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ORIGINAL RESEARCH ARTICLES

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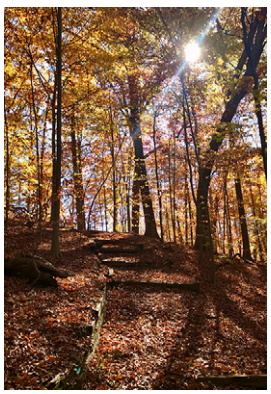

Fall Foliage
photograph
Monica Leigh

In the woods near my house, where I walk my dog on a regular basis, this rustic stairway emerges. It transports one from a narrow foot path to an open field. As COVID-19 has kept us all closer to home, the woods have become a regular sanctuary, a place where I and my dog can roam freely, forgetting about the worries that weigh me down at home. On this sunny day–November 7, 2020–things seemed particularly hopeful. There was talk of a vaccine, and the idea of a new beginning for 2021 emerged. I like to think of this image as a visual reminder that we will find a way out of the depths of disease and into a hopeful future where we can visit and hug our loved ones, travel and discover new places, and meet new friends without fear of infection.

Monica Leigh is a senior managing editor for KWF Editorial and the managing editor for *The Permanente Journal*. When she isn't fostering scientific discovery through scholarly publishing, she photographs families in the Baltimore area and enjoys spending time in nature with her family and their dog.

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ORIGINAL RESEARCH ARTICLE

High Remission Rate with Infliximab and Plant-Based Diet as First-Line (IPF) Therapy for Severe Ulcerative Colitis: Single-Group Trial

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ABSTRACT

Introduction: About one-third of patients with severe ulcerative colitis (UC) do not respond to corticosteroid therapy and receive rescue therapy with infliximab or cyclosporine. Up to 20% of such patients fail to respond to rescue therapy and undergo colectomy.

Objective: We investigated the outcomes of infliximab and a plant-based diet (PBD) as first-line therapy for severe UC.

Methods: Patients with severe UC defined by the Truelove and Witts criteria were admitted and given standard induction therapy with infliximab (5.0 mg/kg-7.5 mg/kg) at 0, 2, and 6 weeks. Additionally, they received a PBD. The primary endpoint was remission or colectomy in the induction phase and 1 year after discharge. Secondary endpoints were changes in inflammatory markers in the induction phase and the PBD score at baseline and follow-up. A higher PBD score indicates greater adherence to a PBD.

Results: Infliximab and PBD as first-line therapy was administered in 17 cases. The remission rate was 76% (13/17), and the colectomy rate was 6% (1/17) in the induction phase. C-reactive protein values and the erythrocyte sedimentation rate significantly decreased at week 6 from 9.42 mg/dL to 0.33 mg/dL and from 59 to 17 mm/h, respectively ($p < 0.0001$). At 1-year follow-up, the cumulative relapse rate was 25%, and there were no additional colectomy cases. Mean PBD scores of 27.7 at 1 year and 23.8 at 4 years were significantly higher than baseline scores of 8.3 and 9.9, respectively ($p < 0.0001$ and $p = 0.0391$).

Conclusion: This new first-line therapy for severe UC demonstrated a higher remission rate and lower colectomy rate than with the current modality.

INTRODUCTION

Newly introduced biologic agents have revolutionized the medical treatment of various conditions, including inflammatory bowel disease (IBD). Antitumor necrosis factor α antibodies (infliximab, adalimumab, and golimumab) and anti-$\alpha_4\beta_7$ antibody (vedolizumab) were introduced for treatment of ulcerative colitis (UC).[1-5] They have been shown to effectively induce and maintain remission in outpatients with moderate to severe UC that is unresponsive to corticosteroids, immunosuppressants, or both. Their induction rates of remission are from 19% to 49%.[1-5] Infliximab is effective in reducing the colectomy rate at 1 year after therapy.[6] The long-term colectomy rate was reported to be reduced in the biologics era (2005-2011) compared with that in the prebiologics era (1998-2004).[7]

Severe UC develops in 10% to 25% of patients with UC.[8-10] It is a potentially life-threatening disease, with a 1% mortality rate.[9,11,12] Therefore, treatment requires hospitalization. First-line therapy is intensive intravenous administration of corticosteroids.[13] In the prebiologics era, colectomy was indicated if patients were unresponsive to corticosteroids in 3 days, which was approximately one-third of patients.[11] Currently, infliximab or cyclosporine is used as rescue second-line treatment of patients who are unresponsive to corticosteroids. This rescue therapy is unsuccessful in approximately 11% to 20% of patients, resulting in colectomy.[14] When remission is successfully induced with infliximab, scheduled maintenance therapy with infliximab is recommended.[10,14,15] Nevertheless, some cases require colectomy, and colectomy rates increase to 26% to 37% at 1 year.[14]

Infliximab is indicated for UC treatment in second-line therapy treatment for outpatients with moderate to severe UC and in treatment for inpatients with acute severe UC. In both situations, corticosteroids are used first, and then biologics are indicated when corticