Korea, demonstrated that DA-9701 decreased dyspeptic symptoms and improved GI function in FD patients.[40] DA-9701 has an affinity for dopamine, serotonin, and adrenergic receptors, thus helps to improve gastric emptying via multiple physiological pathways. However, the side effect profile of the drug is not understood fully. Hence, gastric statis can be reduced with the use of prokinetic agents and consequently reduce bacterial over colonization.

Furthermore, studies looking at directly targeting streptococcal species acid production have created the potential for other treatment modalities. For instance, Senadheera et al.[18] demonstrated that deletion of the VicK sensor kinase in *Streptoccocus* mutans bacterium caused a significant decrease in the bacterium's acid production, but paradoxically increased the bacterium's survival in acidic conditions compared to the wild-type strain. Additionally, Sekiya et al.[41] demonstrated that the compounds piceatannol, curcumin, and demethoxycurcumin strongly reduced the F-ATPase activity of *Streptococcocus* mutans, a proton-pump that is important in the bacteria's acid tolerance abilities. The study showed that these compounds inhibited the growth of *Streptococcus* mutans at a pH of 5.3 and significantly reduced the colony-forming ability at a pH of 4.3. Consequently, with PPI therapy often increasing gastric pH levels to levels greater than 4.0 and allowing overgrowth of *Streptococcocus* species, the findings by Seikya et al.[41] offer a promising potential therapeutic intervention for *Streptococcous* species eradication in FD patients. Finally, the use of probiotics in resetting the gastric microbiome may be another possibility for treatment of patients with FD but warrants further research.[31]

CONCLUSIONS

While PPI therapy is the first line treatment in patients with FD, it may worsen patients' FD through the overgrowth of non-*H. pylori* bacteria in the gastric microbiome, specifically *Streptococcus* species, via gastric acid suppression and delayed gastric emptying. This overgrowth may be translocated to the gut and influence the gut microbiome as well. While the literature is limited, studies have provided promising therapeutic approaches in effectively decreasing symptoms in patients with FD through the inhibition of streptococcal species growth both directly and indirectly. Despite this, further research is warranted to understand the gastric microbiome and its role in FD, explore the highly potential causality of *Streptococcus* species in FD, and develop efficient diagnostic modalities to test patients with FD for different *Streptococcus* species strains in the clinical setting and drug targets against the bacterium.

REFERENCES

[1] Paroni Sterbini F, Palladini A, Masucci L, et al. Effects of proton pump inhibitors on the gastric mucosa-associated microbiota in dyspeptic patients. Appl Environ Microbiol 2016; 82(22):6633-6644. PMID: 27590821.
[2] Vesper BJ, Jawdi A, Altman KW, Haines GK 3rd, Tao L, Radosevich JA. The effect of proton pump inhibitors on the human microbiota. Curr Drug Metab 2009; 10(1):84-89. PMID: 19149516.
[3] Ford AC, Moayyedi P. Dyspepsia. Curr Opin Gastroenterol 2013; 29(6):662-668. PMID: 24100727.
[4] Scarpignato C, Gatta L, Zullo A, et al. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med 2016; 14(1):179. PMID: 27825371.
[5] Tack J, Carbone F. Functional dyspepsia and gastroparesis. Curr Opin Gastroenterol 2017; 33(6):446-454. PMID: 28832359.
[6] Fukui A, Takagi T, Naito Y, et al. Higher levels of streptococcus in upper gastrointestinal mucosa associated with symptoms in patients with functional dyspepsia. Digestion 2020; 101(1):38-45. PMID: 31752012.
[7] Lacy BE, Talley NJ, Locke GR 3rd, et al. Review article: Current treatment options and management of functional dyspepsia. Aliment Pharmacol Ther 2012; 36(1):3-15. PMID: 22591037.
[8] Sanaka M, Yamamoto T, Kuyama Y. Effects of proton pump inhibitors on gastric emptying: A systematic review. Dig Dis Sci 2010; 55(9):2431-2440. PMID: 20012198.
[9] Moayyedi P, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. Cochrane Database Syst Rev 2006; (4):CD001960. PMID: 17054151.
[10] Gantuya B, El-Serag HB, Matsumoto T, et al. Gastric microbiota in Helicobacter pylori-negative and -positive gastritis among high incidence of gastric cancer area. Cancers (Basel) 2019; 11(4):504. PMID: 30974798.
[11] Sgambato D, Miranda A, Romano L, Romano M. Gut microbiota and gastric disease. Minerva Gastroenterol Dietol 2017; 63(4):345-354. PMID: 28206729.
[12] Ianiro G, Molina-Infante J, Gasbarrini A. Gastric microbiota. Helicobacter 2015; 20(Suppl 1):68-71. PMID: 26372828.
[13] Bik EM, Eckburg PB, Gill SR, et al. Molecular analysis of the bacterial microbiota in the human stomach. Proc Natl Acad Sci U S A 2006; 103(3):732-737. PMID: 16407106.
[14] Andersson AF, Lindberg M, Jakobsson H, Bäckhed F, Nyrén P, Engstrand L. Comparative analysis of human gut microbiota by barcoded pyrosequencing. PLoS One 2008; 3(7):e2836. PMID: 18665274.
[15] Li XX, Wong GL, To KF, et al. Bacterial microbiota profiling in gastritis without Helicobacter pylori infection or non-steroidal anti-inflammatory drug use. PLoS One 2009; 4(11):e7985. PMID: 19956741.
[16] Liu J, Xue Y, Zhou L. Detection of gastritis-associated pathogens by culturing of gastric juice and mucosa. Int J Clin Exp Pathol 2018; 11(4):2214-2220. PMID: 31938333.
[17] Guo L, Hu W, He X, Lux R, McLean J, Shi W. Investigating acid production by Streptococcus mutans with a surface-displayed pH-sensitive green fluorescent protein. PLoS One 2013; 8(2):e57182. PMID: 23468929.
[18] Senadheera D, Krastel K, Mair R, et al. Inactivation of VicK affects acid production and acid survival of Streptococcus mutans. J Bacteriol 2009; 191(20):6415-6424. PMID: 19684142.
[19] Snäll J, Linnér A, Uhlmann J, et al. Differential neutrophil responses to bacterial stimuli: Streptococcal strains are potent inducers of heparin-binding protein and resistin-release. Sci Rep 2016; 6:21288. PMID: 26887258.
[20] Wauters L, Nightingale S, Talley NJ, Sulaiman B, Walker MM. Functional dyspepsia is associated with duodenal eosinophilia in an Australian paediatric cohort. Aliment Pharmacol Ther 2017; 45(10):1358-1364. PMID: 28326599.
[21] Liebregts T, Adam B, Bredack C, et al. Small bowel homing T cells are associated with symptoms and delayed gastric emptying in functional dyspepsia. Am J Gastroenterol 2011; 106(6):1089-1098. PMID: 21245834.
[22] Kindt S, Van Oudenhove L, Broekaert D, et al. Immune dysfunction in patients with functional gastrointestinal disorders. Neurogastroenterol Motil 2009; 21(4):389-398. PMID: 19126184.
[23] Hojo M, Asahara T, Nagahara A, et al. Gut microbiota composition before and after use of proton pump inhibitors. Dig Dis Sci 2018; 63(11):2940-2949. PMID: 29796911.
[24] Parsons BN, Ijaz UZ, D'Amore R, et al. Comparison of the human gastric microbiota in hypochlorhydric states arising as a result of Helicobacter pylori-induced atrophic gastritis, autoimmune atrophic gastritis and proton pump inhibitor use. PLoS Pathog 2017; 13(11):e1006653. PMID: 29095917.
[25] Sanduleanu S, Jonkers D, De Bruine A, Hameeteman W, Stockbrügger RW. Non-Helicobacter pylori bacterial flora during acid-suppressive therapy: Differential findings in gastric juice and gastric mucosa. Aliment Pharmacol Ther 2001; 15(3):379-388. PMID: 11207513.
[26] Jackson MA, Goodrich JK, Maxan ME, et al. Proton pump inhibitors alter the composition of the gut microbiota. Gut 2016; 65(5):749-756. PMID: 26719299.
[27] Clooney AG, Bernstein CN, Leslie WD, et al. A comparison of the gut microbiome between long-term users and non-users of proton pump inhibitors. Aliment Pharmacol Ther 2016; 43(9):974-984. PMID: 26923470.
[28] Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. Gut 2016; 65(5):740-748. PMID: 26657899.
[29] Mishiro T, Oka K, Kuroki Y, et al. Oral microbiome alterations of healthy volunteers with proton pump inhibitor. J Gastroenterol Hepatol 2018; 33(5):1059-1066. PMID: 29105152.
[30] Canani RB, Terrin G. Gastric acidity inhibitors and the risk of intestinal infections. Curr Opin Gastroenterol 2010; 26(1):31-35. PMID: 19907324.
[31] Tsuda A, Suda W, Morita H, et al. Influence of proton-pump inhibitors on the luminal microbiota in the gastrointestinal tract. Clin Transl Gastroenterol 2015; 6(6):e89. PMID: 26065717.
[32] Tougas G, Earnest DL, Chen Y, Vanderkoy C, Rojavin M. Omeprazole delays gastric emptying in healthy volunteers: An effect prevented by tegaserod. Aliment Pharmacol Ther 2005; 22(1):59-65. PMID: 15963081.
[33] Benini L, Castellani G, Bardelli E, et al. Omeprazole causes delay in gastric emptying of digestible meals. Dig Dis Sci 1996; 41(3):469-474. PMID: 8617117.
[34] Rasmussen L, Oster-Jørgensen E, Qvist N, Kraglund K, Hovendal C, Pedersen SA. Short report: A double-blind placebo-controlled trial of omeprazole on characteristics of gastric emptying in healthy subjects. Aliment Pharmacol Ther 1991; 5(1):85-89. PMID: 1932485.
[35] Parkman HP, Urbain JL, Knight LC, et al. Effect of gastric acid suppressants on human gastric motility. Gut 1998; 42(2):243-250. PMID: 9536950.
[36] Vanheel H, Carbone F, Valvekens L, et al. Pathophysiological abnormalities in functional dyspepsia subgroups according to the Rome III criteria. Am J Gastroenterol 2017; 112(1):132-140. PMID: 27958284.
[37] DiBaise JK, Patel N, Noelting J, Dueck AC, Roarke M, Crowell MD. The relationship among gastroparetic symptoms, quality of life, and gastric emptying in patients referred for gastric emptying testing. Neurogastroenterol Motil 2016; 28(2):234-242. PMID: 26547484.
[38] Matsueda K, Hongo M, Tack J, Saito Y, Kato H. A placebo-controlled trial of acotiamide for meal-related symptoms of functional dyspepsia. Gut 2012; 61(6):821-828. PMID: 221557329.
[39] Kusunoki H, Haruma K, Manabe N, et al. Therapeutic efficacy of acotiamide in patients with functional dyspepsia based on enhanced postprandial gastric accommodation and emptying: Randomized controlled study evaluation by real-time ultrasonography. Neurogastroenterol Motil 2012; 24(6):540-545; e250-e251. PMID: 22385472.
[40] Jin M, Son M. DA-9701 (Motilitone): A multi-targeting botanical drug for the treatment of functional dyspepsia. Int J Mol Sci 2018; 19(12):4035. PMID: 30551633.
[41] Sekiya M, Izumisawa S, Iwamoto-Kihara A, et al. Proton-pumping F-ATPase plays an important role in Streptococcus mutans under acidic conditions. Arch Biochem Biophys 2019; 666:46-51. PMID: 30930283.

Keywords: dyspepsia, proton pump inhibitors, gastric microbiome, gastroenterology

KANSAS JOURNAL OF MEDICINE

VOLUME 14 • 2021

journals.ku.edu/kjm

Have a manuscript ready to publish?
Visit our website for instructions on submitting a manuscript.

Frontiers: University of Kansas Clinical and Translational Science Institute is a collaborating partner of the Kansas Journal of Medicine

Office of Research
1010 N. Kansas, Wichita, KS 67214
316-293-2617 • Email: kjm@kumc.edu

VOLUME 14 • 2021

WHAT'S INSIDE: ORIGINAL RESEARCH • CASE REPORT

KANSAS JOURNAL of MEDICINE

TABLE OF CONTENTS

KANSAS JOURNAL of MEDICINE

Early Versus Delayed Mobilization Post-Operative Protocols for Primary Lateral Ankle Ligament Reconstruction: A Systematic Review and Meta-Analysis

Matthew L. Vopat, M.D.[1], Alexander Wendling, M.D.[1], Brennan Lee, B.S.[2], Maaz Hassan, B.S.[2], Brandon Morris, M.D.[2], Armin Tarakemeh, B.A.[2], Rosey Zackula, M.A.[3], Scott Mullen, M.D.[2], Paul Schroeppel, M.D.[2], Bryan G. Vopat, M.D.[2]

[1]University of Kansas School of Medicine-Wichita, Wichita, KS
Department of Orthopaedics

[2]University of Kansas Medical Center, Kansas City, KS
Department of Orthopedic Surgery

[3]University of Kansas School of Medicine-Wichita, Wichita, KS
Office of Research

Received Dec. 29, 2020; Accepted for publication March 10, 2021; Published online June 21, 2021
https://doi.org/10.17161/kjm.vol14.15028

ABSTRACT

Introduction. Lateral ankle instability represents a common orthopaedic diagnosis. Nonoperative treatment through focused physical therapy provides satisfactory results in most patients. However, some patients experience persistent chronic lateral ankle instability despite appropriate nonoperative treatment. These patients may require stabilization, which can include primary lateral ligament reconstruction with a graft to restore ankle stability. Optimal post-operative rehabilitation of lateral ankle ligament reconstruction remains unknown, as surgeons vary in how long they immobilize their patients post-operatively. The aim of this review was to provide insight into early mobilization (EM) versus delayed mobilization (DM) post-operative protocols in patients undergoing primary lateral ankle ligament reconstructions to determine if an optimal evidence-based post-operative rehabilitation protocol exists in the literature.

Methods. Following PRIMSA criteria, a systematic review/meta-analysis using the PubMed/Ovid Medline database was performed (10/11/1947 - 1/28/2020). Manuscripts that were duplicates, non-lateral ligament repair, biomechanical, and non-English language were excluded. Protocols were reviewed and divided into two categories: early mobilization (within three weeks of surgery) and delayed mobilization (after three weeks of surgery). Functional outcome scores (American Orthopedic Foot and Ankle Society Score (AOFAS), Karlsson scores), radiographic measurements (anterior drawer, talar tilt), and complications were evaluated using weighted mean differences (pre- and post-operative scores) and mixed-effect models.

Results. After our search, twelve out of 1,574 studies met the criteria for the final analysis, representing 399 patients undergoing lateral ankle reconstruction. Using weighted mean differences the DM group showed superior AOFAS functional scores compared to the EM group (28.0 (5.5) vs. 26.3 (0.0), respectively; $p < 0.001$), although sample size was small. Conversely, no significant differences were found for Karlsson functional score ($p = 0.246$). With regards to radiographic outcome, no significant differences were observed; anterior drawer was $p = 0.244$ and talar tilt was $p = 0.937$. A meta-analysis using mixed-effects models confirmed these results, although heterogeneity was high.

Conclusions. While there are some conflicting results, the findings indicated the timing of post-operative mobilization made no difference in functional outcomes or post-operative stability for patients undergoing lateral ankle ligament reconstruction. Because heterogeneity was high, future studies are needed to evaluate these protocols in less diverse patient groups and/or more consistent techniques for lateral ankle ligament reconstruction. ***Kans J Med 2021;14:141-148***

INTRODUCTION

Lateral ankle instability represents a common orthopaedic injury that can be treated conservatively with good results.[1] However, when lateral ligamentous instability is severe or persists after nonoperative management, surgical management may be indicated. The Brostrom-Gould procedure is the gold standard for repair of lateral ligamentous injuries of the ankle.[2,3] However, in instances where the Brostrom procedure fails, there is insufficient residual anterior talofibular or calcaneofibular ligaments, large athletes or patients exhibit generalized ligamentous laxity, and reconstruction may be indicated.[4,5] Anatomic reconstruction with a graft has shown to be biomechanically similar to the native lateral ligamentous complex and has led to satisfactory outcomes with regards to function and patient satisfaction.[6,7]

However, lateral ankle ligament reconstruction is not without complications. Patients may suffer from graft site morbidity, pain, stiffness, muscle disuse atrophy, or graft failure. Several of these complications may be minimized by optimal post-operative rehabilitation protocols. Many surgeons chose to immobilize patients following their surgery to protect the reconstruction and avoid graft failure. Unfortunately, with prolonged immobilization, rates of stiffness and atrophy are likely to increase.[8,9]

There have been studies investigating outcomes after reconstruction that have allowed early range of motion and studies that have allowed late range of motion. However, there are no randomized studies that have compared early range of motion to late range of motion in the same study. Therefore, the optimal post-operative rehabilitation protocol remains unknown.

The aim of this review was to provide insight into early and delayed mobilization protocols in patients undergoing lateral ankle ligament reconstruction with a graft. We hypothesized that early mobilization post-operative rehabilitation protocols would have equivalent outcomes compared to delayed mobilization post-operative rehabilitation protocols without an increase in complications.

METHODS

Search Strategy and Study Selection. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10] Since this study was a systematic review/meta-analysis of published studies, institutional review board approval was not required. A systematic literature review/meta-analysis was conducted on May 6, 2020 using the PubMed/Ovid MEDLINE database; dates of publication were limited to 10/11/1947 through 1/28/2020. The main keywords "lateral ankle reconstruction" and "lateral ankle ligament reconstruction" were used in the electronic search. Two inves-

tigators performed a separate, manual study selection from this list to exclude repetitions and to select those specifically related to the discussed item. In case of any discrepancies in article selection between the two investigators, a third investigator was involved as the tie-breaking vote. Only studies published in the English language were included in this study. The reference lists of all the articles selected were screened for additional articles.

Eligibility Criteria. Clinical trials that included the following criteria were considered eligible: published in the English language; patients undergoing primary lateral ankle reconstruction; a follow-up of at least one year; reported measured outcomes (American Orthopedic Foot and Ankle Society Score (AOFAS), Karlsson score, and total complications), along with post-operative rehabilitation protocols. Exclusion criteria were studies involving the following procedures: lateral ankle ligament repair, suture tape augmentation (internal brace fixation), revision ligament repair or reconstruction; concomitant talar chondral or osteochondral repair or reconstructive procedures; concomitant peroneal tendon procedures (peroneal tendon debridement, tendon repair); concomitant superior peroneal retinaculum repair; concomitant treatment of hindfoot or forefoot pathology (calcaneal osteotomy for cavovarus reconstruction, subtalar arthrodesis); and/or syndesmosis repair or ankle fracture open reduction and internal fixation (ORIF).

Data Extraction and Quality Appraisal. Post-operative protocols in each article were reviewed and divided into two categories: early mobilization (EM), defined as allowing range-of-motion therapy and/or weight-bearing within three weeks of date of surgery, and delayed mobilization (DM), defined as permitted ankle range of motion after three weeks from date of surgery. Talar tilt, anterior drawer, functional outcome scores (AOFAS, Karlsson scores), and total complications of both populations were recorded. Assessment of methodological quality was conducted by two investigators utilizing the Cochrane Collaboration tool.[11] As before, a third investigator was enlisted to arbitrate disagreements.

Statistical Analysis. Descriptive statistics were conducted using aggregate data from all studies. Categorical data were summarized with frequencies and percentages, and continuous variables with means and standard deviations. Statistical tests were weighted for sample size. To compare early versus delayed mobilization treatment, Levene's test, t-test, and 95% confidence intervals of differences were conducted (equal variances were not assumed in all cases). Analyses were conducted in IBM™ SPSS™ Statistics, version 26, using two-sided tests with an alpha level of 0.05. Because multiple tests were conducted, Bonferroni correction was used to indicate the level of significance: 0.05/13 tests = 0.0038.

Meta-analyses were conducted in RStudio®, using R version 4.0.1, following Harrer, Cuijpers, Furukawa, and Ebert, 2019.[12] Mixed-effects models (random-effects within subgroups and fixed-effects between subgroups) were utilized. The meta-analytical method included the inverse variance method, Sidik-Jonkman estimator for tau^2, Hartung-Knapp adjustment, and Heges's g (bias corrected standardized mean difference). These methods were chosen because the number of studies were few and heterogeneity may be problematic. For each model, mobility measures (delayed vs. early) were compared.

A total of four models were developed: two for the functional measure (AOFAS and Karlsson scores) and two for the radiographic measure (anterior drawer and talar tilt). In addition, a sensitivity analysis was conducted for anterior drawer because mean values differed substantially for the Lee et al. 2018 study.[13]

Results from the quality bias analysis can be found in Figure 6. From our literature review, only one paper evaluated for both EM and DM in their study; however, this was only level III evidence.[14] Thus, the majority of studies included in our analysis were case series, which may skew our study results due to risk of overall bias.

RESULTS

Study Selection. The initial PubMed/Ovid MEDLINE database search identified 1,580 articles; other sources identified 264 (Figure 1). Based on a review of the abstracts, duplicates were removed, 773 articles were excluded for non-lateral ligament repair, and 538 were either non-human studies or not in English. A total of 263 articles were screened using the full-text and 251 were excluded. The result was 12 articles to be analyzed. Of these, two studies utilized early mobilization for their post-op rehabilitation protocol[14,15] and 11 studies utilized delayed mobilization.[8,9,13,14,16-22] One study utilized both early and delayed mobilization.[14]

Study Characteristics. Table 1 shows the demographic characteristics of the 12 studies that met the inclusion criteria. A total of 399 patients had undergone primary lateral ligament reconstruction with at least a one-year follow-up. The DM group included 362 patients; 219 males and 123 females. The EM group included 37 (9%) patients; 23 males and 14 females. Of those categorized as DM, two studies were grouped into two separate categories (Lee et al.[13] and Xu et al.[19]). One study (Miyamoto et al.[14]) evaluated both EM and DM post-operative protocols. Thus, the total number of studies shown for DM was 11 and 2 for EM.

Participants were categorized as either athletes or general population (Table 2). Note that athletes tended to be younger than the general population for both DM and EM, although the sample size was smaller for those classified as athletes, and four studies did not report the type of patient.

Table 3 shows a comparison of pre- and post-surgical outcomes by mobility timing. Averages were weighted by the sample size. Significant differences were observed for age; participants tended to be older for DM compared to EM (29.2 (3.6) vs. 27.1 (0.8), respectively; $p < 0.001$). Regarding differences between pre- and post-operation scores, only AOFAS was significant: mean DM was 28.0 (5.5) vs. mean EM of 26.3 (0.0); $p < 0.001$. However, only one study (Wang et al.[15]) was observed for early mobility and the sample size was small, $n = 19$.

Not shown in the tables are studies by reconstruction technique or complications. All but one study[8] reported using allograft or autograft or compared both. There were 159 patients (five studies) with allograft and 202 patients (seven studies) with autograft reconstruction.

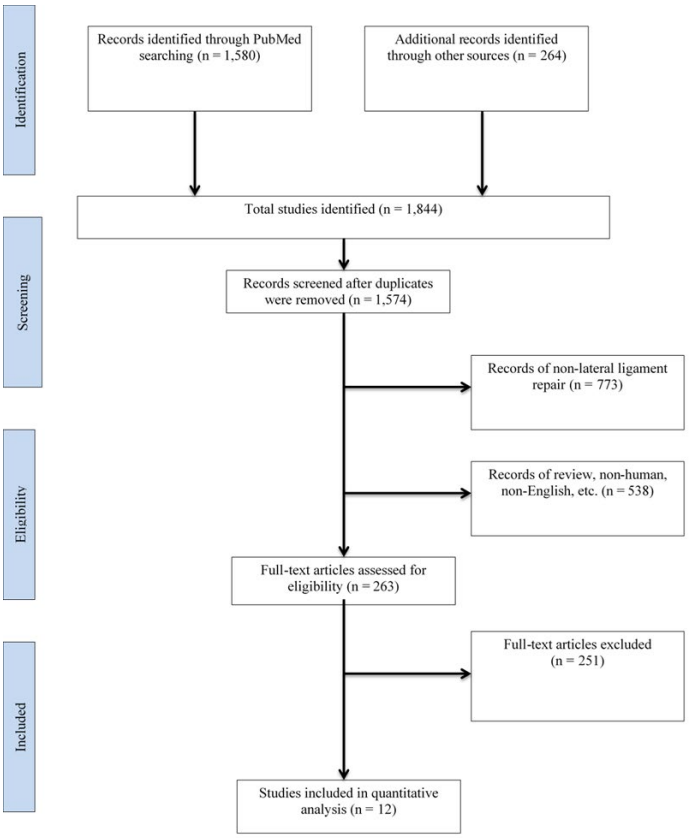


Figure 1. Detailed flowchart of the literature search using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria.

Table 1. Studies by mobility timing.

Author	Year	n	Males	Females	Age range	Level of evidence	Range of follow-up (months)	Average follow-up (months)
Delayed mobility								
Giannini et al.[8]	2014	38	25	13		IV	24-96	60
Lee et al.[13]	2018							
Non-Smokers		47	30	17	16-59		12-68	18.8
Smokers		23	20	3	19-41		12-33	17.3
Miyamoto et al.[14]*	2014	15	10	5	18-43	III	24	24
Nakata et al.[9]	2000	20	n/a	n/a	15-31	IV	37.2-120	50.4
Park et al.[16]	2016	30	23	7	17-54	IV	12-33	20
Sammarco et al.[17]	1999	30	17	13	12-47	IV	24-64	44
Sun et al.[21]	2019	32	18	14	18-43		24-35	28
Ventura et al.[22]	2020	20	12	8	29.2 ± 9.8		180	180
Wang et al.[18]	2013	25	14	11	17-62	IV	12-56	32.3
Xu et al.[19]	2014							
Autograft		32	19	13		III	26.8-40.2	33.5
Allograft		36	22	14		III	21.8-35.2	28.5
Youn et al.[20]	2012	14	9	5	20-53	IV	12-40	18.1
Total delayed mobility	*N = 11*	*362*	*219*	*123*				
Early mobility								
Miyamoto et al.[14]	2014	18	13	5	21-40	III	24	24
Wang et al.[15]	2017	19	10	9	19-41	IV	12-40	18.1
Total early mobility	*N = 2**	*37*	*23*	*14*				

*Miyamoto et al.[14] contained both delayed and early mobility, thus it is listed in both categories.

Table 2. Participant demographics by mobility timing.

Mobility timing	Sample size		Males		Females		Average age
	n = 277	100.0%	n = 162	45.5%	n = 95	34.3%	
Delayed mobility*	240	86.6	139	47.0	81	27.4	28.3
Athletes	53		35		18		26.4
General population	187		104		63		29.2
Early mobility	37	13.3	23	8.3	14	5.1	27.2
Athletes	18		13		5		26.4
General population	19		10		9		27.9

*Four studies from the delayed mobility group (a total of 122 participants) did not report the sample by type.

Table 3. Comparison of pre- and post-surgical outcomes by mobility timing.

Description	Delayed mobility				Early mobility				
	N	n	$mean_w$	SD	N	n	$mean_w$	SD	p**
Average age	11*	362	29.2	3.6	2*	37	27.1	0.8	< 0.001
Functional outcome									
AOFAS Function Score difference	7	283	28.0	5.5	1	19	26.3	n/a	'--
Pre-operation scores			64.5	5.2			64.0	n/a	'--
Post-operation scores			92.5	2.1			90.3	n/a	'--
Karlsson Function Score difference	6	181	32.7	4.1	2	37	34.0	6.3	0.246
Pre-operation scores			58.1	4.7			57.3	6.7	0.490
Post-operation scores			90.8	3.3			91.3	0.4	0.071
Radiographic outcome									
Anterior drawer difference	8	226	4.9	2.9	2	37	5.1	0.7	0.244
Pre-operation scores			17.0	9.8			9.3	0.6	< 0.001
Post-operation scores			12.1	11.6			4.1	0.2	< 0.001
Talar tilt difference	9	294	9.8	1.7	2	37	9.8	3.5	0.937
Pre-operation scores			13.7	1.6			14.0	3.5	0.646
Post-operation scores			3.9	1.1			4.2	0.1	< 0.001

N = number of studies; n = number of participants; $mean_w$ = Weighted means based on number of participants per study.
*Of those categorized as delayed mobility, two studies were grouped into two separate categories (Lee et al.[13] and Xu et al.[19]); one study, Miyamoto et al.[14], contained both delayed and early mobility, thus it is listed in both categories.
**Results from two-sided t-test for equality of means, equal variances not assumed.

Overall complication rates between study groups were significantly different with a complication rate of 1.7% (4/240) in the DM group versus 0.0% (0/37) in the EM. Park et al.[16] reported one complication and Sammarco et al.[17] reported three. In the DM group, three patients had painful hardware that required repeat surgery for removal, and one had sensory nerve damage.

Meta-Analysis Using Random and Mixed-Effects Models: Functional Outcomes. Results of the meta-analysis for the functional outcomes are shown in Figures 2 and 3. Figure 2a shows a random-effects model for AOFAS scores from eight studies[8,13,15,16,18,19,21,22] totaling 302 patients. Of these, 283 patients were in the DM group and 19 patients in EM. Both groups saw improvements in scores after the operation, with a standardized mean difference (SMD) of 3.56 (95% CI (2.56, 4.57); $p < 0.01$), although, heterogeneity was high, (I^2 = 91% (85%, 95%)), indicating that these groups may not be comparable. A subgroup analysis to compare DM with EM using a mixed-effects model showed significant differences between groups in favor of delayed mobilization, (SMD = 2.71, 95% CI (2.12, 3.30); $p < 0.01$). However, high heterogeneity was present, and only one study was included in the EM group (Figure 2b).

Results for Karlsson scores are shown in Figures 3a and 3b. Similarly, the random-effects model showed improvements to scores for these seven studies[13-16,20-22] totaling 218 patients (SMD = 3.52, 95% CI (2.82, 4.23)). Although the mixed-effects model to compare DM and EM was not significant and heterogeneity was high (I^2 = 75% (51%, 87%); p = 0.86).

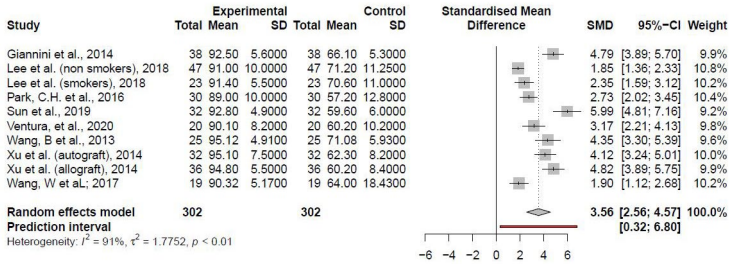


Figure 2a. Functional measure: AOFAS Random-effects model.

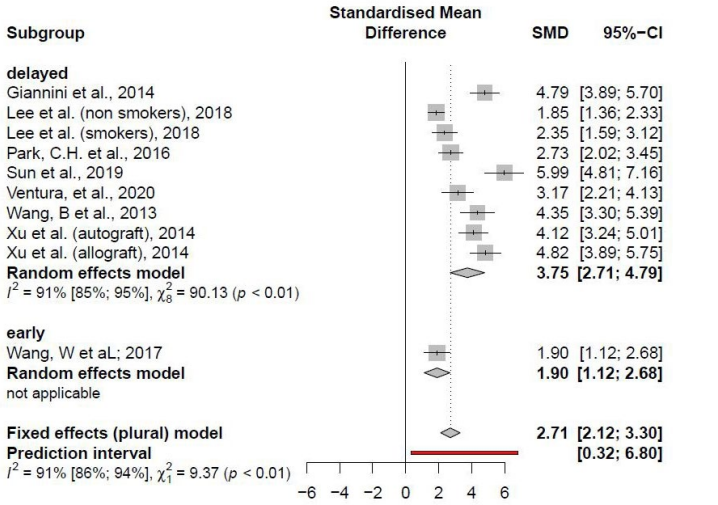


Figure 2b. Functional measure: AOFAS Mixed-effects model delayed vs. early mobilization.
Experimental = post-operational scores; Control = pre-operational scores

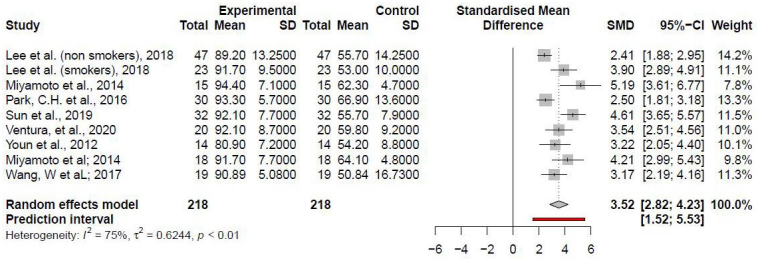


Figure 3a. Functional measure: Karlsson Scores Random-effects model.

Meta-Analysis Using Random and Mixed-Effects Models: Radiographic Outcomes. Results for radiographic outcomes are shown in Figures 4 and 5. Anterior drawer is shown in Figures 4a and 4b, which included 263 patients from nine studies; SMD = -2.35, indicating improved scores from pre- to post-operations. However, group comparisons were not significant, and heterogeneity was high. A second sensitivity analysis was conducted for anterior drawer measures because the scores from Lee et al.[13] were marked higher than all other studies, thus it was removed. Results from this analysis are shown in Figures 4c and 4d. The analysis showed no significant findings and heterogeneity was only slightly reduced from I^2 = 94% to 90% in the random effects model. Results from Talar tilt scores are shown in Figures 5a and 5b. No significant findings were observed.

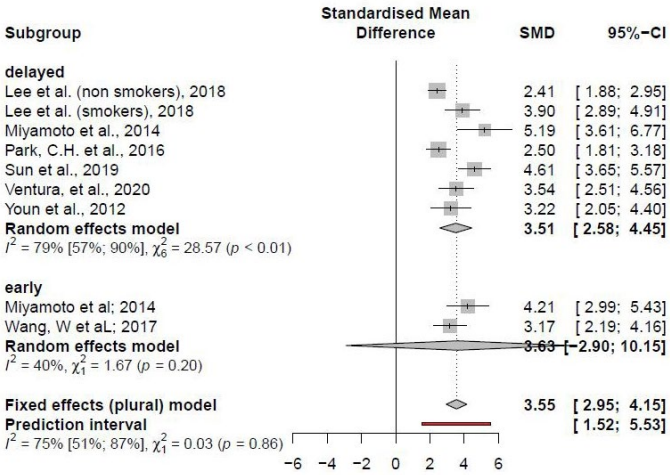


Figure 3b. Figure 3b. Functional measure: Karlsson Scores Mixed-effects model delayed vs. early mobilization.
Experimental = post-operational scores; Control = pre-operational scores
Note: inappropriately wide confidence intervals observed in the early random effects model may be a spurious finding, possibly due to the Hartung-Knapp-Sidik-Jonkman approach, as this produces wider confidence intervals. Although, Higgins and Thompson[23] argued it makes no sense to compare two or more subgroups in a meta-analysis with smaller than 10 studies, as spurious results may occur.

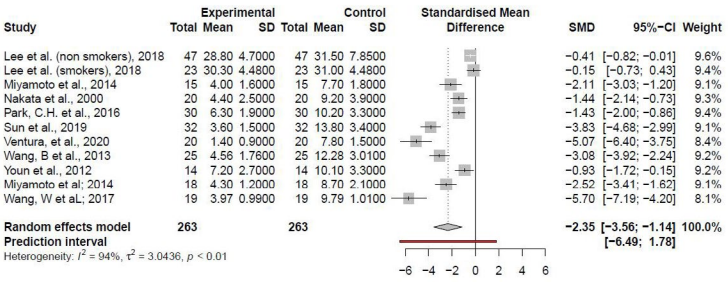


Figure 4a. Radiographic measure: Anterior drawer Random-effects model.

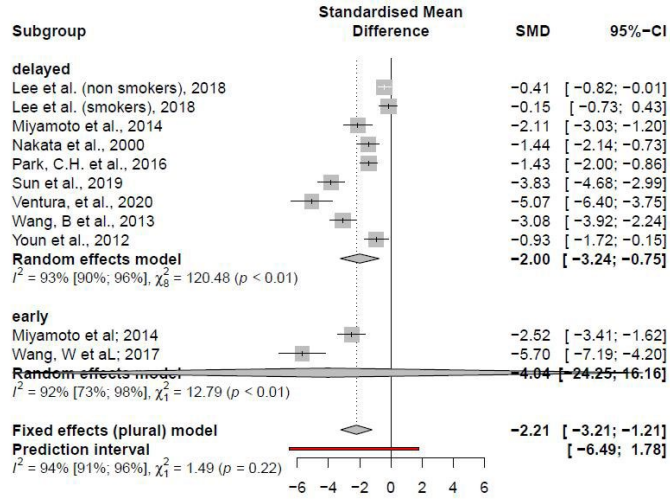


Figure 4b. Radiographic measure: Anterior drawer Mixed-effects model delayed vs. early mobilization.
Experimental = post-operational scores; Control = pre-operational scores
See note in Figure 3b regarding spurious findings for confidence intervals with small studies.

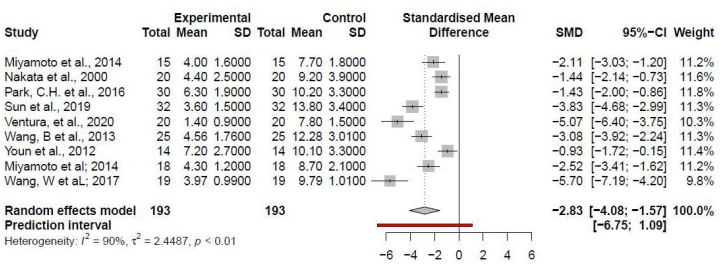


Figure 4c. Radiographic measure: Anterior drawer Random-effects sensitivity model.

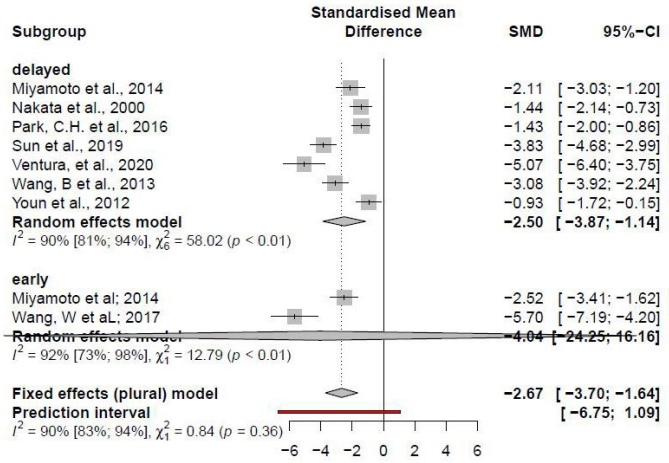


Figure 4d. Radiographic measure: Anterior drawer Mixed-effects sensitivity model delayed vs. early mobilization.
Experimental = post-operational scores; Control = pre-operational scores
See note in Figure 3b regarding spurious findings for confidence intervals with small studies.

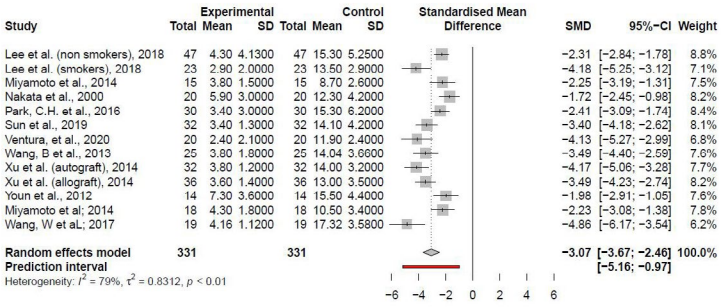


Figure 5a. Radiographic measure: Talar tilt Random-effects model.

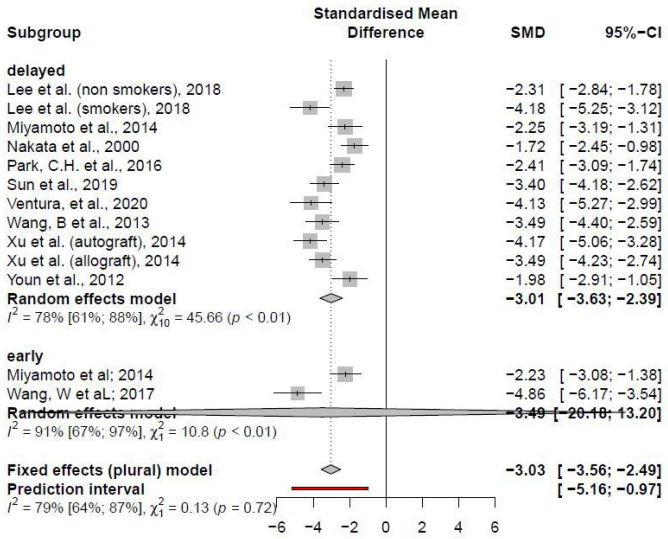


Figure 5b. Radiographic measure: Talar tilt Mixed-effects model delayed vs. early mobilization.
Experimental = post-operational scores; Control = pre-operational scores
See note in Figure 3b regarding spurious findings for confidence intervals with small studies.

DISCUSSION

Overall, our analysis demonstrated that lateral ankle reconstruction can provide significant improvements in functional and radiographic outcomes, regardless of rehabilitation protocols. While no significant differences were found between DM and EM groups for any radiographic outcomes, nor for Karlsson functional scores, a statistically significant greater improvement was observed for AOFAS functional scores, in favor of delayed mobilization. Although, it should be noted the sample size of the EM group was small with only one study.

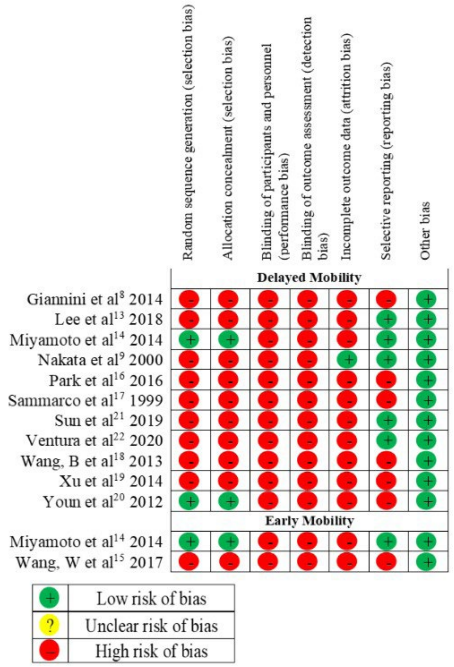


Figure 6. Quantitative bias analysis results for this study.

Results from the meta-analysis showed substantial heterogeneity present in all random and fixed effects models. This may be because study samples were small (some analysis had less than 10 studies) and were underpowered.[23] Furthermore, it is unclear if this difference in AOFAS is clinically significant. Our results demonstrated that EM post-operative protocols may not compromise post-operative instability, with no difference found between EM and DM in terms of both radiographic measures. However, our results also displayed that patients treated with DM may have a higher complication rate compared to the EM group.

The type of patient who undergoes a lateral ankle ligament reconstruction may be one that benefits from DM protocols. Typically, reconstruction is recommended in patients who have longstanding instability and insufficient soft tissue to perform repair or have physical demands that make repair unsuitable. In this type of patient, it would make sense that a period of prolonged immobilization would benefit the patient and give their soft tissues additional time to stabilize. However, our results illustrated that EM did not compromise post-operative stability in terms of both anterior drawer and Talar tilt test. Thus, these results may demonstrate that the use of reconstruction with graft may allow patients to mobilize sooner. It would be beneficial to see if this would correlate into returning to sport or work sooner in patients who are treated with EM. More studies are needed to evaluate this benefit in both graft versus other treatment options such as lateral ligament primary repair.

These findings did not corroborate with the Miyamoto el al.[14] study fully, which directly compared EM versus DM and found no difference in functional outcomes. Our study found a significantly higher change in AOFAS scores in the DM group, but no significant difference in Karlsson scores. Additionally, that study found that patients undergoing EM returned to athletic activity five weeks sooner than patients undergoing

DM. There may be multiple reasons for this, as Miyamoto el al.[14] was the lone study to use a gracilis autograft with an interference screw construct. The authors' goal of this construct was to determine if immediate range of motion could be accommodated. In other EM studies, the aim of the study was not one of length of recovery with a specific technique, but rather to demonstrate a given novel technique was not inferior to established techniques.[15,17]

Three out of the four complications encountered in our analysis were due to painful hardware and these occurred in the DM group.[15,16] Traditionally, it has been thought that delayed mobility can prevent complications. Yet, our analysis showed that all four complications encountered were in the DM group. However, it is not certain that these complications arose due to the timing of post-operative mobilization; rather, they could be due to surgical repair techniques. No studies reported recurrent post-operative ankle instability.

There are several limitations to our study. One was that differences in functional outcomes and ankle stability were not examined by the type of reconstruction. In our analysis, four studies used autografts, three used allografts, and two used a mix of auto and allografts to reconstruct the lateral ligament complex of the ankle. It is possible that differences in reconstruction technique affected outcomes greater than rehabilitation protocols. Also, as stated above, there were a larger number of studies in the DM group compared to the EM group, resulting in a higher number of patients in the DM group. Also, as illustrated by our quantitative analysis, our results were at a high risk from bias due to the lower level of evidence of our studies. Only one paper compared DM and EM; however, this was not a randomized control study design. Another limitation was that our study assumed that protocols were similar in the EM and DM groups. However, there was variability within both groups as to how early (or delayed) each protocol began mobilization. To our knowledge, there are no meta-analyses that compare reconstruction techniques and could provide the basis for future studies. This study suggested that EM post-operative protocols may not compromise patient's function or stability post-operatively. However, future meta-analysis should consider conducting meta-regression to more thoroughly evaluate this. Regardless, further studies are needed to evaluate specific post-operative protocols in patients undergoing lateral ankle ligament reconstruction to help physicians determine how to appropriately treat their patients.

REFERENCES

[1] Waterman BR, Owens BD, Davey S, Zacchilli MA, Belmont PJ Jr. The epidemiology of ankle sprains in the United States. J Bone Joint Surg Am 2010; 92(13):2279-2284. PMID: 20926721.
[2] Clanton TO, Viens NA, Campbell KJ, Laprade RF, Wijdicks CA. Anterior talofibular ligament ruptures, part 2: Biomechanical comparison of anterior talofibular ligament reconstruction using semitendinosus allografts with the intact ligament. Am J Sports Med 2014; 42(2):412-416. PMID: 24280308.
[3] Matheny LM, Johnson NS, Liechti DJ, Clanton TO. Activity level and function after lateral ankle ligament repair versus reconstruction. Am J Sports Med 2016; 44(5):1301-1308. PMID: 26920434.
[4] Karlsson J, Bergsten T, Lansinger O, Peterson L. Reconstruction of the lateral ligaments of the ankle for chronic lateral instability. J Bone Joint Surg Am 1988; 70(4):581-588. PMID: 3356725.
[5] Karlsson J, Bergsten T, Lansinger O, Peterson L. Surgical treatment of chronic lateral instability of the ankle joint. A new procedure. Am J Sports Med 1989; 17(2):268-273; discussion 273-264. PMID: 2667383.
[6] Heikkinen J, Lantto I, Flinkkila T, et al. Soleus atrophy is common after the nonsurgical treatment of acute achilles tendon ruptures: A randomized clinical trial comparing surgical and nonsurgical functional treatments. Am J Sports Med 2017; 45(6):1395-1404. PMID: 28282504.
[7] Nightingale EJ, Moseley AM, Herbert RD. Passive dorsiflexion flexibility after cast immobilization for ankle fracture. Clin Orthop Relat Res 2007; 456:65-69. PMID: 17179787.
[8] Giannini S, Ruffilli A, Pagliazzi G, et al. Treatment algorithm for chronic lateral ankle instability. Muscles Ligaments Tendons J 2014; 4(4):455-460. PMID: 25767783.
[9] Nakata K, Shino K, Horibe S, Natsu-ume T, Mae T, Ochi T. Reconstruction of the lateral ligaments of the ankle using solvent-dried and gamma-irradiated allogeneic fascia lata. J Bone Joint Surg Br 2000; 82(4):579-582. PMID: 10855887.
[10] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009; 6(7):e1000097. PMID: 20171303.
[11] Higgins JPT, Thomas J, Chandler J, et al. (Eds). Cochrane Handbook for Systematic Reviews of Interventions. Version 6.0. London: Cochrane Training, 2019.
[12] Harrer M, Cuijpers P, Furukawa TA, Ebert DD. Doing Meta-Analysis in R: A Hands-on Guide. 2019. https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/.
[13] Lee DO, Eom JS, Jung HG. The effect of smoking on the outcomes of lateral ankle ligament reconstruction. J Orthop Sci 2018; 23(1):88-91. PMID: 28947241.
[14] Miyamoto W, Takao M, Yamada K, Matsushita T. Accelerated versus traditional rehabilitation after anterior talofibular ligament reconstruction for chronic lateral instability of the ankle in athletes. Am J Sports Med 2014; 42(6):1441-1447. PMID: 24723416.
[15] Wang W, Xu GH. Allograft tendon reconstruction of the anterior talofibular ligament and calcaneofibular ligament in the treatment of chronic ankle instability. BMC Musculoskelet Disord 2017; 18(1):150. PMID: 28388886.
[16] Park CH, Lee WC. Donor site morbidity after lateral ankle ligament reconstruction using the anterior half of the peroneus longus tendon autograft. Am J Sports Med 2017; 45(4):922-928. PMID: 27899356.
[17] Sammarco GJ, Idusuyi OB. Reconstruction of the lateral ankle ligaments using a split peroneus brevis tendon graft. Foot Ankle Int 1999; 20(2):97-103. PMID: 10063977.
[18] Wang B, Xu XY. Minimally invasive reconstruction of lateral ligaments of the ankle using semitendinosus autograft. Foot Ankle Int 2013; 34(5):711-715. PMID: 23447511.
[19] Xu X, Hu M, Liu J, Zhu Y, Wang B. Minimally invasive reconstruction of the lateral ankle ligaments using semitendinosus autograft or tendon allograft. Foot Ankle Int 2014; 35(10):1015-1021. PMID: 24951483.
[20] Youn H, Kim YS, Lee J, Choi WJ, Lee JW. Percutaneous lateral ligament reconstruction with allograft for chronic lateral ankle instability. Foot Ankle Int 2012; 33(2):99-104. PMID: 22381340.
[21] Sun Y, Wang H, Tang Y, Zhao H, Qin S, Zhang F. Reconstruction of the lateral ankle ligaments using the anterior half of peroneus longus tendon graft. Foot Ankle Surg 2019; 25(2):242-246. PMID: 29409185.
[22] Ventura A, Legnani C, Corradini C, Borgo E. Lateral ligament reconstruction and augmented direct anatomical repair restore ligament laxity in patients suffering from chronic ankle instability up to 15 years from surgery. Knee Surg Sports Traumatol Arthrosc 2020; 28(1):202-207. PMID: 30377717.
[23] Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. Stat Med 2004; 23(11):1663-1682. PMID: 15160401.

Keywords: lateral ankle ligament, reconstructive surgical procedures, meta-analysis, systematic review

KANSAS JOURNAL of MEDICINE

Residency Prep Course Instills Confidence in Interns

Kelly Winter, M.D.[1], Karson R. Quinn, M.A.[1], Stephen D. Helmer, Ph.D.[1,2], Marilee F. McBoyle, M.D.[1]
[1]University of Kansas School of Medicine-Wichita, Wichita, KS Department of Surgery
[2]Ascension Via Christi Hospital Saint Francis, Wichita, KS Department of Medical Education

Received Nov. 30, 2020; Accepted for publication March 10, 2021; Published online June 21, 2021
https://doi.org/10.17161/kjm.vol14414919

ABSTRACT

Introduction. Physicians entering surgical residency often feel unprepared for tasks expected of them beginning July 1, including responding to pages, writing orders, doing procedures independently, and a multitude of other requirements. Our aim was to design a surgical boot camp to help graduating senior medical students feel more confident entering residency.

Methods. A two-week intensive surgery residency prep course was conducted in the spring of 2019 at an Accreditation Council for Graduate Medical Education-accredited General Surgery residency program. The course was designed combining aspects from existing prep courses and innovative ideas tailored to resources available at our institution. Medical students participated in the Surgery Residency Prep Course as an elective at the end of their fourth year of medical school. An anonymous survey was given pre- and post-prep course completion evaluating confidence in medical knowledge, clinical skills, and surgical skills. Data were compared using Wilcoxon Signed-Rank Test.

Results. Six students completed the course as a medical elective. Students felt more confident at course completion in most aspects, were significantly more confident in all areas of surgical skills taught and evaluated, and nearly all areas of medical knowledge. Subjectively, students felt as though the course was beneficial and helped them feel more prepared for starting internship.

Conclusions. This course designed at our institution was successful in helping prepare and instill confidence in graduating medical students prior to starting their internship. ***Kans J Med 2021;14:149-152***

INTRODUCTION

American surgical societies have long recognized the need for an internship preparatory (prep) course to help graduating medical students' transition to residency. Numerous institutions offer a surgical boot camp, sometimes called a "prep course", for senior medical students entering a surgical residency, and the American College of Surgeons (ACS), American Board of Surgery (ABS), Association of Program Directors in Surgery (APDS), and Association for Surgical Education (ASE) have developed a prep course curriculum with modules deemed necessary for physicians to know prior to beginning residency. However, these prep courses have not been implemented at all institutions and the feasibility of creating these courses at facilities with limited resources has not been addressed.

ACS, ABS, APDS, and ASE issued a joint statement in 2015 indicating that all graduating medical students entering a surgical residency should complete a prep course prior to the beginning of their residency program.[1] Some of the design in these courses has been aimed at helping students achieve core skills or competencies as defined by the Association of American Medical Colleges (AAMC) or Accreditation Council for Graduate Medical Education (ACGME).[2,3] Many other specialties have begun to develop such prep courses as well, and students who have completed these courses recognize their benefit and feel all students should participate in such preparation.[4]

The boot camps taught at different institutions vary in their duration, from one day to four weeks, but are similar in the areas of focus, including basic medical and technical knowledge needed for intern year. The courses previously described have not addressed the success of using all volunteer instructors, and none has described incorporating surgical technology students or their facilities.

Our aim was to utilize the available resources as a model and tailor our own prep course, based on our institution's capabilities, with the goal of increasing students' confidence levels prior to starting residency. We also collaborated with the local surgical technology school and students to enhance the multidisciplinary aspect of the surgical field.

METHODS

This study involved administering a survey prior to and following completion of a two-week intensive surgery residency prep course that was developed for graduating fourth-year medical students entering a surgery internship. The prep course was based on existing "boot camps" at other medical schools, as well as the curriculum developed by the ACS/APDS/ASE. Our course was divided into three broad categories: clinical skills (dictating, writing orders, communication, and answering pages), medical knowledge (pharmacy, radiology interpretation, mechanical ventilation, code management, noninvasive vascular studies, nutrition, and total parenteral nutrition), and surgical skills (sterile technique and setup, wound care, punch biopsies, ultrasound, line access, suturing, knot tying, endoscopy, and anastomoses).

A multidisciplinary approach was used with various medical professionals involved in teaching, including pharmacists, residents, surgical attendings, surgical technology instructors and students, wound care nurses, and dieticians. Didactics and workshops were used throughout the course. The residency program's surgical skills lab was utilized with its existing resources, such as basic sutures and surgical instruments, and students were given access to the Fundamentals of Laparoscopic Surgery machine. Some sessions were held at the local surgical technology school utilizing their simulation materials, such as synthetic bowel and vessels, simulation man, and mock operating rooms. The code management portion was held at the School of Medicine in the code simulation laboratory.

Six students enrolled in the course for Spring 2019. Four were entering a general surgery residency, one entering obstetrics/gynecology, and one entering emergency medicine. Prior to the start of the course, an institutional review board (IRB) approved survey was given to the students evaluating their areas of most interest and their confidence levels on different subjects. Their confidence was ranked on a five-point Likert scale (1 = poor, 2 = fair, 3 = okay, 4 = good, 5 = very good) in

20 different areas under the basic categories of clinical skills, medical knowledge, and surgical skills. They were asked open-ended questions about their biggest concerns for residency. At the completion of the course, they were given a similar IRB approved survey with the same Likert-scale questions regarding confidence levels in each area, with an additional question asking them to list the three most helpful sessions of the course and an area to write additional comments and feedback.

A Wilcoxon signed-rank test was used to assess the difference in confidence level among the medical students. Each area within surgical skills, medical knowledge, and clinical skills were assessed individually. Indexes were created to assess the pre- and post-course survey confidence level within each category (surgical skills, medical knowledge, and clinical skills), as well as assess an overall course confidence level. The rest of the data was listed as frequency counts. All analyses were conducted using SPSS release 19.0 (IBM Corp., Armonk, New York).

This survey study was approved for implementation by the Ascension Via Christi Hospitals Wichita, Inc. Institutional Review Board.

RESULTS

When asked pre-course what three areas were of most interest to them, the most commonly cited responses were "pharmacy" and "anastomoses". Students also were asked about areas of least confidence. The areas of least confidence prior to starting the course were "pharmacy" and "writing orders". Additional responses are detailed in Table 1. The surveys showed students were overall more confident after the course in all areas, increasing their confidence overall from a median score of 2.4 pre-course to a median post-course score of 3.8, for an overall increase in confidence of 58.3% (p = 0.028).

Table 1. Areas of most interest and least confidence identified in pre-course survey.*

Areas of most interest		Areas of least confidence	
Area	**Frequency**	**Area**	**Frequency**
Pharmacy	4	Pharmacy	3
Anastomoses	3	Writing orders	3
Answering pages	2	Anastomoses	2
Medical knowledge	2	Code management	2
Line access	1	Ultrasound	2
Surgical skills	1	Medical knowledge	1
Suturing/Knot tying	1	Dictating	1
Clinical skills	1	Line access	1
Dictating	1	Surgical skills	1
Endoscopy	1	Clinical skills	1
Radiology interpretation	1	Radiology	1
Total	18	Total	18

*Each student allowed to give three answers for each question.

Students demonstrated statistically significant improvement in confidence in all areas of surgical skills with a 70.8% improvement in the overall surgical skills confidence rating increasing from a median of 2.4 to a median of 4.1 (Table 2; p = 0.027). Areas of most significant improvement were ultrasound and anastomoses (both showing 166.7% improvement) and line access and endoscopy (both showing 100.0% improvement).

Table 2. Comparison of surgical skills confidence levels pre- and post-course.

Areas of surgical skills	Pre-course median (IQR)	Post-course median (IQR)	% Improvement	p Value
Ultrasound	1.5 (1.0-2.25)	4 (3.0-5.0)	166.7%	0.023
Anastomoses	1.5 (1.0-2.25)	4 (3.0-4.0)	166.7%	0.026
Line access	2 (1.0-2.0)	4 (3.75-4.25)	100.0%	0.026
Endoscopy	2 (1.75-3.0)	4 (3.0-4.25)	100.0%	0.039
Sterile technique - set up	3 (3.0-4.0)	5 (4.75-5.0)	66.7%	0.024
Wound care/ wound vacs	2.5 (2.0-3.25)	4 (3.75-5.0)	60.0%	0.024
Punch biopsies	3 (2.75-3.5)	4.5 (4.0-5.0)	50.0%	0.039
Suturing/knot tying	3.5 (3.0-4.0)	5 (4.75-5.0)	42.9%	0.023
Overall score	2.4 (2.3-2.8)	4.1 (4.0-4.7)	70.8%	0.027

Students showed statistically significant improvement in their confidence in all areas of medical knowledge except noninvasive vascular study results and electrolytes (Table 3). Their overall confidence score for medical knowledge increased from 2.1 pre-course to 3.8 post-course (p = 0.028), representing an 81.0% overall increase in confidence. Areas of most significant improvement were code management, pressors and sedation, and anticoagulants/reversal (each showing 100% improvement), and mechanical ventilation (75% improvement).

Table 3. Comparison of medical knowledge confidence levels pre-and post-course.

Areas of medical knowledge	Pre-course median (IQR)	Post-course median (IQR)	% Improvement	p Value
Code management	2 (1.75-2.0)	4 (4.0-5.0)	100.0%	0.024
Mechanical ventilation	2 (1.0-2.25)	3.5 (3.0-4.0)	75.0%	0.026
Pharmacy				
Pressors & Sedation	2 (1.0-2.25)	4 (3.75-4.25)	100.0%	0.026
Anticoagulants/ Reversal	2 (2.0-3.0)	4 (3.75-4.0)	100.0%	0.024
Electrolytes	2.5 (1.75-4.0)	4 (3.0-4.0)	60.0%	0.109
Nutrition & TPN	2.5 (1.75-3.0)	4 (3.0-4.0)	60.0%	0.039
Non-invasive vascular studies	2 (2-3.25)	3 (2.75-3.5)	50.0%	0.257
Radiology interpretation	3 (2.0-3.0)	4 (3.75-4.25)	33.3%	0.038
Overall score	2.1 (2.0-2.6)	3.8 (3.4-4.2)	81.0%	0.028

Abbreviation: TPN, total parenteral nutrition.

While not statistically significant, there was a numerical increase in respondents' level of confidence regarding clinical skills in each area measured (Table 4; p = 0.080). Areas of greatest improvement were in answering pages and dictating (both showing 100% improvement) and writing orders (75% improvement). The sessions they felt were most helpful were answering pages and pharmacy (Table 5). The areas identified as least helpful were the noninvasive vascular studies (n = 4), sterile technique (n = 2), and communication (n = 2). Overall, students felt the course was helpful and should continue to be offered in the future.

Table 4. Comparison of clinical skills confidence levels pre- and post-course.

Areas of clinical skills	Pre-course median (IQR)	Post-course median (IQR)	% Improvement	p Value
Answering pages	2 (1.75-3.25)	4 (3.0-5.0)	100.0%	0.078
Dictating	1.5 (1.0-3.5)	3 (2.75-4.0)	100.0%	0.216
Writing orders	2 (1.75-2.25)	3.5 (2.75-4.0)	75.0%	0.066
Communication	3.5 (3.0-4.0)	4 (4.0-5.0)	14.3%	0.102
Overall score	2.1 (1.9-3.3)	3.5 (3.2-4.5)	66.7%	0.080

Table 5. Sessions identified as being most helpful post-course.*

Session	Frequency
Answering pages	5
Pharmacy	4
Medical knowledge (pharmacy, ventilation, codes)	1
Line access	1
Mechanical ventilation	1
Sterile technique/setup (instruments)	1
Anastomoses	1
Line access & anastomoses	1
Pressors/sedation	1
Radiology	1
Ultrasound	1
Total	18

*Each student allowed to give three answers.

DISCUSSION

The importance and need for a prep course, as well as the relative success of such courses, has been established, and our study appeared to be in agreement, although small study size gives a significant limitation to interpretation of our data. Our course showed students gained more confidence in nearly all areas evaluated. Based on responses to open-ended feedback about the course, students felt it was helpful and should be offered again for future students entering a surgery residency. One student wrote, "every fourth-year medical student that wants to apply into General Surgery should be encouraged to take this elective", a sentiment that has been echoed in other survey results from similar prep courses.[4,5]

Clinical skills were the main areas that did not show a statistically significant increase in confidence, although small increases in confidence were observed for each of the categories. This may be due to a relatively high pre-course level of confidence, particularly seen with the communication skills. Other courses similarly have not seen an increase in confidence in areas of communication and writing orders.[4] Additionally, other course evaluations have rated didactics as the weakest portion of the prep course, perhaps reflecting on these students' preference to learn from hands-on or simulation experiences.[6] It may be difficult for students to see the tangible effect of the knowledge gained in these clinical skills areas prior to starting internship and applying them to real clinical scenarios. We may be able to improve these sessions as well by using more case-based teaching to help it seem more applicable.

Another consideration regarding our results was volunteer bias. We cannot say with certainty how closely those who volunteered for the course reflected the general population of graduating fourth year medical students preparing to enter a surgical residency. While it was possible that some component of volunteer bias existed in the study, because the tendency may be to think that those wanting to take the course may have a lower level of confidence than the students who deferred the opportunity, other possibilities were equally likely. For example, those taking the course may have had a more realistic assessment of the demands that were ahead of them and wanted to prepare in advance with every possible modality. This would be a benefit of having a control group who did not take the course to draw comparisons from, and this was a limitation of our study.

As we move forward in ensuring that medical students can meet the core competencies defined by ACGME,[3] it is likely that courses like this will become mandatory rather than an elective. One concern nationwide, as well as in other countries, is the transition that comes with new interns each July. Studies variably have reported on increased morbidity and mortality, decreased efficiency, and increased medical errors with the cohort turnover each year.[7-9] Some have proposed changes in the fourth-year medical school curriculum to decrease this effect. Increasing confidence and preparedness should mitigate some of the "July phenomenon", or the sometimes-controversial increase in morbidity and mortality, or decrease in efficiency seen with cohort turnover.[10]

To expound on the feasibility and basic framework for developing a prep course, our course was organized with the resources at our facility in conjunction with the local surgical technology school. The curriculum from ACS/APDS/ASE was used for several of the didactic sessions and as a guide for some of the workshops, including writing orders, mock pages, communication and handoffs, and radiology interpretation. Students from the local surgical technology school were utilized as assistants in some of the vascular suturing skills sessions, which was found to be beneficial from both medical students' and surgical technology students' viewpoints. We suggest these courses continue to be developed at all medical schools so all students entering residency will have completed a prep course.

Some of the challenge in developing the course came when finding teaching faculty for each session. We were fortunate enough to have interdisciplinary volunteers including surgical attendings and residents. Student feedback was that having residents at the sessions was one of the most valuable pieces. Other institutions have experimented with

mandatory resident-led boot camps;[5] however, we solicited resident help solely on a volunteer basis. Moving forward, our program should be able to encourage more resident participation, although making resident participation mandatory may not be feasible due to their clinical obligations. Challenges in the future of this course include tailoring the course for students entering various surgical specialties, including urology, orthopedics, and obstetrics/gynecology. The number of students at our institution entering these specialties each year is likely not enough to necessitate separate prep courses for each of them, but some adaptations will need to be made to ensure that the material is applicable.

Limitations of this study included a small sample size and no control group for comparison. Ideally, the course will continue to garner interest and more students will be enrolled in subsequent years for further analysis and course development. We plan to continue future studies and will be able to make comparisons with control groups of students who did not take the course. We also would like to extend the study period and follow the students at least six months into residency to evaluate if their confidence remains elevated compared to controls. There have been mixed reviews on whether this increase in confidence is sustained. At least one study showed statistically significant sustained increase in confidence in only two out of nine surgical skills when compared to controls over a six-month period.[10] In contrast, a neurosurgery course demonstrated that knowledge taught in the course was retained at six months and students continued to feel the course was beneficial.[11]

CONCLUSIONS

Our study added to the evidence that prep courses increase confidence and preparedness in medical students before entering surgical residency. We developed and adapted our course with limited resources and believe that all medical schools can create a prep course utilizing curricula already available and examples published from various institutions. We also believe that incorporating multidisciplinary teams is a key component to early development of interpersonal relationships.

ACKNOWLEDGMENTS

The authors thank the many individuals from varied disciplines who volunteered their time in conducting this course and the Skills Labs at the University of Kansas School of Medicine-Wichita and Wichita State University TECH for use of their facilities.

REFERENCES

[1] American Board of Surgery; American College of Surgeons; Association of Program Directors in Surgery; Association for Surgical Education. Statement on surgical pre-residency preparatory courses. World J Surg 2014; 38(11):2743-2745. PMID: 25288032.
[2] Heimroth J, Jones VM, Howard JD Jr, Sutton ERH. Utilizing surgical bootcamps to teach core entrustable professional activities to senior medical students. Am Surg 2018; 84(6):783-788. PMID: 29981602.
[3] Prerequisite objectives for graduate surgical education: A study of the Graduate Medical Education Committee American College of Surgeons. J Am Coll Surg 1998; 186(1):50-62. PMID: 9449600.
[4] Burns R, Adler M, Mangold K, Trainor J. A brief boot camp for 4th-year medical students entering into pediatric and family medicine residencies. Cureus 2016; 8(2):e488. PMID: 27014522.
[5] Ting DS, Lee JC, Loo BK, et al. A nationwide, resident-led teaching programme for medical students in Singapore: SingHealth Student Internship Programme Bootcamp. Singapore Med J 2016; 57(5):233-237. PMID: 27211310.
[6] Singh P, Aggarwal R, Pucher PH, Darzi A. Development, organisation and implementation of a surgical skills 'boot camp': SIMweek. World J Surg 2015; 39(7):1649-1660. PMID: 25665671.
[7] Young JQ, Ranji SR, Wachter RM, et al. "July Effect": Impact of the academic year-end changeover on patient outcomes: A systematic review. Ann Int Med 2011; 155(5):309-315. PMID: 21747093.
[8] Mongelli F, Fischer H, Stickel M, et al. Surgical residents' proficiency and turnover may affect the overall efficiency in an emergency department. World J Surg 2019; 43(10):2365-2370. PMID: 31214832.
[9] Bahl A, Hixson CC. July phenomenon impacts efficiency of emergency care. West J Emerg Med 2019; 20(1):157-162. PMID: 30643619.
[10] Okusanya OT, Kornfield ZN, Reinke CE, et al. The effect and durability of a pregraduation boot cAMP on the confidence of senior medical student entering surgical residencies. J Surg Educ 2012; 69(4):536-543. PMID: 22677594.
[11] Selden NR, Anderson VC, McCartney S, et al. Society of Neurological Surgeons boot camp courses: Knowledge retention and relevance of hands-on learning after 6 months of postgraduate year 1 training. J Neurosurg 2013; 119(3):796-802. PMID: 23590128.

Keywords: internship and residency, surgical procedures, teaching methods, self confidence, formative feedback

KANSAS JOURNAL of MEDICINE

Post-Biopsy Pneumothorax Incidence in Patients Treated with Biosentry™ Plug Device

Hythem Abouodah[1], Gregg Werner, M.D.[1,2], Thomas M. Fahrbach, M.D.[1,2], Cameron Fox, Ph.D.[1], Jared Mazurek[1], Jeremy Lott, M.D.[1], Carissa N. Walter, MPH[1,2], Lauren Clark, M.S.[1,3], Brandon Custer, M.D.[1,2]
University of Kansas Medical Center, Kansas City, KS
[1]School of Medicine, Kansas City, KS
[2]Department of Radiology
[3]Department of Biostatistics and Data Science

Received Jan. 12, 2021; Accepted for publication March 12, 2021; Published online June 21, 2021
https://doi.org/10.17161/kjm.vol14.15093

ABSTRACT

Introduction. This study aimed to determine if the Biosentry™ Plug Device (BPD), a prophylactic sealant used to prevent pneumothorax after lung biopsies, reduced post-lung biopsy pneumothorax rates, and other complications compared to no device utilization.

Methods. This single institution, retrospective cohort study included patients who received a lung biopsy in the Department of Interventional Radiology from May 1, 2015 to August 31, 2017. Data such as sex, race, ethnicity, chronic obstructive pulmonary disease status, degree of lung bullae if present, smoking status, and use of BPD were recorded. Decisions to use BPD were based on operator preference. A chi squared analysis was used with a p value greater than 0.05 considered significant.

Results. The study included 521 patients who underwent a lung biopsy during the study timeframe. Of these, 74 (14.2%) received the BPD, while 447 (85.8%) did not. One-hundred ninety (36.4%) had a pneumothorax within one month of the lung biopsy. Of the total 190 that experienced pneumothorax, 36.7% of non-BPD biopsies resulted in pneumothorax, while 35.1% of BPD biopsies resulted in pneumothorax (p value = 0.7970; degrees of freedom = 1).

Conclusions. These findings indicated that BPD may not reduce pneumothorax incidence nor limit the severity of complications in patients.
Kans J Med 2021;14:153-155

INTRODUCTION

Transcutaneous lung biopsies, performed in Interventional Radiology, are the gold standard for diagnosing suspected lung malignancies that cannot be reached bronchoscopically.[1] This type of biopsy is important both for diagnosis and detection of tumor receptor type, which can influence treatment options.[2] Pneumothorax is a common complication that occurs after 8 - 54% of all lung biopsies.[3] Many pneumothoraces are small and can resolve with time, although others can require additional clinical monitoring, hospital admission, chest tube placement, or surgery. Therefore, reducing the rate of pneumothoraces could improve patient outcomes and decrease cost.

Most lung biopsies require immediate pre- and post-biopsy computed tomography (CT) chest scans to assess for biopsy feasibility and complications. A treatment for pneumothoraces is frequently chest tube placement. Published rates of chest tube placement vary between 2 - 18% of patients who have had a pneumothorax post-biopsy, which requires hospital admission.[5-8]

At the end of the biopsy procedure, a Biosentry™ Plug (BPD; AngioDynamics, Latham, New York, USA), a hydrogel plug that expands and forms an airtight seal in the lung pleura and cutaneous biopsy tract, can be placed where the biopsy was performed to prevent pneumothoraces from occurring.[4] In study, the BPD demonstrated a 16% absolute risk reduction in pneumothorax rate post-biopsy, although the study was not powered to analyze the association of the use of the plug and other important outcomes, such as admission rates, chest tube placements, or cardiothoracic surgery consultation. Another study documented a significant reduction in post-procedure chest tube insertions associated with the BPD and a near significant reduction in length of hospital stay.[9] Few studies have examined the benefits of BPD on preventing post-biopsy pneumothorax and chest tube placement, but no other studies have focused on admission and surgery consult rates.

This study aimed to determine whether the BPD is efficacious in decreasing post-lung biopsy pneumothorax rates compared to cases where no device was used at one institution. Secondary aims were to determine whether inpatient admission, chest tube placement, and surgery consultation rates differ between patients who received the BPD and those who did not.

METHODS

Institutional review board approval was obtained, and patient medical records were reviewed in compliance with Health Care Portability and Accountability Act guidelines. This retrospective cohort study included patients who received a lung biopsy from May 1, 2015 to August 31, 2017 and had at least one follow-up image after biopsy to document presence or lack of pneumothorax. Patients who met any of the following criteria were excluded from this study: were under 18 years of age, had an existing pneumothorax when undergoing the lung biopsy, had no available post-biopsy imaging, or had a history of extensive bullous emphysema.

The decision to use BPD was determined by the attending physician's preference. Four interventional radiologists conducted the biopsies with 8 - 24 years of experience. The BPD was used according to its instructions for use.

Patient demographics, clinical history (chronic obstructive pulmonary disease (COPD), bulla, and smoking status), and imaging information were obtained from the electronic medical record and Picture Archiving and Communications Systems (PACS). Pre- and post-procedure CT and chest radiographs were analyzed and clinical notes were checked for mention of the presence of a pneumothorax, COPD, and bullous disease as per regular post-biopsy protocol. Post-procedure complications that occurred within one month of the biopsy and resulted in pneumothorax, surgical consults, chest tube placements, and admissions were recorded.

Patients were grouped based on use of BPD and a chi-squared test of independence analysis was conducted to determine the association of pneumothorax incidence and BPD use. SAS 9.4 was the analytic platform used to analyze the data sets. A p value of greater than 0.05 was considered statistically significant.

RESULTS

Six-hundred forty-eight patients initially were identified as having undergone a lung biopsy and 127 were excluded for having a pre-existing pneumothorax, no available post-biopsy imaging, or having a history of extensive bullous emphysema. In total, 521 patients were included in the study. Of these, 74 (14.2%) received the Biosentry™ Plug device, while 447 (85.8%) did not. Other patient characteristics are found on Table 1. Two-hundred eleven patients (40.5%) had some degree of COPD. Five patients (< 1%) had some history of lung bulla. Three-hundred eighty-four patients (73.7%) had a smoking history.

One-hundred ninety (36.4%) suffered a pneumothorax within one month of the lung biopsy. Of these 190, 187 (98.4%) had pneumothorax occur within one week and 185 (97.4%) occurred within 24 hours of biopsy. Of the total 190 that experienced pneumothorax, 36.7% of non-BPD biopsies resulted in pneumothorax, while 35.1% of BPD biopsies resulted in pneumothorax (p value = 0.7970; degrees of freedom = 1; Table 2).

Of the 190 pneumothorax patients, 48 (25.3%) were admitted as inpatients due to pneumothorax. There was no difference in admission rates between those who did and did not have the device (p = 0.5555). Fifty-three (27.9%) patients had chest tubes inserted. There was also no statistical difference between those that did and did not have the device (p = 0.2121). Of the 521 total subjects, 17 (3.3%) required a cardiothoracic surgery consultation and no statistical difference was found between the two groups who did and did not have the device (p = 0.4887; Table 3).

DISCUSSION

This study found no association in BPD use and pneumothorax rates within one month of biopsy. Additionally, the data showed no significant differences in rates of chest tube placement, admission for pneumothorax, or cardiothoracic surgery consultations sought between those who received the BPD and those who did not. However, the rates were lower in the BPD group for all outcomes studied (36.7% versus 35.1% for overall incidence of pneumothorax, 28.7% versus 23.1% for chest tube placement, 26.8% versus 15.4% for admission rate, and 3.6% versus 1.4% for cardiothoracic consults). Future studies with larger sample sizes should explore whether the BPD lowers rates for these two complications.

Though this study did not find a statistically significant difference in outcomes between those who received and did not receive the BPD, a lower rate was seen for the BPD group in all outcomes studied including pneumothorax, chest tube placement, admission rates, and cardiothoracic consults. This trend compared with the findings from other studies. Of four other studies that explored the efficacy of BPD in preventing pneumothorax, three[4,9,10] found a significant decrease in post-biopsy pneumothorax and all studies noted significant decreases in chest tube insertion for patients treated with BPD.[4,9,10,11] Like our study, Grage et al.[11] also found that there was no statistical significance in pneumothorax reduction with BPD use. An increase in sample size for this study, particularly the group that received BPD, may have resulted in different findings.

Table 1. Patient characteristics.

	No Biosentry™ Plug used 447 (85.8%)	Biosentry™ Plug used 74 (14.2%)	All 521 (100%)
Age, mean (SD)	65.4 (12.3)	67.3 (12.1)	65.7 (12.3)
Sex, n (%)			
Male	234 (52.35%)	36 (48.65%)	270 (51.82%)
Female	213 (47.65%)	38 (51.35%)	251 (48.18%)
Race, n (%)			
American Indian/ Alaskan Native	2 (0.45%)	0 (0.00%)	2 (0.38%)
Asian/Pacific Islander	1 (0.22%)	1 (1.35%)	2 (0.38%)
Black	34 (7.61%)	7 (9.46%)	41 (7.87%)
White	385 (86.13%)	61 (82.43%)	446 (85.60%)
Other	5 (1.12%)	1 (1.35%)	6 (1.15%)
Unknown	20 (4.47%)	4 (5.41%)	24 (4.61%)
Ethnicity, n (%)			
Non-Hispanic/Latino	433 (96.87%)	73 (98.65%)	506 (97.12%)
Hispanic/Latino	12 (2.68%)	1 (1.35%)	13 (2.50%)
Unknown	2 (0.45%)	0 (0.00%)	2 (0.38%)
COPD status, n (%)			
None	262 (58.61%)	48 (64.86%)	310 (59.50%)
Mild	103 (23.04%)	13 (17.57%)	116 (22.26%)
Moderate	67 (14.99%)	10 (13.51%)	77 (14.78%)
Severe	15 (3.36%)	3 (4.05%)	18 (3.45%)
Bulla status, n (%)			
Unknown	1 (0.22%)	0 (0.00%)	1 (0.19%)
None	443 (99.11%)	73 (98.65%)	516 (99.04%)
Mild	3 (0.67%)	1 (1.35%)	4 (0.77%)
Moderate	0 (0.00%)	0 (0.00%)	0 (0.00%)
Severe	0 (0.00%)	0 (0.00%)	0 (0.00%)
Smoking status at time of biopsy, n (%)			
Current	103 (23.04%)	11 (14.86%)	114 (21.88%)
Former	228 (51.01%)	42 (56.76%)	270 (51.82%)
Never	116 (25.95%)	21 (28.38%)	137 (26.30%)

Table 2. Pneumothorax rates with and without Biosentry™ plug device use.

	No Biosentry™ Plug used 447 (85.8%)	Biosentry™ Plug used 74 (14.2%)	p Value	Degrees of freedom
Is pneumothorax present within one month after biopsy?*			0.7970	1
Yes	164 (36.69%)	26 (35.14%)		
No	283 (63.31%)	48 (64.86%)		

*97.4% of pneumothoraxes occurred within 24 hours of biopsy.

Table 3. Differences in pneumothorax inpatient admission, chest tube placement, and cardiothoracic surgery consultation related to Biosentry™ Plug Device use.*

	No Biosentry™ Plug used	Biosentry™ Plug used	p Value
Was a chest tube placed within one month after biopsy? (After pneumothorax)			0.5555
Yes	47 (28.66%)	6 (23.08%)	
No	117 (71.34%)	20 (76.92%)	
Was patient admitted because of the pneumothorax?			0.2121
Yes	44 (26.83%)	4 (15.38%)	
No	120 (73.17%)	22 (84.62%)	
Was cardiothoracic surgery consulted?			0.4887**
Yes	16 (3.58%)	1 (1.35%)	
No	431 (96.42%)	73 (98.65%)	

*The initial two questions include the 190 patients with pneumothorax, while question three incorporates all 512 patients.
**Fisher's exact test was used because of small expected cell count.

Limitations to this study included a lack of randomization and unequal sample sizes in the BPD and non-BPD groups. Another limitation may be that different patient characteristics may have played a role in who received the BPD and who did not, biasing the results. However, the decision to use the BPD was not based on patient characteristics, but on operator preference (two operators preferred to use the device and two did not).

This study found that there was no statistically significant association between BPD use and pneumothorax and chest tube placement rates within one month of biopsy. Though this was on trend with other studies, future studies may want to explore use of the BPD further.

REFERENCES

[1] Otto S, Mensel B, Friedrich N, et al. Predictors of technical success and rate of complications of image-guided percutaneous transthoracic lung needle biopsy of pulmonary tumors. PLoS One 2015; 10(4):e0124947. PMID: 25855983.
[2] Schulze R, Seebacher G, Enderes B, Kugler G, Fischer JR, Graeter TP. Complications in CT-guided, semi-automatic coaxial core biopsy of potentially malignant pulmonary lesions. Rofo 2015; 187(8):697-702. PMID: 26062172.
[3] Khankan AA, Al-Muaikeel M. Image-guided percutaneous transthoracic biopsy in lung cancer – Emphasis on CT-guided technique. J Infect Public Health 2012; 5(Suppl 1):S22-S30. PMID: 23244183.
[4] Zaetta JM, Licht MO, Fischer JS, Avelar RL, Bio-Seal Study Group. A lung biopsy tract plug for reduction of postbiopsy pneumothorax and other complications: Results of a prospective, multicenter, randomized, controlled clinical study. J Vasc Interv Radiol 2010; 21(8):1235-1243.e1-3. PMID: 20656223.
[5] Klein JS, Salomon G, Stewart EA. Transthoracic needle biopsy with a coaxially placed 20-gauge automated cutting needle: Results in 122 patients. Radiology 1996; 198(3):715-720. PMID: 8628859.
[6] Collings CL, Westcott JL, Banson NL, Lange RC. Pneumothorax and dependent versus nondependent patient position after needle biopsy of the lung. Radiology 1999; 210(1):59-64. PMID: 9885587.
[7] Wu CC, Maher MM, Shepard JO. Complications of CT-guided percutaneous needle biopsy of the chest: Prevention and management. AJR Am J Roentgenol 2011; 196(6):W678-682. PMID: 31606253.
[8] Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: An analysis of discharge records. Ann Intern Med 2011; 155(3):137-144. PMID: 21810706.
[9] Grage RA, Naveed MA, Keogh S, Wang D. Efficacy of a dehydrated hydrogel plug to reduce complications associated with computed tomography-guided percutaneous transthoracic needle biopsy. J Thorac Imaging 2017; 32(1):57-62. PMID: 27870824.
[10] Ahrar JU, Gupta S, Ensor JE, et al. Efficacy of a self-expanding tract sealant device in the reduction of pneumothorax and chest tube placement rates after percutaneous lung biopsy: A matched controlled study using propensity score analysis. Cardiovasc Intervent Radiol 2017; 40(2):270-276. PMID: 27826786.
[11] Grage RA, Keogh S, Naveed MA. Comparison analysis pre and post implementation of a BioSentry tract sealant system after percutaneous transthoracic CT guided needle biopsy. J Vasc Interv Radiol 2015; 26(2):S149.

Keywords: pneumothorax, chest tube, thoracostomy, lung, biopsy

KANSAS JOURNAL of MEDICINE

Gastrointestinal Stromal Tumor or Malignant Peripheral Nerve Sheath Tumor? An Enigmatic Mass

Yasmine Hussein Agha, M.D.[1], Ali Taleb, M.D.[1], Sachin Srinivasan, M.D.[1], Ali Ahmad, M.D.[2], Nathan Tofteland, M.D.[1,3]
University of Kansas School of Medicine-Wichita, Wichita, KS
[1]Department of Internal Medicine
[2]Department of Surgery
[3]Department of Internal Medicine, Division of Gastroenterology

Received Jan. 8, 2021; Accepted for publication March 8, 2021; Published online June 21, 2021
https://doi.org/10.17161/kjm.vol1415071

INTRODUCTION

Neurofibromatosis type 1 (NF-1) frequently has been associated with sarcomas, leukemias, and lymphomas.[1] Benign or malignant, the expansive growth of these tumors is often one of the reasons why these patients have a shortened life expectancy.[2] Particularly, the incidence of gastrointestinal stromal tumor (GIST) and malignant peripheral nerve sheath tumor (MPNST) in patients with NF-1 tends to be higher than the general population.[1,3-5] Cases of NF-1 with cancer reported in the literature described patients who develop one of these tumors.[1,4,6] We present a patient with a perihilar hepatic mass with features of both GIST and MPNST concomitantly in the setting of NF-1.

CASE REPORT

The patient was a 39-year-old male with a history of NF-1 and known neurofibromas of the intra-medullary cervical region and along the cauda equina nerve roots, in addition to the muscle and subcutaneous tissues of the thorax. Given this extensive disease, he had chronic intractable shoulder pain, back pain, peripheral neuropathy, and headaches.

He presented to the emergency department with new-onset right upper quadrant abdominal pain, nausea, vomiting, and findings of obstructive jaundice. Computed tomography (CT) of the abdomen and magnetic resonance cholangiopancreatography (MRCP) showed intrahepatic bile duct dilatation with obstruction of the common bile duct (Figure 1). During endoscopic retrograde cholangio-pancreatography (ERCP), a localized biliary stricture was found, and a stent was placed. The upper third of the main bile duct, the left and right hepatic ducts, and all intrahepatic branches were dilated. Brush cytology was non-diagnostic. Subsequently, endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) was also non-diagnostic. The patient was advised to follow-up within four weeks for re-assessment.

Magnetic resonance imaging (MRI) of the abdomen was obtained one month later; a lesion measuring 25.40 mm x 35.66 mm compressing the porta hepatis was seen (Figure 2). The patient was referred to surgery for exploratory laparotomy during which two tumors were found: a perihilar mass (50 mm x 50 mm) involving the entire common bile duct and part of the left lobe of the liver and a mass in the small bowel (20 mm x 20 mm). The patient had a radical resection of the perihilar mass, small bowel, and common bile duct, Roux-en-Y hepaticojejunostomy to the intra-hepatic bile ducts, retroperitoneal and peri-portal lymphadenectomy, and left partial hepatectomy.

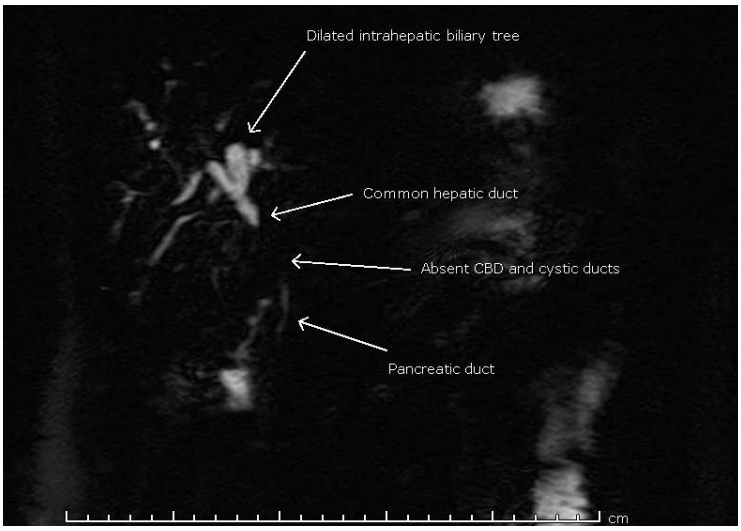


Figure 1. Magnetic resonance cholangiopancreatography showed intrahepatic bile duct dilatation with obstruction of the common bile duct.

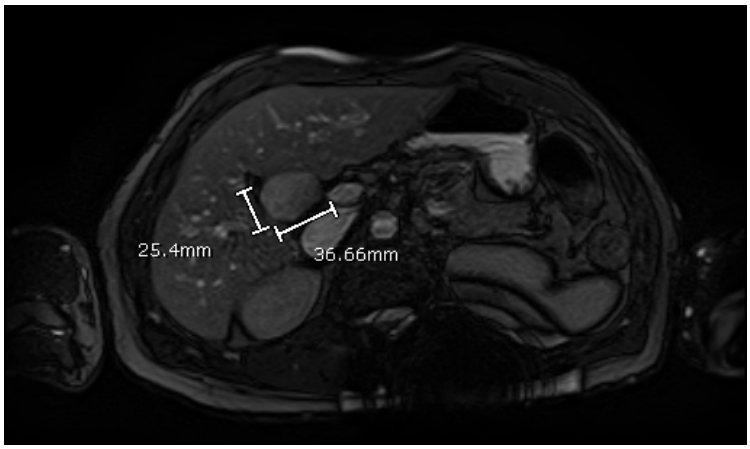


Figure 2. Magnetic resonance imaging of the abdomen showed a lesion measuring 25.40 mm x 35.66 mm compressing the porta hepatis.

Histology of the small bowel tumor was consistent with a typical GIST morphology and immunophenotype with expression of CD-117 and DOG-1. The tumor had a low mitotic rate, negative epithelial membrane antigen, rare expression of SOX-10, and retention of the gene transcription repressor H3-K27-me3.

The perihilar tumor's histology showed mitotically active malignant-appearing spindle cell neoplasm with necrosis infiltrating into the liver. This tumor's morphology is seen in MPNST. However, its immunophenotype was not concordant with its morphologic features. There was complete loss of expression of H3-K27-me3 as would be expected in MPNST but CD-117, DOG-1, and SOX-10 were positive, which are diagnostic for GIST.

Three months following the Whipple procedure, MRI of the abdomen showed three hepatic lesions with high grade spindle cell neoplasm on histology. He was initiated on gemcitabine and taxotere to treat MPNST. However, the patient's disease progressed on chemotherapy. He was switched to ifosfamide and etoposide. Despite current treatment, his malignancy has metastasized further.

DISCUSSION

Our patient presented with a mass that had features of both GIST and MPNST, making the diagnosis difficult and rendering its management uncertain. While rare in the general population, these tumors have a greater prevalence among patients with NF-1.[1,3-5]

GIST is the most common NF-associated gastrointestinal tumor, its incidence in NF-1 is significantly higher than that of the general population.[1,7] While cases of GIST have been reported in all age groups, they are diagnosed most commonly in the 6th decade of life.[6] These tumors are found predominantly in the stomach (60%) followed by the small intestine (20 - 30%). However, in patients with NF-1, GIST is found predominantly in the small intestine and diagnosed at a younger age, as seen in our patient.[4,8] The diagnosis of GIST usually is established with immunohistochemistry that demonstrates a gain-of-function mutation of the receptor tyrosine kinase protein, KIT, also known as CD-117.[9] DOG-1, a transmembrane protein, is sensitive and specific to GIST and more sensitive than CD-117 for gastric GIST, while CD-117 is more sensitive than DOG-1 in intestinal GIST.[10,11]

MPNST is an aggressive spindle cell neoplasm associated with NF-1; 50 - 60% of MPNST cases have a known diagnosis of NF-1.[12] Approximately 2 - 5% of patients with NF-1 develop MPNST in the second or third decade of life.[3] These tumors commonly arise from pre-existing plexiform neurofibromas, which are prevelant in patients with NF-1.[3,5] The diagnosis of MPNST involves nonspecific histologic features; no pathognomonic immunohistochemical stain has been defined for MPNST.[13] Since it is difficult to distinguish MPNST from plexiform neurofibromas, loss of H3-K27-me3 has been studied as a possible diagnostic marker for MPNST.[14] Loss of H3-K27-me3 has a high specificity for the diagnosis of MPNST, particularly NF1-associated MPNST.[14-16] However, studies have reported variable sensitivity levels for this test.[15,16] Consequently, loss of H3-K27-me3 should be considered in the setting of a spindle-cell neoplasm.[16]

Our patient was found to have two tumors, both expressing DOG-1 and CD-117, which are diagnostic for GIST.[8] However, the perihilar tumor exhibited loss of H3-K27-me3 in addition to spindle cell morphology. Since this marker is specific for MPNST, the possibility that the second tumor had two simultaneous NF-associated malignancies cannot be ruled out.[15,16]

The hilar mass could represent a NF-associated GIST with loss of H3-K27-me3 due to high mitotic activity. However, no previous studies were found discussing such an occurrence. Loss of H3-K27-me3 could serve as a marker of an aggressive variant of GIST as well, however, no prior cases were described in the literature.

GIST and MPNST carry devastating prognoses. Malignant GIST has a median five year relative survival rate of 45% and is resistant to conventional radiation and chemotherapy.[9,17] This has made surgery the primary treatment modality for localized tumors, with a cure rate of 60%.[9,17] The tyrosine kinase inhibitor imatinib has been used prior to surgery to decrease tumor size and as adjuvant chemotherapy with a response rate of 82%.[9] MPNST's five-year survival rate is 35 - 50% and decreases to 10% in patients with NF-1.[18] To the best of our knowledge, this is the first case of NF-1 presenting with a tumor carrying features of both GIST and MPNST.

REFERENCES

1 Zoller ME, Rembeck B, Oden A, Samuelsson M, Angervall L. Malignant and benign tumors in patients with neurofibromatosis type 1 in a defined Swedish population. Cancer 1997; 79(11):2125-2131. PMID: 9179058.
2 Zoller M, Rembeck B, Akesson HO, Angervall L. Life expectancy, mortality and prognostic factors in neurofibromatosis type 1. A twelve-year follow-up of an epidemiological study in Goteborg, Sweden. Acta Derm Venereol 1995; 75(2):136-140. PMID: 7604643.
3 Ferner RE, Gutmann DH. International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis. Cancer Res 2002; 62(5):1573-1577. PMID: 11894862.
4 Miettinen M, Fetsch JF, Sobin LH, Lasota J. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: A clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol 2006; 30(1):90-96. PMID: 16330947.
5 Rossiter JP, Fenton PV. Malignant peripheral nerve sheath tumor in neurofibromatosis type 1. JAMA Neurol 2014; 71(2):242. PMID: 24343189.
6 Nishida T, Blay JY, Hirota S, Kitagawa Y, Kang YK. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. Gastric Cancer 2016; 19(1):3-14. PMID: 26276366.
7 Fuller CE, Williams GT. Gastrointestinal manifestations of type 1 neurofibromatosis (von Recklinghausen's disease). Histopathology 1991; 19(1):1-11. PMID: 1916682.
8 Andersson J, Sihto H, Meis-Kindblom JM, Joensuu H, Nupponen N, Kindblom LG. NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics. Am J Surg Pathol 2005; 29(9):1170-1176. PMID: 16096406.
9 Mantese G. Gastrointestinal stromal tumor: Epidemiology, diagnosis, and treatment. Curr Opin Gastroenterol 2019; 35(6):555-559. PMID: 31577561.
10 Cheng SP, Huang MJ, Yang TL, et al. Neurofibromatosis with gastrointestinal stromal tumors: Insights into the association. Dig Dis Sci 2004; 49(7-8):1165-1169. PMID: 15387340.
11 Hemminger J, Iwenofu OH. Discovered on gastrointestinal stromal tumours 1 (DOG1) expression in non-gastrointestinal stromal tumour (GIST) neoplasms. Histopathology 2012; 61(2):170-177. PMID: 22571292.
12 Evans DG, Baser ME, McGaughran J, Sharif S, Howard E, Moran A. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet 2002; 39(5):311-314. PMID: 12011145.
13 Farid M, Demicco EG, Garcia R, et al. Malignant peripheral nerve sheath tumors. Oncologist 2014; 19(2):193-201. PMID: 24470531.
14 Cleven AH, Sannaa GA, Briaire-de Bruijn I, et al. Loss of H3K27 tri-methylation is a diagnostic marker for malignant peripheral nerve sheath tumors and an indicator for an inferior survival. Mod Pathol 2016; 29(6):582-590. PMID: 26990975.
15 Otsuka H, Kohashi K, Yoshimoto M, et al. Immunohistochemical evaluation of H3K27 trimethylation in malignant peripheral nerve sheath tumors. Pathol Res Pract 2018; 214(3):417-425. PMID: 29482987.
16 Schaefer IM, Fletcher CD, Hornick JL. Loss of H3K27 trimethylation distinguishes malignant peripheral nerve sheath tumors from histologic mimics. Mod Pathol 2016; 29(1):4-13. PMID: 26585554.
17 Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: An analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol 2005; 100(1):162-168. PMID: 15654796.
18 Venkatachala S, Rajeshkumar S, Premkumar S, et al. Malignant peripheral nerve sheath tumorin neurofibromatosis type I: Unusual presentation as mesenteric mass. Indian J Cancer 2015; 52(3):318-319. PMID: 26905125.

Keywords: neurofibromatosis 1, neurofibrosarcoma, gastrointestinal stromal tumor

KANSAS JOURNAL of MEDICINE

Clinical Characteristics of Necrotizing Soft Tissue Infection and Early Toxic Shock-Like Syndrome Caused by Group G *Streptococcus*: Case Report and Review of Literature

Khalil Choucair, M.D., M.Sc.[1], Katia El Jurdi, M.D., M.Sc.[1], K. James Kallail, Ph.D.[1], Thomas A. Moore, M.D.[1,2]
[1]University of Kansas School of Medicine-Wichita, Wichita, KS Department of Internal Medicine
[2]Infectious Disease Consultants, Wichita, KS

Received Jan. 2, 2021; Accepted for publication March 10, 2021; Published online June 21, 2021
https://doi.org/10.17161/kjm.vol14153038

INTRODUCTION

Necrotizing soft tissue infections (NSTIs) are uncommon, but rapidly spreading infections, that involve the fascia and subcutaneous tissue.[1] NSTIs can be complicated by toxic shock syndrome (TSS), which usually are caused by β-hemolytic streptococci, mostly attributed to group A *Streptococcus* (GAS).[2,3] In fact, the original definition of streptococcal TSS in 1993 required the isolation of GAS, along with parameters indicative of multi-organ dysfunction.[4] TSS remains associated with high mortality rates exceeding 40 - 50%, despite adequate antimicrobial treatment.[5-7] However, group G β-hemolytic streptococci (GGS), historically identified as part of the normal flora of the pharynx, gastrointestinal tract and skin, are an uncommon cause of NSTI-TSS.[8] We report the case of a male with NSTI of the penile shaft, and toxic shock-like syndrome (TSLS) attributable to GGS. Only 16 similar cases have been reported.

CASE REPORT

A 32-year-old previously healthy male presented with penile pain following a 36-hour entrapment of the penile shaft by a plastic ring. He received amoxicillin-clavulanate with urgent surgical ring removal and exploratory flexible cystoscopy. On postoperative day one, he developed fever, chills, and excruciating pain with guarding across the pelvic area. The penile shaft was disproportionately swollen distally, cold to touch, necrotic, and devoid of sensation, with formation of new tense blisters. A new, erythematous skin rash overlying the pubic symphysis and both inguinal canals was observed, with well-demarcated, flat borders (Figure 1). Bilateral inguinal lymphadenopathy was present; identification of crepitus was limited by tenderness.

Labs were remarkable for mild lactic acidosis (2.1 mmol/L), hyperazotemia (25 mmol/L), hyponatremia (126 mEq/L), and thrombocytopenia (107 x 10^3/uL). Interval examination revealed worsening symptoms and rash progression, raising suspicion for NSTI superimposed by early stage streptococcal-induced TSLS. Peripheral blood, fluid from bullae, and penile skin swabs were cultured. IV immunoglobulin (IVIG) was administered and antibiotic therapy was modified to IV piperacillin-tazobactam and clindamycin.

On postoperative day two, he became afebrile and rash progression halted. He underwent penile/scrotum fasciotomy and debridement. Blood cultures remained negative, but fluid from the bullae, the penile skin, and surgical tissue specimen grew GGS. On postoperative day three, the rash receded. Antibiotic therapy was discontinued on day six, and he received a skin graft on day seven.

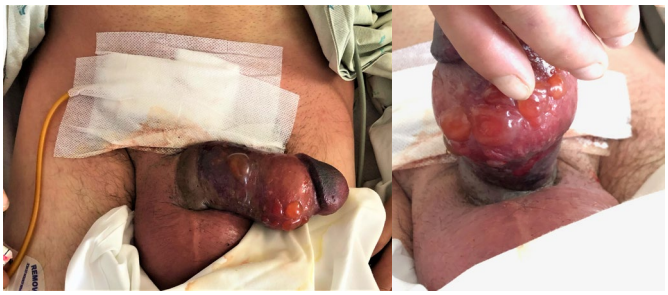


Figure 1. View of the G β-hemolytic *Streptococci* necrotizing soft tissue infection involving the penile area with necrosis of distant shaft, prior to therapy and surgical debridement. (Left) A new, erythematous skin rash overlying the pubic symphysis and both inguinal canals was observed, with well-demarcated, flat borders. (Right) Figure illustrates disproportionate swelling and necrosis distally, with formation of new tense blisters.

DISCUSSION

A review of the English literature revealed 16 additional cases of NSTI caused by GGS.[9-17] Clinical characteristics and outcomes are summarized in Table 1. The mean age of the total of 16 cases was 62.9 years (range: 46 - 80 yrs.). The majority were males (n = 9; 56.2%) and had other co-morbidities (n = 10; 62.5%), including liver cirrhosis (n = 1), malignancy (n = 1), multiple sclerosis (n = 1), syringomyelia (n = 1),[18] arthritis (n = 1), and diabetes mellitus which was the most common co-morbidity (n = 5; 50%).

The mean duration of symptoms prior to presentation was 3.2 days (± 2.2 days) and ranged from one to seven days. Common presenting manifestations were swelling with redness (n = 16; 100%), severe acute pain (n = 8; 50%), and blister formation (n = 7; 43.75%). The lower extremities (leg, ankle, and foot) were the most commonly involved sites (n = 12; 75%), with one case involving the arm,[12] two cases involving the knees,[10] and one case involving multiple sites simultaneously.[13] Progression to TSS or TSLS occurred in nine cases (56.3%). The diagnosis was established by isolating GGS from the site of involvement in all cases (n = 16; 100%): tissue (n = 12), bullae/blisters (n = 2), and joint fluid (n = 2). Bacteremia occurred in 25% of patients (n = 4).[11-13] Treatment included penicillin-based antibiotic regimen in all patients and varying degrees of surgical debridement (n = 15; 93.75%). Four patients received IVIG therapy. The overall mortality rate was 25% (n = 4), with equal rates in those who received IVIG (n = 1/4) and those who did not (n = 3/12); all patients who died developed TSLS.

Our patient presented with less than two days history of penile shaft entrapment with no clear sign of infection. He was treated solely based on clinical presentation which was highly suggestive of streptococcal TSS. Implication of GGS as the organism responsible for this illness and clinical progression was only later established based on an isolated specimen from surgical tissue and blister fluid which showed Gram-positive cocci and GGS growth on culture. The case thus highlighted the importance of early TSLS signs recognition, and the ensuing prompt management based on pure clinical presentation.

Table 1. Characteristics of Group G *Streptococcus* necrotising fasciitis.

Age (years)/sex	Co-morbidities	Site	Source of culture	TSS/TSLS? (Y/N)	Therapy	Outcome	Reference
75/F	Syringomyelia	Left leg	Tissue	N	Antibiotics, debridement	Survived	[36]
80/F	None	Right leg	Tissue	N	Antibiotics, debridement	Survived (skin graft)	[9]
49/F	None	Left ankle	Tissue	N	Antibiotics, debridement	Survived	[9]
75/M	None	Right leg	Tissue	N	Antibiotics, debridement	Survived	[9]
71/M	None	Left foot	Skin/bulla	N	Antibiotics, debridement	Survived (skin graft)	[14]
59/M	Unknown	Right leg	Skin/blister	Y	Antibiotics, debridement	Died	[15]
64/F	DM	Both legs	Tissue	Y	Antibiotics	Died	[17]
65/F	RA	Right arm	Blood/tissue	Y	Antibiotics, amputation	Died	[12]
52/M	DM	Right leg	Tissue	Y	Antibiotics. debridement	Survived	[16]
52/M	DM	Right leg	Tissue	N	Antibiotics, debridement	Survived	[13]
59/M	HCL/FN	Left leg	Blood/tissue	N	Antibiotics, debridement	Survived	[13]
58/M	Liver cirrhosis	Left knee, forearm, wrist, digits	Blood/tissue	Y	Antibiotics, IVIG, debridement	Died	[13]
73/F	Morbid obesity, HTN, DM, PVD	Left leg/ankle	Blood/tissue	Y	Antibiotics, debridement	Survived	[11]
46/F	MS, LLL	Right leg	Tissue	Y	Antibiotics, IVIG, debridement	Survived	[10]
63/M	None	Both knee joints	Joint fluid	Y	Antibiotics, IVIG, arthroscopic washes	Survived	[10]
66/M	DM, TKR	Prosthetic knee	Prosthetic knee/ fluid	Y	Antibiotics, IVIG, debridement	Survived	[10]
32/M	None	Penis	Bulla/tissue	Y	Antibiotics, IVIG, debridement	Survived	Present work

M = Male; F= Female; Y: Yes; N: No; DM: Diabetes Mellitus; RA: Rheumatoid Arthritis; HCL: Hairy Cell Leukemia; FN: Febrile Neutropenia; HTN: Hypertension; PVD: Peripheral Vascular Disease; MS: Multiple Sclerosis; LLL: Lower limb lymphedema; TKR: Total Knee Replacement

While originally identified and described by Lancefield and Hare as part of the normal flora, previous case reports have indicated that GGS also could cause complicated infections, such as cellulitis, osteomyelitis, septic arthritis, meningitis, endocarditis, and bacteremia.[19-22] Invasive disease due to GGS has been reported mostly in patients with underlying debilitating conditions including malignancy, rheumatoid arthritis, diabetes mellitus, injection drug use, and HIV infection, as well as in more elderly patients (Table 1).[10,11,13,16-18]

Our patient was young and healthy with no known history of co-morbid conditions. Whether the penile shaft entrapment and the ensuing low blood flow and necrosis could mimic the low terminal vascular supply and/or local impairment in defense mechanism observed in diabetes mellitus patients remains a plausible hypothesis, particularly in light of the observation that most cases had lower extremity involvement and diabetes mellitus (Table 1). Our review of literature did not always suggest an apparent precipitating cause of GGS-NSTI and TSS.

The presented case was unique in respect to two aspects. The first one pertains to the rarity of the underlying causative organism (only 16 reported cases in the English literature); as mentioned earlier GGS historically has been characterized as part of the normal flora with rare cases describing its involvement in pathologic states. Our case was one of these rare occurrences. Second, within the different reported cases, invasive GGS invariably has been linked to existing underlying co-morbidities. In contrast, our case was unique in that it reflected the occurrence of this potentially lethal infection in an otherwise young and healthy individual, hence highlighting the importance of a low clinical suspicion threshold for GGS-NSTI.

Over the past years, the number of reported GGS-NSTI cases, with or without TSS, has been on the rise. In fact, this observation prompted Wong et al.[18] to conduct a retrospective chart review of patients admitted to Long Island College Hospital in Brooklyn, New York, between January 2003 and December 2007. Only adult patients with microbiologically documented GGS infection were included in the study. A total of 73 patients with GGS infections were admitted to the hospital during the five-year study period, with the number increasing yearly and in an incremental fashion from three cases in 2003 to 28 in 2007. This study, along with the different cases reported (Table 1), reflects a clear increase in trend, and raises the possibility of GGS being an emerging human pathogen. The reasons of this increase remain

unknown and could relate to increase in potential risk factors, such as increased prevalence of diabetes mellitus or cancer, or to improved detection methods. Furthermore, emergence of resistance patterns in response to increased antibiotics use worldwide may explain possible changes/increases in GGS virulence. Hashikawa et al.[23] microbiologically characterized 12 strains of group C and G streptococci that caused TSS. Despite GGS TSS manifesting clinically in a similar fashion to GAS, only the *spegg* gene, which encodes a super-antigen found in GAS stains, was detected in *S. dysgalactiae* (GGS strain), but no other apparent virulence factor responsible for the TSS pathogenesis was identified. Further multi-center studies are warranted to characterize the increasing trend of GGS and define underlying host risk factors, and strain virulence factors.

As mentioned, NSTI and TSS treatment in our patient was initiated solely based on clinical presentation and high index of suspicion with no imaging to characterize the depth of tissue involvement.[24] Prompt initiation of therapy took precedence over establishing a clear diagnosis, based on both high clinical suspicion and the significantly high morbidity/mortality associated with delayed initiation of therapy. The actual diagnosis was validated clinically later when the patient positively responded to therapy and shock progression halted.

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) is a score used in the setting of early infection to define the likelihood of NSTI; it is based on indicators including white blood cell count (WBC), hemoglobin (Hgb), sodium (Na), glucose, creatinine (Cr.), and C-reactive protein (CRP).[25,26] A score greater than six is suggestive of NSTI while less than six is indicative of low risk (but does not exclude risk), suggesting IV antibiotics and serial laboratory monitoring without the need for surgical debridement.

We did not calculate a LRINEC score for our patient. In hindsight, and with the available laboratory values (CRP not obtained), the calculated LRINEC would have been five (WBC = 10.3 x 10^3/ uL; Cr. = 1.8; Na: 126 mEq/L; and Hgb = 12 d/dL), suggestive of low risk. This discrepancy between the low LRINEC score and the actual clinical picture reveals yet again the importance of clinical history and physical exam in clinical decision making. High suspicion for NSTI on clinical ground warrants a straight operative debridement approach, regardless of LRINEC score.

A recent assessment of the LRINEC score has recommended its cautious use given a poor performance in external validation.[27] In this study which involved patients with established diagnoses of cellulitis (n = 948) and necrotizing fasciitis (n = 135), a retrospective computation of the LRINEC score revealed poor predictive value of the score for differentiating between both diseases with a 10.7% false diagnoses of moderate-to-high risk of necrotizing fasciitis in patients with a confirmed diagnosis of cellulitis. Similarly, and within the group of patients with confirmed necrotizing fasciitis, 63.8% were categorized as low risk for necrotizing fasciitis using the LRINC score.

Similar to all NSTI, broad spectrum antibiotics and surgical debridement are necessary for a good outcome. Our patient received piperacillin-tazobactam as a regimen, along with both clindamycin and IVIG. Beyond its antibacterial effects, clindamycin is added for its ability to suppress bacterial toxin production.[28] In fact, use of clindamycin in patients with invasive GAS infection was associated with lower 30-day mortality (15% vs. 39% in those who did not receive clindamycin).[29] Linezolid or tedizolid alternatively can be used in patients with known resistance to clindamycin.[1] The use of IVIG in patients with streptococcal TSS often has been a subject of debate. The proposed rationale for use of IVIG is to boost antibody levels (passive immunity) in the setting of the overwhelming infection seen in TSS. Several mechanisms have been proposed, including bacterial opsonisation, toxin neutralization, inhibition of T cell proliferation, and inhibition of inflammatory cytokines.[30,31] Clinically, IVIG super-antigen neutralizing activity reduced mortality rates in streptococcal TSS.[32-34] A recent meta-analysis including five studies of patients with streptococcal TSS treated with clindamycin revealed an association between IVIG use and 30-day reduction in mortality (33.7 vs. 15.7 %).[35]

In summary, this work illustrated how NSTI due to GGS can progress, similar to GAS-induced fasciitis, to TSS/TSLS and can be life-threatening. Clinicians should keep a high index of suspicion, especially in patients with underlying co-morbid conditions, and understand the crucial role of early IVIG therapy, the choice of antibiotics with anti-toxin properties, and the increasing trend of GGS infections.

REFERENCES

1 Stevens DL, Bryant AE. Necrotizing soft-tissue infections. N Engl J Med 2017; 377(23):2253-2265. PMID: 29211672.
2 Rowlands J, Dufort EM, Blog DS, Zansky SM. Underreporting of necrotizing fasciitis and streptococcal toxic shock syndrome in invasive group A streptococcus cases in New York State, 2007-2016. Open Forum Infect Dis 2017; 4(suppl 1):S240-S240.
3 Ikebe T, Tominaga K, Shima T, et al. Increased prevalence of group A streptococcus isolates in streptococcal toxic shock syndrome cases in Japan from 2010 to 2012. Epidemiol Infect 2015; 143(4):864-872. PMID: 25703404.
4 Breiman RF, Davis JP, Facklam RR, et al. Defining the group A streptococcal toxic shock syndrome: Rationale and consensus definition. JAMA 1993; 269(3):390-391. PMID: 8418347.
5 Davies HD, McGeer A, Schwartz B, et al. Invasive group A streptococcal infections in Ontario, Canada. N Engl J Med 1996; 335(8):547-554. PMID: 8684408.
6 McCormick JK, Yarwood JM, Schlievert PM. Toxic shock syndrome and bacterial superantigens: An update. Annu Rev Microbiol 2001; 55(1):77-104. PMID: 11544350.
7 O'Loughlin RE, Roberson A, Cieslak PR, et al. The epidemiology of invasive group A streptococcal infection and potential vaccine implications: United States, 2000-2004. Clin Infect Dis 2007; 45(7):853-862. PMID: 17806049.
8 Vartian C, Lerner PI, Shlaes DM, Gopalakrishna KV. Infections due to Lancefield group G streptococci. Medicine 1985; 64(2):75-88. PMID: 3974442.
9 Barker F, Leppard BJ, Seal DV. Streptococcal necrotising fasciitis: Comparison between histological and clinical features. J Clin Pathol 1987; 40(3):335-341. PMID: 3558868.
10 Baxter M, Morgan M. Streptococcal toxic shock syndrome caused by group G streptococcus, United Kingdom. Emerg Infect Dis 2017; 23(1):127-129. PMID: 27983491.
11 Gupta S, Mansuri N, Kowdley G. Group G streptococcus leading to necrotizing soft tissue infection after left lower extremity radiofrequency venous ablation. J Vasc Surg Cases Innov Tech 2019; 5(2):110-112. PMID: 31193488.
12 Hirose Y, Yagi K, Honda H, Shibuya H, Okazaki E. Toxic shock-like syndrome caused by non-group A beta-hemolytic streptococci. Arch Intern Med 1997; 157(16):1891-1894. PMID: 9290550.

[13] Humar D, Datta V, Bast DJ, Beall B, De Azavedo JCS, Nizet V. Streptolysin S and necrotising infections produced by group G streptococcus. Lancet 2002; 359(9301):124-129. PMID: 11809255.
[14] Jarrett P, Rademaker M, Duffill M. The clinical spectrum of necrotising fasciitis. A review of 15 cases. Aust N Z J Med 1997; 27(1):29-34. PMID: 9079250.
[15] Kugi M, Tojo H, Haraga I, Takata T, Handa K, Tanaka K. Toxic shock-like syndrome caused by group G Streptococcus. J Infect 1998; 37(3):308-309. PMID: 9892544.
[16] Sharma M, Khatib R, Fakih M. Clinical characteristics of necrotizing fasciitis caused by group G Streptococcus: Case report and review of the literature. Scand J Infect Dis 2002; 34(6):468-471. PMID: 12160177.
[17] Wagner JG, Schlievert PM, Assimacopoulos AP, Stoehr JA, Carson PJ, Komadina K. Acute group G streptococcal myositis associated with streptococcal toxic shock syndrome: Case report and review. Clin Infect Dis 1996; 23(5):1159-1161. PMID: 8922817.
[18] Wong SS, Lin YS, Mathew L, Rajagopal L, Sepkowitz D. Increase in group G streptococcal infections in a community hospital, New York, USA. Emerg Infect Dis 2009; 15(6):991. PMID: 19523319.
[19] Liao CH, Liu LC, Huang YT, Teng LJ, Hsueh PR. Bacteremia caused by group G streptococci, Taiwan. Emerg Infect Dis 2008; 14(5):837. PMID: 18439377.
[20] Venezio FR, Gullberg RM, Westenfelder GO, Phair JP, Cook FV. Group G streptococcal endocarditis and bacteremia. Am J Med 1986; 81(1):29-34. PMID: 3728552.
[21] Mohan P, Shanmugam J, Nair A, Tharakan J. Fatal outcome of group-G streptococcal meningitis (a case report). J Postgrad Med 1989; 35(1):49. PMID: 2585338.
[22] Burkert T, Watanakunakorn C. Group G streptococcus septic arthritis and osteomyelitis: Report and literature review. J Rheumatol 1991; 18(6):904-907. PMID: 1895274.
[23] Hashikawa S, Iinuma Y, Furushita M, et al. Characterization of group C and G streptococcal strains that cause streptococcal toxic shock syndrome. J Clin Microbiol 2004; 42(1):186-192. PMID: 14715751.
[24] Turecki MB, Taljanovic MS, Stubbs AY, et al. Imaging of musculoskeletal soft tissue infections. Skeletal Radiol 2010; 39(10):957-971. PMID: 19714328.
[25] El-Menyar A, Asim M, Mudali IN, et al. The laboratory risk indicator for necrotizing fasciitis (LRINEC) scoring: The diagnostic and potential prognostic role. Scand J Trauma Resusc Emerg Med 2017; 25(1):28. PMID: 28270166.
[26] Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: A tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 2004; 32(7):1535-1541. PMID: 15241098.
[27] Neeki MM, Dong F, Au C, et al. Evaluating the laboratory risk indicator to differentiate cellulitis from necrotizing fasciitis in the emergency department. West J Emerg Med 2017; 18(4):684-689. PMID: 28611889.
[28] Stevens DL, Maier KA, Mitten JE. Effect of antibiotics on toxin production and viability of Clostridium perfringens. Antimicrob Agents Chemother 1987; 31(2):213-218. PMID: 2882731.
[29] Carapetis JR, Jacoby P, Carville K, Ang SJ, Curtis N, Andrews R. Effectiveness of clindamycin and intravenous immunoglobulin, and risk of disease in contacts, in invasive group a streptococcal infections. Clin Infect Dis 2014; 59(3):358-365. PMID: 24785239.
[30] Norrby-Teglund A, Kaul R, Low DE, et al. Plasma from patients with severe invasive group A streptococcal infections treated with normal polyspecific IgG inhibits streptococcal superantigen-induced T cell proliferation and cytokine production. J Immunol 1996; 156(8):3057-3064. PMID: 8609429.
[31] Norrby-Teglund A, Kaul R, Low DE, et al. Evidence for the presence of streptococcal-superantigen-neutralizing antibodies in normal polyspecific immunoglobulin G. Infect Immun 1996; 64(12):5395-5398. PMID: 8945593.
[32] Darenberg J, Ihendyane N, Sjolin J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: A European randomized, double-blind, placebo-controlled trial. Clin Infect Dis 2003; 37(3):333-340. PMID: 12884156.
[33] Kaul R, McGeer A, Norrby-Teglund, et al. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome - A comparative observational study. Clin Infect Dis 1999; 28(4):800-807. PMID: 10825042.
[34] Linnér A, Darenberg J, Sjolin J, Henriques-Normark B, Norrby-Teglund A. Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: A comparative observational study. Clin Infect Dis 2014; 59(6):851-857. PMID: 24928291.
[35] Parks T, Wilson C, Curtis N, Norrby-Teglund A, Sriskandan S. Polyspecific intravenous immunoglobulin in clindamycin-treated patients with streptococcal toxic shock syndrome: A systematic review and meta-analysis. Clin Infect Dis 2018; 67(9):1434-1436. PMID: 29788397.
[36] Gaunt N, Rogers K, Seal D, Denham M, Lewis J. Necrotising fasciitis due to group C and G haemolytic streptococcus after chiropody. Lancet 1984; 323(8375):516. PMID: 6142243.

Keywords: soft tissue infections, toxic shock syndrome, Streptococcus sp. 'group G'

KANSAS JOURNAL of MEDICINE

Gastric Metastasis of Breast Cancer Found on Routine Esophageal Variceal Screening

Luke Johnson, M.D., Ryan Ford, M.D., Nathan Tofteland, M.D.
University of Kansas School of Medicine-Wichita, Wichita, KS
Department of Internal Medicine

Received Dec. 30, 2020; Accepted for publication March 12, 2021; Published online June 21, 2021
https://doi.org/10.17161/kjm.vol14.15032

INTRODUCTION

Esophageal varices are the most common fatal complication of cirrhosis. Screening with esophagogastroduodenoscopy (EGD) is recommended at initial diagnosis of cirrhosis and every one to three years depending on the patient's level of hepatic compensation and presence of varices. The incidence of metastatic cancer to the stomach is exceedingly rare, about 0.2 to 0.7%.[1] Among these occurrences, breast cancer, lung cancer, and renal cell cancer are the most prevalent. Symptoms of metastatic cancer to the stomach are atypical. They include epigastric pain, gastrointestinal hemorrhage, and dysphagia.

We report on a unique case of a female with cirrhosis presenting five years after achieving breast cancer remission for initial esophageal variceal screening. She underwent routine gastric biopsy for *H. pylori*, which incidentally showed metastatic breast cancer.

CASE REPORT

A 50-year-old female presented to her gastroenterologist in 2020 for routine screening for esophageal varices. She had a history of cirrhosis and invasive ductal carcinoma (T1c, N2, M0) diagnosed in 2014 status-post lumpectomy, adjuvant radiation, and chemotherapy. The patient had undergone four months of chemotherapy with doxorubicin and cyclophosphamide in 2014 prior to remission. She was then on maintenance therapy with tamoxifen beginning in 2015 with no signs of metastatic disease.

The patient had no early satiety, unintentional weight loss, or other concerning symptoms at the time of her endoscopy. EGD showed moderate portal hypertensive gastropathy with increased mucosal friability, normal esophagus, and no other gross abnormalities. Microscopically, an Indian file pattern with signet ring appearance primarily in the serosal, muscular, and submucosal layers was seen. Immunohistochemistry was positive for ER, CK7, GCDFP-15, and CK20. Biopsies of the mucosa showed large, uniform cells with prominent nucleoli and foamy cytoplasm. Routine biopsies taken for evaluation of *H. pylori* demonstrated metastatic breast carcinoma.

DISCUSSION

While the incidental finding of metastatic breast cancer during routine gastric biopsy is exceedingly rare, it is important to appreciate the diversity of diagnostic findings and the role immunohistochemical staining plays in differentiating primary gastric cancer from metastatic breast cancer. The overall incidence of metastatic cancer to the stomach is 0.2 - 0.7%.[1] Primary sites include breast cancer (27%), lung cancer (23%), renal cell carcinoma (7.6%), and malignant melanoma (7%). Additionally, average time between primary breast malignancy and metastatic disease is 50 - 78 months, with an average patient age of 75.6.

Endoscopically, breast cancer metastasis exhibits the following patterns: (1) localized, such as large ulcers/polyps, (2) diffusely infiltrating, and (3) extrinsic compression.[2] In the setting of breast cancer, immunohistochemical staining suggesting a breast origin typically will show positive markers for ER, PR, CK7, GCDFP-15, and negative markers for CK20, CA19-9, CDX-2.[3] Additionally, the presence of ERα combined with the absence of HER-2 ECD can suggest metastasis from the breast.

Key differences in the immunohistochemistry of our case versus standard metastatic breast cancer is the presence of CK20. While immunohistochemistry is a key part of the diagnostic process, this further highlighted the spectrum of possible findings that necessitates consideration of the patient's clinical picture as a whole.

In general, the risk of distant recurrence in patients who underwent endocrine treatment, such as tamoxifen, steadily increased over the next 15 years and correlated with tumor size, tumor grade, and lymph node status.[4] Annual risk of distant recurrence increased 3% each year for those with > 3 positive lymph nodes, 2% each year for one to three positive lymph nodes, 1% each year for negative lymph nodes with tumor grade 2 or greater, and 0.5 - 1.0% for all others. Our patient's findings were consistent with an annual risk of metastasis increasing 3% per year.

The heterogenous nature of tumor lesions, lack of endoscopic classification system that clearly can identify metastases, and variability in microscopy highlighted the importance of adequate biopsy sampling combined with immunohistochemical analysis as the only way to differentiate primary gastric cancer consistently from metastatic disease.[1-3] In addition, for patients with history of a primary malignant lesion, it is important to obtain histologic sampling of even subtle areas of mucosal abnormalities to detect the presence of metastatic disease.

REFERENCES

1 Weigt J, Malfertheiner P. Metastatic disease in the stomach. Gastrointest Tum 2015; 2(2):61-64. PMID: 26674003.
2 Namikawa T, Hanazaki K. Clinicopathological features and treatment outcomes of metastatic tumors in the stomach. Surg Today 2013; 44(8):1392-1399. PMID: 23896636.
3 Villa Guzman JC, Espinosa J, Cervera R, Delgado M, Paton R, Cordero Garcia JM. Gastric and colon metastasis from breast cancer: Case report, review of the literature, and possible underlying mechanisms. Breast Cancer (Dove Med Press) 2016; 9:1-7. PMID: 28096693.
4 Pan H, Gray R, Braybrooke J, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. New Engl J Med 2017; 377(19):1836-1846. PMID: 29117498.

Keywords: breast cancer, neoplasm metastasis, esophageal and gastric varices, stomach

KANSAS JOURNAL of MEDICINE

KANSAS JOURNAL OF MEDICINE

VOLUME 14 • 2021

journals.ku.edu/kjm

Have a manuscript ready to publish?
Visit our website for instructions on submitting a manuscript.

Frontiers: University of Kansas Clinical and Translational Science Institute is a collaborating partner of the Kansas Journal of Medicine

Office of Research
1010 N. Kansas, Wichita, KS 67214
316-293-2617 • Email: kjm@kumc.edu

VOLUME 14 • 2021

WHAT'S INSIDE: ORIGINAL RESEARCH • CASE REPORT • IMAGES

KANSAS JOURNAL of MEDICINE

TABLE OF CONTENTS

KANSAS JOURNAL of MEDICINE

A Pilot and Feasibility Study to Evaluate Small and Large Bite Fascial Closure Techniques

Clint R. Gates, M.D.[1], Gina M. Berg, Ph.D., MBA[2,3], Kyle B. Vincent, M.D.[1,4], David L. Acuna, D.O.[1,3,5], Kamran Ali, M.D.[6,7]
University of Kansas School of Medicine-Wichita, Wichita, KS
[1]Department of Surgery
[2]Department of Family and Community Medicine
[3]Wesley Medical Center, Wichita, KS
[4]Ascension Medical Group, Wichita, KS
[5]Kansas Surgical Consultants, Wichita, KS
[6]University of Kansas School of Medicine-Wichita, Wichita, KS
Department of Radiology
[7]Wichita Radiological Group, Wichita, KS

Received March 2, 2021; Accepted for publication March 31, 2021; Published online July 9, 2021
https://doi.org/10.17161/kjm.vol14152236

ABSTRACT

Introduction. Few randomized controlled studies have been conducted comparing a small to large fascial bite technique, yet recommendations have been made to standardize small bite closures. However, large scale randomized controlled trials require considerable effort and may benefit from a pilot study.

Methods. This multi-center randomized controlled pilot study of adult patients undergoing median laparotomy incision investigated the feasibility of studying the outcomes between small and large surgical closure techniques.

Results. Fifty of 100 planned patients consented, 32 patients completed surgery, and 19 patients completed the one-year ultrasound. Enrollment was 2.7 versus 8 patients per month pre/post addition of a study coordinator. Clinical results are summarized for feasibility demonstration purposes, but not analyzed for hypothesis testing. The total cost of the pilot study was $19,152.50 and took 22 months from first surgery to final one-year ultrasound.

Conclusions. This feasibility assessment demonstrated the complexity of planning a large-scale randomized trial evaluating small and large bite surgical closure technique. To expand this pilot study to a full scaled sample size study would require dedicated personnel and large grant funding. ***Kans J Med 2021;14:163-169***

INTRODUCTION

The incidence of incisional hernia following a median laparotomy incision is 11 - 20%.[1-4] Incisional hernias can be symptomatic or life threatening when they incarcerate, strangulate, or lead to bowel obstructions and may require surgical repair (45% chance of recurrence)[5] and incurs cost.[6] Risk factors include diabetes, malignancy, wound infection, malnutrition, previous laparotomy, use of corticosteroids, and surgical technique.[2,3,7] Modifiable surgical technique components include suture material,[8] running versus interrupted suture,[3,9-12] and suture length to wound length ratio (SL:WL).[8,12-15] The SL:WL can vary based on suture bite width, advancement length, and applied tension. A larger bite incorporates more tissue within the suture line distributing tension over more tissue, theoretically decreasing tissue strangulation. However, a larger bite incorporates tissue that offers no tensile strength allowing the suture material to cut through and loosening the closure. A smaller bite aims to grab precisely only the fascia, the tissue that provides the tensile strength.[16] Small bite versus large bite was studied in the Netherlands (the STITCH Trial) and demonstrated an 8% absolute reduction in the occurrence of incisional hernia at one year in the small bite group.[17] The authors concluded that the small bite technique should become standard clinical practice closure technique for midline incisions.

Clinical practice guidelines to standardize care are developed by a systematic review of multiple studies rather than a single study.[18] The STITCH Trial was a randomized controlled trial (RCT) of 560 patients, ten surgical centers, from 2009 to 2012,[17] and has been criticized for variability in SL:WL,[19] non-standardized suture material and needles,[20] and length of follow-up period.[21] The feasibility of replicating large multi-center RCTs to corroborate findings can be assessed by a pilot trial to reveal the challenges of study protocols.[22-24] Jeray et al.[22] indicated objectives of a pilot study include: 1) integrity of study protocol; 2) consent and recruitment; 3) acceptability of intervention/randomization; 4) safety; 5) economically justifiable; and 6) data collection and management. Pilot studies also may include a feasibility assessment to make a determination to proceed with the full scale study[22,23,25,26] and may de-risk large scale funding.[27]

This was a multi-center pilot study to assess the feasibility of replicating the STITCH Trial.[17] The primary outcomes were to follow objectives as previously listed by Jeray et al.[22] Due to low sample size of pilot data, the clinical data are presented only to demonstrate Jeray's objective #6.

METHODS

This feasibility study was approved by the Wichita Medical Research and Education Foundation, Via Christi St. Francis, University of Kansas School of Medicine-Wichita, and Wichita State University Institutional Review Boards. All participants underwent the informed consent process and participation was voluntary.

Participants. Patients undergoing surgery at two tertiary hospitals were eligible if adult (age 18 - 75) and scheduled for a potential operation through a midline incision. Exclusion criteria included: previous incisional hernia or fascial dehiscence with secondary healing after midline incision, pregnant, body mass index (BMI) over 50, laparotomy within one year, expected to live less than 24 hours, systolic blood pressure < 90 mmHg, and an American Society of Anesthesiologists (ASA) Physical Status score ≥ 4.[28] Study participants were to be enrolled in their clinic office or in the hospitals. Enrollment was monitored monthly.

Procedure. Data were collected at: Stage 1) Enrollment (pre-surgery, patient demographics); Stage 2) Surgery (closure details); Stage 3) Discharge (hospital course); Stage 4) Six week post-operative (outpatient follow-up, complications); and Stage 5) One-year ultrasound (presence or absence of hernia). Patients were blinded to closure technique and closure type was revealed to the surgeon at the time of fascial closure. Post-operative ultrasonography was performed at one year by a radiologist blinded to closure technique. Participants were offered a $30 incentive for completing Stage 4 and a $100 incentive for completing Stage 5. There was no charge for the one-year ultrasound.

Protocol education was provided to staff at each facility, including videos demonstrating the separate closure techniques. The small bite technique used 0.5 cm bite width and 0.5 cm inter-suture spacing using 2-0 PDS®II suture on an SH 26 mm taper needle (Product Number: Z317, Ethicon, Cincinnati, OH). The large bite closure technique used 1 cm bite width and 1 cm inter-suture spacing with 1 PDS®II suture on a CT-1 36 mm taper needle (Product Number: Z347, Ethicon, Cincinnati, OH). Running suture was used in all participants and nine knots were used at each of the three tie-off locations (center and both ends). Remaining suture was retained for SL:WL ratio calculation. The wound length and number of bites taken were recorded and calculated to verify that the proper technique was employed.

Statistical Analysis. Feasibility and clinical findings were summarized with descriptive statistics using means (standard deviations) and frequencies (percentages) as appropriate. This feasibility study was not designed to conduct clinical hypothesis testing; thus, no comparison statistics are reported.

RESULTS

Enrollment. Figure 1 demonstrates participant attrition. Only 50 of the planned 100 participants were enrolled in 10 months. Of those, 18 (36%) were excluded for ineligibility (no midline incision), surgeon discretion, missing surgery data, or complications (return to the operating room, anastomotic leak, or missing data). Of the 32 patients who completed surgery, 13 (41%) participants were randomized into the small bite group and 19 (59%) were randomized into the large bite group. Thirteen participants were lost to one-year ultrasound follow-up. Thus, the final ultrasound sample was 19 (38%). In the final ultrasound group (n = 19), eight (42.1%) had been randomized into the small bite group and eleven (57.8%) in the large bite group.

Clinical Data Only for Feasibility Demonstration Purposes. Table 1 describes the participant demographics. Of the 32 patients that completed the surgery, 14 (40%) were male and the average age was 56.9 years (SD 13.1). Of the 19 participants that completed the ultrasound, there were eight males (42%) and the average age was 61.8 years (SD 9.4).

Table 2 describes surgery data. The mean incision length was 19.9 cm and 11.9 cm in the small and large bite groups, respectively. Mean stitches per centimeter of incision were 2.2 cm for small bite and 1.1 cm for large bite group. Mean suture length/wound length ratios were 3.6 cm and 5.6 cm for the small and large bite groups, respectively.

Of the 32 participants that completed surgery, one received a blood transfusion and one had a surgical site infection, both in the large bite group (Table 3). One patient who completed surgery expired due to reasons unrelated to the study. The mean hospital length of stay was 7.4 days and 6.9 days for the small and large bite groups, respectively. One patient (5.2%) required intensive care unit admission and one (5.2%) was readmitted for suspected anastomotic leak, both in the large bite group.

Two complications were reported in the post-operative clinic visits (Table 4): one wound infection and one superficial skin dehiscence, both were in the large bite group. There were no incisional hernias appreciated on physical exam for either group. Nineteen of the 33 participants that completed the surgery also completed the one-year ultrasound (Table 5). The average maximum distance between the rectus muscles was 2.7 cm in the small bite group and 2.2 cm in the large bite group. Radiology readings indicated that 19 (100%) had an intact linea alba, but there was one (5.2%) fascial defect in the small bite group. Clinical data were presented only to demonstrate Jeray's objective #6.[22]

Table 1. Study participant demographics and pre-operative characteristics.

		Stage 5 (US) completed (N = 19)	
	(N = 32)	Small (n = 8)	Large (n = 11)
Age, mean (SD)	56.94 (13.1)	60.8 (10.8)	62.6 (8.7)
Height, cm, mean (SD)	169.7 (9.2)	168.5 (11.6)	170.1 (9.0)
Weight, kg, mean (SD)	77.4 (18.9)	75.5 (12.1)	85.9 (20.4)
BMI, mean (SD)	27.3 (6.3)	28.0 (5.8)	29.5 (6.4)
	f(%)	*f*(%)	f(%)
Sex, male	14 (40.0)	3 (37.5)	5 (45.5)
Medical history			
Current smoker	9 (28.1)	0	4 (36.4)
History of COPD	3 (9.4)	0	1 (9.1)
Diabetes mellitus	10 (31.3)	4 (50.0)	3 (27.3)
Heart disease	3 (9.4)	2 (25.0)	1 (9.1)
Pre-operative			
Radiation therapy	4 (12.5)	1 (12.5)	1 (9.1)
Chemotherapy	5 (15.6)	1 (12.5)	1 (9.1)
Corticosteroids	2 (6.3)	0	1 (9.1)
Previous procedures			
Abdominal operations	17 (53.1)	4 (50.0)	6 (54.5)
Other hernias	2 (6.3)	0	1 (9.1)
ASA classification			
1 Normal healthy	21 (65.6)	5 (62.5)	9 (81.8)
2 Mild systemic disease	6 (18.8)	1 (12.5)	0
3 Severe systemic disease	4 (12.5)	1 (12.5)	2 (18.2)

Note: Percentages may not total 100% due to missing patient data. Patients not eligible if pregnant, previous incisional hernia, laparotomy within past year, BMI over 50, or moribund. Other hernias include umbilical or ventral hernia in distant past. ASA = American Society of Anesthesiologists (http://www.asahq.org/resources/clinical-information/asa-physical-statusclassification-system).

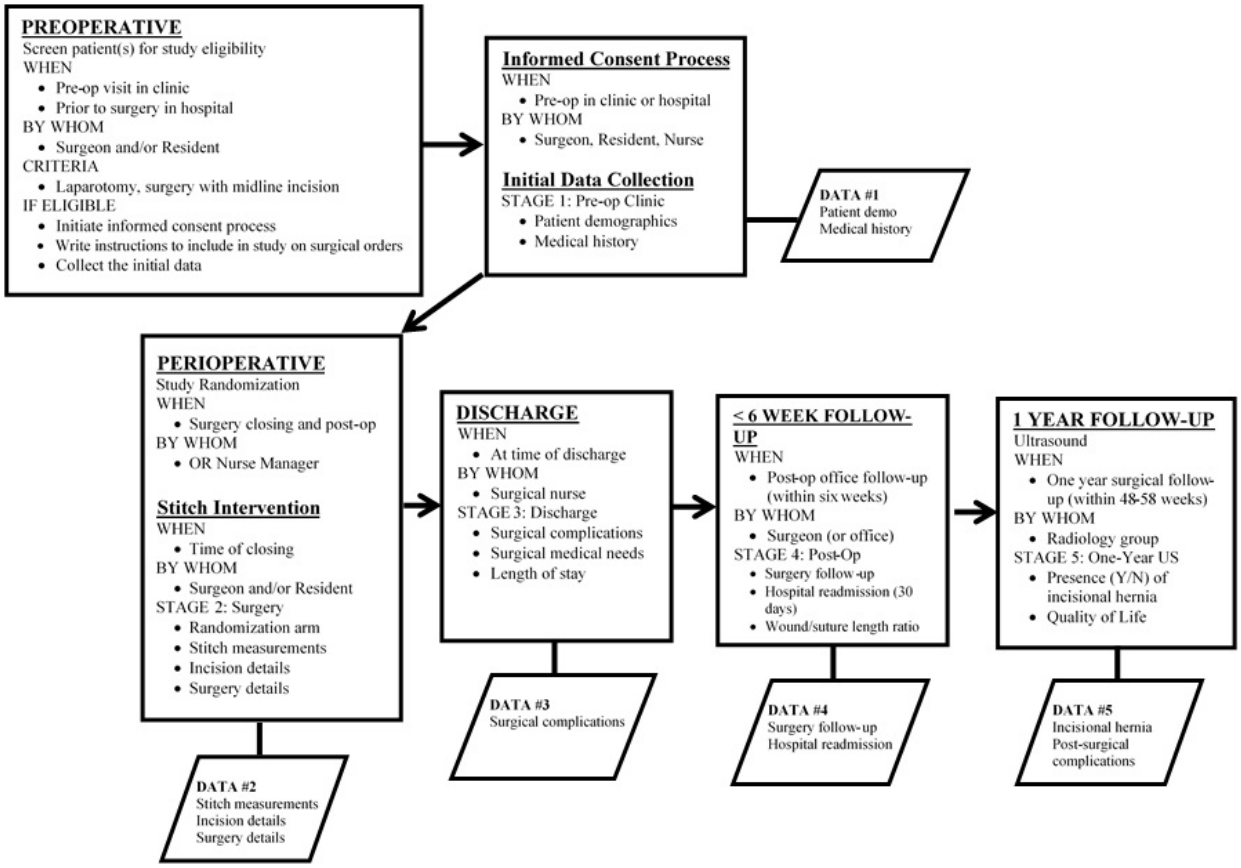


Figure 1. BITES (Better Incisional closure Technique Evolution in Surgery) study flowchart.

Table 2. Operative data.

	Surgery completed (N = 32)		Ultrasound completed (N = 19)	
	Small (n = 13)	Large (n = 19)	Small (n = 8)	Large (n = 11)
Facility				
Hospital 1	2 (15.4)	7 (36.8)	1 (12.5)	6 (54.5)
Hospital 2	11 (84.6)	12 (63.2)	7 (87.5)	5 (45.5)
Closure details				
Number of stitches, *f* (%)	40.6 (16.1)	15.1 (11.0)	43.5 (15.4)	13.6 (7.6)
Length of incision, mean (SD)	18.7 (6.3)	14.2 (7.3)	19.9 (5.5)	11.9 (6.3)
Range of incision	6.0 - 26.0	3.5 - 28.0	8.0 - 25.0	6.0 - 25.00
Stitches per incision cm	2.2 (.5)	1.2 (.2)	2.2 (.57)	1.14 (.2)
Range of stitch per incision cm	1.6 - 3.0	1.0 - 1.6	1.64 - 3.06	1.0 - 1.47
Length of suture, mean (SD)	72.3 (23.4)	62.9 (18.9)	84.0 (20.1)	55.4 (17.7)
SL:WL, mean (SD)*	3.8 (1.0)	4.5 (1.1)	3.6 (.97)	5.6 (2.6)
SL:WL range	2.7 - 5.9	3.1 - 7.7	2.68 - 4.86	3.30 - 11.88
Surgical details				
EBL (cc), mean (SD)	188.8 (206.8)	97.9 (96.4)	85.6 (60.0)	9 (81.8)
Antibiotic prophylaxis, *f*(%)	13 (100.0)	19 (100.0)	8 (100.0)	11 (100)
Thrombosis prophylaxis, *f*(%)	8 (61.5)	15 (78.9)	5 (62.5)	9 (81.8)
Drains, *f*(%)	6 (46.2)	6 (31.6)	2 (25.0)	3 (30.0)
Death during surgery, *f*(%)	0	0	0	0

Note: *Three patients excluded due to missing suture pieces.

Table 3. Hospital course.

	Surgery completed (N = 32)		Ultrasound completed (N = 19)	
	Small (n = 13)	Large (n = 19)	Small (n = 8)	Large (n = 11)
Post-operative complications				
Ileus	4 (30.8)	7 (36.8)	2 (25.0)	6 (54.5)
Blood transfusion	0	1 (5.2)	0	0
Surgical site infection	0	1 (5.2)	0	0
Wound hematoma	0	0	0	0
Pulmonary infection	0	0	0	0
Ventilation	0	0	0	0
Corticosteroids	0	0	0	0
Other	0	1 (5.2)		
Hospital course				
Hospital length of stay	7.5 (4.3)	6.3 (4.5)	7.38 (4.6)	6.9 (5.7)
ICU admission, *f*(%)	1 (7.7)	2 (10.5)	0	1 (9.1)
ICU length of stay	5.0 (0.0)	3.5 (2.1)	0	5.0 (0.0)
Readmission with 30 days, *f*(%)	0	2 (10.5)[1]	0	1 (9.1)[2]
Death post surgery	0	0		

[1]Anastomotic leak; abdominal pain/constipation.
[2]Anastomotic leak and suspected anastomotic leak.

Table 4. Six-week post-operative complications.

	Surgery completed (N = 32)		Ultrasound completed (N = 19)	
	Small (n = 13)	Large (n = 19)	Small (n = 8)[1]	Large (n = 11)
Incisional hernia (palpated)	0	0	0	0
Wound dehiscence	0		0	0
Wound infection	0	1 (5.2)[2]	0	1 (9.1)
Seroma formation	0	0	0	0
Other wound problems	0	1 (5.2)[3]	0	1 (9.1)

Note: Frequencies (%).
[1]One of the ultrasound (small bite) patients did not attend the post-operative clinic visit.
[2]Superficial.
[3]Superficial skin dehiscence.

Table 5. One-year ultrasound follow-up contacts (n = 32).

	Ultrasound eligible (N = 19)	
	Attrition (n = 13, 40.6%)	Completed (n = 19, 59.3%)
Letters returned, *f*(%)	3 (23.0)	1 (5.3)[1]
Number of letters sent, mean (SD)	2.9 (.3)	1.4 (.8)
Number of letters, *f*(%)		
1	0	14 (73.7)
2	1 (7.7)[2]	2 (10.5)
3	12 (92.3)	3 (15.8)

[1]Patient called to follow-up.
[2]Letter returned before third letter sent.

Feasibility Study Development. This study required the approval of four IRBs. Study design, logistic planning, and grant and IRB application preparation required over 16 team meetings. Twelve education sessions were conducted. The planning phase took 18 months until the first patient was enrolled.

Study Personnel. This was a surgery resident directed study. Three research personnel contributed to grant and protocol development. Three surgeons/attendings served as principal investigators. Twenty-two surgeons agreed to participate in the study, 14 participated, and the number of cases per surgeon ranged from one to eight. Two surgeons performed nearly 40% of the cases. Three physician assistant students assisted with suture measurement and data entry. One medical student was hired as study coordinator. The number of clinic and operation room nurses and managers who were educated on the study protocol and participated were not collected. Radiology technicians performed the ultrasounds which were assessed by an attending radiologist.

Recruitment. Only half (50/100) of the expected participants were enrolled at ten months, thus new participant enrollment was terminated (Figure 2). Early enrollment in surgeon offices was not successful. The monthly average enrollment was 2.7 which increased to 8 after a part-time study coordinator was hired as shown in Figure 3. The study took 22 months from the first surgery until the last one-year ultrasound was completed.

Participant Attrition. Figure 2 demonstrates participant attrition. Sixty-four percent (32/50) completed surgery. Only 19/50 (38%) of those enrolled completed the entire study. Three follow-up invitation letters were sent to the 13 participants who were lost to ultrasound follow-up.

Costs. Table 6 lists the costs of the current feasibility study and projected costs extrapolated to the large-scale sample sizes based on actual costs.

DISCUSSION

This was a surgery resident-driven feasibility assessment of a randomized controlled trial evaluating small and large bite closure techniques. Clinical results were reported for demonstration only as it is not appropriate to interpret feasibility data for hypothesis testing; thus, this discussion is focused on the feasibility assessment according to Jeray et al.[22]

Integrity of Study Protocol. All personnel received protocol education; however, investigators suspected there may have been a few inaccuracies in data collection (e.g., Stage 5: One-year ultrasound: intact linea alba noted with an incisional hernia). Surgical technique was evaluated and deemed adequate by a preliminary assessment at six months evaluating the SL:WL ratio and the number of stitches placed per centimeter of wound length.

Consent and Recruitment. The plan was for participant enrollment to be performed during pre-operative clinic visits and when not successful by operation room staff and/or surgery residents. Both options required changes in staff workflow. When low enrollment was noted, a study coordinator was hired. At ten months, only half of the planned 100 participants had been enrolled, thus enrollment was terminated due to time constraints. Barriers to successful enrollment included case volume availability predictions that were too high, but primarily, expectations of the volunteer staff were too much.

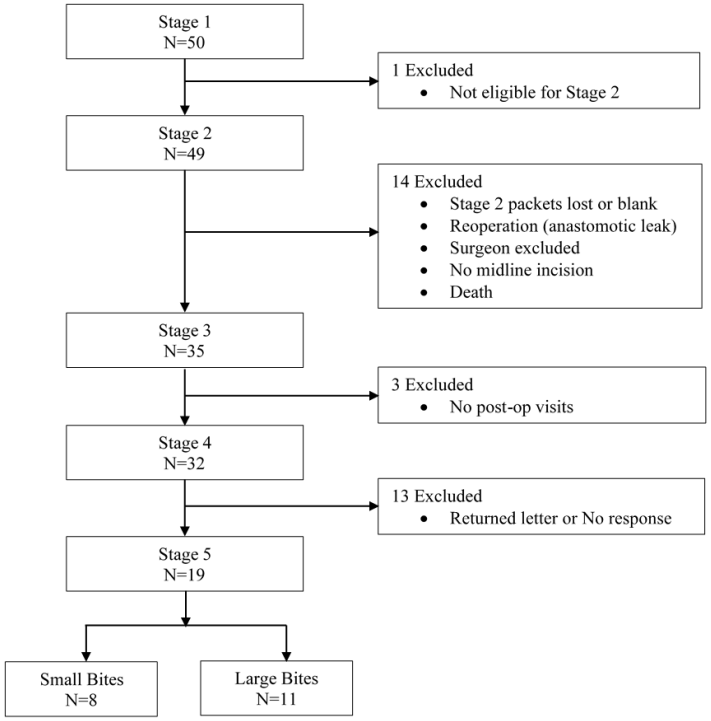


Figure 2. STARD diagram for flow of patients.

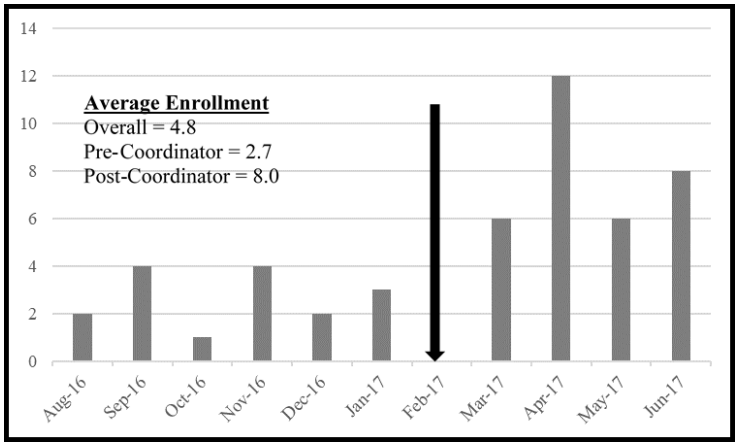


Figure 3. Participant enrollment with and without study coordinator.

Acceptability of Intervention/Randomization. One surgeon excluded a patient at the point of randomization based on patient characteristics, even though he had participated with other patients. Had this been the full-scale study, the exclusion would have been reviewed and surgeons re-educated to prevent potential bias.

Safety. There were no adverse events relevant to this study. The single incisional hernia observed was within the reported incidence (11-20%) of incisional hernia following a median laparotomy incision.[1-4] One patient expired, unrelated to study.

Economically Justifiable. Costs were extrapolated from this study (n = 19) to the sample size indicated (n = 576) in the full scale STITCH Trial[17] or 690 estimated by sample size calculation. Sample size was calculated on the incidence of incisional hernia in the STITCH Trial[17] (21% large bite vs. 13% small bite), study power was set at 80%, and alpha was set at 5%. A total of 690 patients are needed for a large-scale

RCT. The projected full-scale study was estimated to cost $586,954.65 (N = 576) or $704,050.00 (N = 690). The cost likely was inflated due to short-term process inefficiencies, but also under-reported as all academic support was provided in-kind. The original STITCH Trial, having 560 patients and ten sites, took three years.[17] Replicating with only two sites, such as this feasibility study, would take significantly longer.

Table 6. Projection for full scale study extrapolated from 19 (38%) patients completed.

	Current feasibility (N = 19)	STITCH[18] (N = 576)	Estimated sample size (N = 690)
Projected enrollment (based on 62% feasibility attrition)	50	1,515	1,863
Costs			
Data collection packets (5 packets per enrolled)	$102.50	$3,105.75	$3,819.15
Stage 4 incentives (actual $30*64% enrolled)	$960.00	$29,070.00	$35,760.00
Stage 5 incentives (actual $100*100% completed)	$1,900.00	$57,600.00	$69,000.00
Stage 5 ultrasounds (actual $100*100% completed)	$1,900.00	$57,600.00	$69,000.00
Coordinator cost ($753 per 19 completed)	$14,500.00	$439,578.90	$526,470.00
Total costs (projected for replication)	$19,362.50	$586,954.65	$704,049.15

Note: Not all patients who completed Stage 4 (Post-operative) completed Stage 5 (Ultrasound). Coordinator cost included enrollment and data entry.

Data Collection and Management. Data collection was not ideal and required frequent reliability checks. Stage 3 (Surgery) data collection packets were lost resulting in excluding consented patients from the study. Stage 4 (Post-operative) data were not collected consistently during the post-operative visit and instead abstracted from the patient medical record. Data management was effective to report the pilot statistics presented here.

Limitations. Pilot studies are not recommended for calculating sample sizes or response rates for large scale studies.[24] Hypothesis testing is not valid without an appropriate sample size. This feasibility study replicated the STITCH Trial in using two different needles and suture materials, a criticism noted by Gajjar and Shafi.[20]

CONCLUSIONS

This pilot study, with feasibility assessment, was a good demonstration of potential issues in planning a large scale randomized controlled multi-center trial, in this case evaluating small and large bite surgical closure techniques. As planned, there were not enough data to derive any clinical conclusions and were presented only for feasibility demonstration. This was time and resource intensive and required dedicated study personnel for enrollment success. To expand this pilot study to a full-scaled sample size appropriate study would require dedicated personnel and large grant funding. Depending on in-kind resources likely would not result in a successful and timely study. These results did not preclude the necessity of a confirmation study to generate evidence supported guidelines for best practice closure technique.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the following supporters of this study: Felecia Lee, Ph.D., Ashley Hervey, M.Ed., Jimmie Stewart, M.D., Sue Nyberg, PA-C, MPH, Megan Holick, PA-C, Lauren Simmons, PA-C, Calder Young, PA-C, Rita Railing, Jacqueline Osland, M.D., Noel Sanchez, M.D., Ali Ahmad, M.D., Paul Harrison, M.D., William Waswick, M.D., Lindsey Strader, D.O., Michael Porter, M.D., Aaron Nilhas, M.D., J.L. Smith, M.D., Brent Lancaster, M.D., Jeremy Howes, M.D., and the University of Kansas School of Medicine-Wichita, Wesley Medical Center, Via Christi St Francis Hospital, Wichita Surgical Specialists, and Kansas Surgical Consultants.

This study was funded by a grant from the Kansas Biosciences Authority via the University of Kansas School of Medicine-Wichita as well as funds from Wesley Medical Center Trauma Services.

REFERENCES

[1] Mudge M, Hughes LE. Incisional hernia: A 10 year prospective study of incidence and attitudes. Br J Surg 1985; 72(1):70-71. PMID: 3155634.
[2] Sugerman HJ, Kellum JM Jr., Reines HD, DeMaria EJ, Newsome HH, Lowry JW. Greater risk of incisional hernia with morbidly obese than steroid-dependent patients and low recurrence with prefascial polypropylene mesh. Am J Surg 1996; 171(1):80-84. PMID: 8554156.
[3] van 't Riet M, Steyerberg EW, Nellensteyn J, Bonjer HJ, Jeekel J. Meta-analysis of techniques for closure of midline abdominal incisions. Br J Surg. 2002; 89(11):1350-1356. PMID: 12390373.
[4] Wissing J, van Vroonhoven TJ, Schattenkerk ME, Veen HF, Ponsen RJ, Jeekel J. Fascia closure after midline laparotomy: Results of a randomized trial. Br J Surg 1987; 74(8):738-741. PMID: 3307992.
[5] Geçim IE, Koçak S, Ersoz S, Bumin C, Aribal D. Recurrence after incisional hernia repair: Results and risk factors. Surg Today 1996; 26(8):607-609. PMID: 8855493.
[6] Park AE, Roth JS, Kavic SM. Abdominal wall hernia. Curr Probl Surg 2006; 43(5):326-375. PMID: 16679124.
[7] Ellis H, Gajraj H, George CD. Incisional hernias: When do they occur? Br J Surg 1983; 70(5):290-291. PMID: 6850263.
[8] Israelsson LA, Jonsson T. Suture length to wound length ratio and healing of midline laparotomy incisions. Br J Surg 1993; 80(10):1284-1286. PMID: 8242299.
[9] Ceydeli A, Rucinski J, Wise L. Finding the best abdominal closure: An evidence-based review of the literature. Curr Surg 2005; 62(2):220-225. PMID: 15796944.
[10] Hodgson NC, Malthaner RA, Ostbye T. The search for an ideal method of abdominal fascial closure: A meta-analysis. Ann Surg 2000; 231(3):436-442. PMID: 10714638.
[11] Rucinski J, Margolis M, Panagopoulos G, Wise L. Closure of the abdominal midline fascia: Meta-analysis delineates the optimal technique. Am Surg 2001; 67(5):421-426. PMID: 11379640.
[12] Weiland DE, Bay RC, Del Sordi S. Choosing the best abdominal closure by meta-analysis. Am J Surg 1998; 176(6):666-670. PMID: 9926810.
[13] Israelsson LA, Jonsson T. Overweight and healing of midline incisions: The importance of suture technique. Eur J Surg 1997; 163(3):175-180. PMID: 9085058.
[14] Israelsson LA, Jonsson T, Knutsson A. Suture technique and wound healing in midline laparotomy incisions. Eur J Surg 1996; 162(8):605-609. PMID: 8891617.
[15] Jenkins TP. The burst abdominal wound: A mechanical approach. Br J Surg 1976; 63(11):873-876. PMID: 137024.
[16] Harlaar JJ, van Ramshorst GH, Nieuwenhuizen J, et al. Small stitches with small suture distances increase laparotomy closure strength. Am J Surg 2009; 198(3):392-395. PMID: 19285296.
[17] Deerenberg EB, Harlaar JJ, Steyerberg EW, et al. Small bites versus large bites for closure of abdominal midline incisions (STITCH): A double-blind, multicentre, randomised controlled trial. Lancet 2015; 386(10000):1254-1260. PMID: 26188742.

[18] Lim W, Arnold DM, Bachanova V, et al. Evidence-based guidelines--An introduction. Hematology Am Soc Hematol Educ Program 2008; 26-30. PMID: 19074050.
[19] Fujita T. Closure of abdominal midline incisions: STITCH Trial. Lancet 2016; 387(10018):534. PMID: 26867444.
[20] Gajjar K, Mahmood S. Closure of abdominal midline incisions: STITCH Trial. Lancet 2016; 387(10018):534-535. PMID: 26867443.
[21] Hayashi K, Ozaki A, Tanimoto T. Closure of abdominal midline incisions: STITCH Trial. Lancet 2016; 387(10018):535. PMID: 26867446.
[22] Jeray KJ, Tanner SL. Pilot randomized trials: Is there a need? J Bone Joint Surg Am 2012; 94 (Suppl 1):15-18. PMID: 22810441.
[23] Arnold DM, Burns KE, Adhikari NK, et al. The design and interpretation of pilot trials in clinical research in critical care. Crit Care Med 2009; 37(1 Suppl):S69-74. PMID: 19104228.
[24] Cope DG. Conducting pilot and feasibility studies. Oncol Nurs Forum 2015; 42(2):196-197. PMID: 25806886.
[25] Whitehead AL, Sully BG, Campbell MJ. Pilot and feasibility studies: Is there a difference from each other and from a randomised controlled trial? Contemp Clin Trials 2014; 38(1):130-133. PMID: 24735841.
[26] Eldridge SM, Lancaster GA, Campbell MJ, et al. Defining feasibility and pilot studies in preparation for randomised controlled trials: Development of a conceptual framework. PLoS One 2016; 11(3):e0150205. PMID: 26978655.
[27] Morgan B, Hejdenberg J, Hinrichs-Krapels S, Armstrong D. Do feasibility studies contribute to, or avoid, waste in research? PLoS One 2018; 13(4):e0195951. PMID: 29684043.
[28] American Society of Anesthesiologists. ASA Physical Status Classification System. October 15, 2014.. https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system. Accessed April 9, 2019.

Keywords: pilot study, surgical closure techniques, suture techniques, treatment outcome, abdominal wound closure techniques

KANSAS JOURNAL of MEDICINE

Intra-operative Radiation Therapy versus Whole Breast External Beam Radiotherapy: A Comparison of Patient-Reported Outcomes

Jo Leatherman, MS-3[1], Christina Nicholas, M.D.[1,2], Therese Cusick, M.D.[1,2], Ellen Cooke, M.D.[1,3], Elizabeth Ablah, Ph.D.[1,4], Hayrettin Okut, Ph.D.[1,4,5], Diane Hunt, M.D.[1,2]

[1]University of Kansas School of Medicine-Wichita, Wichita, KS

[2]Department of Surgery

[3]Department of Radiology

[4]Department of Population Health

[5]Office of Research

Received Feb. 2, 2021; Accepted for publication April 7, 2021; Published online July 9, 2021
https://doi.org/10.17161/kjm.vol1415147

ABSTRACT

Introduction. This project sought to compare patient-reported outcomes between patients who received intra-operative radiation therapy (IORT) and those who qualified for IORT but received whole-breast external beam radiation therapy (EBRT) following breast-conserving surgery (BCS).

Methods. Three scales from the BREAST-Q Breast Cancer BCT Module Version 2.0 questionnaire were used to collect patient-reported outcomes regarding post-operative physical well-being of the chest, post-operative satisfaction with breast cosmesis, and post-operative adverse effects of radiation.

Results. Patients who received EBRT travelled farther on average than patients who received IORT to complete treatment. Respondents who received IORT reported better physical well-being of the chest than those who received EBRT. Regression revealed that the respondent's age was the determining factor in the difference between IORT and EBRT post-operative physical well-being scores, where younger patients report poorer well-being. There was no difference in patient-reported outcomes regarding post-operative satisfaction with breast cosmesis or adverse effects of radiation.

Conclusions. Patients who received IORT reported better physical well-being of the chest than patients who received EBRT. There appeared to be a relationship between age and physical well-being of chest. This study suggested that there was no difference in patient-reported outcomes concerning post-operative satisfaction with breast cosmesis or post-operative adverse effects of radiation between patients who received IORT and those who received EBRT.

Kans J Med 2021;14:170-175

INTRODUCTION

In 2015, there were approximately 3,418,124 women living in the United States with breast cancer.[1] In 2019, approximately 268,600 new cases were diagnosed, and 41,760 U.S. women died due to breast cancer-related complications.[2] Among Kansans, an estimated 2,420 women were diagnosed with breast cancer in 2019, and 350 died due to breast cancer-related complications.

Since the 1990s, breast-conserving therapy (BCT), a combination of breast-conserving surgery (BCS) and radiation therapy (RT), has been the preferred treatment for patients with breast cancer.[3] Traditional whole-breast external beam radiation therapy (EBRT) has been the primary form of RT following BCS. Adjuvant EBRT involves the patient receiving treatment at a radiation oncology center five days a week for three to six weeks. Up to 21% of patients who undergo BCS do not complete the prescribed RT,[4] and failure to complete RT is associated with higher mortality and a 25% relative increase in local recurrence.[5,6] Those least likely to complete this therapy included patients who are African American, resided in a rural community, or were single.[7] In addition, travel burden, adverse effects of treatment (e.g., fatigue, rib fractures, arm lymphedema),[8] and the complex multidisciplinary nature of breast cancer treatment likely contribute to failure of completion of adjuvant EBRT.[4]

In 2000, intra-operative radiation therapy (IORT) was introduced, a technique that uses a targeted, one-time, high-dose RT performed concurrently with BCS for low-risk patients.[9,10] Two randomized control trials, TARGIT-A and ELIOT, suggested IORT is non-inferior to EBRT in terms of local recurrence risk for low-risk patients.[9,10] To be considered for IORT, the patient's tumor profile must fit the following criteria: estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (Her2) negative, size less than 2 cm on pre-operative imaging, negative lymph nodes,[11] and no evidence of ductal carcinoma in-situ (DCIS) or invasive lobular carcinoma on initial core biopsy.[12] The overall toxicity profile was lower for IORT patients, and quality-adjusted life-years were improved among IORT patients compared to EBRT patients.[13,14] IORT patients reported excellent outcomes but did not offer comparison to EBRT patients.[15] Another study suggested IORT patients reported less general pain and better societal role functioning than EBRT patients,[16] and a third suggested IORT patients reported fewer breast symptoms and body image concerns than EBRT patients.[17] A lifetime cost-effectiveness analysis suggested IORT was a more valuable strategy than EBRT and was preferential among low-risk patients.[18]

IORT has a higher risk of ipsilateral breast tumor recurrence compared to EBRT if used inappropriately,[19] so it is essential to stratify patients based on risk of local recurrence and metastases before choosing this strategy.[12] Post-operative discovery of predefined factors (e.g., positive sentinel node) could result in the addition of EBRT (expected for approximately 15% of patients);[10] in this situation, IORT serves as a tumor bed boost dose and has been demonstrated to further lower the risk of local recurrence.[11]

More research is needed regarding the comparison of patient-reported outcomes based on RT type (IORT versus EBRT), including post-operative satisfaction with breast cosmesis, post-operative physical well-being of the chest, adverse effects of radiation, and travel burden. This project sought to compare patient-reported outcomes between patients who received IORT and patients who qualified for IORT but received EBRT.

METHODS

Participants. All IORT-eligible patients of three Wichita-area surgeons from May 1, 2017 through April 17, 2019 were considered

for this study. Inclusion criteria were women 50 years or older with tumors that were ER-positive, Her2-negative, size less than 2 cm on pre-operative imaging, and without identification of DCIS or invasive lobular carcinoma on initial core biopsy. No incentive was provided for participation in this study. This case-control study was approved by the Human Subjects Committee at the University of Kansas School of Medicine-Wichita.

Instruments. Office staff at participating clinics used ICD-10 codes (19294, 19297, and 19301) to identify eligible patients within their respective electronic health records (EHRs). The abstracted variables included patient identifiers (e.g., name, address, phone number, date of birth, medical record number), patient demographics (e.g., race, insurance coverage), tumor information (e.g., ER and Her2 status, size), and therapy details (e.g., IORT vs. EBRT, date of surgery). Study data were collected and managed using REDCap® electronic data capture tools hosted at the University of Kansas Medical Center.[20]

A survey was developed to collect patient-reported outcomes including breast satisfaction, adverse effects of radiation, and travel burden. The survey included questions from the BREAST-Q Breast Cancer BCT Module Version 2.0 questionnaire,[21] as well as additional questions created by the research team, all of which used Likert scales.

The BREAST-Q has been used since 2009 to collect meaningful and reliable data regarding patient-reported outcomes.[22,23] Three scales from the BREAST-Q BCT module were used to assess outcomes at the time of the survey. The first scale included 11 questions about post-operative satisfaction with breast cosmesis (e.g., appearance when clothed, breast shape when wearing a bra, feeling normal in clothes, being able to wear fitting clothing, how the breast sits/hangs, how smoothly shaped the breast looks, the contour of the breast, whether breasts are equal in size, how normal the breast looks, whether breasts look the same, and appearance when unclothed). The second scale included nine questions about post-operative physical well-being of the chest (e.g., difficulty lifting or moving arms; difficulty sleeping because of breast discomfort; tightness, pulling, tenderness, sharp pain, or aching feeling in the breast area; difficulty lying on the side of lumpectomy breast; or swelling of the arm (lymphedema)). The third scale included six questions about post-operative adverse effects of radiation at the time of the survey (e.g., amount of bother from breast skin looking different, marks on breast skin caused by radiation, radiated breast skin feeling dry, radiated breast skin feeling sore/sensitive when touched, radiated breast skin feeling unnaturally thick, and radiated breast skin feeling irritated by clothing). Additionally, the authors modified these questions to assess adverse effects at the time of RT (n = 6) to address the discrepancy regarding time since surgery among patients in the nearly two-year study period. An additional eight of questions addressed complications related to RT. Participants were asked to provide the geographic location of their RT, the number of weeks they received RT, and the number of days per week they received RT.

Procedures. Case sample size was limited to the 23 patients receiving IORT from May 1, 2017 through April 17, 2019. All patients who qualified for IORT but instead received EBRT during the same time period were identified as possible controls. These patients were matched to the IORT study arm by age and surgeon, then randomized, using a random number generator to create a control arm of equal size.

After the study and control arms were established, patients were called and invited to participate in the study. A maximum of three attempts were made, including voicemails. Upon agreement to participate, patients were given the option to complete the questionnaire over the phone, through the mail, or through an online survey. A REDCap® database was used to log completed calls and collect additional information (e.g., best time to call, current mailing address, e-mail address). All participants gave informed consent.

Likert scale responses to the BREAST-Q were summed and converted into an equivalent Rasch-transformed score (0-100). Higher equivalent Rasch-transformed scores reflect a better outcome. To determine travel burden, the roundtrip distance from each patient's home address at the time of BCT to the patient's radiation oncology center was calculated using Google Maps.[14] The shortest roundtrip route was recorded in miles as the patient's travel distance. The travel distance was multiplied by the number of radiation treatments completed to determine the total number of miles traveled for RT.

Statistical Analysis. SAS version 9.4 was used to generate descriptive statistics for nominal, categorical, and continuous variables (SAS Int. Inc., Cary, NC). Prior to data analysis, outcomes were tested for normal distribution using Shapiro-Wilk's method. Comparisons across the two groups were made using t-tests and analysis of variance (ANOVA) tests for normally distributed variables. For non-normal distribution with appropriate transformation operations, non-parametric approaches such as Mann-Whitney U test and Kruskal-Wallis test were conducted. Data were reported as frequencies, percentages, means, standard deviations, observed t's, F and Likelihood Ratio Chi-square values, and corresponding significance levels (p).

Multiple linear regression was used to model the relationship between post-operative physical well-being, and immediate adverse effects of radiation with age, tumor size, RT type, and durgeon by fitting a linear equation to observed data. All statistical tests at $p \leq 0.05$ were considered significant.

RESULTS

Of the 155 women who had BCS during the study time period, 54.8% (n = 85) were excluded due to not meeting IORT criteria (Figure 1). The 70 remaining patients were given the option to choose IORT or EBRT based on their preferences. Of the 70 patients who were candidates for IORT based on their tumor characteristics, 32.9% (n = 23) received IORT (identified from ICD codes 19294 and 19297) and were invited to participate by completing a survey. Those who received EBRT during the same period (67.1%, n = 47) were matched to the study arm and invited to participate (n = 22). One patient declined participation, one was ineligible as she was undergoing chemotherapy prior to radiation, and 10 did not respond. Six participants elected not to undergo RT (five EBRT and one IORT due to technical difficulties) and were not asked to complete the survey. Altogether, 27 of the 45 surveys were returned, for a response rate of 60%.

One patient who received IORT had positive margins and subsequently underwent 25 EBRT treatments; she was included in the analysis of the IORT group on an intent-to-treat basis. This singular exception representing 6% of the IORT group remains well below the expected 15% of patients who require addition of EBRT after IORT.[10]

Participants ranged from 51 to 81 years, with a mean age of 64.0 years (SD = 6.8). Caucasians accounted for the majority of the population (94% of IORT participants and 100% of EBRT participants, n = 27; Table 1). Most IORT patients were insured by Medicare (83%, n = 15), and the largest insurer of EBRT patients was Blue Cross and Blue Shield of Kansas (44%, n = 4). Table 2 provides an age comparison by radiation therapy type.

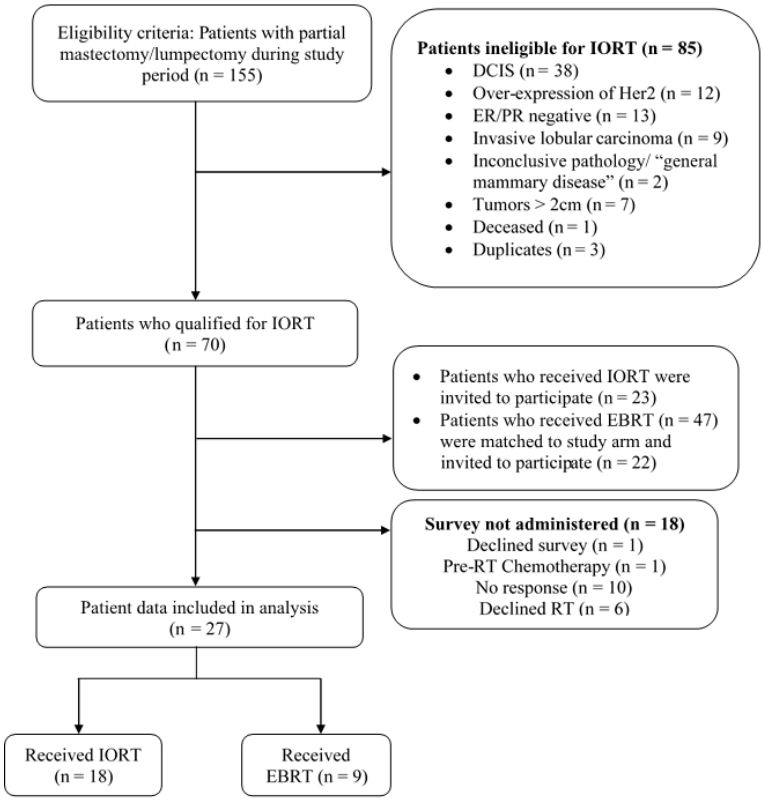


Figure 1. Flow diagram.

More participants who received IORT (11.8%, n = 2) reported being bothered "a lot" by the necessity to limit work or activity than those who received EBRT (0%, n = 0), $\chi^2(3, n = 27) = 8.9$, $p = 0.03$. The number of respondents who required additional therapies to address the side effects of their radiation therapy (e.g., topical moisturizers) was greater among those who received EBRT (22.2%, n = 6) than those who received IORT (7.4%, n = 2), $\chi^2(1, n = 27) = 7.04$, $p < 0.01$.

Of the four BREAST-Q scales used, only post-operative physical well-being equivalent Rasch-transformed scores were associated with RT type (Table 3). Respondents who received IORT reported better physical well-being of the chest (mean = 86.2) than those who received EBRT (mean = 66.4), $Z = -1.73$, $p = 0.05$.

Table 1. Participant demographics.

	IORT		EBRT		
	Frequency	%	Frequency	%	p value
Age					0.25
50 - 59 years	2	11%	3	33%	
60 - 69 years	11	61%	6	67%	
70 - 79 years	3	17%	0	0%	
80 years or older	2	11%	0	0%	
Race					0.47
White/Caucasian	17	94%	9	100%	
Black/African American	1	6%	0	0%	
Ethnicity					0.29
Not Hispanic or Latino	16	89%	9	100%	
Hispanic or Latino	2	11%	0	0%	
Insurance					0.01
Medicare	15	83%	2	22%	
Blue Cross Blue Shield of Kansas	0	0%	4	44%	
Aetna	1	6%	1	11%	
Miscellaneous	1	6%	0	0%	
United Healthcare	1	6%	1	11%	
Ascension	0	0%	1	11%	

Table 2. Age comparison by radiation therapy type.

RT type	N	Mean age (years)	SD	Median	Quartile range	p value
IORT	18	66.6	7.1	67.2	4.7	0.008
EBRT	9	61.5	5.2	61.9	7.4	

Table 3. Comparison of BREAST-Q mean equivalent Rasch-transformed scores between IORT and EBRT participants.[a]

BREAST-Q Scale	IORT (SD)	EBRT (SD)	p value
Post-op satisfaction with breast cosmesis	85.9 (16.4)	70.5 (26.8)	0.10
Post-op physical well being: Chest	86.2 (19.6)	66.4 (30.9)	0.05
Post-op adverse effects of radiation at treatment time	88.2 (16.6)	84.6 (9.3)	0.18
Post-op adverse effects of radiation at survey time	84.7 (23.8)	82.2 (28.6)	0.49

[a]Higher equivalent Rasch-transformed scores denote better outcome.

Table 4. Questions included in the BREAST-Q Version 2.0 for Physical Well-Being: Chest.

In the past week, how often have you experienced:	None of the time	Some of the time	All of the time
a. Difficulty lifting or moving your arms?	1	2	3
b. Difficulty sleeping because of discomfort in your breast area?	1	2	3
c. Tightness in your breast area?	1	2	3
d. Pulling in your breast area?	1	2	3
e. Tenderness in your breast area?	1	2	3
f. Share pains in your breast area?	1	2	3
g. Aching feeling in your breast area?	1	2	3
h. Difficulty laying on the side of your lumpectomy breast?	1	2	3
i. Swelling of the arm (lymphedema) on the side(s) that you had your breast surgery?	1	2	3

All patients who received IORT (100%, n = 18) were insured by companies that cover IORT (e.g., Medicare, UnitedHealthcare), whereas 44% (n = 4) of those who received EBRT were insured by companies that cover IORT, $\chi^2(1, n = 27) = 12.3, p < 0.01$. More patients who received EBRT (18%, n = 6) did not complete RT as prescribed by their physician. One patient who was prescribed IORT (3%) did not receive her treatment due to equipment malfunction, and she thereafter elected not to complete EBRT, $\chi^2(1, n = 33) = 6.19, p = 0.01$. The average age of patients who elected to forgo EBRT was 65.7 years.

For all patients, the median total travel distance to complete RT was 100 miles, with a mean of 598 miles (SD = 1778.39) and a range of three to 9,520 miles. Participants who received EBRT travelled farther (mean = 1351 miles ± 2783.52) than participants who received IORT (mean = 138 miles ± 247), $Z = 2.99, p < 0.01$ to complete treatment.

Age, tumor size, RT type, and surgeon explained the 39% variability in post-operative well-being of chest. After adjusting for tumor size, RT type, and surgeon, only age ($\beta = 1.93$, SE = 0.64, t = 2.99 and p = 0.007) was associated significantly with this variability, with younger patients reporting poorer well-being, $F(4,22) = 3.48, p = 0.02, R^2 = 0.39$. Though the model was not significant ($F(4,22) = 1.14, p = 0.36$), immediate adverse effects of radiation as defined by the Rasch-transformed score were associated solely with the participant's age (p = 0.05).

DISCUSSION

The current study suggested that IORT patients reported better post-operative physical well-being than EBRT patients. This was an expected outcome as IORT has minimal chest wall and pulmonary radiation exposure. While tangential beams are used with EBRT, often the physical shape of the chest wall requires inclusion of the underlying ribs, superficial lung, and more rarely, portions of the anterior aspect of the heart within the treatment fields to deliver dose to all of the breast tissue adequately. There are well-documented secondary effects of this potential exposure of these organs.[24,25]

There were no differences between patients who received IORT or EBRT in post-operative satisfaction with breast cosmesis or post-operative adverse effects of radiation. This was consistent with one study which suggested that IORT patients have a comparable quality of life to EBRT patients,[17] but inconsistent with another study which suggested that IORT patients reported better quality of life than EBRT patients.[13] This variability may be due to the different tools used to assess patient-reported outcomes; other studies have used the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 and Breast 23 (QLQ-C30 and BR23).[13,17] The current study used the BREAST-Q because the scales were more specific to the adverse effects of radiation, which was more pertinent to the research question, and fewer questions were included, requiring less time commitment for participants.

The current study suggested that fewer women who are prescribed adjuvant EBRT complete their RT than those who are prescribed IORT. Participants reported a mean difference of 1,000 miles of traveling between EBRT and IORT patients to complete RT. This was consistent with previous studies that reported that travel distance to a radiation center was inversely related to prescribed RT receipt.[7,26] If a woman is not willing to undergo radiation, she often will select a mastectomy over driving that many miles and potentially losing her job (according to participating surgeons, email communication, August 2020). A previous study suggested one-step IORT is associated with an advantage in work resumption.[27] This is particularly relevant in a state such as Kansas with concerns surrounding rural patients' access to treatment. Among the 18% of EBRT patients in this study who chose not to receive adjuvant EBRT after surgery, the average age was 65.7 years. Patients aged 70 and over are typically not offered EBRT, however, particularly healthy patients in this age range may be considered for IORT as a single dose may be considered more reasonable. It also should be considered that a one-time visit rather than multiple appointments limits possible SARS-CoV-2 exposure for patients.

The current study suggested that IORT recipients were bothered "a lot" by the necessity to limit work or activity at the time of their treatment, more than EBRT recipients. The wording of this question may have been confusing as to whether patients were bothered by travel, radiation, or post-operative restrictions. This likely was motivation for the patient choice for a single dose of radiation (IORT) over multiple trips to a radiation center (EBRT) over many weeks in a rural state.

The current study suggested that the number of respondents who required additional therapies to address the side effects of their RT (e.g., topical emu oil, Cetaphil® lotion) was greater among those who received EBRT. When given the option (i.e., their insurance covers the treatment), the current study suggested that women will choose IORT over EBRT. This was consistent with a previous study that indicated that patients chose IORT, and they were willing to travel for it.[28] The current study showed that women who receive EBRT travel farther over the course of their treatment than patients who receive IORT. This was consistent with a previous study done in the UK correlating the greater distance with more time travelled and higher CO_2 emissions.[29] IORT's one-time nature could ease treatment burden on patients substantially, particularly those who live in rural areas and must travel long

distances to the nearest radiation oncology center for repeated EBRT treatments.

Limitations. Recall bias may have contributed to participants' responses regarding adverse effects of radiation at the time of surgery, further amplified for participants who had surgery at the beginning of the study period. Sample size was limited by the number of patients who received IORT. Risk-adapted criteria necessarily limited the patient pool, as only 45% of BCS patients were considered eligible for IORT. Whereas 78% (18/23) of IORT patients responded to the survey, only 41% (9/22) of EBRT patients responded. This discrepancy further limited the comparison of the data. The small sample size also can be attributed partly to some private insurers considering IORT to be experimental or investigational. In this study, only 32% (23/70) of IORT-eligible patients had insurance coverage for IORT. Most of the surveyed patients who qualified for IORT but received EBRT had insurance through Blue Cross and Blue Shield of Kansas (54.5%, n = 12), the largest insurance carrier in Kansas. Medicare and private insurers in several states have concluded that IORT is reasonable and medically necessary for suitable patients and cover this treatment.[30-32]

CONCLUSIONS

Most patients who had insurance coverage for IORT chose IORT over EBRT. This study showed that patients who received EBRT travelled farther on average than patients who received IORT to complete treatment. Patients who received IORT reported better physical well-being of the chest than patients who received EBRT. There was no difference in patient-reported outcomes concerning post-operative satisfaction with breast cosmesis or adverse effects of radiation between patients who received IORT and those who received EBRT.

ACKNOWLEDGEMENTS

The authors thank to Rosalee Zackula for her assistance with REDCap®.

DATA AVAILABILITY STATEMENT

The datasets generated during and analyzed during the current study are not publicly available as these data were abstracted from medical charts and contain information that could compromise research participant privacy.

REFERENCES

[1] National Cancer Institute, DCCPS, Surveillance Research Program. Surveillance, Epidemiology, and End Results (SEER) Program Populations (1969-2016). December 2017. www.seer.cancer.gov/popdata.
[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69(1):7-34. PMID: 30620402.
[3] No authors. NIH consensus conference. Treatment of early-stage breast cancer. JAMA 1991; 265(3):391-395. PMID: 1984541.
[4] Tuttle TM, Jarosek S, Habermann EB, Yee D, Yuan J, Virnig BA. Omission of radiation therapy after breast-conserving surgery in the United States: A population-based analysis of clinicopathologic factors. Cancer 2012; 118(8):2004-2013. PMID: 21952948.
[5] Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002; 347(16):1233-1241. PMID: 12393820.
[6] Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. Lancet 2005; 366(9503):2087-2106. PMID: 16360786.
[7] Hershman DL, Buono D, McBride RB, et al. Surgeon characteristics and receipt of adjuvant radiotherapy in women with breast cancer. J Natl Cancer Inst 2008; 100(3):199-206. PMID: 18230795.
[8] Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, Abeloff MD. Abeloff's Clinical Oncology. Fifth edition. Philadelphia: Elsevier, 2014. ISBN: 1455728659.
[9] Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. Lancet Oncol 2013; 14(13):1269-1277. PMID: 24225155.
[10] Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): An international, prospective, randomised, non-inferiority phase 3 trial. Lancet 2010; 376(9735):91-102. PMID: 20570343.
[11] Harris EER, Small W Jr. Intraoperative radiotherapy for breast cancer. Front Oncol 2017; 7:317. PMID: 29312887.
[12] Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2014; 383(9917):603-613. PMID: 24224997.
[13] Corica T, Nowak AK, Saunders CM, et al. Cosmesis and breast-related quality of life outcomes after intraoperative radiation therapy for early breast cancer: A substudy of the TARGIT-A Trial. Int J Radiat Oncol Biol Phys 2016; 96(1):55-64. PMID: 27511847.
[14] Sosin M, Gupta SS, Wang JS, et al. A prospective analysis of quality of life and toxicity outcomes in treating early breast cancer with breast conservation therapy and intraoperative radiation therapy. Front Oncol 2018; 8:545. PMID: 30560085.
[15] Olsen JR, Ridings JW, Dickinson J, et al. Patient reported outcomes from a prospective risk-adapted breast IORT registry trial. Int J Radiat Oncol 2018; 102(3):E591-E592.
[16] Welzel G, Boch A, Sperk E, et al. Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: Results from the randomized phase III trial TARGIT-A. Radiat Oncol 2013; 8:9. PMID: 23294485.
[17] Wetzel G, Hofmann F, Blank E, et al. Health-related quality of life after breast-conserving surgery and intraoperative radiotherapy for breast cancer using low-kilovoltage x-rays. Ann Surg Oncol 2010; 17(Suppl 3):S359-S367. PMID: 20853059.
[18] Patel R, Ivanov O, Voigt J. Lifetime cost-effectiveness analysis of intraoperative radiation therapy versus external beam radiation therapy for early stage breast cancer. Cost Eff Resour Alloc 2017; 15:22. PMID: 29151818.
[19] Zhang L, Zhou Z, Mei X, et al. Intraoperative radiotherapy versus whole-breast external beam radiotherapy in early-stage breast cancer: A systematic review and meta-analysis. Medicine (Baltimore) 2015;94(27): e1143. PMID: 26166124.
[20] Harris PA, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42(2):377-381. PMID: 18929686.
[21] Google Maps. Google Maps. 2019. https://maps.google.com.
[22] Cohen WA, Mundy LR, Ballard TNS, et al. The BREAST-Q in surgical research: A review of the literature 2009-2015. J Plast Reconstr Aesthet Surg 2016; 69(2):149-162. PMID: 26740288.
[23] Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a new patient-reported outcome measure for breast surgery: The BREAST-Q. Plast Reconstr Surg 2009; 124(2):345-353. PMID: 19644246.
[24] Taylor C, Correa C, Duane FK, et al. Estimating the risks of breast cancer radiotherapy: Evidence from modern radiation doses to the lungs and heart and from previous randomized trials. J Clin Oncol 2017; 35(15):1641-1649. PMID: 28319436.
[25] Yi A, Kim HH, Shin HJ, Huh MO, Ahn SD, Seo BK. Radiation-induced complications after breast cancer radiation therapy: A pictorial review of multimodality imaging findings. Korean J Radiol 2009; 10(5):496-507. PMID: 19721835.
[26] Athas WF, Adams-Cameron M, Hunt WC, Amir-Fazli A, Key CR. Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. J Natl Cancer Inst 2000; 92(3):269-271. PMID: 10655446.
[27] Sorrentino L, Fissi S, Meaglia I, et al. One-step intraoperative radiotherapy optimizes conservative treatment of breast cancer with advantages in quality of life and work resumption. Breast 2018; 39:123-130. PMID: 29674010.

[28] Larson KE, Valente SA, Shah C, et al. Are patients traveling for intraoperative radiation therapy? Int J Breast Cancer 2017; 2017:6395712. PMID: 29130001.
[29] Coombs NJ, Coombs JM, Vaidya UJ, et al. Environmental and social benefits of the targeted intraoperative radiotherapy for breast cancer: Data from UK TARGIT-A trial centres and two UK NHS hospitals offering TARGIT IORT. BMJ Open 2016; 6(5):e010703. PMID: 27160842.
[30] IntraOp. Medicare Increases Coverage for IORT. September 20, 2018. https://intraop.com/news-events/medicare-increases-coverage-for-iort/. Accessed May 21, 2019.
[31] IntraOp. AETNA adds single treatment Electron IORT to its Medical Policy. October 02, 2018. https://intraop.com/news-events/aetna-adds-single-treatment-electron-iort-to-its-medical-policy/. Accessed May 21, 2019.
[32] IntraOp. Anthem Blue Cross and Blue Shield coverage update increases access to electron IORT. January 30, 2018. https://intraop.com/news-events/anthem-blue-cross-blue-shield-coverage-update-increases-access-electron-iort/. Accessed May 21, 2019.

Keywords: breast cancer, radiation therapy, patient-reported outcomes

KANSAS JOURNAL of MEDICINE

momHealth: A Feasibility Study of a Multi-behavioral Health Intervention for Pregnant and Parenting Adolescent Mothers

Karen A. Wambach, Ph.D.[1], Ann M. Davis, Ph.D.[2], Eve Lynn Nelson, Ph.D.[1], Kelli Snow, M.S.[3], Annie Yungmeyer, BSN[1], Rachel Muzzy, M.S.[2], Karman Romero, Ph.D.[1], Megan Murray, M.S.[2]
University of Kansas Medical Center, Kansas City, KS
[1]School of Nursing
[2]School of Medicine, Department of Pediatrics
[3]Children's Mercy Hospital, Kansas City, MO

Received Oct. 7, 2020; Accepted for publication April 7, 2021; Published online July 9, 2021
https://doi.org/10.17161/kjm.vol14147738

ABSTRACT

Introduction. In 2016, 209,809 babies were born to mothers 15 - 19 years of age, for a live birth rate of 20.3 per 1,000 in this age group. Many health issues surround adolescent mothers and their infants, many of which can be addressed through behavioral change. The main purpose of this study was to examine the feasibility, acceptability, usability, and relevance of momHealth, an innovative multiple health behavior change (MHBC) education and support mHealth intervention, focused on breastfeeding, healthy eating and active living, and depression prevention among pregnant and parenting adolescents. We also evaluated the proposed online surveys and physical outcome measures for feasibility and acceptability (burden, time, ease of use).

Methods. A one-group quasi-experimental longitudinal design was used to examine the intervention components and the breastfeeding, diet/activity, and depression outcome measures. Nine iPad-delivered education modules, text messaging, and virtual individual and group support were provided for 12 weeks, beginning at 32 weeks of pregnancy, with follow-up to three months postpartum. Data on the main behaviors and outcomes were collected at three in-home visits, one telephone call soon after birth, and ten postpartum weekly and biweekly online surveys.

Results. Although recruitment and attrition presented challenges, six participants enrolled in the study during prenatal clinic visits; all were pregnant with their first child, single, and had a mean age of 17.7 years (SD = 1.4). Intervention participation ranged from 59% to 91% for educational module completion, text message reading, and individual virtual support meetings and three virtual peer support groups were held. Intervention acceptability, relevance, and delivery was supported by reports of clear and relevant content, reasonable time burden, iPad ease of use, and acceptable intervention length. Data collection was reported as convenient and non-burdensome, but the diet recall method and activity monitoring challenged some.

Conclusions. This was the first MHBC research in adolescent pregnant women designed to improve breastfeeding outcomes, healthy eating/active living, and depression prevention. Findings demonstrated strengths and challenges of the interventions and methods, support feasibility and acceptability of momHealth, and informed the recruitment and intervention protocols of our pilot randomized trial.

Kans J Med 2021;14:176-181

INTRODUCTION

Although the rate of teenage pregnancy in the United States has declined greatly over the past two decades, teen pregnancy remains a significant public health problem.[1] In 2016, 209,809 babies were born to mothers 15 - 19 years of age, for a live birth rate of 20.3 per 1,000 women in this age group.[2] Multiple health behavior issues more greatly impact pregnant and parenting adolescent mothers in comparison to mothers over the age of twenty. For example, suboptimal breastfeeding initiation and continuation persist[3]; in 2016, 70.5% of adolescent mothers under age 20 initiated breastfeeding in comparison to 80% among mothers over 20 years of age and 27.9% versus 48.2% continued to breastfeed to six months. Second, adolescent mothers tended toward excess pregnancy weight gain,[4] postpartum weight retention,[5-7] and physical inactivity after giving birth.[8] Third, these mothers were at higher risk and had elevated rates of postpartum depression.[9-10] Between 25 and 36% of adolescent mothers' experience postpartum depression, higher than adult postnatal mothers and non-perinatal adolescents. All these health behaviors and/or conditions influence maternal and child long-term health.

The multiple health behavior change paradigm (MHBC)[11] offers a framework to address multiple health behaviors through simultaneous intervention. Despite the significance of adolescent pregnancy and the behavioral health issues noted, there is no known MHBC research involving this vulnerable population. Therefore, we designed and conducted a technology-based intervention and assessed its feasibility (i.e., can it be done?), acceptability (i.e., is it desirable?), usability (i.e., does it work?), and relevance for a sample of middle- to late-adolescent pregnant and parenting women.

METHODS

This study was approved by the university's Institutional Review Board. A one-group, quasi-experimental, longitudinal design was used and conducted between July 2016 and March 2017 in a metropolitan area in Kansas. Recruitment took place in prenatal clinics at two university affiliated family medicine and obstetric practices. Recruitment efforts and assessment of the sampling pool was tracked by the research team throughout the study; after two months of recruitment efforts, the age criterion was changed from an upper limit of 18 years to 19 years, due to low numbers of pregnant adolescents under 19 years. Therefore, the final sample inclusion criteria included English-speaking, pregnant adolescents between 15 - 19 years of age, low risk pregnancy, intending to keep their first baby, and between 26 - 34 weeks gestation at screening. Exclusion criteria included prenatal complications and/or high-risk pregnancy conditions, such as preterm labor and gestational diabetes, diagnosed depression, and other untreated clinical mental health conditions. Participants provided their own informed consent; parental/guardian consent was not required because of the "no more than minimal risk nature" of the study and on the basis that recruitment and enrollment would be impaired because most pregnant adolescents attend their prenatal visits without a parent.

Study Timeline, Data Collection, and Measures. The time frame for study participation from enrollment to final data collection was 20 weeks. Data collection was conducted during three home visits at baseline (32 weeks), five weeks postpartum, and three months postpartum. A single telephone call was made to participants shortly after giving birth to collect birth information and hospital infant-feeding data. In addition, after giving birth, participants received automated e-mail invitations for 10 weekly brief online surveys for the main study outcomes. All data were collected using the Research Electronic Data Capture (REDCap®) secure web platform, including the home-visit measures that were collected by research staff.[12-13] Further detail regarding data collection, time points, and interventions are included in Figure 1 and Table 1.

Demographic data included age, education level, marital status, and Women and Infant Supplemental Nutrition (WIC) program eligibility and status collected at the baseline home visit. Physical data included pre-pregnancy weight and current weight and height at the home visits. Main outcome data regarding breastfeeding intention (prenatal), initiation, and continuation were self-reported post-birth and at the postpartum home visits. Healthy eating and physical activity data were collected with three 24-hour diet recalls and Actigraph monitoring sessions (initiated at each home visit). Depression symptoms were self-reported using the Edinburg Postnatal Depression Scale (all home visits). During the second post-intervention home visit and final home visit at three months, interviews/surveys were used to evaluate the acceptability, relevance, usefulness, and burden of the intervention and convenience and burden of data collection measures, respectively.

Data Management and Analysis. Data were stored securely in REDCap® and a secure web server. Descriptive statistics were used for demographic data presentation. Frequencies and percentages were used to describe participation counts for the intervention components (actual number of completed interventions divided by total number of potential components). Content analysis was used for text-based narratives regarding evaluation of the intervention and data collection measures.

Intervention. All participants were consented at clinic recruitment or at the baseline home visit. Participants were lent an iPad Mini™ tablet with a cellular data connection and provided with instructions for tablet use and care, a phone number to call for technical support, instruction on the project timeline, how to use the education modules, text messaging, and virtual support meetings. The intervention period covered approximately eight weeks prenatally and four weeks postpartum (Figure 1). Nine educational modules, three in each area (breastfeeding, healthy eating/active living, and stress management and self-care for depression prevention) were delivered via narrated slide presentations pre-loaded on the tablet and web-based applications and resources. Health professionals (i.e., two psychologists and a board-certified lactation consultant) and trained research assistants provided the content and narration for each topical area. Daily text messages, sent Monday through Friday, accompanied and mirrored each module to provide additional tips and web-based resources. Weekly individual professional support and counseling tied to the content areas were provided via teleconferencing using the tablet. Finally, a weekly virtual support group among study participants to enhance content sharing was planned; however, with limited numbers of participants simultaneously enrolled, only three groups were conducted.

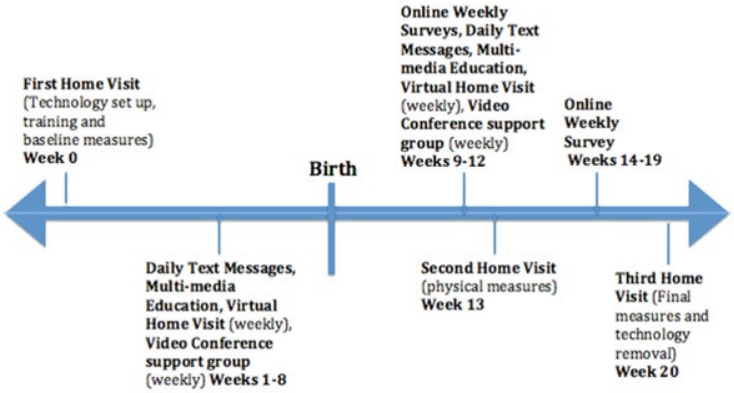


Figure 1. Study timeline including intervention and data collection points.

RESULTS

Participants. A sample size of eight to ten was desired; nine teens were screened and eight consented. Two participants (25%) withdrew prior to baseline data collection, and six (75%) were enrolled for the final sample. Post-enrollment attrition occurred for two participants (33%); one did not complete any intervention and withdrew prior to giving birth and one completed the intervention and withdrew at five weeks postpartum following the second home visit. Participant ages ranged from 16 - 19; the mean age was 17.7 years (SD = 1.4). All were single (100%) and two (33%) were living with the father of the baby. Four (67%) had completed middle school and two completed high school (33%). All were eligible for the Women and Infant Supplemental Nutrition (WIC) program and 50% received WIC benefits.

Feasibility. As noted in the methods section, some challenges in recruiting from the medical center clinics were experienced and altered our sampling criterion for age. Notes and observations were recorded along with the listing of potential recruits each week during recruitment. Challenges included slower than expected recruitment, a limited number of eligible potential recruits despite adequate pre-study estimates, and twice to three times weekly recruitment coverage in each clinic. Limited clinical staff support was experienced for assisting our research personnel during recruitment visits. On the participant side, some potential recruits did not show for appointments, some study recruits decided not to participate after agreeing to take part and/or before the home visit for baseline data collection, and refused participation due to being too busy.

Rate of intervention component completion for the five participants who completed the intervention were as follows: 28 out of 45 education module presentations (62%), module texts received and read (response = yes/no) in 42 of 45 cases (93%), and 35 out of 45 individual support sessions attended (78%). Individual participant rates of completion, including the participant who dropped out of the study before giving birth, ranged from 0 to 100% for each intervention approach (Table 2).

Table 1. Study measures and educational modules description.

Measure	Baseline - home visit	Birth (telephone self-report)	5-weeks postpartum home visit	3-months postpartum home visit	Weekly or bi-weekly online brief surveys via REDCap®	Educational module description
Demographic, physical, and social data	Age, race, education, pre-pregnancy weight, and current weight	Infant gender, birth weight, and gestational age	Return to work and/or school (yes/no)	-	-	-
Breastfeeding	5-point rating scale for self-report prenatal intention to breastfeed, intention to exclusively breastfeed (yes/no); intended duration of breastfeeding (months).	Breastfeed only, breastfeed partial (mother's milk and formula) or formula feed in hospital	Breastfeeding Experience Scale[14] to assess early breastfeeding problems and severity, as well as feeding patterns and weaning.	2 items on infant feeding method	10 weekly post- birth online surveys including items on breast and/or formula feeding. If discontinued breastfeeding, when?	The decision: Benefits of breastfeeding and exclusive breastfeeding, planning for breastfeeding, getting help from professionals and others. Early breastfeeding in hospital and after hospital discharge, early challenges, who to call for help. Maintaining milk supply, getting help from family and professionals, dealing with baby's growth spurts, return to work and school, family planning.
Healthy Eating/ Active Living	24-hour diet recall during the home visit with the National Cancer Institute Automated Self-Administered 24-hour Recall™ (ASA24™), a free, multiple-pass food recall tool for research and clinical practice based upon the USDA Automated Multiple-Pass Method.[15] ActiGraph activity monitoring[16] for 7 days following visit. Weight and height via scale and stadiometer.	-	24-hour diet recall during visit and ActiGraph activity monitoring for 7 days following visit. Weight and height via scale and stadiometer.	24-hour diet recall during visit and ActiGraph activity monitoring for 7 days following visit. Weight and height via scale and stadiometer.	Weekly: Number of red food servings previous day.[17] Minutes of physical activity the previous day.	Stop Light Diet 3 parts, making healthy food choices, diet planning, reading food labels. Exercise and keeping balance. Self-esteem and positive body image. Planned and incidental exercise.
Depression	Edinburg Postnatal Depression Scale (EPDS).[18] Ten item scale to assess depressive symptoms over the previous two weeks. Widely used among adult and adolescent mothers (post- and antenatal) with adequate psychometrics, sensitivity, and specificity.[18-20]	-	Edinburg Postnatal Depression Scale (EPDS)			
Perceptions of the content, technology ease of use, and participant burden.			Structured interview - example questions: What did you find useful or helpful about the breastfeeding education program? Was the technology user-friendly?			

Table 2. Individual rates of component completion.

Participant	Education Module Completion (completed independently by each participant)	Module Text Messages Received and Read (Yes/No)	Module Individual Support Received (mean length of session in minutes)
#1	4/9 (44%)	7/9 (78%)	8/9 (89%) (X = 20.1 min., SD = 11.7)
#2	9/9 (100%)	9/9 (100%)	9/9 = 100% (X = 24.2 min., SD = 2.2)
#3 (Dropped prior to giving birth)	0/9 (0%)	0/9 (0%)	0/0 (0%)
#4 (Dropped after intervention)	2/9 (22%)	4/9 (44%)	7/9 = 78% (X = 35.3 min., SD = 14.7)
#5	4/9 (44%)	9/9 (100%)	5/9 = 56% (X = 24 min., SD = 4.2)
#6	9/9 (100%)	9/9 (100%)	9/9 = 100% (X = 24.4 min., SD = 14.8)

Challenges of intervention delivery were recorded by research team members in module completion notes and included participant issues in scheduling and keeping support appointments including not responding to study personnel to schedule, not showing up for scheduled support meetings, and delayed responsiveness owing to reported "busy or hectic lives" (see Results on rates of intervention completion and Table 2). Technology issues included periodic limited internet bandwidth/connectivity during teleconference support meetings, tablet operation difficulty by one participant (e.g., charger failure), and one case of difficulty retrieving equipment at study completion (one lost activity monitor and one iPad charger).

Intervention Acceptability, Relevance, Burden, and Usefulness. Of the five participants who received the intervention, four (80%) completed the intervention evaluation interview. All (100%) reported that the content provided was understandable and relevant, and no changes were suggested. All four respondents reported that the tablet was easy to use (one tablet charger needed replacement during the intervention, but this was not mentioned in the evaluation). No burden of time for the interventions was reported. No changes for study design were recommended except for one of the four (25%) respondents who recommended shortening the study to less than three months after the birth of baby. The individual component evaluation (i.e., education modules, texts, individual support, and peer support) were appraised as most useful and least useful. Participants reported the module presentations (n = 3) and individual support (n = 2) were most useful with daily text messages only getting one "most useful rating". The peer support meetings were rated the least useful by three of the four respondents (75%). Regarding the text messaging, two of the four respondents thought more "new" information would be useful as opposed to information already shared in the education modules.

Evaluation of Data Collection Measures. Four of the five participants (80%) who completed the intervention provided responses to the survey regarding the study measures at the final home visit. First, convenience of home visits was reported as positive (n = 3), but one reported inconvenience stating the final visit was difficult to schedule due to responsibilities of work, school, and the baby. One participant noted that in-home visits were better than going outside the home for data collection and intervention. The weekly post birth online surveys were described by all four participants as easy to access using the REDCap® e-mail invitations; two participants noted that reminder emails did not always "pop up" as expected. Among the five participants who completed the online weekly surveys, four (80%) completed all ten surveys and one (20%) completed only two surveys.

The 24-hour diet recalls were judged as convenient by three of the four respondents (80%), however, one reported having difficulty remembering the schedule for the recalls. Activity monitoring issues were reported by three of the four (75%) respondents; two had difficulty remembering to put on the monitor in the morning or remove it at night and one had difficulty remembering to mail the monitor back to the project staff. One participant felt there were no barriers (25%), that project staff reminders helped, and the device was easy to wear.

Outcomes-Selected Results. Detailed data analysis for effectiveness was not intended for the behavioral outcomes for this feasibility study. However, some selected outcomes are reported here. Five participants (100%) who maintained post-birth study participation breastfed their infants; one (20%) maintained breastfeeding until three months postpartum and four (80%) discontinued breastfeeding before the final data collection (one at 3 weeks, one at 1 month, and two at 2.5 months). Also notable was prenatal baseline data indicated that one participant was unsure about feeding prenatally and another planned to formula-feed, yet these two mothers breastfed their newborns. For the healthy eating outcome, based in the online weekly surveys, five participants (100%) reported eating 0 - 4 red food servings (X = 1.3, SD = 1.3) and between 0 and 120 minutes of physical activity for the previous day (X = 27.7 minutes, SD = 24.9; median/mode = 30 minutes). For the depression symptom outcomes, EPDS scores were highest at the prenatal baseline (X = 5.7, SD = 3.7 [n = 6]), lowest at five weeks postpartum (X = 1.6, SD = 2.19 [n = 5]), and increased again at three months postpartum (X = 3.5, SD = 2.21 [n = 4]).

DISCUSSION

This feasibility study provided important data on several aspects of the momHealth project for sample recruitment and retention; intervention e-delivery feasibility (ease of use); content acceptability, relevance, burden, and usefulness; and our data collection and online survey methods convenience and burden.

We experienced challenges of slower-than-expected sample recruitment and apparent recruitment pool inadequacy within the two clinic settings. We suspected that the significant decline in teenage pregnancy rates across the United States was manifested in our local area and our sample. According to Martin and colleagues[2], "since 2009, the teen

birth rate has fallen to a new low each year. The rate for this group has declined 51% (or an average of 8% per year) since 2007 (p. 4)". In addition, two months after recruitment began, the limited numbers of potential recruits in our original age range of 15 to 18 years required us to modify our age criterion to 15 to 19 years. Indeed, the final sample included no 15-year-olds, one 16-year-old, one 17-year-old, one 18-year-old, and three 19-year-olds. In response to these issues, for our subsequent pilot randomized controlled trial (RCT), the expanded age range was used and the number of recruitment sites increased to six in medical centers and county health department clinics across our bi-state metropolitan area and two out-state sites. "Word of mouth" recruitment also was included to the sampling protocol.

We experienced attrition after screening and/or enrollment. However, based on our previous research with an adolescent pregnant and parenting sample in a longitudinal experimental design[22] and other work,[23-24] this was not completely unexpected. To address this in our pilot RCT, we enhanced our recruitment staff training to focus on clear, unrushed explanation of study requirements during the invitation and consent processes, and improved our study advertising flyer to include a clearer, simple description of study requirements and a photograph of a pregnant adolescent on the flyer.[24] We also built in additional training for our research staff in relation to communicating and working with pregnant and parenting adolescent mothers, including flexibility and persistence in scheduling and clarifying response expectations with participants.[23] Finally, enhanced engagement methods for participant retention were incorporated, including larger monetary incentives.

Our electronic mHealth intervention was judged acceptable, relevant, useful, and the technology was easy to use. Other researchers of feasibility of technology-based interventions for adolescent mothers or mother/infant dyads have had similar favorable outcomes, including interventions for depression treatment[23-25] and education for infant feeding.[26] The intervention in our subsequent pilot RCT was largely unchanged from the pilot although some of the text messaged information was enhanced with less repetitive information.

Likewise, our online automated data collection methods were reported as non-burdensome in number and easy to use. For the subsequent pilot RCT, our REDCap® surveys and reminders were revised and fixed where necessary. Our measures of healthy eating and physical activity were accomplished using standard dietary recall and activity monitoring and compared similarly to other research in adolescent mothers.[27] However, those measures appeared to be more challenging to our sample according to their reports. Thus, we incorporated enhanced instruction for participants in those measures and included automated e-mail reminders in our subsequent pilot RCT for both measures. We also gave participants the choice to do diet recalls by telephone or via online automated approach.

Limitations of the Study. We had a small sample from two university-affiliated prenatal clinics and fewer participants than we planned. However, our previous research indicated that this type of intervention focusing on multiple behaviors was attractive to pregnant women and pregnant adolescents.[28] Thus, it was important to gain feasibility information before going forward to a larger pilot RCT.

In conclusion, the findings partially supported the feasibility of the momHealth intervention. Although recruitment and retention were our greatest challenges, we have used that information in our pilot RCT to great benefit. Finally, the e-intervention and physical data collection were largely supported by our sample. We believe that the feasibility findings were useful in our securing our pilot RCT funding and conduct of that study.

ACKNOWLEDGEMENTS

This work was supported by the MacArthur Interprofessional Research Award (University of Kansas Medical Center Endowment Association). It was presented in 2017 as a poster at the Midwest Nursing Research Society Annual Conference, Minneapolis, MN.

REFERENCES

[1] Power to Decide. National and State Data. The National Campaign to Prevent Teen and Unplanned Pregnancy. https://powertodecide.org/what-we-do/information/national-state-data/national.%20Accessed%207-1-2020. Accessed November 2, 2020.
[2] Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: Final data for 2016. Natl Vital Stat Rep 2018; 67(1):1-55. PMID: 29775434.
[3] U.S. Centers for Disease Control and Prevention. Rates of Any and Exclusive Breastfeeding by Sociodemographics Among Children Born in 2017 2020. October 4, 2020. https://www.cdc.gov/breastfeeding/data/nis_data/rates-any-exclusive-bf-socio-dem-2017.html. Accessed November 2, 2020.
[4] Howie LD, Parker JD, Schoendorf KC. Excessive maternal weight gain patterns in adolescents. J Am Diet Assoc 2003; 103(12):1653-1657. PMID: 14647096.
[5] Black MM, Papas MA, Bentley ME, et al. Overweight adolescent African-American mothers gain weight in spite of intentions to lose weight. J Am Diet Assoc 2006; 106(1):80-87. PMID: 16390669.
[6] Lemay CA, Elfenbein DS, Cashman SB, Felice ME. The body mass index of teen mothers and their toddler children. Matern Child Health J 2008; 12(1):112-118. PMID: 17551821.
[7] Chang T, Choi H, Richardson CR, Davis MM. Implications of teen birth for overweight and obesity in adulthood. Am J Obstet Gynecol 2013; 209(2):110.e1-e7. PMID: 23587742.
[8] Behrens TK, Bradley JE, Kirby JB, Nanney MS. Physical activity among postpartum adolescents: A preliminary report. Percept Mot Skills 2012; 114(1):310-318. PMID: 22582698.
[9] Lanzi RG, Bert SC, Jacobs BK, Centers for the Prevention of Child Neglect. Depression among a sample of first-time adolescent and adult mothers. J Child Adolesc Psychiatr Nurs 2009; 22(4):194-202. PMID: 19930300.
[10] Logsdon MC, Birkimer JC, Simpson T, Looney S. Postpartum depression and social support in adolescents. J Obstet Gynecol Neonatal Nurs 2005; 34(1):46-54. PMID: 15673645.
[11] Prochaska JJ, Spring B, Nigg CR. Multiple health behavior change research: An introduction and overview. Prev Med 2008; 46(3):181-188. PMID: 18319098.
[12] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42(2):377-381. PMID: 18929686.
[13] Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019; 95:103208. PMID: 31078660.
[14] Wambach KA. Breastfeeding intention and outcome: A test of the theory of planned behavior. Res Nurs Health 1997; 20(1):51-59. PMID: 9024477.
[15] Subar AF, Kirkpatrick SI, Mittl B, et al. The Automated Self-Administered 24-hour dietary recall (ASA24): A resource for researchers, clinicians, and educators from the National Cancer Institute. J Acad Nutr Diet 2012; 112(8):1134-1137. PMID: 22704899.
[16] Brage S, Brage N, Wedeerkopp N, Froberg K. Reliability and validity of the computer science and applications accelerometer in a mechanical setting. Meas Phys Educ Exerc Sci 2003; 7(2):101-119.

[17] Epstein L, Squires S. The Stoplight Diet for Children: An Eight-week Program for Parents and Children. New York: Little Brown & Co., 1988. ISBN: 978-0316245753.
[18] Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987; 150(6):782-786. PMID: 3651732.
[19] Wisner KL, Parry BL, Piontek CM. Clinical practice. Postpartum depression. N Engl J Med 2002; 347(3):194-199. PMID: 12124409.
[20] Gaynes BN, Gavin N, Meltzer-Brody S, et al. Perinatal depression: Prevalence, screening accuracy, and screening outcomes. Evid Rep Technol Assess (Summ) 2005; (119):1-8. PMID: 15760246.
[21] Richardson LP, Rockhill C, Russo JE, et al. Evaluation of the PHQ-2 as a brief screen for detecting major depression among adolescents. Pediatrics 2010; 125(5):e1097-e1103. PMID: 20368315.
[22] Wambach KA, Aaronson L, Breedlove G, Domian EW, Rojjanasrirat W, Yeh HW. A randomized controlled trial of breastfeeding support and education for adolescent mothers. West J Nurs Res 2011; 33(4):486-505. PMID: 20876551.
[23] Pinto-Foltz MD, Logsdon MC, Derrick A. Engaging adolescent mothers in a longitudinal mental health intervention study: Challenges and lessons learned. Issues Mental Health Nurs 2011; 32(4):214-219. PMID: 21355755.
[24] Logsdon MC, Martin VH, Stikes R, et al. Lessons learned from adolescent mothers: Advice on recruitment. J Nurs Scholarsh 2015; 47(4):294-299. PMID: 25968179.
[25] Logsdon MC, Barone M, Lynch T, et al. Testing of a prototype web based intervention for adolescent mothers on postpartum depression. Appl Nurs Res 2013; 26(3):143-145. PMID: 23473677.
[26] Taki S, Lymer S, Russell CG, et al. Assessing user engagement of an mHealth intervention: Development and implementation of the growing healthy app engagement index. JMIR mHealth uHealth 2017; 5(6):e89. PMID: 28663164.
[27] Davis AM, Gallagher K, Taylor M, et al. An in-home intervention to improve nutrition, physical activity, and knowledge among low-income teen mothers and their children: Results from a pilot study. J Dev Behav Pediatr 2013; 34(8):609-615. PMID: 24131884.
[28] Davis AM, Wambach KA, Nelson EL, et al. Health behavior change in pregnant women: A two-phase pilot study. Telemed J E Health 2014; 20(12):1165-1169. PMID: 25289706.

Keywords: adolescent pregnancy, breastfeeding, health behaviors, healthy nutrition, depression

KANSAS JOURNAL of MEDICINE

Recognizing Pseudocholinesterase Deficiency in the Post-operative Patient: Diagnosis and Management in the ICU

Jared A. Ojile, M.D., Ashlie A. Elver, B.S.
University of Kansas School of Medicine-Wichita, Wichita, KS
Department of Internal Medicine

Received Feb. 7, 2021; Accepted for publication March 30, 2021; Published online July 9, 2021
https://doi.org/10.17161/kjm.vol1415169

INTRODUCTION

Succinylcholine is a paralytic drug commonly used during general surgery.[1] It is a depolarizing paralytic, meaning that it achieves its paralytic effect by overstimulating the neuromuscular endplate and thereby blocking neuromuscular junction-released acetylcholine from causing muscular contraction. The onset of action is typically within seconds of injection and usually declines and clears over a course of a few minutes. Clearance of the drug is dependent on the enzyme pseudocholinesterase, which degrades succinylcholine. Genetic or acquired deficiency of pseudocholinesterase therefore results in unexpected prolongation of succinylcholine clearance and prolonged flaccid paralysis.

Management of pseudocholinesterase deficiency centers on re-initiating or maintaining the patient's intubated status until the patient's ability to draw proper tidal volumes spontaneously returns as the drug is slowly cleared.[2] Depending on whether the patient is heterozygous or homozygous for the genetic enzyme deficiency, the duration of extended flaccid paralysis can last up to a few hours. Acquired forms of pseudocholinesterase deficiency can occur during trauma, organ failure, malignancy, certain medication, and other metabolically demanding disease states, but are not discussed in detail here.

CASE REPORT

A 53-year-old male presented to the intensive care unit (ICU) directly from the operating room due to delay of extubation. Medications used for general anesthesia included the following systemic drugs: midazolam 2 mg, fentanyl 250 mcg, lidocaine 100 mg, and propofol 540 mg. Surgical paralysis was achieved using succinylcholine 120 mg and rocuronium 10 mg. Other medications given intraoperatively and perioperatively included cefazolin 2000 mg, ephedrine 80 mg, ondansetron 4 mg, abuterol HFA inhaler 8 puffs, hydromorphone 1 mg, and 1500 ml of crystalloid fluids.

The surgery was without complication. Upon completion of the procedure, the patient failed to meet criteria for extubation. Per the anesthesiologist's description, the patient was highly tachypneic, but failed to draw appropriate tidal volumes while on appropriate pressure support. Sugammadex was given to reverse rocuronium blockade but had no effect. He was transferred to the intensive care unit while still intubated for further monitoring. Labs obtained upon transferring, including blood counts and electrolytes, were unremarkable. Approximately three hours later the patient passed a spontaneous breathing trial and was extubated successfully. The patient required no further oxygen supplementation. He was able to reposition himself in his hospital bed with ease shortly after extubation, limited only by expected post-operative pain.

The patient's past medical history was significant for recovery from opioid use disorder. He received methadone 80 mg PO daily from the local methadone clinic. Of note, he did not take his daily dose on day of surgery as instructed but was given 250 mcg of fentanyl during the surgery. He also reported being diagnosed with Guillain-Barre Syndrome in 2006 and was treated on multiple occasions over subsequent years with IVIG, plasmapheresis, and oral steroids. He ultimately received the diagnosis of chronic inflammatory demyelinating polyneuropathy in 2013 and took neuropathic pain agents daily.

The patient has an otherwise unremarkable surgical history. He previously had undergone arthroscopy of the knee at an outside hospital under local anesthesia presumably without the use of systemic paralytics. After the patient had an opportunity to talk to his family, further interview revealed an event where he was in a "coma" following a procedure as an infant. He learned from his sister that she also had recently experienced similar prolonged paralysis during a hysterectomy and had been diagnosed with presumed pseudocholinesterase deficiency. The patient had eight children with unknown surgical and anesthesia histories.

DISCUSSION

Since genetic analysis of this patient was unfeasible due to the resources available, pseudocholinesterase deficiency was an inclusion and exclusion clinical diagnosis. Due to the patient's history of opiate abuse, current methadone use, and history of Guillain-Barre Syndrome, it is important to differentiate how each of these and other neuromuscular etiologies would present and how they differed from the patient's case. The anesthesiologist noticed that while the patient was on appropriate pressure support before extubation, he was tachypneic and failed to draw proper tidal volumes. It is unclear whether the patient was fully alert at this time, but upon arrival to the ICU on ventilatory support approximately 20 minutes later, the patient was able to follow basic movement commands consistently and answer basic questions with nods and shakes of head.

The first possibility ruled out was opioid-induced respiratory depression. The patient took 80 mg of methadone per day, which he was instructed to hold on day of surgery. No information to the contrary indicated that the patient was noncompliant with this instruction. During the procedure, the patient received 250 mcg of fentanyl. The team was confident in ruling out narcotic toxicity as the etiology due to the patient's tachypnea, which indicated an intact central respiratory drive. While opioid toxicity can cause poor tidal volumes due to opioid binding patterns in the pons, it would be unusual for a patient to have compensatory tachypnea in this kind of toxicity.[3] Because of lack of evidence of opioid toxicity, naloxone was not attempted at this time.

Myasthenia gravis and myasthenic crisis are conditions that could present with a similar symptom profile as our patient. While multiple forms of myasthenia gravis exist based on the type of autoantibodies produced, the most common are those directed against the acetylcholine receptor (AChR) on the neuromuscular endplate.[4] These autoantibodies produce flaccid paralysis by blocking true acetylcholine binding as well as by degrading these receptors that are necessary for

neuromuscular signal translation. This is similar to the action of succinylcholine with one important distinction. While the autoantibodies of myasthenia gravis bind AChR on the neuromuscular endplate, they do not activate the receptor but instead block and degrade it. While succinylcholine binds and blocks acetylcholine receptors, it also activates these receptors repeatedly. This repetitive stimulation initially causes a fasciculation-induced paralysis followed by true flaccid paralysis. Unlike in myasthenia gravis, acetylcholinesterase inhibitors do not produce increased levels of true muscular contractions, but rather prolong succinylcholine's paralytic effect. Acetylcholinesterase inhibitors, therefore, cannot be used as an antidote when pseudocholinesterase levels are deficient.[5]

Myasthenic crisis, which involves severe respiratory compromise as the muscles of respiration become involved in the myasthenic process, mimics our patient case very closely. As noted by the anesthesiologist, the patient appeared to have an intact respiratory drive, as he was tachypneic and in distress, but his poor tidal volumes indicated poor respiratory muscle capacity. Surgical procedures are known precipitants of myasthenic crisis. While management of myasthenic crisis can include IVIG and plasma exchange, a mainstay of management for both myasthenic crisis and pseudocholinesterase deficiency resulting in respiratory compromise is intubation with mechanical ventilation. Myasthenic crisis was low on our differential diagnosis given the patient's lack of history of myasthenia gravis, as well as his spontaneous full recovery within hours of the initial event. In either scenario, empiric acetylcholinesterase inhibitor use should be avoided given that these medications are contraindicated in both myasthenic crisis (as they can cause overproduction of lung secretions in a vulnerable patient)[6] and pseudocholinesterase deficiency (as this will prolong the paralysis induced by succinylcholine).[5]

The patient's history of Guillain-Barre Syndrome (GBS)/Chronic Inflammatory Demyelinating Polyneuropathy was a factor to consider, especially given the relatively prolonged nature of his clinical course with that disease. The history of GBS was not discovered until after patient had recovered. Guillain-Barre was ruled out for several reasons. First, Guillain-Barre's clinical course usually extends over multiple weeks. The hyperacuity of the patient's symptoms, with him being neurologically intact before the procedure and complete neural recovery within hours indicated an etiology other than GBS. While GBS can produce respiratory distress through diaphragmatic involvement that would mimic his clinical symptoms, it would be unusual for a GBS patient not to have previously experienced other non-diaphragmatic muscle weakness as well. As mentioned previously, the patient was grossly neurologically intact before his surgical procedure. He was able to follow basic movement commands while on a ventilator but appeared diffusely weak rather than the ascending flaccid paralysis typical of GBS.[7] Once extubated, he had full function of all muscles return equally, limited only by expected post-operative pain.

Because the patient received succinylcholine and rocuronium for intraoperative paralysis, the possibility of rocuronium toxicity had to be ruled out. Sugammadex is the preferred antidote for rocuronium toxicity.[8] While still in the operating room, the patient was administered 100 mg sugammadex without effect. Given these factors, it was determined that pseudocholinesterase deficiency was the most likely etiology of the patient's compromised status. This diagnosis was supported by the patient's spontaneous recovery within hours.

Inherited pseudocholinesterase deficiency severity depends on the homozygosity vs. heterozygosity of the patient. Heterozygotes for the deficient enzyme occur in about 1 in 500 persons, and homozygotes for the deficient enzyme occur in about 1 in 2,000 - 5,000 persons.[2] Homozygotes have more prolonged paralysis with succinylcholine than heterozygotes. Since genetic analysis of each pre-surgical patient is unfeasible and the genetic variant resulting in deficiency of pseudocholinesterase is relatively common, the surgical and anesthesia team must be on the lookout for this possibility. Preoperative screening should include a family history of delayed extubation. While this mutation is of less importance in the intraoperative phase due to the patient having continuous respiratory support, it is of supreme importance post-operatively, as the surfacing patient can begin to experience severe respiratory distress and accompanying mental terror. This requires immediate recognition, continuation of respiratory support, and possible mild sedation for patient comfort. Understanding the differential diagnosis and pathophysiology related to different causes of neuromuscular respiratory failure are critical to the ICU physician, as failure to recognize the correct etiology and administer the appropriate drug could harm the patient further.

REFERENCES

[1] Hager HH, Burns B. Succinylcholine Chloride. November 16, 2020. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing, 2020. PMID: 29763160.
[2] Trujillo R, West WP. Pseudocholinesterase Deficiency. July 15, 2020. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing, 2020. PMID: 31082076.
[3] Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. Anesthesiology 2010; 112(1):226-238. PMID: 20010421.
[4] Huijbers MG, Lipka AF, Plomp JJ, Niks EH, van der Maarel SM, Verschuuren, JJ. Pathogenic immune mechanisms at the neuromuscular synapse: The role of specific antibody-binding epitopes in myasthenia gravis. J Intern Med 2014; 275(1):12-26. PMID: 24215230.
[5] U.S. National Library of Medicine. ANECTINE® (Succinylcholine Chloride Injection, USP): A short-acting depolarizing skeletal muscle relaxant. Civica, Inc. July 2020. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=0b990f84-9515-44bd-a97d-a97bbead065c&type=display. Accessed February 20, 2021.
[6] Wendell LC, Levine JM. Myasthenic crisis. Neurohospitalist 2011; 1(1):16-22. PMID: 23983833.
[7] Arcila-Londono X, Lewis RA. Guillain-Barré syndrome. Sem Neurol 2012; 32(03):179-186. PMID: 23117942.
[8] Wu X, Oerding H, Liu J, et al. Rocuronium blockade reversal with sugammadex vs. neostigmine: Randomized study in Chinese and Caucasian subjects. BMC Anesthesiol 2014; 14:53. PMID: 25187755.

Keywords: pseudocholinesterase deficiency, airway extubation, intensive care unit

KANSAS JOURNAL of MEDICINE

An 8-Month-Old Girl with Prolonged Fever

Fatima Abdo, M.D., Catherine Bshouty, M.D.,
Charles W. Coffey, M.D., Robert R. Wittler, M.D.
University of Kansas School of Medicine-Wichita, Wichita, KS
Department of Pediatrics

Received Feb. 18, 2021; Accepted for publication April 1, 2021; Published online July 9, 2021
https://doi.org/10.17161/kjm.vol1415208

INTRODUCTION

Francisella tularensis is an aerobic Gram-negative coccobacillus, which causes acute febrile illness of humans and other mammals, most commonly rabbits. Exposure may occur through direct contact with infected animals, arthropod bites including ticks, deer flies, and mosquitoes, contaminated soil, or ingestion of contaminated meats or water, and, in some cases, via inhalation of aerosolized organisms. Based on a retrospective study, arthropod bite was identified in 77% of cases, which was consistent with the mode of transmission in our current case.[1]

Manifestation of tularemia infection varies. Of the seven forms of tularemia, the classic clinical presentation is ulcero-glandular.[1] Of note, each form is associated with symptoms consistent with an influenza-like illness, consisting of fevers, chills, headache, and myalgia. "Typhoidal" symptoms were reported in 47% of cases, double the proportion of the more classic manifestation of lymphadenopathy, which was contrary to the expectations.

Fever is defined as a core temperature of at least 38.0°C (100.4°F). Febrile illness in the pediatric population has a broad differential diagnosis. Fever can be due to infections (bacterial, viral, fungal, or tick-borne), autoimmune disorders, or malignancy. A detailed history and physical examination are needed to narrow the differential diagnosis.

The following was a case of an 8-month-old presenting with fever which was found later to be due to a tick-borne illness although initial serologies for tick-borne illness were negative.

CASE REPORT

An 8-month-old girl with gross motor delay presented with febrile illness of unknown origin. The patient initially presented to a regional emergency department with lethargy, excessive sleepiness, and multiple episodes of vomiting at home for one day. At the time, parents also reported fevers of greater than 100.4°F. The infant was admitted to the community hospital for supportive care and further evaluation. Blood and urine cultures along with a nasopharyngeal viral pathogen assay were obtained. The nasopharyngeal swab was positive for Parainfluenza 3. She was discharged following three days of hospitalization with presumptive viral illness although she remained intermittently febrile while hospitalized.

On day seven of illness, she was seen at her primary care provider's office for continued fever and was started on a course of amoxicillin to cover empirically for possible bacterial infection. However, persistent fevers, decreased oral intake, and decreased number of wet diapers prompted parents to have her re-evaluated at the local emergency department on day 11 of illness. In the emergency room, the patient was noted to have a scar with a scab at the left postauricular area where a tick had been removed. The scar had not been visualized at the initial emergency department visit (Figure 1).

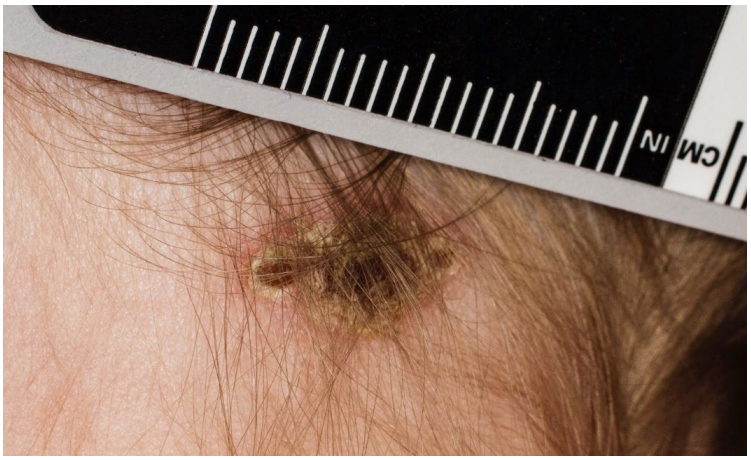


Figure 1. Left postauricular tick bite site.

Of note, there was no recent travel outside of the United States, however, the family was in Colorado a month prior to her illness. The patient was exposed to a cat and a dog at home, but there was no recollection of an animal bite or scratch. The infant's past medical history was noncontributory, and immunizations were up to date.

Given the clinical findings, the patient was admitted for parenteral antimicrobial therapy for suspected tick-borne disease with doxycycline. Pertinent lab findings from the regional hospital included an elevated white blood count of 19.1 K/cumm (5.0 - 18.0), decreased Hgb level of 8.6 gm/dL (11.0 - 14.0), elevated platelet count of 630 K/cumm (150 - 450), elevated liver enzymes of AST 463 IU/L (0 - 40) and ALT of 202 IU/L (0 - 30), as well as a decreased sodium level of 126 mmol/L (135 - 148), and decreased albumin of 2.1 g/dL (4.1 - 5.2). Serologic assays were obtained for Epstein Barr Virus, Cytomegalovirus, *Bartonella henselae*, *Francisella tularensis*, and *Rickettsia ricketsiia*. The patient was transferred to a tertiary care center for further management on day four of hospitalization due to persistent symptoms on day 14 of illness.

On admission to the tertiary care center, the patient remained on IV doxycycline. Significant lab findings on admission were remarkable for elevated lactate dehydrogenase of 931 units/L (reference range 180 - 430), low uric acid of 1.1 mg/dL (2.6 - 6.0), elevated c-reactive protein of 123 mg/L (< 8.0), increased prothrombin time of 16.6 sec (9.8 - 13.0), and a low hemoglobin of 7.4 gm/dL (11.0 - 14.0). Pertinent imaging included a CT of the abdomen which showed multiple hypo-attenuated foci in the spleen and a CT of the pelvis which showed prominent inguinal lymph nodes. Flow cytometry on peripheral blood obtained at the time did not show any evidence of leukemia. The above noted serologic assays from the referring hospital were all negative.

The patient continued to be febrile despite six days of therapy with IV doxycycline. Due to suspicion for tularemia infection, antimicrobial therapy was switched to IV gentamicin. The initial serology for tularemia, which was obtained at day 14 of illness, was negative. The patient was treated for an additional six days on IV gentamicin. After being afebrile for greater than 24 hours, the patient was discharged home

with a 10-day course of ciprofloxacin. Prior to discharge on day 21 of illness, tularemia antibody was re-tested and was positive at a titer of 2560 (negative < 20).

DISCUSSION

Our case presented with the less common manifestation of the typhoidal form of tularemia based on her clinical symptoms of persistent fever, no apparent lymphadenopathy or lymphadenitis, no pharyngitis, and no pneumonia.[1] Ulcero-glandular tularemia is the most frequent clinical presentation of tularemia which presents with an ulcerative lesion at the inoculation site (tick or animal bite) and a regional lymphadenitis. Tularemia is particularly endemic to areas in south-central United States and most frequently is transmitted by ticks rather than by animals such as rabbits. There are many limiting factors in diagnosing tularemia; its clinical presentation is nonspecific and similar to other more frequent summer febrile illnesses such as enterovirus infection. Other differential diagnoses for prolonged fever include rheumatologic diseases or malignancy.

Antibodies to *Francisella tularensis* often remain negative for the first 7 to 14 days of infection as observed in our patient.[2] Those factors contribute to a prolonged time to diagnosis and a delay in appropriate treatment for tularemia. For that reason, in the pediatric population, it is imperative to have a high suspicion of typhoidal tularemia infection in the setting of a febrile illness even without lymphadenopathy, especially during tick season in an endemic region.[1,2] Complications associated with tularemia include pneumonia, sepsis, and meningitis.[1]

Interestingly, the CT scan of our patient's abdomen was significant for hematogenous spread with focal lesions involving the spleen. A PubMed (pubmed.gov) search of tularemia, human, and splenic lesion or splenic nodule found only one prior case.[3] Imaging of the liver and spleen should be considered in cases of fever of unknown origin given the possibility of tularemia and hepatosplenic *Bartonella henselae* infection.

Early detection or suspicion of tularemia and initiation of appropriate antibiotic therapy plays a significant role in success of treatment. Antibiotics such as ceftriaxone or other beta-lactam antibiotics that commonly are given for empiric treatment of children with persistent fever have not been shown to be effective treatment for tularemia. Aminoglycosides, such as streptomycin or gentamicin, are first line drugs of choice.[4] Doxycycline is the drug of choice for tickborne Rickettsial infections and monocytic erlichiosis which have some overlapping presentations with typhoidal tularemia, however, concern for relapse occurs when used as monotherapy for tularemia.[5] Although aminoglycosides are effective in treating tularemia, they only can be administered parentally, requiring prolonged hospitalization. In addition, the toxicity associated with the use of aminoglycosides is of concern.[6] In comparison to gentamicin, streptomycin has been shown to be more effective in the treatment of oropharyngeal tularemia.[7] Patients with mild to moderate cases of tularemia have been treated successfully with oral ciprofloxacin.[8] Aminoglycosides should be given for 7 - 10 days, whereas ciprofloxacin would be given for 10 - 14 days.[6]

Our patient was switched from intravenous doxycycline to intravenous gentamicin on day 15 of illness due to a high suspicion for tularemia despite negative initial serological tests for tularemia, which was obtained on day 11 of illness. Our patient had clinical improvement within 24 hours of initiating gentamicin and remained on gentamicin therapy for a total of six days prior to transitioning to oral therapy with ciprofloxacin. As mentioned earlier, repeated serology for tularemia at day 19 of illness was positive with a titer of 2560 confirming the diagnosis of tularemia.

Tick-borne illness should be considered as part of a broad differential diagnosis for fever of unknown origin, especially in endemic regions within the pediatric population. Similar to Rocky Mountain Spotted Fever, tularemia antibodies may not be detected within the first 14 days of illness and sometimes may take up to 21 days to be detected.[2] Since early antibiotic treatment decreases the morbidity associated with tularemia, a high index of suspicion should prompt early antibiotic use even in the absence of positive serology. It is worth noting that the clinical presentation of tularemia may be variable and may present with unusual manifestations, such as the splenic involvement as seen in our case.

REFERENCES

[1] Lester Rothfeldt LK, Jacobs RF, Wheeler JG, Weinstein S, Haselow DT. Variation in tularemia clinical manifestations-Arkansas, 2009-2013. Open Forum Infect Dis 2017; 4(1):ofx027. PMID: 28480295.
[2] Snowden J, Stovall S. Tularemia: Retrospective review of 10 years' experience in Arkansas. Clin Pediatr 2010; 50(1):64-68. PMID: 20837613.
[3] Garver MK, St. Geme JW, Siegel MJ. Tularemia presenting with splenic nodules. Pediatr Infect Dis J 1994; 13(9):830-832. PMID: 7808857.
[4] Nigrovic LE, Wingerter SL. Tularemia. Infect Dis Clin North Am 2008; 22(3):489-504. PMID: 18755386.
[5] Caspar Y, Maurin M. Francisella tularensis susceptibility to antibiotics: A comprehensive review of the data obtained in vitro and in animal models. Front Cell Infect Microbiol 2017; 7:122. PMID: 28443249.
[6] Kimberlin DW, Brady MT, Jackson MA, Long SS, American Academy of Pediatrics. Committee on Infectious Diseases. Red Book: 2018-2021 Report of the Committee on Infectious Diseases. American Academy of Pediatrics; 2018.
[7] Kaya A, Uysal IO, Guven AS, et al. Treatment failure of gentamicin in pediatric patients with oropharyngeal tularemia. Med Sci Monit 2011; 17(7):CR376-CR380. PMID: 21709631.
[8] Johansson A, Berglund L, Gothefors L, Sjostedt A, Tarnvik A. Ciprofloxacin for treatment of tularemia in children. Pediatr Infect Dis J 2000; 19(5):449-453. PMID: 10819342.

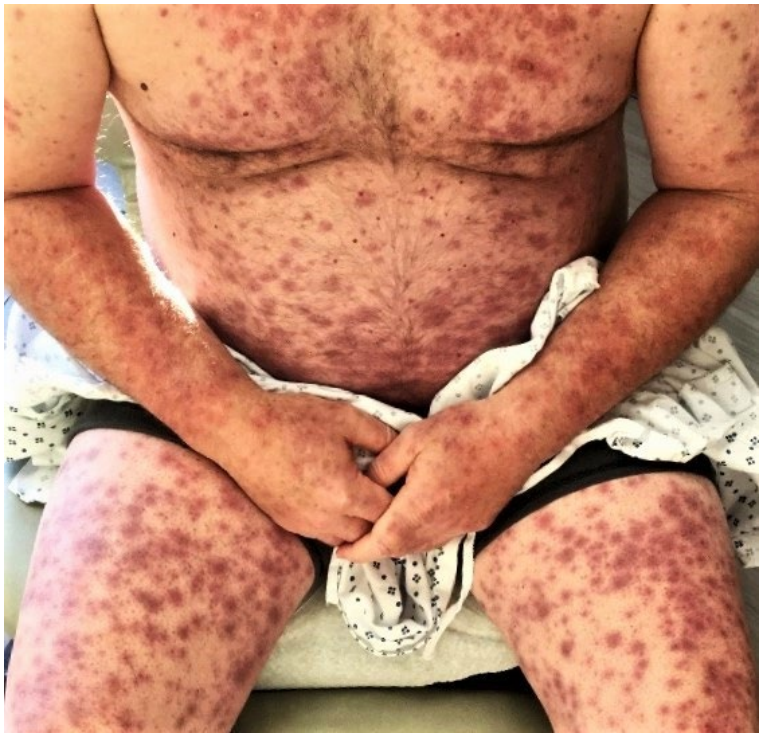
Keywords: tick-borne disease, Francisella tularensis, tularemia, fever of unknown origin, splenic disease

KANSAS JOURNAL of MEDICINE

Rocky Mountain Spotted Fever Misdiagnosed as an Acute Drug Reaction: Diagnostic Clues and Evaluation Recommendations

Atieh Jibbe, M.D.[1], Brett C. Neill, M.D.[1], Stan N. Tolkachjov, M.D.[2]
[1]University of Kansas Medical Center, Kansas City, KS
Department of Internal Medicine, Division of Dermatology
[2]Epiphany Dermatology, Dallas, TX

Received Feb. 24, 2021; Accepted for publication April 1, 2021; Published online July 9, 2021
https://doi.org/10.17161/kjm.vol1415223



CASE DESCRIPTION

History and Exam. A 52-year-old healthy male presented to the dermatology clinic with fever, rash, and myalgias. Two days prior, he had been discharged from the hospital for a presumed drug rash secondary to an opiate. The petechial rash initially involved his hands, wrists, and ankles, and was spreading centripetally, involving the proximal upper and lower extremities and trunk (Figure). Of note, the patient recently started summer gardening at his home in the southeast U.S. which caused worsening back pain for which he took oxycodone/acetaminophen. He denied a tick bite history.

Presumptive Diagnosis. Further workup was unremarkable except for mildly elevated AST/ALT. Based on a high clinical suspicion with the characteristic petechial rash and systemic symptoms, Rocky Mountain Spotted Fever (RMSF) was the presumptive diagnosis and empiric treatment was begun with doxycycline.

Confirmatory Diagnosis. After initiating doxycycline, the patient had a skin biopsy with direct immunofluorescence consistent with vasculitis and subtle features of RMSF histopathology: basal layer vacuolar degeneration with mild interface and lymphocytic exocytosis. Serum RMSF titers via indirect immunofluorescence, drawn one week after likely infection, were positive confirming the diagnosis.

DISCUSSION

RMSF is the most common fatal tickborne disease in the U.S.[1] Incidence of Spotted Fever Rickettsiosis has increased from 2000 to 2017 with 495 to 6,248 cases, respectively. RMSF is transmitted by the Dermacentor variabilis tick most prevalent in the eastern U.S.[2,3] The incubation period ranges from 3 - 12 days. RMSF presents with a classic triad of fever, headache, and rash, however, this triad is not identified often. It is estimated that only 3% of patients present with this triad within the first three days of illness. Early disease presents with non-specific symptoms including fever, headache, malaise, myalgia, nausea, vomiting, and photophobia.[3] RMSF rash usually presents two to five days after the onset of symptoms with blanching erythematous macules that progress to form petechiae and spread centrifugally.[3,4] This rash can be absent in 10 - 15% of patients, typically older adults and African-Americans.[3] Labs in RMSF can vary with possible leukocytosis, thrombocytopenia, elevated liver enzymes, and hyponatremia.[5]

Our case was challenging due to the lack of tick bite history. In a 1995 study of 79 RMSF patients, only 40% of patients recalled a tick bite.[4] In our case, the history of summertime gardening in an endemic area, purpuric rash starting on wrists and spreading centripetally, elevated AST/ALT, myalgias, and the rarity of oxycodone/acetaminophen causing a rash provided the index of suspicion for RMSF.

The mainstay of diagnosis for RMSF is serology with indirect immunofluorescence assay. Antibodies to RMSF usually develop 7 - 10 days after illness onset, but serologies should be obtained 14 - 21 days after symptom onset due to the likelihood of false negatives in the acute phase. A single reactive titer may suggest RMSF, but a four-fold increase in IgG titers from acute to convalescent phase can confirm the diagnosis.[4] A skin biopsy can assist in the diagnosis but is not confirmatory. In a study of 26 cases of RMSF, the major histopathologic features were lympho-histiocytic capillaritis and venulitis with extravasation of erythrocytes, edema, predominantly perivascular with some interstitial infiltrate, and leukocytoclastic vasculitis.[6]

Empiric treatment comprises of doxycycline 100 mg (2.2 mg/kg for children) twice-daily for > 3 days after defeverence with 5 - 7-day minimum duration.[3] Treatment should be initiated if RMSF is suspected even if symptoms are mild or laboratory evidence is lacking. The importance of early treatment is highlighted by a study of 94 patients that revealed patients treated within five days of symptoms onset had lower mortality rates than those treated after the fifth day (6.5% vs. 22.9%).[7] Chloramphenicol (50 mg/kg/day in four divided doses) is the only known alternative agent for the treatment of RMSF. It appears to be less effective than doxycycline and typically is used in the rare setting when an individual has a history of a severe adverse reaction to doxycycline.

RMSF is suspected in patients with fever, headache, and constitutional symptoms, during the summer in endemic areas, and known tick-bite history. This diagnosis remains a clinical challenge for providers due to its non-specific symptoms, absence or delayed rash, lack of tick-bite history, and sporadic distribution of the disease in endemic areas.

REFERENCES

[1] U.S. Centers for Disease Control and Prevention. Rocky Mountain Spotted Fever (RMSF). April 7, 2020. http://www.cdc.gov/rmsf/stats/#geography. Accessed June 7, 2019.
[2] Lin L, Decker CF. Rocky Mountain spotted fever. Dis Mon 2012; 58(6):361-369, PMID: 22608123.
[3] Gottlieb M1, Long B, Koyfman A. The evaluation and management of Rocky Mountain spotted fever in the emergency department: A review of the literature. J Emerg Med 2018; 55(1):42-50. PMID: 29685474.
[4] Blanton LS. The rickettsioses: A practical update. Infect Dis Clin North Am 2019; 33(1):213-229. PMID: 30712763.
[5] Helmick CG, Bernard KW, D'Angelo LJ. Rocky Mountain spotted fever: Clinical, laboratory, and epidemiological features of 262 cases. J Infect Dis 1984; 150(4):480-486. PMID: 6491365.
[6] Kao GF, Evancho CD, Ioffe O, Lowitt MH, Dumler JS. Cutaneous histopathology of Rocky Mountain spotted fever. J Cutan Pathol 1997; 24(10):604-10. PMID: 9449487.
[7] Kirkland KB, Wilkinson WE, Sexton DJ. Therapeutic delay and mortality in cases of Rocky Mountain spotted fever. Clin Infect Dis 1995; 20(5):1118-1121. PMID: 7619985.

Keywords: Rocky Mountain spotted fever, adverse drug reaction, diagnosis, misdiagnosis

KANSAS JOURNAL of MEDICINE

KANSAS JOURNAL OF MEDICINE

VOLUME 14 • 2021

journals.ku.edu/kjm

Have a manuscript ready to publish?
Visit our website for instructions on submitting a manuscript.

Frontiers: University of Kansas Clinical and Translational Science Institute is a collaborating partner of the Kansas Journal of Medicine

Office of Research
1010 N. Kansas, Wichita, KS 67214
316-293-2617 • Email: kjm@kumc.edu

VOLUME 14 • 2021

WHAT'S INSIDE: ORIGINAL RESEARCH • CASE REPORT

KANSAS JOURNAL of MEDICINE

TABLE OF CONTENTS

KANSAS JOURNAL of MEDICINE

An Evaluation of a Kansas Open Streets Event's Impact on Businesses

Danielle Gauna, MPH[1], Jack Brown, MUA, R.S.[1], Kelsey Lu, M.S.[1], Matthew Martinez[2], Elizabeth Ablah, Ph.D., MPH[1]
[1]University of Kansas School of Medicine-Wichita, Wichita, KS Department of Population Health
[2]City of Wichita Park and Recreation, Wichita, KS

Received Sept. 22, 2020; Accepted for publication April 9, 2021; Published online Aug. 4, 2021
https://doi.org/10.17161/kjm.vol1414662

ABSTRACT

Introduction. Open Streets is an event that promotes physical activity among populations by encouraging city residents to walk and bicycle in streets blocked from motor vehicles. Engagement of businesses is a critical component of Open Streets. This study sought to evaluate the Open Streets ICT 2019 event's impact on adjacent businesses.

Methods. A 12-item novel survey was developed for this study. Businesses eligible for study participation included retail and non-retail (e.g., non-profits, churches) sites along the Open Streets ICT route in Wichita, Kansas. To understand how Open Streets ICT impacted businesses, the survey used Likert scale questions to prompt respondents to report sales and visitors experiences during the event. Additionally, respondents reported a percent difference in sales compared to a typical Sunday. A phenomenological approach was used to convey the experiences among study participants during Open Streets ICT.

Results. A total of 102 surveys were completed, a 42% response rate. Most businesses (56%, n = 56) reported being open during Open Streets ICT. Many businesses (72%) reported having "more" visitors compared to a typical Sunday. More than half reported they experienced new and regular visitors (54%, n = 30) from the event. Most businesses (64%, n = 36) reported a positive financial impact, and (52%, n = 29) having more sales than a typical Sunday.

Conclusions. Open Streets ICT increased sales and the number of visitors among businesses. Respondents reported they plan to participate in the 2020 Open Streets ICT, and if Open Streets ICT was offered twice a year. Finally, most participating businesses reported they recommend that other businesses participate in Open Streets ICT.

Kans J Med 2021;14:187-191

INTRODUCTION

As the United States population becomes increasingly physically inactive, active transportation (human powered modes of transportation such as walking or bicycling)[1] serve as reasonable opportunities to increase activity among populations. However, an important barrier to engaging in recreational and active transportation is a concern for safety from motor vehicles.[2]

Open Streets is a public health initiative that aims to create safe environments from motor vehicles and promote recreational activity, with the potential for promoting active transportation long-term. The event temporarily closes streets from motorized vehicles to encourage hosting city residents to walk and bicycle along the closed streets.[3-6] The event is designed for residents to engage with neighbors, local businesses, and event sponsors.

Open Streets have the potential to transform communities by creating cultures of health, where all members of society are able to lead healthier lives now and in the future.[7] Scholars suggested this can be accomplished by increasing the awareness of the importance of active transportation and creating a sense of community through social cohesion by bringing people from different backgrounds and ages together through activity in the community.[5,8-11] In fact, many past Open Streets event attendees return to the next event because they have such a positive experience in a safe and active environment.[12] Approximately 497 Open Streets events occur in 27 countries with most occurring in Latin America.[8,13]

The first Open Streets, "Ciclovia," emerged from a protest in Bogotá, Colombia on December 15, 1974.[14] Five thousand Bogotáns protested against air pollution, traffic congestion, and the lack of public space for recreational activities. Between 1995 and 2000, the route was increased from 20 km (12 mi) to 121 km (75 mi) to reach different socioeconomic populations. In fact, participants in two Open Streets in Latin America, Bogotá and Santiago de Cali, were more likely to visit higher or lower social economic status neighborhoods than their neighborhood of origin.[15] The Open Streets in Bogotá attracts about one million participants every Sunday.[16] The event occurs every Sunday and holiday from 7 a.m. to 2 p.m., with a route length of 127.69 km (79 mi).[14]

Although Open Streets events are gaining popularity in the United States, many do not meet the definition from Sarmiento and colleagues: two events per month, with a minimum street closure of one kilometer (0.62 miles).[9] However, Kuhlberg and colleagues[10] used a broader definition for Open Streets in the United States: any free event held in a city where streets were closed to motorized traffic for a period of time and opened to residents to encourage physical activity. Previous studies in the United States have evaluated Open Streets events in major urban cities including: Los Angeles,[17] San Francisco,[12,18,19] San Diego,[20] Atlanta,[21] and St. Louis,[22] to rural cities such as Brownsville, Texas.[23] Each study reported positive public health impacts such as improved air quality,[17] increased physical activity among event attendees,[12,20-23] perceptions of safety during the event,[12,21] and benefits among businesses.[18-22]

Open Streets events often promote the services and products from businesses along the local route. Hosting an Open Streets on a route where businesses are located can be advantageous to the local economy.[12,18] In fact, 68% of event attendees from an Open Streets event in St. Louis reported an increased awareness of participating businesses.[22] Additionally, 82% of event attendees in Atlanta reported spending more than $10 at Open Streets.[21]

The annual Open Streets event in Wichita, Kansas, "Open Streets ICT", began on a Sunday in September of 2017, from 12 p.m. to 5 p.m.[24] Open Streets ICT temporarily closed a four-mile route on Douglas Avenue, a major street in downtown Wichita, from motor vehicles.[25] The event was free to attend and designed to bring the community together to enjoy live music, food, street vendors, and support local businesses, all while residents were engaging in recreational or active transportation. Douglas Avenue is home to more than 300 local businesses, dozens of pieces of art, including 31 bronze sculptures, and includes the ICT

Pop-Up Urban Park, a gathering place for picnics and food trucks.[25] Douglas Avenue connects two diverse neighborhoods, Delano on the west end and College Hill on the east end.

Local businesses along the event route are critical stakeholders to the success and sustainability of Open Streets, as they can promote it and benefit from participating in the event. However, little was known about how Open Streets events impacted adjacent businesses and their revenue. Therefore, this study sought to evaluate the 2019 Open Streets ICT event's impact on adjacent businesses.

METHODS

Participants. Businesses eligible for participation in Open Streets ICT 2019 included any business two blocks (0.5 miles) north and two blocks south from the 4.1-mile route on Douglas. The route's endpoints were West Douglas and Glenn Street in the Delano neighborhood and East Douglas and Bluff Street in the College Hill neighborhood. Eligible businesses could participate in Open Streets ICT at no cost and qualified for a free 10 × 10-foot booth during the event.

Businesses eligible for participation in this study included any retail businesses and non-retail (e.g., non-profits, churches) sites along the route, or less than one block (0.25 miles) from the route, with the furthest business being 0.1 mile from the route. Participants eligible to complete the survey included owners, managers, or employees representing the businesses along the route, regardless of whether they participated in the 2019 Open Streets ICT.

Instrument. A 12-item novel assessment was designed for this study to understand how Open Streets ICT impacted businesses. The survey was created in Research Electronic Data Capture (REDCap®).[26] The survey prompted respondents to identify the type of business they represented (e.g., grocery, restaurant, service industry such as roofing). Respondents were prompted to report if the business was open during Open Streets ICT. If respondents reported that the business was not open during Open Streets ICT, they were prompted to provide a reason as to why the business was not open. Respondents who reported that the business was open during the event were asked additional questions to understand how the event impacted their business.

The survey prompted respondents who were open during the event to estimate the proportions of sales and visitors they experienced during the event compared to a typical Sunday afternoon (far fewer, fewer, about the same, more, or many more). To understand how Open Streets ICT 2019 influenced sales, the survey prompted respondents to report a percent difference in sales compared to a typical Sunday. To understand the type of visitors who visited the businesses during the event, respondents were asked if they experienced no increase in visitors, new visitors, regular visitors, or new plus regular visitors. Respondents also were asked if Open Streets ICT 2019 impacted their business financially (strongly negatively, somewhat negatively, no impact, somewhat positively, or strongly positively). Also, respondents were prompted to indicate if they would recommend that other businesses participate in Open Streets ICT. Finally, the survey offered open-ended questions: please provide your reason for not wanting to be open during Open Streets ICT or extend hours, please briefly describe these impacts, do you have any feedback or suggestions for improving Open Streets ICT? These open-ended questions allowed the research team to collect qualitative data about how Open Streets ICT 2019 affected businesses and how Open Streets ICT can be improved.

Procedures. The recreation supervisor for the City of Wichita's Park and Recreation identified the need to conduct the survey and recommended that respondents would be more responsive to an anonymous online survey than an in-person administration of the survey. Several survey questions from a previous study were included.[18] Additionally, questions were added by a Master of Public Health (MPH) student and the principal investigator to tailor the survey to Open Streets ICT. The study was approved by the Human Subjects Committee at the University of Kansas School of Medicine-Wichita.

An MPH student used Google Maps to identify the businesses on the Douglas route. A list of businesses with mailing addresses and telephone numbers was created to contact potential respondents. First, potential respondents were contacted by telephone to discuss the survey and consent process. If the respondent could not be reached by telephone, then the MPH student visited the business to make them aware of the project. If respondents agreed to participate in the study, they were asked to provide an e-mail address to receive the survey.

The survey data were managed in REDCap® hosted by the University of Kansas School of Medicine.[26] Data were collected between September 26 and October 20, 2019. The survey could be completed in less than five minutes, and participants could discontinue participation at any time.

Statistical Analysis. Data were analyzed using IBM® SPSS Statistics 25. Frequencies and percentages were generated for all quantitative variables. The average was calculated for the percent difference in sales compared to a typical Sunday. Two outliers were removed due to potential overestimation (1000%) or underestimation (-288%) of reported percent differences. Qualitative data were collected from respondent quotes derived from three open-ended items in the survey. An MPH student coded the quotes into themes and subthemes which were reviewed by the principal investigator. To analyze the qualitative data, the principal investigator and MPH student used an interpretive phenomenological approach to convey the experiences among respondents and how those experiences impacted their businesses during Open Streets ICT 2019.

RESULTS

Two hundred forty-six businesses were e-mailed a link to the online survey, and 102 surveys were completed; a 42% response rate. After removing two surveys where more than half of the items were not completed, the final sample size was 100 businesses. Most of the businesses from the sample (n = 95), were categorized as "retail" (64%, n = 61) as they sell tangible products. Another 36% (n = 34) were "non-retail businesses", which consisted of churches (n = 3), non-profits (n = 7), art galleries (n = 2), and businesses that provide services or do not sell tangible products (e.g., roofing, education; n = 22).

Fifty-six percent (n = 56) reported that their business was open during Open Streets ICT 2019 (Table 1). In fact, 46% of these businesses (n = 26) reported being open or extending their business' hours specifically because of Open Streets ICT.

Table 1. Responses from businesses along the Open Streets ICT route.

Survey item	Yes n (%)	No n (%)	Missing n (%)
Business opened or extended hours specifically for Open Streets ICT	26 (46)	30 (54)	0 (0)
Beneficial for business to participate in Open Streets ICT	46 (82)	7 (13)	3 (5)
Recommend other businesses participate in Open Streets ICT	50 (89)	4 (7)	2 (4)
Business will participate in Open Streets ICT next year	47 (84)	6 (11)	3 (5)

Nearly two-thirds of respondents (64%, n = 36) reported a positive financial impact from the event (Table 2). In fact, 52% (n = 29) reported having "more" sales than they would have on a typical Sunday. Respondents reported a percent difference in sales compared to a typical Sunday ranging from -80% to 200%. The average percent difference in sales was a 47% increase. The median percent difference in sales was 20%. Nearly three-fourths of respondents (71%, n = 40) reported having "more" visitors than a typical Sunday. More than half of respondents (54%, n = 30) reported they experienced new and regular visitors compared to a typical Sunday.

Table 2. Reported sales and visitors compared to a typical Sunday.

Survey item	Fewer n (%)	About the same n (%)	More n (%)	Missing n (%)
Proportion of sales compared to a typical Sunday	7 (13)	14 (25)	29 (52)	6 (11)
Proportion of visitors compared to a typical Sunday	8 (14)	7 (13)	40 (71)	1 (2)

Overall, 89% of respondents (n = 50) reported they would recommend that other businesses participate in Open Streets ICT, and 82% (n = 46) reported it was beneficial for them to participate in Open Streets ICT. Another 84% (n = 47) reported that their business planned to participate in the next Open Streets ICT.

Finally, three themes emerged from the qualitative data: reasons for closed businesses, impacts of Open Streets ICT on businesses, and recommended improvements for Open Streets ICT (Table 3). Subthemes for each theme also were captured. The first theme included reasons why businesses were not open, with five subthemes: closed on Sundays, not enough staff, closed but personally participated in Open Streets ICT, not a business that relies on foot traffic, and other event or circumstance.

The second theme included the impacts of Open Streets ICT on businesses with three subthemes: decreases in business, increase in sales, and increased awareness. Respondents reporting a decrease in business described decrease in sales, reservations canceled, or not enough visibility from the event having too many vendors. Respondents reporting an increase in sales suggested a return of investment on coupons, selling more products, or because they had an increase in sales. Respondents reporting increased awareness suggested Open Streets ICT is an event that brings awareness and support of their business or products rather than an increase in their sales.

The third theme recommended improvements for Open Streets ICT with four subthemes: have Open Streets ICT more often, offer more activities, promote participating business and the event, and improve streets prior to Open Streets ICT. Respondents who reported to have Open Streets ICT more often suggested promoting the event. Respondents reported advertising for the Open Streets ICT was not sufficient. Those reporting that more activities needed to be added to Open Streets ICT suggested they want more activities in general, or they wanted activities implemented on both east and west sides of Douglas. Respondents reporting to improve streets prior to the event, suggested cleaning the streets, closing a major intersection (Hydraulic Street and Douglas), using detour signs, and having designated parking.

Table 3. Themes and subthemes in the qualitative data.

Theme (n = 3)	Subtheme (n = 12)
Reasons that some businesses were closed	Closed on Sunday (n = 27) Not enough staff (n = 4) Closed but personally participated in Open Streets ICT (n = 2) Not a business that relies on foot traffic (n = 5) Other event or circumstance (n = 3)
Impacts of Open Streets ICT on businesses	Decrease in business (n = 7) Increase in sales (n = 9) Increased awareness or new visitors (n = 17)
Recommended improvements for Open Streets ICT	Offer Open Streets ICT more often (n = 5) Offer more activities (n = 4) Promote participating businesses and event (n = 8) Improve streets prior to Open Streets ICT (n = 4)

Theme 1: Reasons that Some Businesses Were Closed. Businesses that were not open for Open Streets ICT 2019 (n = 44) reported the reasons that their businesses were closed for the event. Many respondents (n = 27) reported that the event was not held during normal business hours, or that their business usually was closed on Sundays. Additionally, respondents (n = 4) reported having insufficient personnel to staff the event: "We typically open for this event. This year we didn't have enough staff available to work it. It's always been good for business in the past." Two respondents reported that although their businesses were not open for Open Streets ICT, the businesses did participate. One reported, "while our office was not open, we did have a table with water set up outside of our building so we could participate." Another reported that their business is "normally closed on Sundays. We still celebrated with a Mariachi band and candy and games for passer-byes." Two respondents reported their businesses do not rely on foot traffic. One reported, "it's on the weekend and everyone is on bikes and looking to ride along the street, not enter buildings. ICT Open Streets seems more about activity outside vs. being open for people to come in off the street inside." Another respondent reported, "people aren't shopping for our items during this event and we aren't generally open on Sundays. Promoted the business with outdoor displays two years ago and people were curious but that was it." Some respondents reported they had to attend another event, such as a church event or family reunion, and some reported that the "timing was not good".

Theme 2: Impacts of Open Streets ICT on Businesses. Few businesses (n = 7) reported a decrease in business during Open Streets ICT. The businesses described slower sales from streets being closed, reservations canceled, or not enough visibility from the event having too many vendors. One of these respondents reported as a restaurant, café, or bar, "last year we were packed for Open Streets, but this year it seemed that most of the people stayed on Douglas. We saw a $4,000 drop in sales compared to open streets last year." Additionally, a theatre company reported, "it made it incredibly difficult for our audience to get to the theatre. A lot of people called and canceled their reservations as this was our last show, and they could not exchange their date." Another respondent reported, "so many vendors out there that we were completely overlooked."

However, more respondents (n = 9) reported an increase in sales by either stating an increase in sales from a return of coupons, selling more products, or because they had an increase in sales. One respondent reported, "this is our favorite Sunday of the year. It is so great to see everyone on Douglas and we see a lot of new visitors too. Lots of beer sales and some merchandise sales too." Another respondent reported, "doubled average sales for Sunday." A respondent of a new business reported, "we've only been open 90 days, but it was our second busiest day."

Another common sub-theme increased awareness of new visitors because businesses would identify Open Streets ICT as an event that brings awareness and support of their business or products. Specifically, they noted a lot of new or first-time visitors, and how those visitors learned about their business or product. One respondent reported, "We have seen more new customers come back to our store since the event. The event was very good for us in generating more awareness for our business." Another respondent shared, "new customers, better visibility as people were walking instead of driving." Also, another respondent reported, "Open streets ICT is amazing! Please continue to do this. It gets everyone out and about to help support local businesses."

Theme 3: Recommended Improvements for Open Streets ICT. Offering Open Streets ICT more often was a recurring subtheme among respondents. One respondent reported, "Everyone seemed to enjoy the day and was having fun with family, friends, or pets on Douglas. We had a lot of fun, too. Afterward, we discussed that it would make sense to have the event twice a year also."

Other suggestions for improvment commonly reported by respondents included improving the streets prior to Open Streets ICT, such as providing "detour signage when streets are blocked off" and offering more activities. One respondent reported, "The crowd on the west end was smaller than years past and there was very little engagement." Another respondent reported, "bring more things to both ends not just downtown." Additionally, one respondent reported cleaning the streets prior to the event would be helpful. "Yes, it would be great to have the city sweepers clean the street and sidewalks prior to Open Streets so that the boulevard looks its best. Our volunteer team cleaned the sidewalk and street area near the curb so that walkers, bikers, and all didn't trip over debris piles."

Respondents reported the need to promote Open Streets ICT by "continuing to promote it to people outside the city core. We feel as though people that don't live in the area would really enjoy the day, but probably don't know about it." Also, respondents suggested that participating businesses could be promoted better. One respondent suggested a potential scavenger hunt for event attendees. "Encourage people to stop at our business. A map or list of participating businesses to check off might be cool and encourage an increase in business."

DISCUSSION

This study suggested that businesses that participated or were open during the event reported an increase in visitors. This information was consistent with studies of Open Streets events in San Diego (CicloSDias), which reported an increase in the number of customers,[20] and San Francisco (Sunday Streets), which reported an increase in walk-in customer activity.[19] This suggested that Open Streets events can promote local businesses by increasing the foot traffic along the route and attract new visitors. Additional research is needed to estimate the future economic impact of these additional visitors to participating businesses.

This study suggested that, on average, businesses that participated in Open Streets ICT in 2019 increased their sales by approximately 47% compared to a typical Sunday. This information was consistent with evaluations of CicloSDias, which reported a 50% increase in sales,[20] and Sunday Streets, which reported a 44% increase in sales and customer activities.[19] The Sunday Streets evaluation also reported that every dollar spent at the event generated an output of $9.32. This suggested that Open Streets events can impact participating businesses' revenues positively. The increase in revenue might prompt business owners to participate in, promote, or sponsor the event. Moreover, engaging businesses' interests in increased revenue may catalyze these critical event stakeholders to advocate for an increased number of Open Street offerings, therefore contributing energy and strength to grow and sustain the event. This could have significant public health consequences because these events promote recreational activity, active transportation,[27] and health equity.[6]

Scholars suggested Open Streets events are potential opportunities to increase physical activity and engage vulnerable populations who may not have access to recreational opportunities.[13,18] Studies propose strategies to improve health equity through Open Streets such as increasing the length of the route,[15] the duration of the event,[15] or the frequency of the event.[6] However, these strategies would require additional funding for the event, primarily for barricades and a police presence to ensure the streets are safe during the event. Unlike Latin American countries, in the United States, cities hosting Open Streets events are responsible for the expenses of police presence and liability insurance.[4,15] These additional costs serve as a critical barrier to improving health equity through and sustainability of Open Streets events.

Implications for Future Research. Although previous studies have reported benefits among business during Open Streets events, few have used qualitative methods to understand the economic implications of an Open Streets event on adjacent businesses. Researchers must continue to explore the impact of Open Streets events economic outcomes

for businesses, the promotion of active transportation, and improvements to health and health equity. An advantage of this study was its use of qualitative survey questions to understand how Open Streets ICT impacted businesses. Future studies of Open Streets events may extend the literature by using open-ended questions to understand how Open Streets impacts businesses and, more importantly, how businesses can impact Open Streets.

For Open Streets events to grow and/or be sustained, they need buy-in from businesses along the route. Future research could explore how to engage various types of businesses better and determine which types of businesses might be willing to sponsor the event. Businesses are stakeholders and may be willing to increase funding for barriers and police presence. Additionally, research needs to explore how businesses could contribute meaningfully to the Open Streets planning process. This could involve identifying which streets to close, extending the Open Streets routes to reach vulnerable populations, proposing more activities during and throughout the event, and determining the frequency and duration of the event. This collaboration can lead to greater public health impacts such as addressing insufficient physical activity, health inequity, and safer streets.

Limitations. There were two primary limitations to this study. First, the sample size was small. Not all businesses throughout the entire two-block width were surveyed. Thus, results might not be representative of all businesses participating in the event. However, this study had a larger sample size of businesses than the CicloSDias event (n = 26),[20] albeit much smaller than Sunday Streets (n = 317).[19] Second, the survey included subjective questions about the event's impact on businesses. We avoided asking respondents to report the specific revenue in sales or the number of visitors, as conducted in previous Open Streets evaluations, due to concerns that specifying dollar amounts might dissuade respondents from completing the survey.

CONCLUSIONS

Compared to other Sundays, Open Streets ICT 2019 increased the number of visitors and improved sales for participating businesses. These businesses reported it was beneficial for their business, and they recommended that other businesses participate in Open Streets ICT.

REFERENCES

[1] Strategies for Health-Oriented Transportation Projects and Policies Promote Active Transportation. 2011. https://www.cdc.gov/healthyplaces/transportation/promote_strategy.htm. Accessed December 19, 2020.
[2] Sallis JF, Floyd MF, Rodríguez DA, Saelens BE. Role of built environments in physical activity, obesity, and cardiovascular disease. Circulation 2012; 125(5):729-737. PMID: 22311885.
[3] Zieff SG, Hipp JA, Eyler AA, Kim MS. Ciclovía initiatives: Engaging communities, partners, and policy makers along the route to success. J Public Health Manag Pract 2013; 19(3 Suppl 1):S74-82. PMID: 23529059.
[4] Eyler AA, Hipp JA, Lokuta J. Moving the barricades to physical activity: A qualitative analysis of Open Streets initiatives across the United States. Am J Health Promot 2015; 30(1):e50-e58. PMID: 25162326.
[5] Hipp JA, Eyler AA, Zieff SG, Samuelson MA. Taking physical activity to the streets: The popularity of Ciclovía and Open Streets initiatives in the United States. Am J Health Promot 2014; 28(3 Suppl):S114-115. PMID: 24380455.
[6] Hipp JA, Bird A, van Bakergem M, Yarnall E. Moving targets: Promoting physical activity in public spaces via Open Streets in the U.S. Prev Med 2017; 103S:S15-S20. PMID: 27773707.
[7] Robert Wood Johnson Foundation. Building A Culture of Health – Lessons Learned from Global Efforts. National Collaborative on Childhood Obesity Research. 2016. https://www.nccor.org/wp-content/uploads/2016/09/NCCOR_GlobalLessons_Booklet_web-1.pdf. Accessed December 3, 2020.
[8] Sarmiento OL, Díaz del Castillo A, Triana CA, Acevedo MJ, Gonzalez SA, Pratt M. Reclaiming the streets for people: Insights from Ciclovías Recreativas in Latin America. Prev Med 2017; 103S:S34-S40. PMID: 27497659.
[9] Sarmiento O, Torres A, Jacoby E, Pratt M, Schmid TL, Stierling G. The Ciclovía-Recreativa: A mass-recreational program with public health potential. J Phys Act Health 2010; 7(Suppl 2):S163-180. PMID: 20702905.
[10] Kuhlberg JA, Hipp JA, Eyler A, Chang G. Open Streets initiatives in the United States: Closed to traffic, open to physical activity. J Phys Act Health 2014; 11(8):1468-1474. PMID: 24384529.
[11] Torres A, Sarmiento OL, Stauber C, Zarama R. The Ciclovia and Cicloruta programs: Promising interventions to promote physical activity and social capital in Bogotá, Colombia. Am J Public Health 2013; 103(2):e23-30. PMID: 23237179.
[12] Zieff SG, Kim MS, Wilson J, Tierney P. A "Ciclovia" in San Francisco: Characteristics and physical activity behavior of Sunday Streets participants. J Phys Act Health 2014; 11(2):249-255. PMID: 23363639.
[13] Meisel JD, Sarmiento OL, Montes F, et al. Network analysis of Bogotá's Ciclovía Recreativa, a self-organized multisectorial community program to promote physical activity in a middle-income country. Am J Heal Promot 2014; 28(5):e127-136. PMID: 23971523.
[14] Instituto Distrital de Recreación y Deporte. Historia Ciclovia Bogotana. https://www.idrd.gov.co/historia-ciclovia-bogotana. 2017. Accessed January 2, 2021.
[15] Mejia-Arbelaez C, Sarmiento OL, Vega RM, et al. Social inclusion and physical activity in Ciclovía Recreativa programs in Latin America. Int J Environ Res Public Health 2021; 18(2):655. PMID: 33466637.
[16] Montero S. Worlding Bogotá's Ciclovía: From urban experiment to international "Best Practice". Lat Am Perspect 2016; 44(2):111-131.
[17] Shu S, Batteate C, Cole B, Froines J, Zhu Y. Air quality impacts of a CicLAvia event in downtown Los Angeles, CA. Environ Pollut 2016; 208(Pt A):170-176. PMID: 26493865.
[18] Chaudhuri A, Zieff SG. Do Open Streets initiatives impact local businesses? The case of Sunday Streets in San Francisco, California. J Transp Health 2015; 2(4):529-539.
[19] Zieff S, Chaudhuri A. Sunday Streets SF: An economic impact assessment. March 1, 2013. https://papers.ssrn.com/sol3/papers. Accessed September 30, 2020.
[20] Engelberg JK, Carlson JA, Black ML, Ryan S, Sallis JF. Ciclovía participation and impacts in San Diego, CA: The first CicloSDias. Prev Med 2014; 69(Suppl1):S66-S73. PMID: 25459488.
[21] Torres A, Steward J, Strasser S, Lyn R, Serna R, Stauber C. Atlanta Streets Alive: A movement building a culture of health in an urban environment. J Phys Act Heal 2016; 13(2):239-246. PMID: 26180931.
[22] Hipp JA, Eyler AA, Kuhlberg JA. Target population involvement in Urban Ciclovias: A preliminary evaluation of St. Louis Open Streets. J Urban Health 2013; 90(6):1010-1015. PMID: 22948790.
[23] Salazar-Collier CL, Reininger B, Gowen R, Rodriguez A, Wilkinson A. Evaluation of event physical activity engagement at an Open Streets initiative within a Texas–Mexico border town. J Phys Act Heal 2018; 15(8):605-612. PMID: 29741429.
[24] Erickson C. FREE Open Streets ICT event. https://wichitaonthecheap.com/open-2019. Accessed December 16, 2019.
[25] Wichita's CORE: 2020 Wichita Official Visitors Guide. Wichita, Kansas: Madden Media, LLC, 2020.
[26] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42(2):377-381. PMID: 18929686.
[27] The Streets Plan Collaborative & The Alliance for Biking and Walking. The Open Streets Guide. The Alliance for Biking and Walking. February 2012. https://nacto.org/docs/usdg/smaller_open_streets_guide_final_print_alliance_biking_walking.pdf. Accessed December 16, 2019.

Keywords: physical activities, built environment, businesses, economics

KANSAS JOURNAL of MEDICINE

Analysis of Patient Handoff Between Providers at a Tertiary Urban Medical Center

Candice Metzinger, MS-2[1], Sam Antonios, M.D.[2,3], K. James Kallail, Ph.D.[3,4], Hayrettin Okut, Ph.D.[4], Rosey Zackula, M.A.[4], Brianna Cline, D.O.[3]

[1]University of Kansas School of Medicine-Wichita, Wichita, KS
[2]Ascension Via Christi St. Francis, Wichita, KS
University of Kansas School of Medicine-Wichita, Wichita, KS
[3]Department of Internal Medicine
[4]Office of Research

Received Feb. 7, 2021; Accepted for publication April 14, 2021; Published online Aug. 4, 2021
https://doi.org/10.17161/kjm.vol1415170

ABSTRACT

Introduction. Few studies have quantified the total number of attending and consulting physicians involved in inpatients' care, and no other research quantifies the total number of all providers participating in inpatients' care. The purpose of this study was to calculate the number of attending hand-offs, the attending encounter time, and the total number of providers participating in inpatients' care for all admitted patients at a tertiary urban medical center.

Methods. The study design was an observational retrospective cohort. Subjects included pediatric and adult patients who were admitted to and discharged from Ascension Via Christi St. Francis (AVCSF) in Wichita, Kansas between November 1, 2019 and January 31, 2020. Data were abstracted from the Cerner Electronic Medical Record. Variables included: patient demographics, admitting diagnosis, diagnosis related group (DRG), admission service, and duration of inpatient stay. Provider variables abstracted included provider type and provider specialty. Categorical variables were presented as frequencies and percentages, while continuous variables were presented as means ± standard deviation.

Results. The sample included information from 200 patient charts. Patients' ages ranged from 5 to 94 years, with a mean of 61 years. Approximately 52% were female and 74.9% were admitted to a surgical service. The length of all inpatients' stays ranged from less than 1 day to 31 days, with a mean of 4 days. Seventy-six different DRGs were recorded. The most frequent attending specialties were hospital medicine, internal medicine, general surgery, and interventional cardiology. Consulting physicians had more patient encounters than any other healthcare provider. For all inpatients, an average of two attending physicians participated in care over the duration of their stay with a range of one to six attending physicians. There was an average of one hand-off between attending physicians. Patients had an average of five consulting physicians, two resident physicians, two physician assistants, and two nurse practitioners during a stay. There was an average of 10 total providers, with a range of one to 46 total providers participating in care.

Conclusions. Understanding the provider data surrounding an inpatient stay is a foundational step in assessing the quality of the provider-inpatient encounter and potential areas for improvement. In this study, the average number of attending physicians and handoffs was reasonable; however, the total number of providers involved in care was relatively high. Assessment of staffing and scheduling requirements by hospital administration could identify areas of improvement to reduce the potential for medical error caused by multiple providers being involved in patient care. ***Kans J Med 2021;14:192-196***

INTRODUCTION

During an inpatient stay, more than one healthcare provider participates in patient care.[1] Collectively, these providers form a multidisciplinary healthcare team,[2] lead by the attending physician. This provider is ultimately responsible for the diagnosis, treatment, and management of the patient. Consulting physicians (sometimes referred to as specialists) are those who are highly trained in a specific area of medicine and are utilized by attending physicians to help with diagnosis and treatment of the patient. Resident physicians are licensed physicians participating in further specialty training after completing medical school. Advanced practice professional providers, such as nurse practitioners and physician assistants, have advanced training and assist physicians in the management of patients.

Over the course of an inpatient stay, attending physicians may transfer, or hand-off, care to another physician who assumes the attending physician role. Increased frequencies of hand-offs may lead to medical errors and/or adverse events.[3] The primary causes for these errors and adverse events are low quality hand-off procedures and multiple physicians participating in inpatients' care.[4] The quality and content of patient hand-offs has been studied, especially in emergency departments (ED) and intensive care units (ICU);[3,5] however, there is minimal research investigating the number of attending hand-offs, the length of time an attending is responsible for a patient (defined as attending encounter time), and the total number of providers (physicians and advanced practice professional providers) participating in a patients' care during a hospitalization.[4]

Although some research described the impact of the number of attending physicians on inpatients' outcomes and satisfaction,[6] few quantified the total number of attending and consulting physicians involved in inpatients' care, and no other research quantified the total number of providers participating in inpatients' care, including attending physicians, consulting physicians, resident physicians, physician assistants, and nurse practitioners. Quantitative analysis of attending encounter time, which has the potential to impact the number of attending hand-offs, also is lacking. The purpose of this study was to calculate the number of attending hand-offs, the attending encounter time, and the total number of providers participating in inpatients' care for all admitted patients at a tertiary urban medical center.

METHODS

The study design was an observational retrospective cohort. The study was approved by the Institutional Review Board at Ascension Via Christi.

Participants. Pediatric and adult patients who were admitted to and discharged from Ascension Via Christi St. Francis (AVCSF) in Wichita, Kansas between November 1, 2019 and January 31, 2020 were included in this study. Those who were admitted for labor and delivery, including

the infants born during the admission, were excluded.

Procedures. Data were abstracted from the hospital's electronic medical record. The abstracted variables included: patient demographics (age and sex), admitting diagnosis (ICD-10), diagnosis related group (DRG), admission service (medical or surgical), and duration of inpatient stay (in days). Abstracted provider variables included provider type (e.g., attending physician, nurse practitioner) and provider specialty (e.g., hospitalist, diagnostic radiology, general surgery).

Duration of care was abstracted for attending physicians only. These data were calculated by subtracting intake and hand-off dates. Intake date (defined as the date and time the attending physician assumed responsibility for the patient) was identified in two ways. The admitting physician was identified as the first attending physician, so the admission date and time were recorded as the intake date. If an attending physician was not the admitting physician, the intake date was recorded as the date and time of the provider's first documentation in the patient chart. The date and time recorded as the second attending physician's intake date also was used as the hand-off date for the first attending physician. Patient discharge date and time was recorded as the hand-off date for the last attending physician to document in the chart prior to discharge.

Any repeat attending physicians (i.e., attending physicians who participated in patient care for two non-contiguous periods during the patient stay) were flagged in the database to ensure the repeat instance was subtracted from the total number of providers. All other providers (e.g., consulting physicians, resident physicians, physician assistants, and nurse practitioners) were recorded once, whether or not they had multiple encounters with the patient.

Statistical Analysis. Sample size was determined through a power analysis using summary statistics for 32,342 inpatient discharges over one fiscal year. The length of stay from the summary statistics was assumed to have a lognormal distribution, with the mean length of stay and the coefficient of variation used to estimate sample sizes for different power levels. From these calculations, a power of 0.938 for a sample of 200 patients resulted. A report of all patients admitted and discharged during the study timeframe was produced. A data report generated by AVCSF containing a random sample of 250 patients from the study timeframe was obtained, and the first 200 patients were entered into a REDCap® database.[7] The remaining 50 patients in the report were not included in the initial chart abstraction and were kept as backup in the event that any of the initial 200 patients were excluded from the study. Data were abstracted from patient charts, and REDCap® was used to calculate age at admission, length of stay, attending encounter time, and the number of providers per inpatient stay.

De-identified data were exported from REDCap® into SAS version 9.4 for statistical analysis. Categorical variables were presented as frequencies and percentages, while continuous variables were presented as means ± standard deviation (SD). A 2-sided p value of less than 0.05 was considered statistically significant. Statistical analysis was conducted using SAS 9.4 (SAS 9.4, SAS Inc, Cary, NC, 2020).

RESULTS

Of the initial 200 patient charts that were reviewed, 5.5% (n = 11) were omitted due to admission dates that were prior to the study timeframe. To satisfy the power requirement for statistical significance, 11 additional patient charts from the original randomized report were added to the data abstraction, and the final sample consisted of 200 patient charts.

Patient Characteristics. Patients' ages ranged from 5 to 94 years, with a mean of 61 years (SD = 15.3). Approximately 52% (n = 103) were female and most (74.9%, n = 158) were admitted to a surgical service. When subdivided by admission service, average age was similar to the overall average for medical and surgical patients (62 years and 61 years, respectively). The majority of patients admitted to the surgical service were female (53.8%, n = 85) and the majority of patients admitted to the medical service were male (57.1%, n = 24). The length of all inpatients' stays ranged from less than 1 day to 31 days, with a mean of four days (SD = 3.75). Patients admitted to the medical service had a mean stay of five days (SD = 3.85) and those admitted to the surgical service had a mean stay of four days (SD = 3.75).

There were 76 different Diagnosis Related Groups (DRGs) recorded for this sample. The most frequent for all patients were "Major Hip and Knee Joint Replacement or Reattachment of Lower Extremity without Major Complication or Comorbidity" (12.0%, n = 24), "O.R. Procedures for Obesity without Complication or Comorbidity/Major Complication or Comorbidity" (11.5%, n = 23), "Major Small & Large Bowel Procedures with Complication or Comorbidity" (8.0%, n = 16), and "Major Small & Large Bowel Procedures without Complication or Comorbidity/Major Complication or Comorbidity" (5.0%, n = 10). When subdivided by admission service, patients admitted to the surgical service had the same most frequent DRGs as the total patient population. The most frequent DRGs for patients admitted to the medical service were "Seizures without Major Complication or Comorbidity" (14.3%, n = 6), "Percutaneous Cardiovascular Procedure with Drug Eluting Stent without Major Complication or Comorbidity" (11.9%, n = 5), and "Septicemia or Severe Sepsis without Mechanical Ventilation Greater than 96 Hours" (11.6%, n = 5).

When all DRGs were categorized by Major Diagnostic Categories (MDC), the most frequent were "Diseases & Disorders of the Musculoskeletal System & Connective Tissue" (31.0%, n = 61), "Diseases & Disorders of the Digestive System" (18.0%, n = 35), "Diseases & Disorders of the Circulatory System" (15.0%, n = 30), and "Endocrine, Nutritional & Metabolic Diseases & Disorders" (15.0%, n = 30; Table 1).

Table 1. Major diagnostic categories for all patients.

Major diagnostic categories	Frequency	Percent
08 Diseases & Disorders of the Musculoskeletal System & Connective Tissue	61	30.5%
06 Diseases & Disorders of the Digestive System	35	17.5%
05 Diseases & Disorders of the Circulatory System	30	15.0%
10 Endocrine, Nutritional & Metabolic Diseases & Disorders	30	15.0%
01 Diseases & Disorders of the Nervous System	14	7.0%
All other	30	15.0%

Provider Characteristics. Attending physicians comprised 15.0% (n = 304) of all provider types (Table 2). The most frequent attending specialties for medical patients were hospital medicine (62.0%, n = 49), internal medicine (11.4%, n = 9), general surgery (8.9%, n = 7), and interventional cardiology (7.6%, n = 6). The most frequent attending specialties for surgical patients were general surgery (42.9%, n = 82), orthopedic surgery (23.0%, n = 44), cardiothoracic surgery (11.0%, n = 21), and neurosurgery (9.4%, n = 18; Table 3).

Table 2. Provider type for all patients.

Provider type	Frequency	Percent
Attending Physician	304	15.0%
Consulting Physician	952	46.9%
Resident Physician	291	14.3%
Physician Assistant	150	7.4%
Nurse Practitioner	333	16.4%

Table 3. Attending specialty by service.

Type of service	Frequency	Percent
Medical		
Hospitalist	49	62.0%
Internal Medicine	9	11.4%
General Surgery	7	8.9%
Interventional Cardiology	6	7.6%
Cardiology	4	5.1%
Neuro Critical Care	2	2.5%
Orthopedic Surgery	1	1.3%
Pediatrics	1	1.3%
Surgical		
General Surgery	82	42.9%
Orthopedic Surgery	44	23.0%
Cardiothoracic Surgery	21	11.0%
Neurosurgery	18	9.4%
Interventional Cardiology	11	5.8%
Vascular Surgery	10	5.2%
Plastic Surgery	2	1.0%
Urology	2	1.0%
Cardiology	1	0.5%

Consulting physicians had more patient encounters than any other healthcare provider, comprising 46.9% (n = 952) of all providers in the study (Table 2). The most frequent consultant specialties for medical patients were nephrology (9.2%, n = 20), cardiology (8.3%, n = 18), and pulmonary disease (5.0%, n = 11; Table 4). The most frequent consultant specialties for surgical patients were cardiology (8.7%, n = 64), hospital medicine (8.7%, n = 64), and interventional cardiology (4.2%, n = 31). Diagnostic radiology and anesthesiology were counted as consultant specialties during chart abstraction and represented large frequencies of consultants for both medical and surgical patients; however, these specialties were included in the "All Other" category because these physicians are inherent to the inpatient experience and are not considered consultants in the traditional sense (Table 4).

Table 4. Consulting specialty by service.

Type of service	Frequency	Percent
Medical		
Nephrology	20	9.2%
Cardiology	18	8.3%
Pulmonary Disease	11	5.0%
General Surgery	10	4.6%
Infectious Diseases	10	4.6%
Cardiology Electrophysiology	9	4.1%
Interventional Cardiology	9	4.1%
Neurology	8	3.7%
All other	113	56.4%
Surgical		
Cardiology	64	8.7%
Hospitalist	64	8.7%
Interventional Cardiology	31	4.2%
Pathology	21	2.9%
Pulmonary Disease	16	2.2%
All other	491	73.2%

Resident physicians accounted for 14.3% (n = 291) of the total providers, and of the advanced practice professional providers, nurse practitioners had the most patient encounters (16.4%, n = 333; Table 2). For all providers, including attending physicians, consulting physicians, resident physicians, physician assistants, and nurse practitioners, the most represented specialties were anesthesiology (22.3%, n = 453), diagnostic radiology (17.6%, n = 358), general surgery (12.2%, n = 247), and hospital medicine (10.7%, n = 217).

For all inpatients, an average of two (SD = 1.0) attending physicians participated in care over the duration of their stay with a range of one to six attending physicians. There was an average of one (SD = 1.0) handoff between attending physicians. The mean duration of an attending physician encounter was 94.5 hours (SD = 90.0) for all inpatients. Patients in the study had an average of five (SD = 4.4) consulting physicians, two (SD = 2.0) resident physicians, two (SD = 0.9) physician assistants, and two (SD = 1.7) nurse practitioners during a stay. There was an average of 10 total providers (SD = 6.6), with a range of 1 to 46 total providers participating in care.

DISCUSSION

Patients admitted to a midwestern tertiary medical center with approximately 400 inpatient beds had an average of 10 healthcare providers. The patient population's demographics were comparable to both state and national inpatient demographics from the Healthcare Cost and Utilization Project (HCUP), a federal aggregation of state inpatient data.[8] The majority of the current study population was female (52%), which was similar to both national (56.7%) and state (58.3%) HCUP inpatient data and paralleled estimated 2019 census information for Sedgwick County, Kansas where approximately half

(50.6%) of the population was female.[9] However, the current study reported a mean age of 61 years, whereas national and state HCUP inpatient data reported 49 years as the mean age.[8] This difference in age could be attributed to the timeframe of the study; the sample included patients hospitalized from November through January. Hospital admissions increase during the winter months, with the largest increase seen in patients 65 years or older.[10] The difference in the average age of patients also could relate to insurance. Most individuals meet their insurance deductibles by the end of the calendar year, and some choose to undergo non-emergent elective procedures during this time. As the main consumers of elective orthopedic procedures are the elderly,[11] this could explain the shift in the current study's demographics, especially considering that most patients were admitted to a surgical service.

The two most frequent MDCs under which patients were admitted were "Diseases and Disorders of the Musculoskeletal System and Connective Tissue" and "Diseases and Disorders of the Digestive System". Most of these MDCs included DRGs for surgical procedures. This result was concordant with 2016 national and state HCUP data, which ranked "Diseases and Disorders of the Musculoskeletal System and Connective Tissue" as the fourth most frequent MDC and "Diseases and Disorders of the Digestive System" as the sixth most frequent MDC for discharged patients.[8]

In the current study, the mean length of stay (LOS) was four days. This was slightly less than the mean LOS from national and state HCUP data reported in 2016 (4.6 and 4.3 days, respectively), as well as the American Hospital Association's data from 2018 (4.9 days).[8,12] This difference could be explained by the high volume of patients admitted to the hospital for elective surgery. In addition to the most common MDC, "Diseases and Disorders of the Musculoskeletal System and Connective Tissue" (the majority of which include surgical procedures), another common MDC in the current study, "Endocrine, Nutritional & Metabolic Diseases & Disorders", includes procedures for the treatment of obesity and laparoscopic gastric bypass surgeries, which account for most bariatric procedures and have a mean LOS of two days.[13] Although mean LOS data vary for orthopedic- and abdominal-related elective surgeries, patients in high income countries who are admitted for these procedures have better outcomes and fewer postoperative complications,[11,14-17] which could decrease the amount of time needed for inpatient postoperative recovery.

Co-management of surgical patients, where hospitalists and surgeons partner in the leadership of inpatient care during the perioperative period, was demonstrated in the current study. Aside from anesthesiology and diagnostic radiology, hospitalist medicine was one of the most frequent consultant physician specialties for patients admitted to the surgical service. This style of patient management has been studied frequently in the setting of orthopedic and neurosurgery with varying results;[18] however, a 2015 study reported that co-management in orthopedic and neurosurgical patients significantly decreased the proportion of patients with at least one postoperative medical complication.[19] Another study reported a decrease in one-year mortality in geriatric patients with hip fractures who were co-managed in an "orthogeriatric" team. These patients also showed better functional outcomes and a decreased risk of additional fractures.[20] When taking into account that the majority of the patients in the current study were surgical patients undergoing orthopedic procedures, it is understandable that hospitalists would participate frequently in patient care to maximize patient outcomes.

The current study suggested there was an average of two attending physicians per patient stay, with one handoff between them. This result was concordant with similar research. In one study, inpatients admitted for pneumonia and heart failure had, on average, 2.05 and 1.78 hospitalists per stay, respectively.[1] A 2016 study of patients with hospital stays longer than 21 days reported a mean number of attending and consulting physicians during the entire stay of 4.5 and 7.3, respectively.[6]

Implications and Future Research. This quantification of attending physicians, attending encounter time, total providers, and number of handoffs for inpatients' stays is a critical quality improvement and research metric. When more providers participate in patient care, length of inpatients' stays are longer, and patients' satisfaction with physician-to-patient communication is poorer.[1,6] Identification of these variables is a foundational step in the improvement of healthcare delivery and patient satisfaction. For example, one study indicated that a relatively simple intervention of scheduling emergency department providers in overlapping shifts resulted in a 25% reduction in patient hand-offs, a decrease in 72-hour patient readmissions, improved charting times, and improved provider satisfaction.[4]

This study functions as a starting point for further research into quantifiable provider data and the impact of this data on inpatients' experience. As national healthcare spending is projected to grow to 20% of the total national gross domestic product by the year 2025,[21] careful analysis of resources used during an inpatient stay could help to control costs. Future research could investigate the number and types of providers participating in the care of patients admitted for specific MDCs and/or DRG; it also could hone the focus on specific outcomes like expenditures or patient mortality. Other future research could identify if communication gaps between providers exist, the effect(s) of these gaps on inpatients' care and indicate where process improvements could be initiated to maximize both inpatients' outcomes and the use of healthcare resources.

Limitations. There are several limitations that must be acknowledged. First, more medically complex patients inherently will require longer lengths of stay, more providers, and more handoffs. This inherent limitation to the study may have influenced the statistical interpretation of the data. Another limitation arises when considering that aggregate data for both medical and surgical patients were analyzed as one group. Again, because these groups may have inherent differences in the composition of their care teams and the amount/type of care needed, this may have skewed certain results such as number of attending physicians and total providers, length of stay, and attending encounter duration. Future studies can improve these limitations by stratifying patients per admission service (medical or surgical) or by analyzing specific DRGs/MDCs.

CONCLUSIONS

Understanding the quantitative provider data surrounding an inpatient stay is a foundational step in assessing the quality of the provider-inpatient encounter and potential areas for improvement. In this study, the average number of attending physicians and handoffs were reasonable; however, the total number of providers (including attending physicians, consulting physicians, resident physicians, and advanced practice professionals) involved in care were relatively high. Assessment of staffing and scheduling requirements by hospital administration could identify areas of improvement to reduce the potential for medical error caused by multiple providers being involved in patient care.

REFERENCES

[1] Epstein K, Juarez E, Epstein A, Loya K, Singer A. The impact of fragmentation of hospitalist care on length of stay. J Hosp Med 2010; 5(6):335-338. PMID: 20803671.
[2] Traub O. Hospital Care Team Members. https://www.merckmanuals.com/home/special-subjects/hospital-care/hospital-care-team-members#. 2018. Accessed June 26, 2020.
[3] Colvin MO, Eisen LA, Gong MN. Improving the patient handoff process in the intensive care unit: Keys to reducing errors and improving outcomes. Semin Respir Crit Care Med 2016; 37(1):96-106. PMID: 26820277.
[4] Yoshida H, Rutman LE, Chen J, et al. Waterfalls and handoffs: A novel physician staffing model to decrease handoffs in a pediatric emergency department. Ann Emerg Med 2019; 73(3):248-254. PMID: 30287122.
[5] Cheung DS, Kelly JJ, Beach C, et al. Improving handoffs in the emergency department. Ann Emerg Med 2010; 55(2):171-180. PMID: 19800711.
[6] Schmocker RK, Holden SE, Vang X, et al. The number of inpatient consultations is negatively correlated with patient satisfaction in patients with prolonged hospital stays. Am J Surg 2016; 212(2):282-288. PMID: 26792276.
[7] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42(2):377-381. PMID: 18929686.
[8] U.S. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project. https://hcupnet.ahrq.gov/#setup. Accessed July 26, 2020.
[9] U.S. Census Bureau. Quick Facts: Sedgwick County, Kansas; Kansas. https://www.census.gov/quickfacts/fact/table/sedgwickcountykansas,KS/PST045219. 2019. Accessed July 10, 2020.
[10] Patterson S. Do hospital admission rates increase in colder winters? A decadal analysis from an eastern county in England. J Public Health (Oxf) 2018; 40(2):221-228. PMID: 29106572.
[11] McDermott K, Freeman WJ, Elixhauser A. Overview of Operating Room Procedures During Inpatient Stays in U.S. Hospitals, 2014: Statistical Brief #233. 2017. In: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US), 2006. https://www.ncbi.nlm.nih.gov/books/NBK487976/. Accessed February 9, 2021.
[12] American Hospital Association. AHA Hospital Statistics. https://guide.prod.iam.aha.org/stats/states. 2021. Accessed July 25, 2020.
[13] Baker MT, Lara MD, Larson CJ, Lambert PJ, Mathiason MA, Kothari SN. Length of stay and impact on readmission rates after laparoscopic gastric bypass. Surg Obes Relat Dis 2006; 2(4):435-439. PMID: 16925375.
[14] Moghadamyeghaneh Z, Carmichael JC, Smith BR, et al. A comparison of outcomes of emergent, urgent, and elective surgical treatment of diverticulitis. Am J Surg 2015; 210(5):838-845. PMID: 26116319.
[15] International Surgical Outcomes Study Group. Global patient outcomes after elective surgery: Prospective cohort study in 27 low-, middle- and high-income countries. Br J Anaesth 2016; 117(5):601-609. PMID: 27799174.
[16] Le Manach Y, Collins G, Bhandari M, et al. Outcomes after hip fracture surgery compared with elective total hip replacement. JAMA 2015; 314(11):1159-1166. PMID: 26372585.
[17] Beverly A, Brovman EY, Urman RD. Comparison of postoperative outcomes in elderly patients with a do-not-resuscitate order undergoing elective and nonelective hip surgery. Geriatr Orthop Surg Rehabil 2017; 8(2):78-86. PMID: 28540112.
[18] Auerbach AD, Wachter RM, Cheng HQ, et al. Comanagement of surgical patients between neurosurgeons and hospitalists. Arch Intern Med 2010; 170(22):2004-2010. PMID: 21149758.
[19] Rohatgi N, Loftus P, Grujic O, Cullen M, Hopkins J, Ahuja N. Surgical comanagement by hospitalists improves patient outcomes: A propensity score analysis. Ann Surg 2016; 264(2):275-282. PMID: 26764873.
[20] Gosch M, Hoffmann-Weltin Y, Roth T, Blauth M, Nicholas JA, Kammerlander C. Orthogeriatric co-management improves the outcome of long-term care residents with fragility fractures. Arch Orthop Trauma Surg 2016; 136(10):1403-1409. PMID: 27501701.
[21] U.S. Centers for Medicare and Medicaid Services. National Health Expenditure Data. https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata. 2019. Accessed July 27, 2020.

Keywords: patient handoff, health care providers, inpatients, tertiary healthcare

KANSAS JOURNAL of MEDICINE

How Much Education and Training do Residents Across Specialties Receive in Neuropsychology?

Seher Chowhan, D.O.[1], Phillip K. Martin, Ph.D.[1], Matthew Macaluso, D.O.[2], Christina Bowman, M.D.[1], Ryan W. Schroeder, Psy.D.[1]

[1]University of Kansas School of Medicine-Wichita, Wichita, KS
Department of Psychiatry and Behavioral Sciences

[2]The University of Alabama at Birmingham School of Medicine, Birmingham, AL
Department of Psychiatry and Behavioral Neurobiology

Received Feb. 13, 2021; Accepted for publication April 16, 2021; Published online Aug. 4, 2021
https://doi.org/10.17161/kjm.vol1415200

ABSTRACT

Introduction. Neuropsychologists play an important role on multidisciplinary teams with physicians from multiple specialties. The extent of residency training on the use of neuropsychological services is unclear. Medical residents across multiple specialties throughout the United States were surveyed to assess resident education, training, and understanding of neuropsychological services, along with their intent to consult neuropsychologists in the future.

Methods. A survey was sent to residents in accredited psychiatry, neurology, family medicine, and internal medicine programs. After data were collected, chi-square group level analyses with post-hoc pairwise comparisons were used to analyze the data.

Results. A total of 434 residents took the survey. The proportion of residents exposed to neuropsychology during residency varied significantly according to specialty (χ^2 (3, N = 419) = 51.4, p < 0.001), with more psychiatry and neurology residents reporting exposure than residents in family medicine or internal medicine. Similarly, the proportion of psychiatry and neurology residents who 'agree' or 'strongly agree' that they understand the nature of neuropsychological services differed significantly from family medicine and internal medicine residents (χ^2 (3, N = 415) = 40.4, p < 0.001). The majority of residents across all specialties (85.7%) reported they are likely to consult/order neuropsychological services in future practice.

Conclusions. The majority of residents in all specialties reported exposure to neuropsychological services in some manner, but forms of exposure varied. Results indicated a need for increased education and training in neuropsychological services, especially within family medicine and internal medicine programs. ***Kans J Med 2021;14:197-200***

INTRODUCTION

Clinical neuropsychology is a sub-specialty of clinical psychology that applies an understanding of brain-behavior relationships to the evaluation of cognitive, behavioral, and emotional disorders, typically by use of standardized assessments.[1] According to Schoenberg and Scott, patients typically are referred for neuropsychological evaluations for (1) diagnostic clarification, (2) description of neuropsychological status, (3) treatment planning/program placement (e.g., nursing home placement), (4) monitoring effects of treatment, (5) identification of underlying processes for cognition and/or effects of treatments/other agents, and (6) forensic applications.[2]

Physicians from multiple specialties refer patients to neuropsychologists, with neuropsychologists receiving most of their referrals from neurologists, psychiatrists, and primary care physicians.[3] In a survey of physicians, the majority of respondents (89%) reported that they had referred patients for neuropsychological evaluations.[4] When broken down by physician specialty type, anywhere from 99% (neurologists) to 70% (primary care physicians) of responding physicians indicated they had referred patients to neuropsychologists. Previous surveys also documented that neuropsychological services are viewed positively by physicians and that neuropsychological evaluation results, when available, often are incorporated into patient treatment plans. For example, one study examining the use of neuropsychology services in inpatient hospital care showed that 78% of discharge summaries included information regarding the neuropsychological evaluation and that placement outcomes coincided with neuropsychology recommendations 80% of the time.[5]

Although past research has examined physician's attitudes and practices regarding utilization of neuropsychological services, no such studies have been conducted with medical residents. Additionally, it is unknown to what degree medical residents are exposed to neuropsychology during residency or whether residents' exposure to and understanding of neuropsychology differs according to specialty. Therefore, the objective of this study was to assess resident exposure to and understanding of neuropsychological services across residency specialties. By doing so, the study aimed to identify avenues for further development in current residency training curriculum.

METHODS

A survey study was developed, which included multiple questions including those related to demographic information (i.e., degree, residency year, residency specialty, and region), type of exposure to neuropsychology, understanding of neuropsychological services, and likelihood of utilizing neuropsychology services in future practice. With regard to demographic information and items about exposure to neuropsychology, questions were asked in a "select all that apply" format. With regard to questions relating to understanding of neuropsychological services and likelihood of utilizing neuropsychological services, Likert scales were utilized, allowing survey respondents to select "Strongly Agree", "Agree", "Disagree", and "Strongly Disagree".[6] Responses to the survey were collected and managed using Research Electronic Data Capture (REDCap®) tools hosted at the author's institution. REDCap® is a secure, web-based application designed to support data capture for research studies.[7] No identifying information was asked in the questionnaire. Survey data was stored on REDCap® and data analyses were conducted in IBM SPSS Statistics Version 23.

Coordinators of accredited residency training programs were identified using the lists available at the Accreditation Council for Graduate Medical Education (ACGME) website. The initial invitation to participate in the study was emailed to 1,420 residency program coordinators across residency programs training in psychiatry, neurology, internal medicine, and family medicine, and they were asked to distribute the

survey to residents in their program. Those coordinators not wishing to participate were allowed to opt out without consequence. The survey originally was sent to coordinators on February 1, 2019. Upon receiving the email, residents were self-selected by clicking "yes" or "no" in providing consent, which was the opening screen on the e-survey. The survey instructions stated that responses were anonymous, that participation was optional, and that the survey would take about three to five minutes. Access to the survey was only granted to those residents who consented to participate. Participants were encouraged to fill out the survey completely, but were not required to answer all questions to complete the survey. Two subsequent reminder emails were sent approximately one week apart, and data collection ended February 28, 2019. The study utilized a convenience sample comprised of residents who both opened the survey and decided to respond.

Based on a prior survey conducted using a similar format, a power analysis conducted in IBM® SPSS Sample Power, found that a minimum of 328 resident responses would be required to have power at 90%.[8] In total, 434 residents ultimately completed the survey. Data were not collected regarding the number of residency programs who elected to disseminate the survey to their residents or the number of residents who ultimately received the survey email. Of the residents who received the survey, there was no way of knowing how many opened the email and were aware of the survey. As such, neither a program participation rate nor a survey response rate could be calculated.

Consenting respondents' data were summarized and reported as frequency and percentages. Descriptive statistics overall and by medical subspecialty were conducted on all responses. To allow for easier comparison and given that some cells contained very few participants, Likert scale-based response sets were collapsed into the binary categories of agree/strongly agree and disagree/strongly disagree. Comparisons were made between the four medical specialties using Chi-square tests at $p < 0.01$, using this more stringent critical value to account for inflated familywise error rate in the context of multiple comparisons. The local Institutional Review Board approved the design and conduct of the study.

RESULTS

A total of 434 residents consented: 70% MDs, 27.7% DOs, 2.3% other; 35.1% were first year residents, 31.4% second year residents, 23.6% third year residents, 9.0% fourth year residents, and 0.9% did not indicate their year of training. By specialty, 22.4% were from psychiatry programs (n = 97), 32.8% were from family medicine programs (n = 142), 30.0% were from internal medicine programs (n = 130), 11.5% were from neurology programs (n = 50), and 3.2% (n = 14) did not indicate their specialty. By region, 27.1% (n = 117) were from the Northeast, 21.8% (n = 94) were from the Southeast, 36.4% (n = 157) were from the Midwest, 5.8% (n = 25) were from the Southwest, and 8.8% (n = 38) were from the West.

The proportion of residents exposed to neuropsychology during residency varied significantly according to resident specialty (χ^2 (3, N = 419) = 51.4, $p < 0.001$). Psychiatry (96.9%) and neurology (90.0%) residents did not differ significantly regarding exposure to neuropsychology; however, more psychiatry and neurology residents reported exposure to neuropsychology during residency than residents in family medicine (71.8%) or internal medicine (58.8%; $p < 0.01$). As noted in Table 1, common avenues for exposure, irrespective of specialty, included clinical experiences where neuropsychological services were utilized (32.5%), didactics (31.8%), writing orders for neuropsychological evaluations (30.9%), and reading of the medical literature (28.8%).

Table 1. Exposure to neuropsychology during residency by specialty*.

Forms of exposure	Neuro	Psych	FM	IM	Total
Any exposure	90%	97%	72%	59%	76%
Multiple lectures, seminars, or other didactic teaching	48%	59%	28%	9%	32%
A clinical rotation or other clinical experience in which neuropsychological services were ordered or utilized	40%	57%	24%	18%	33%
Writing orders/consultations for neuropsychological evaluations	36%	56%	23%	19%	31%
Reading of medical literature	30%	49%	21%	21%	29%
A single lecture, seminar, or other didactic teaching	12%	11%	20%	11%	14%
A clinical rotation or other clinical experience in which shadowing of a neuropsychologist occurred	16%	23%	8%	4%	11%
Other	2%	2%	0%	1%	1%

*Neurology, Psychiatry, Family Medicine, Internal Medicine

Differences between specialties were found regarding the proportion of residents who 'agree' or 'strongly agree' that they understand the nature of services provided by a neuropsychologist (χ^2 (3, N = 415) = 40.4, $p < 0.001$). Pairwise comparisons found psychiatry (76.3%) and neurology (71.4%) residents more commonly agree or strongly agree that they "understand the nature of the services provided by a neuropsychologist" than family medicine (48.6%) and internal medicine (38.0%) residents ($p < 0.01$), with the overall proportion of residents (55.0%) reporting they understand the nature and services provided by neuropsychology. Regardless, the majority of residents across specialties (85.7%) reported that they are likely to consult/order neuropsychological services when they practice independently, with psychiatry (95.9%), neurology (87.8%), family medicine (85.7%), and internal medicine (78.3%) agreeing, by specialty. Psychiatry residents indicated being more likely to consult neuropsychology than internal medicine residents (χ^2 (1, N = 226) = 14.1, $p < 0.001$), with other group differences being non-significant.

DISCUSSION

The majority of residents from neurology, psychiatry, family medicine, and internal medicine residency programs were exposed to neuropsychology during residency through some combination of clinical experiences, didactics, writing orders/referring patients, and/or reading medical literature. That said, some residents reported having

no exposure to neuropsychology, with residents in internal medicine and family medicine, particularly, being less likely to be exposed than residents in psychiatry and neurology. This disparity in training experience is likely due to various factors. For one, psychiatry and neurology specialties are more likely to consult neuropsychology due to overlapping patient populations: both psychiatry and neurology specialties commonly evaluate and treat patients with dementia, mild cognitive impairment, stroke, traumatic brain injury, psychiatric disturbance, and delirium/encephalopathy. Patients with such conditions are more likely to be referred to neuropsychology to clarify diagnoses, identify salient personality and emotional features, assess capacity to make decisions, aid in treatment strategies, and provide guidance in potential placement. A previous study revealed that physicians in the acute inpatient hospital setting documented specific neuropsychological evaluation recommendations 68% of the time in discharge summaries, with placement outcomes consistent with explicit recommendations 80% of the time.[5] Second, academic medical centers are more likely to have neuropsychologists on faculty within neurology or psychiatry departments than other departments (e.g., family medicine). Thus, residents in psychiatry and neurology departments are more likely to interact both clinically and academically with neuropsychology faculty.

Unsurprisingly, the results indicated that residents within those specialties with more exposure to neuropsychology (i.e., neurology and psychiatry) were more likely to report understanding neuropsychological services than those residents within specialties reporting less exposure (i.e., family medicine and internal medicine). These findings would suggest that increasing exposure to neuropsychology via formal education or clinical practice might enhance residents' understanding of neuropsychological services.

An interesting finding of this study was that a greater proportion of residents indicated that they likely would refer to neuropsychologists than those who indicated that they understood the services provided by neuropsychologists. This was true both of the overall sample and for each specialty. This finding appeared to signify a couple of points: first, that the neuropsychology field is regarded positively even if not fully understood; and second, that residents across these four specialties believe they would have a need to utilize neuropsychology services in practice. Despite this finding, successful utilization of any clinical diagnostic service, including neuropsychology, likely requires some understanding of how that service can enhance patient care and for which patient groups the service is appropriate. Thus, the finding that less than 50% of internal medicine and family medicine residents reported that they understand the nature of the services provided by neuropsychology could portend poor utilization of neuropsychological services despite residents indicating that they would likely refer.

When combined, the findings suggested a need and potential opportunity to increase knowledge of neuropsychological services in residencies within family medicine and internal medicine by increasing exposure. It is likely important that family medicine and internal medicine residents understand neuropsychological services given that primary care physicians are commonly first-line providers when patients first experience cognitive and psychiatric symptoms.[1] Further, previous research indicated that when primary care physicians refer patients for neuropsychological services, the vast majority find the evaluations to be helpful.[3,4] Given the demonstrated significance of neuropsychological services in family medicine and internal medicine care, the current findings suggested that exposure to neuropsychology should be increased in family medicine and internal medicine residencies. The various formats of exposure noted in this survey study could serve as a guide for residency programs for how further education regarding neuropsychological services might be provided.

There are several limitations in this survey study. Although we sought to determine and contact an inclusive list of residency program directors, there was no means of determining how many program directors forwarded the survey to their residents. Of the residents who received the survey, there was no way of knowing how many opened the email and were aware of the survey. This approach was utilized to increase the overall number of respondents; however, the number of residents who saw the survey email but neglected to respond is unknown, which precludes calculation of a response rate. Additionally, the possibility that the results were impacted by selection bias cannot be excluded. For example, program directors more familiar with neuropsychology or with specific perceptions of neuropsychology might have been more likely to forward the survey and encourage residents to complete it. Similarly, it is possible that residents already familiar with neuropsychological services were more likely to complete the survey than those with less experience or with less favorable opinions.

CONCLUSIONS

While the majority of residents in all specialties reported being exposed to neuropsychological services in some manner, specific types of exposure varied. Results indicated an increased need for specific types of education and training in neuropsychological services, especially within family medicine and internal medicine programs where residents less clearly understand the use of neuropsychological services. Interestingly, despite not having a clear understanding of neuropsychological services, the majority of these residents still agreed that they would utilize them in future practice.

REFERENCES

[1] Schroeder RW, Martin PK, Walling A. Neuropsychological evaluations in adults. Am Fam Physician 2019; 99(2):101-108. PMID: 30633479.
[2] Schoenberg MR, Scott JG. The Little Black Book of Neuropsychology: A Syndrome-Based Approach. New York: Springer Science+Business Media, LLC, 2011. ISBN 978-0-387-70703-7.
[3] Sweet JJ, Benson LM, Nelson NW, Moberg PJ. The American Academy of Clinical Neuropsychology, National Academy of Neuropsychology, and Society for Clinical Neuropsychology (APA Division 40) 2015 TCN professional practice and 'salary survey': Professional practices, beliefs, and incomes of U.S. neuropsychologists. Clin Neuropsychol 2015; 29(8):1069-1162. PMID: 26878229.
[4] Temple RO, Carvalho J, Tremont G. A national survey of physicians' use of and satisfaction with neuropsychological services. Arch Clin Neuropsychol 2006; 21(5):371-382. PMID: 16844340.

[5] Bishop CL, Temple RO, Tremont G, Westervelt HJ, Stern RA. Utility of the neuropsychological evaluation in an acute medical hospital. Clin Neuropsychol 2003; 17(4):468-473. PMID: 15168912.
[6] Burns KE, Duffett M, Kho ME, et al. A guide for the design and conduct of self-administered surveys of clinicians. CMAJ 2008; 179(3):245-252. PMID: 18663204.
[7] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42(2):377-381. PMID: 18929686.
[8] Bowman C, Zackula R, Nutting R, Macaluso M. Perceptions among family medicine residents: The quantity, quality, and effectiveness of training on diagnosing and treating mental disorders. 2018 Annual Meeting of the American Association of Directors of Psychiatry Residency Training. New Orleans, LA. March 1, 2018.

Keywords: neuropsychology, internship and residency, curriculum, education, surveys and questionnaires

KANSAS JOURNAL of MEDICINE

A Case of Autoimmune Myocarditis Treated with IL-17 Inhibition

Atieh Jibbe, M.D.[1], Brett C. Neill, M.D.[1], Anand Rajpara, M.D.[1], Jacob Whitsitt, M.D.[2], Mark Hamblin, M.D.[1]
[1]University of Kansas Medical Center, Kansas City, KS
Department of Internal Medicine, Division of Dermatology
[2]UCHealth Cherry Creek Medical Center, Denver, CO

Received Feb. 24, 2021; Accepted for publication April 7, 2021; Published online Aug. 4, 2021
https://doi.org/10.17161/kjm.vol1415225

INTRODUCTION

Myocarditis is an inflammatory process affecting the heart muscle.[1] Myocarditis, however, occurs because of an external antigen exposure, such as viruses, bacteria, fungi, parasites, toxins, or drugs, with viruses being the most common, or internal triggers.[2,3] Autoimmune myocarditis can occur as an isolated entity in which the primary targeted organ is the heart, as is seen in giant cell myocarditis and eosinophilic myocarditis, or as part of a systemic autoimmune disease which can affect heart tissues, generating myocarditis in the context of a broader autoimmune phenomenon.[1] These diseases include systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, Sjogren's syndrome, vasculitis, polymyositis, and psoriasis as seen in our case.[1,4,5] There is a surplus of literature detailing the specific immune mechanism targets in autoimmune myocarditis including that of the Th17 and IL-17 mediated pathways. A case of a patient diagnosed with autoimmune myocarditis in the setting of psoriasis was treated successfully with the IL-17 inhibitor, secukinumab, thus directly targeting the immune mechanisms found to be involved in autoimmune myocarditis and its progression.

CASE REPORT

A 35-year-old woman presented with heart palpitations and excessive fatigue. She had frequent premature ventricular contractions (PVCs) with no apparent cause which eventually self-resolved. One year later, she developed new onset shortness of breath and had a recurrence of heart palpitations with Holter monitoring revealing occasional to frequent single, unifocal PVCs. She was started on flecainide 50 mg twice daily, which controlled her PVCs. Symptomatic PVCs recurred anytime flecainide was held.

She underwent an electrophysiologic study which mapped PVCs to the anteroseptal right ventricular outflow tract region. This area was ablated with symptoms controlled, and flecainide was discontinued.

A few months after the ablation, the patient experienced recurrent palpitations. Holter monitoring showed frequent monomorphic PVCs and a PVC burden at 20%. The patient was re-started on flecainide 50 mg twice daily. At this time, she underwent advanced imaging studies to evaluate the possibility of myocarditis. A fluorine-18, fluoro-deoxyglucose (18f-FDG) PET-CT scan showed diffuse heterogeneous increased FDG uptake involving the left ventricular myocardium, involving the mid-basal inferolateral wall of the left ventricle with a standardized uptake value (SUV) max of 12.83. The max SUV at basal septal wall was 8.8 and apex was 10.24 (Figure 1).

Given the presence of myocarditis on PET imaging, she underwent a comprehensive workup to rule out alternative causes of myocarditis. Cardiac biomarkers were unremarkable with a troponin of 0 ng/mL and a brain natriuretic peptide less than 15 pg/ml. Extensive workup for viral etiologies was unremarkable.

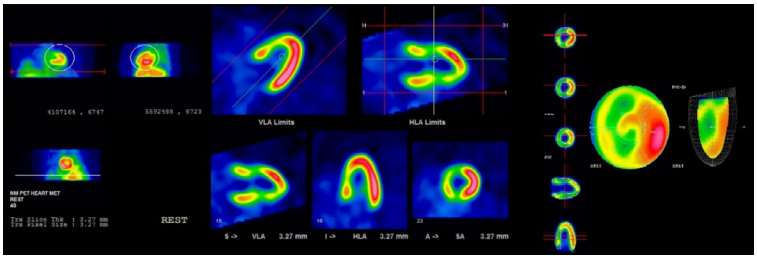


Figure 1. Increased diffuse heterogeneous increased fluoro-deoxyglucose uptake involving the left ventricular myocardium which was consistent with moderate acute myocarditis. No metabolically active mediastinal or hilar nodes, or pulmonary nodules noted.

The patient's autoimmune serologies revealed only a mildly elevated antinuclear antibody panel of 80. CT imaging of the chest, abdomen, and pelvis was within normal limits. A stress test was negative for ischemia and showed left ventricular volume decrease and systolic function that improved with exercise. PVCs only were noted at rest but did not appear during exercise. A 2D Doppler echocardiogram showed normal left ventricular function with an ejection fraction of 55%. Of note, she had a past medical history of psoriasis since early childhood and was being treated with apremilast and narrowband ultraviolet phototherapy at that time.

The negative laboratory evaluation and lack of other clinical signs and symptoms led to the diagnosis of an autoimmune myocarditis secondary to psoriasis. She was started on 30 mg prednisone. PVCs improved, but due to weight gain and hyperglycemia, methotrexate was added a few months later. Repeat cardiac 18f-FDG PET-CT showed persistent disease with a similar uptake pattern. The max SUV in the left basal lateral ventricular myocardium improved from 12.83 to 7.20 (Figure 2).

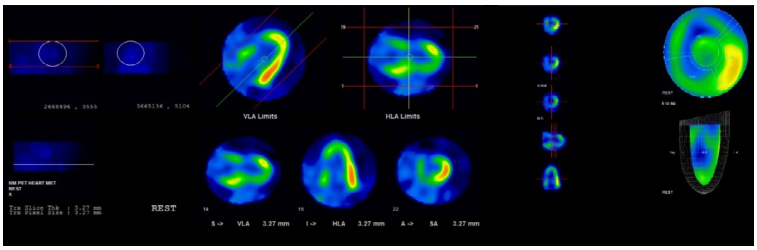


Figure 2. Continued heterogeneous uptake throughout the left ventricular myocardium suggestive of myocarditis.

Despite six months of treatment with methotrexate, the patient's PVC burden increased anytime her prednisone was decreased below 20 mg daily. Our multidisciplinary team attempted biologic therapy to treat the myocarditis. She was treated initially with adalimumab, but she could not tolerate it after two months, developing chest pain, shortness of breath, headache, and dizziness. Adalimumab and methotrexate were discontinued, and she was started on secukinumab 150 mg every two weeks. Within a month of therapy, the patient noticed significant improvement in her psoriasis and PVC burden. She was able to taper prednisone, but palpitations recurred when prednisone was tapered below 10 mg daily. Methotrexate was restarted two months after start-

ing secukinumab, and she was able to taper prednisone further. She had repeat cardiac PET imaging, which showed near complete resolution of the myocarditis (Figure 3). A repeat Holter monitor showed near complete resolution of PVC burden.

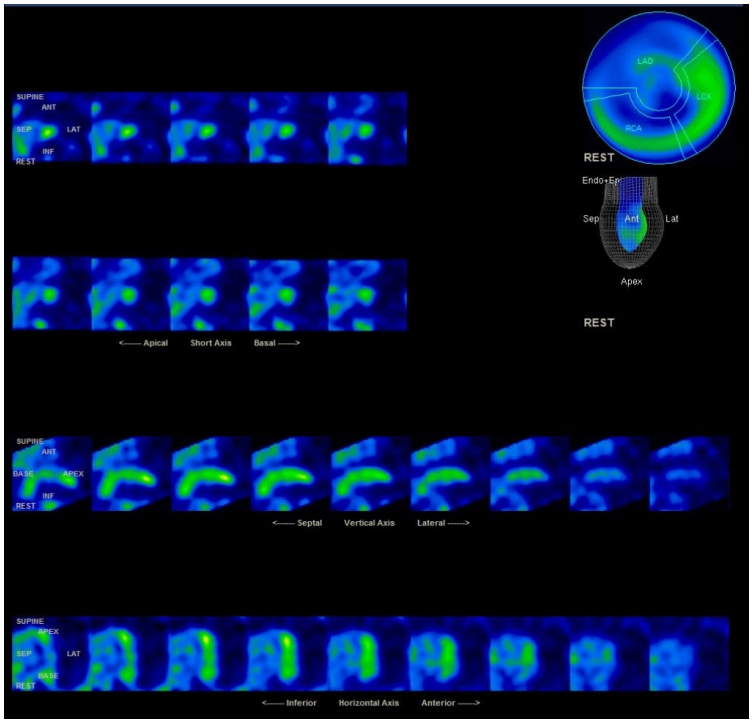


Figure 3. Near complete resolution of increased uptake in the left ventricular myocardium reflective of favorable response to therapy.

DISCUSSION

The PET imaging consistent with acute myocarditis along with an extensive negative workup (negative autoimmune and viral serologies) led to a diagnosis of autoimmune myocarditis secondary to psoriasis. The possibility of a viral myocarditis cannot be ruled out, though it is unlikely as there was no acute episode at onset of symptoms, and the symptoms were progressive and developed insidiously.

Psoriasis is an inflammatory disease with IL-17 as the major effector cytokine in its pathogenesis.[6] Similarly, the Th17 arm of the immune system is linked to the pathogenesis of myocarditis and dilated cardiomyopathy (DCM), which would explain both the likely etiology of the autoimmune myocarditis, and the success of treatment with secukinumab, an IL-17 inhibitor.

Several studies have utilized a mouse model, experimental autoimmune myocarditis (EAM), to establish the connection between Th17 cells and IL-17 cytokines in the development of autoimmune myocarditis and its progression to DCM.[1,7-11] Targeting of IL-17 and subsequent improvement of myocarditis in EAM mice suggested a role for direct inhibition of IL-17 in human patients with myocarditis. In multiple studies, Th17 cells were elevated in patients with myocarditis and DCM.[7-11] Elevated Th17 cells correlated with heart failure were evidenced by the fact that biopsies with detectable IL-17A+ cells trended toward heavier fibrosis, while biopsies with no detectable IL-17A+ cells showed weaker fibrosis.

In our patient, an endomyocardial biopsy was spared given that biopsies are high risk and usually reserved for patients presenting with major clinical syndromes, such as severe heart failure and/or life-threatening arrhythmias that are refractory to conventional therapies, which was not the case in our patient. The radiographic evidence and underlying autoimmune disease, which was the likely related cause of the autoimmune myocarditis, further negated the need for a biopsy.

CONCLUSIONS

While the pathogenesis of autoimmune myocarditis and DCM and their association with the Th17 and IL-17 mediated processes were well documented in the literature, the use of direct inhibition of IL-17 within humans with myocarditis had not been reported. This case highlighted the success of IL-17 inhibition in treating autoimmune myocarditis, a disease with no truly effective treatment and with potentially devastating consequences. Thus, it provided an exciting avenue for future research in larger patient populations to assess the efficacy of this treatment modality.

REFERENCES

[1] Bracamonte-Baran W, Čiháková D. Cardiac autoimmunity: Myocarditis. Adv Exp Med Biol 2017; 103:187-221. PMID 28667560.
[2] Sagar S, Liu PP, Cooper LT Jr. Myocarditis. Lancet 2012; 379(9817):738-747. PMID: 22185868.
[3] Lilly LS. Braunwald's Heart Disease: Review and Assessment. Eleventh Edition. Philadelphia: Elesevier, 2018. ISBN: 9780323546348.
[4] Kakturskii L, Belova E, Polosova T, Skatnikova V. [Cardiac lesion in psoriasis]. [Russian] Arkh Patol 2004; 66(6):22-24. PMID 15648162.
[5] Prakash A, Deepshikha. Psoriasis and cardiomyopathy: An intriguing association. Indian J Dermatol 2010; 55(3):271-273. PMID: 21063523.
[6] Blauvelt A, Chiricozzi A. The immunologic role of IL-17 in psoriasis and psoriatic arthritis pathogenesis. Clin Rev Allergy Immunol 2018; 55(3):379-390. PMID: 30109481.
[7] Sinagra G, Anzini M, Pereira NL, et al. Myocarditis in clinical practice. Mayo Clin Proc 2016; 91(9):1256-1266. PMID: 27489051.
[8] Donermeyer D, Beisel K, Allen P, Smith S. Myocarditis-inducing epitope of myosin binds constitutively and stably to I-Ak on antigen-presenting cells in the heart. J Exp Med 1995; 182(5):1291-1300. PMID: 7595200.
[9] Pummerer CL, Luze K, Grässl G, et al. Identification of cardiac myosin peptides capable of inducing autoimmune myocarditis in BALB/c mice. J Clin Invest 1996; 97(9):2057-2062. PMID: 8621795.
[10] Baldeviano GC, Barin JG, Talor MV, et al. Interleukin-17A is dispensable for myocarditis but essential for the progression to dilated cardiomyopathy. Cir Res 2010; 106(10):1646-1655. PMID:20378858.
[11] Daniels MD, Hyland KV, Wang K, Engman DM. Recombinant cardiac myosin fragment induces experimental autoimmune myocarditis via activation of Th1 and Th17 immunity. Autoimmunity 2008; 41(6):490-499. PMID: 18781477.

Keywords: autoimmune diseases, myocarditis, IL-17

KANSAS JOURNAL of MEDICINE

Concurrent Dermatomyositis, Celiac Disease, and Dermatitis Herpetiformis in a Patient with a History of Morphea

Atieh Jibbe, M.D.[1], Brett C. Neill, M.D.[1], Stan N. Tolkachjov, M.D.[2]
[1]University of Kansas Medical Center, Kansas City, KS
Department of Internal Medicine, Division of Dermatology
[2]Epiphany Dermatology, Dallas, TX

Received Feb. 24, 2021; Accepted for publication April 12, 2021; Published online Aug. 4, 2021
https://doi.org/10.17161/kjm.vol14.15224

INTRODUCTION

Dermatomyositis is a type of idiopathic inflammatory myopathy (IIM), characterized by an autoimmune response primarily against skin and muscle tissues.[1,2] A variety of cutaneous manifestations can be seen in dermatomyositis, although Gottron's papules, Gottron's sign, and a heliotrope rash are considered pathognomonic.[1,3] Gottron's papules are flat-topped, red-to-purple papules and plaques involving the skin, metacarpophalangeal, and interphalangeal joints of the dorsal aspect of both hands. These lesions resolve, leaving areas of dyspigmentation, atrophy, and scarring. Gottron's papules should be differentiated from similar lesions, such as verruca vulgaris, lichen planus, knuckle pads, sarcoidosis, and erythema elevatum diutinum.[1,3] If a clinician initially suspects a Gottron's mimicker and treats with the standard treatment for that diagnosis (i.e., verruca without resolution), a biopsy should be considered.

Morphea, dermatomyositis, celiac disease, and dermatitis herpetiformis are autoimmune disorders that share similar pathogenesis and triggers. The diagnosis of multiple autoimmune syndrome (MAS) is given to patients with at least three autoimmune disorders with involvement of one or more autoimmune endocrine disorders.[4] We present a case describing a patient with morphea, dermatomyositis, and celiac disease/dermatitis herpetiformis, suggesting a constellation of autoimmune disorders not subclassified by the MAS classification and not reported in the literature.

CASE REPORT

A 40-year-old male with fibromyalgia was seen with a three-month history of "warts" on his right knuckles. The patient was treated initially with cryotherapy, but the lesions did not resolve. Upon evaluation, the clinician had an index of suspicion that the warts had a unique distribution and surprisingly had not responded to therapy.

Upon additional questioning, his past medical history was significant for a 10-year history of multifocal morphea. No additional information was known about his morphea history. He did not take any medications, and his family history was unremarkable for autoimmune conditions.

On physical exam, multiple inconspicuous areas of hyperkeratotic, lichenified, violaceous plaques were seen on the dorsal surface of the metacarpophalangeal and distal interphalangeal joints. There was a small, flat-topped, scaly papule with central atrophy located on his right 2nd metacarpophalangeal joint (Figure 1a). Nailbed findings were significant for dystrophic growth with "ragged" cuticles (Figure 1b). Of note, areas of hyper- and hypo-pigmented indurated plaques were noted on the trunk and upper extremities, consistent with morphea (Figure 1c).

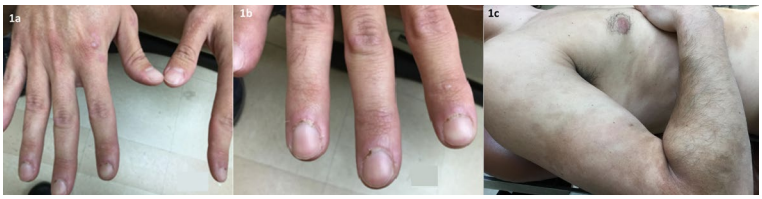


Figure 1. (a and b) Gottron's papules and dystrophic "ragged" cuticles of dermatomyositis. (c) Morphea: Hyper- and hypo-pigmented indurated plaques were noted on the trunk and upper extremities.

Due to the lack of resolution and the clinical appearance/distribution of the lesions, a scoop shave biopsy was performed. Histopathologic findings included acanthosis, basal layer vacuolization, and perivascular lymphocytic infiltrates with increased mucin deposition in the dermis. The biopsy was consistent with features of a connective tissue disease, and in this case, Gottron's papule. The patient was diagnosed with amyopathic dermatomyositis with mild myopathy initially thought to be secondary to his history of fibromyalgia. Creatine kinase and aldolase were normal; however, there was a mild elevation of AST, which can be seen in myopathy or myositis. Complete blood count and the rest of the comprehensive metabolic panel were within normal limits. Antinuclear antibodies were positive and extractable nuclear antigens were remarkable for antibodies against nuclear matrix protein 2 (NXP2).

The patient was referred for malignancy screening. Upon evaluation with esophagogastroduodenoscopy and small bowel follow-through, duodenal biopsy exhibited villous atrophy, crypt hyperplasia, and intraepithelial lymphocytic infiltrate. The diagnosis of celiac disease was confirmed after serologic studies were positive for tTG-IgA autoantibody. A gluten-free diet was recommended to the patient, and he was referred to a nutritionist. Dapsone therapy was discussed, but the patient preferred to try a gluten-free diet.

Five months later, he returned for evaluation of a new rash. The rash differed from the previous dermatoses in that the lesions were notably itchy. An erythematous papulovesicular eruption with excoriations on the knees, elbows, and buttock was observed (Figure 2). A 4-mm punch biopsy of the buttock was performed, which showed subepidermal vesicles and accumulation of neutrophils at the tips of dermal papillae with some features of folliculitis. Granular deposits of IgA within the dermal papillae and along the basement membrane were noted on direct immunofluorescence, consistent with dermatitis herpetiformis. The patient was not compliant with the gluten-free diet during that period. Treatment with dapsone was again offered but was declined by the patient. He preferred to recommit to the gluten-free diet and start topical clobetasol therapy and agreed for routine follow-up.

DISCUSSION

The diagnosis of Gottron's papules is important because it can assist in diagnosis of dermatomyositis and hasten a malignancy workup. The risk of malignancy in association with dermatomyositis is well known, with 20 - 25% of dermatomyositis cases having coexisting cancer, typically in an older population. Cancer of the breast, ovary, cervix, colon, stomach, and lung are common cancers associated with dermatomyositis.[3] As in our case, a diagnosis of Gottron's papules and subsequently

dermatomyositis led to a malignancy workup which resulted in the identification of celiac disease in the patient. Making the diagnosis of celiac disease was important to avoid its complications if untreated, including osteoporosis, enteropathy-associated intestinal T-cell lymphoma, collagenous sprue, ulcerative jejunoileitis, and non-Hodgkin lymphoma, among others.

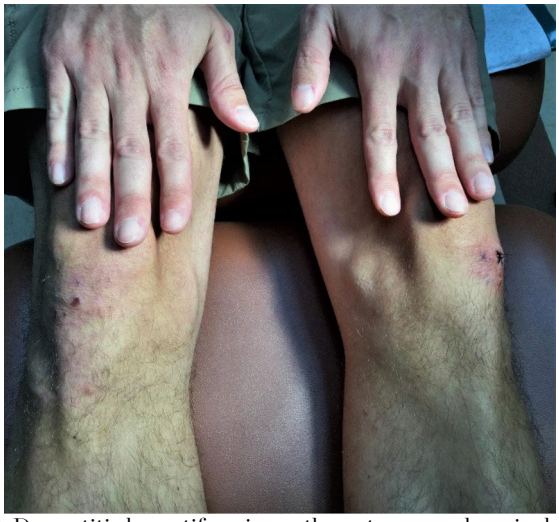


Figure 2. Dermatitis herpetiformis; erythematous papulovesicular eruption with excoriations predominantly on the knees.

The discovery of myositis-specific autoantibodies (MSA) has provided further stratification of dermatomyositis based on clinical findings and prognostic values. Autoantibodies associated with dermatomyositis include transcriptional intermediary factor 1γ (TIF-1γ), nucleosome-remodeling deacetylase complex (Mi-2), melanoma differentiation-associated gene 5 (MDA5), small ubiquitin-like modifier activating enzyme (SAE1/2), and NXP2.[1] Compared to adults, anti-NXP2 antibodies are seen more commonly in juvenile dermatomyositis.

NXP2 has been identified as an autoantibody target in a subset (1.6 - 30%) of adult dermatomyositis patients.[5-7] An association has been suggested between anti-NXP2 and an increased risk of malignancy.[8] However, a recent meta-analysis of 20 cohort studies found no association between anti-NXP2 and malignancy.[9] Autoantibodies against TIF-1γ are associated with cancer occurrence with a sensitivity of 78% and specificity of 89%.[8] The presence of anti-MDA5 autoantibodies is associated with a higher risk of developing interstitial lung disease,[10] and 50% of those with this autoantibody will die from respiratory failure in the first six months following diagnosis.[11] The presence of SAE1/2 autoantibodies is associated clinically with severe dysphagia.[12] Lastly, patients with anti-Mi-2 antibodies may have a better response to immunosuppressive treatment.[13]

Characteristic muscle biopsy findings in dermatomyositis are perivascular and perimysial infiltration of CD4 T-cells and B-cells, suggesting a production of autoantibodies involved in the pathogenesis. Dermatomyositis likely develops in patients who are predisposed genetically and commonly is triggered by factors such as infection, medication, radiation, or malignancy.[1,2]

Morphea is an autoimmune connective tissue disorder characterized by inflammation and fibrosis of the skin and soft tissues.[14,15] Patients with generalized morphea rarely may involve muscle and joints, causing myalgia and arthritis. The pathogenesis of morphea is unknown, but the combination of vascular dysfunction and autoimmunity may result in an abnormal recruitment of inflammatory cells and an increase production of collagen. Morphea, like dermatomyositis, commonly develops after an extrinsic insult such as infection, trauma, radiation, or medication.

Celiac disease is a multifactorial condition caused by an abnormal immune response to gluten at the level of the intestinal mucosa.[16] Celiac disease is associated with HLA-DQ2 and/or HLA-DQ8 though these allele associations alone are not sufficient for the diagnosis, given that 30% to 40% of the general population are carriers for at least one of these alleles. Exposure to gliadin in genetically predisposed individuals results in the production of IgA autoantibodies that target tissue transglutaminase 1(tTG).

Dermatitis herpetiformis is associated with celiac disease and is thought to be due to cross reaction of anti-tTG IgA against tissue transglutaminase 3 found in the dermis, resulting in the deposition of IgA in the dermal papilla and the accumulation of neutrophils and eosinophils.[17] Environmental factors play a major role in the development of celiac disease such as breastfeeding, gastrointestinal infections, antibiotics, and proton-pump inhibitors.

There were no known previously published reports of dermatomyositis, celiac disease, and dermatitis herpetiformis concurrently in a patient with a history of morphea. Celiac disease was associated with juvenile dermatomyositis and cases of celiac disease in adult-onset dermatomyositis have been emerging.[18-20] Similarly, a case report described a patient with morphea and celiac disease.[21] The common pathogenesis, triggering factors, and genetic background associated with morphea, dermatomyositis, celiac disease, and dermatitis herpetiformis may suggest a common etiology consisting of both genetic and autoimmune components.

Individuals with at least three autoimmune diseases fall under the diagnosis of multiple autoimmune syndrome.[4] MAS can be classified into three types determined by the cluster of autoimmune conditions most commonly seen together. This classification requires the involvement of at least one endocrine gland dysfunction. The autoimmune nature of the diseases in our case, the common triggers associated with disease onset, and the lack of glandular involvement in our patient may suggest an autoimmune syndrome that has not been reported.

CONCLUSIONS

In conclusion, this unique patient with multiple confirmed autoimmune diagnoses may suggest an autoimmune constellation not reported in the literature and not compliant with the MAS classification. Three major points of consideration in this case are: 1) a clinician should have a high index of suspicion to biopsy a lesion that does not respond to standard therapy or clinically fit the rendered diagnosis; 2) when evaluating a patient with an autoimmune disease, additional autoimmune diseases should be considered; and 3) while clusters of autoimmune disorders have been reported, the nature and variety of autoimmune conditions may lead to new associations and potential for therapeutic targets.

REFERENCES

[1] Bogdanov I, Kazandjieva J, Darlenski R, Tsankov N. Dermatomyositis: Current concepts. Clin Dermatol 2018; 36(4):450-458. PMID: 30047429.
[2] Thompson C, Piguet V, Choy E. The pathogenesis of dermatomyositis. Br J Dermatol 2018; 179(6):1256-1262. PMID: 28542733.
[3] Muro Y, Sugiura K, Akiyama M. Cutaneous manifestations in dermatomyositis: Key clinical and serological features - A comprehensive review. Clin Rev Allergy Immunol 2016; 51(3):293-302. PMID: 26100618.
[4] Cojocaru M, Cojocaru IM, Silosi I. Multiple autoimmune syndrome. Maedica (Bucur) 2010; 5(2):132-134. PMID: 21977137.
[5] Ceribelli A, Fredi M, Taraborelli M, et al. Anti-MJ/NXP-2 autoantibody specificity in a cohort of adult Italian patients with polymyositis/dermatomyositis. Arthritis Res Ther 2012; 14(2):R97. PMID: 22546500.
[6] Ichimura Y, Matsushita T, Hamaguchi Y, et al. Anti-NXP2 autoantibodies in adult patients with idiopathic inflammatory myopathies: Possible association with malignancy. Ann Rheum Dis 2012; 71(5):710-713. PMID: 22258483.
[7] Ishikawa A, Muro Y, Sugiura K, Akiyama M. Development of an ELISA for detection of autoantibodies to nuclear matrix protein 2. Rheumatology (Oxford) 2012; 51(7):1181-1187. PMID: 22427409.
[8] Fiorentino DF, Chung LS, Christopher-Stine L, et al. Most patients with cancer-associated dermatomyositis have antibodies to nuclear matrix protein NXP-2 or transcription intermediary factor 1γ. Arthritis Rheum 2013; 65(11):2954-2962. PMID: 24037894.
[9] Zhong L, Yu Z, Song H. Association of anti-nuclear matrix protein 2 antibody with complications in patients with idiopathic inflammatory myopathies: A meta-analysis of 20 cohorts. Clin Immunol 2019; 198:11-18. PMID: 30445156.
[10] Oldroyd AGS, Allard AB, Callen JP, et al. A systematic review and meta-analysis to inform cancer screening guidelines in idiopathic inflammatory myopathies. Rheumatology (Oxford) 2021; keab166. PMID: 33599244.
[11] Nakashima R, Imura Y, Kobayashi S, et al. The RIG-I-like receptor IFIH1/MDA5 is a dermatomyositis-specific autoantigen identified by the anti-CADM-140 antibody. Rheumatology (Oxford) 2010; 49(3):433-440. PMID: 20015976.
[12] Betteridge ZE, Gunawardena H, Chinoy H, et al. Clinical and human leucocyte antigen class II haplotype associations of autoantibodies to small ubiquitin-like modifier enzyme, a dermatomyositis-specific autoantigen target, in UK Caucasian adult-onset myositis. Ann Rheum Dis 2009; 68(10):1621-1625. PMID: 18930994.
[13] Petri MH, Satoh M, Martin-Marquez BT, et al. Implications in the difference of anti-Mi-2 and -p155/140 autoantibody prevalence in two dermatomyositis cohorts from Mexico City and Guadalajara. Arthritis Res Ther 2013; 15(2):R48. PMID: 23557279.
[14] Florez-Pollack S, Kunzler E, Jacobe HT. Morphea: Current concepts. Clin Dermatol 2018; 36(4):475-486. PMID: 30047431.
[15] Fett N, Werth VP. Update on morphea: Part I. Epidemiology, clinical presentation, and pathogenesis. J Am Acad Dermatol 2011; 64(2):217-228; quiz 229-230. PMID: 21238823.
[16] Green PHR, Lebwohl B, Greywoode R. Celiac disease. J Allergy Clin Immunol 2015; 135(5):1099-1106; quiz 1107. PMID: 25956012.
[17] Jakes AD, Bradley S, Donlevy L. Dermatitis herpetiformis. BMJ 2014; 348:g2557. PMID: 24740905.
[18] Iannone F, Lapadula G. Dermatomyositis and celiac disease association: A further case. Clin Exp Rheumatol 2001; 19(6):757-758. PMID: 11791656.
[19] Marie I, Lecomte F, Hachulla E, et al. An uncommon association: Celiac disease and dermatomyositis in adults. Clin Exp Rheumatol 2001;19(2):201-203. PMID: 11326486.
[20] Song MS, Farber D, Bitton A, Jass J, Singer M, Karpati G. Dermatomyositis associated with celiac disease: Response to a gluten-free diet. Can J Gastroenterol 2006; 20(6):433-435. PMID: 16779462.
[21] Firoz EF, Kamino H, Lehman TJA, Orlow SJ. Morphea, diabetes mellitus type I, and celiac disease: Case report and review of the literature. Pediatr Dermatol 2010; 27(1):48-52. PMID: 20199410.

Keywords: dermatomyositis, morphea, celiac disease, dermatitis herpetiformis

KANSAS JOURNAL of MEDICINE

Screening for Barrett's Esophagus in Patients with Cirrhosis Using WATS^{3D}

Yasmine Hussein Agha, M.D.[1], Ali Taleb, M.D.[1], Sachin Srinivasan, M.D.[1], Nathan Tofteland, M.D.[1,2], William Salyers, M.D., MPH[1,2]
University of Kansas School of Medicine-Wichita, Wichita, KS
[1]Department of Internal Medicine
[2]Division of Gastroenterology

Received Jan. 8, 2021; Accepted for publication April 12, 2021; Published online Aug. 4, 2021
https://doi.org/10.17161/kjm.vol1415074

INTRODUCTION

Barrett's esophagus (BE) is a premalignant condition that arises from longstanding gastroesophageal reflux disease (GERD). It can lead to esophageal adenocarcinoma (EAC), a cancer with incidence rates that continue to rise in the Western world.[1] The gold standard for screening for BE requires endoscopic evaluation and 4-quadrant esophageal forceps biopsy (Seattle protocol).[2] However, endoscopists have a higher tendency to refrain from performing forceps biopsies (FB) in patients with an increased risk of bleeding such as patients with cirrhosis.[3]

Wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS^{3D}) is an abrasive cytology brush capable of taking full transepithelial samples and is able to cover a wide circumferential area of esophageal mucosa.[4,5] Compared to forceps biopsies, WATS^{3D} covers a wider surface area of the esophagus and acquires deep mucosal tissue where pre-malignant cells develop without reaching the submucosal veins. In this case series, seven patients with cirrhosis and GERD are reported that underwent routine surveillance for BE using WATS^{3D} with no post-procedural complications.

CASE REPORT

Seven patients with cirrhosis had risk factors associated with bleeding (Table 1) and underwent screening for BE by upper endoscopy using WATS^{3D}. The first patient was a 70-year-old female with a history of cirrhosis secondary to autoimmune hepatitis along with portal hypertension and gastropathy. She underwent a liver and kidney transplant three years prior to presentation. Given her longstanding history of GERD, she was scheduled for routine surveillance of BE by upper endoscopy. A BE segment (C1 M3) was biopsied per Seattle protocol using traditional forceps and sampled using WATS^{3D} as well. No varices were noted during the procedure. Both modalities revealed intestinal metaplasia and were negative for dysplasia.

The second patient was a 65-year-old male with a history of alcoholic cirrhosis, grade 1 esophageal varices, and portal hypertensive gastropathy. He also had a history of GERD and was due for variceal surveillance. During the procedure, grade 2 esophageal varices and a BE segment (C1 M2) were noted. WATS^{3D} brushing alone was obtained since the patient was at high risk of bleeding. Pathology was consistent with intestinal metaplasia and was negative for dysplasia. The patient was treated with a daily proton pump inhibitor. The patient underwent repeat esophagogastroduodenoscopy (EGD) one year later. Sampling was repeated with WATS^{3D} only and yielded the same results.

The third patient was a 69-year-old male with a history of cirrhosis due to untreated hepatitis C and alcoholism. He also had a history of GERD and BE and was due for variceal surveillance. His procedure revealed a salmon-colored segment (C0 M6), congestive gastropathy, and grade 1 esophageal varices. WATS^{3D} sampling of the segment was consistent with goblet cell metaplasia and low-grade dysplasia. FB was not done due to concerns for bleeding. Subsequently, he was initiated on a daily proton pump inhibitor. EGD with WATS^{3D} sampling was repeated six months later and yielded the same results.

The fourth patient was a 61-year-old male with a history of alcoholic cirrhosis who was discharged recently from the hospital following a gastrointestinal bleed. An emergent EGD revealed bleeding esophageal varices (Grade 3) that were banded and ultimately required a transjugular intrahepatic portosystemic shunt for management of varices. Upper endoscopy was repeated eight weeks later and showed grade 1 esophageal varices and a distal island of salmon colored mucosa. Sampling of the distal esophagus with WATS^{3D} yielded columnar epithelium with no evidence of BE.

The fifth patient was a 49-year-old male with a history of alcoholic cirrhosis. His previous two EGDs showed portal hypertensive gastropathy and grade 1 esophageal varices. He also had a salmon-colored mucosal segment in the distal esophagus, consistent with Prague class C0 M2 BE. However, no biopsies were taken owing to concerns for hemorrhagic complications. During his most recent endoscopy, the segment and esophageal varices were unchanged. Sampling was performed with both modalities and revealed intestinal metaplasia without evidence of dysplasia. He was prescribed a daily proton pump inhibitor.

The sixth patient was a 63-year-old male known to have celiac sprue and alcoholic cirrhosis. His previous EGD showed portal hypertensive gastropathy and grade 2 esophageal varices. During his variceal surveillance endoscopy, a BE segment (C0 M2) was noted in addition to grade 2 esophageal varices. Sampling was done with WATS^{3D} only. Pathology revealed intestinal metaplasia without evidence of dysplasia, which prompted treatment with daily proton-pump inhibition therapy.

The seventh patient was a 65-year-old male who was newly diagnosed with cirrhosis due to untreated hepatitis C. Upper endoscopy revealed a BE segment (C20 M21) and a nodularity with ulcerations that were suspicious for high grade dysplasia (HGD) and confirmed by FB and WATS^{3D}. No varices were seen during the procedure. Endoscopic mucosal resection was unsuccessful since the mucosa was tacked down to deeper tissues at the site of ulcerations.

All patients (except for the last patient) followed-up in our gastroenterology clinic multiple times within the first year after the EGD. None had any immediate or delayed post-procedural complications such as bleeding, infections, and perforation. The last patient did not display any early complications, however, was lost to follow-up for further management.

Table 1. Patient characteristics.

Patient Number	Age (Years)	Gender	Variceal Grade	Prague Score	Sampling by FB	FB Pathology	Sampling by WATS[3D]	WATS Pathology
1	70	F	0	C1 M3	Yes	Non-dysplastic BE	Yes	Non-dysplastic BE
2	65	M	2	C1 M2	No	N/A	Yes	Non-dysplastic BE
3	69	M	1	C0 M6	No	N/A	Yes	LGD + BE
4	61	M	3	N/A	No	N/A	Yes	Columnar mucosa
5	49	M	1	C0 M2	Yes	Non-dysplastic BE	Yes	Non-dysplastic BE
6	63	M	2	C0 M2	No	N/A	Yes	Non-dysplastic BE
7	65	M	0	C20 M21	Yes	HGD + BE	Yes	HGD + BE

Abbreviations: forceps biopsy (FB); Prague criteria Circumferential Barrett's segment (C) and longest tongue of Barrett's (M); High grade dysplasia (HGD); Low grade dysplasia (LGD); Barrett's Esophagus (BE); Not applicable (N/A).

DISCUSSION

GERD is associated with a 10 - 15% risk for developing BE.[2] The rate of progression to EAC depends on the degree of dysplasia. The annual incidence rate of EAC in patients with HGD is 7% according to the American College of Gastroenterology.[2] Other randomized studies have shown that this rate can be as high as 19%.[3] While GERD is very common in the general population, several studies have demonstrated a higher prevalence of GERD in patients with cirrhosis and an incidence rate of dysplasia ranging from 33% to 64%.[6-11]

Studies initially had attributed this association to the presence of esophageal varices (EV) mechanically impeding lower esophageal sphincter (LES) closure and reported no association between GERD and cirrhosis in the absence of EV.[11,12] However, a more recent study showed that cirrhosis causes GERD in the absence of EV by demonstrating a negative correlation between LES pressures and Child-Pugh scores.[7] The increased intra-abdominal pressure from ascites and the increased generation of nitrous oxide in advancing liver disease are two of the main contributing factors.[6,7] We can infer that GERD in patients with liver disease is a progressive outcome and unpreventable. Cirrhotic patients occupy a significant proportion of the total population of patients that require screening for BE. With the increased risk of neoplastic progression in patients with GERD and cirrhosis, it is necessary to adhere to screening guidelines for BE in patients with cirrhosis.

Unfortunately, physicians often refrain from taking biopsies in patients with advanced liver disease due to the anticipated risk of bleeding from esophageal varices and coagulopathy. Consequently, BE may be underdiagnosed in this subpopulation.[3] Clinically-significant bleeding following FB in the general population is rare and has an incidence rate of 0.03 to 0.16%.[13-15] However, no studies have evaluated the risk of bleeding in patients with cirrhosis following esophageal FB.

WATS[3D] is less traumatic and associated with minimal post-procedural bleeding complications.[4,16] Studies have demonstrated improved rates of detection of BE when WATS[3D] is used as an adjuvant to the standard 4-quadrant forceps biopsy protocol by about 18% in community settings and up to 83% in referral centers.[4,15,17] This provided a significant improvement to standard FB, which has a reported accuracy of 35% to 68% and correlated positively with the number of biopsy samples taken.[2]

CONCLUSIONS

With the added benefits of WATS[3D] and no increased risk of bleeding, it would be beneficial to use this modality in patients with cirrhosis. Future studies assessing the risk of bleeding in patients with cirrhosis using WATS[3D] and FB are needed to establish a clear recommendation as to what modality would be most appropriate to use for screening in this patient population.

REFERENCES

[1] Hur C, Hayeck TJ, Yeh JM, et al. Development, calibration, and validation of a U.S. white male population-based simulation model of esophageal adenocarcinoma. PloS One 2010; 5(3):e9483. PMID: 20208996.
[2] Shaheen NJ, Falk GW, Iyer PG, Gerson LB, American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and management of Barrett's esophagus. Am J Gastroenterol 2016; 111(1):30-50. PMID: 26526079.
[3] Apfel T, Lopez R, Sanaka MR, Thota PN. Risk of progression of Barrett's esophagus in patients with cirrhosis. World J Gastroenterol 2017; 23(18):3287-3294. PMID: 28566888.
[4] Schechter RB, Lemme EMO, Coelho HSM. Gastroesophageal reflux in cirrhotic patients with esophageal varices without endoscopic treatment. Arq Gastroenterol 2007; 44(2):145-150. PMID: 17962861.
[5] Zhang J, Cui P-L, Lv D, Yao S-W, Xu Y-Q, Yang Z-X. Gastroesophageal reflux in cirrhotic patients without esophageal varices. World J Gastroenterol 2011; 17(13):1753-1758. PMID: 21483637.
[6] Suzuki K, Suzuki K, Koizumi K, et al. Effect of symptomatic gastroesophageal reflux disease on quality of life of patients with chronic liver disease. Hepatol Res 2008; 38(4):335-339. PMID: 18021233.
[7] Theocharidou E, Dhar A, Patch D. Gastrointestinal motility disorders and their clinical implications in cirrhosis. Gastroenterol Res Pract 2017; 2017:8270310. PMID: 28584525.
[8] Li B, Zhang B, Ma JW, et al. High prevalence of reflux esophagitis among upper endoscopies in Chinese patients with chronic liver diseases. BMC Gastroenterol 2010; 10:54. PMID: 20525368.
[9] Ahmed AM, al Karawi MA, Shariq S, Mohamed AE. Frequency of gastroesophageal reflux in patients with liver cirrhosis. Hepatogastroenterology 1993; 40(5):478-480. PMID: 8270239.
[10] Passaretti S, Mazzotti G, de Franchis R, Cipolla M, Testoni PA, Tittobello A. Esophageal motility in cirrhotics with and without esophageal varices. Scand J Gastroenterol 1989; 24(3):334-338. PMID: 2734592.
[11] Vu CK, Korman MG, Bejer I, Davis S. Gastrointestinal bleeding after cold biopsy. Am J Gastroenterol 1998; 93(7):1141-1143. PMID: 9672346.
[12] Gross SA, Smith MS, Kaul V, US Collaborative WATS[3D] Study Group. Increased detection of Barrett's esophagus and esophageal dysplasia with adjunctive use of wide-area transepithelial sample with three-dimensional computer-assisted analysis (WATS). United European Gastroenterol J 2018; 6(4):529-535. PMID: 29881608.
[13] Johanson JF, Frakes J, Eisen D, EndoCDx Collaborative Group. Computer-assisted analysis of abrasive transepithelial brush biopsies increases the effectiveness of esophageal screening: A multicenter prospective clinical trial by the EndoCDx Collaborative Group. Dig Dis Sci 2011; 56(3):767-772. PMID: 21132367.

[14] Anandasabapathy S, Sontag S, Graham DY, et al. Computer-assisted brush-biopsy analysis for the detection of dysplasia in a high-risk Barrett's esophagus surveillance population. Dig Dis Sci 2011; 56(3):761-766. PMID: 20978843.
[15] Vennalaganti PR, Kaul V, Wang KK, et al. Increased detection of Barrett's esophagus-associated neoplasia using wide-area trans-epithelial sampling: A multicenter, prospective, randomized trial. Gastrointest Endosc 2018; 87(2):348-355. PMID: 28757316.
[16] Smith MS, Ikonomi E, Bhuta R, et al. Wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS) markedly improves detection of esophageal dysplasia and Barrett's esophagus: Analysis from a prospective multicenter community-based study. Dis Esophagus 2019; 32(3):doy099. PMID: 30541019.
[17] Srinivasan S, Hussein Agha Y, Hyder J, et al. WATS^{3D} vs. traditional forceps biopsy in screening of Barrett's esophagus: A community hospital experience. [Abstract] Am J Gastroenterol 2019; 114:S212-S213.

Keywords: Barrett esophagus, gastroesophageal reflux, liver cirrhosis, diagnosis computer-assisted, digestive system endoscopy

KANSAS JOURNAL of MEDICINE

KANSAS JOURNAL OF MEDICINE

VOLUME 14 • 2021

journals.ku.edu/kjm

Have a manuscript ready to publish?
Visit our website for instructions on submitting a manuscript.

Frontiers: University of Kansas Clinical and Translational Science Institute is a collaborating partner of the Kansas Journal of Medicine

Office of Research
1010 N. Kansas, Wichita, KS 67214
316-293-2617 • Email: kjm@kumc.edu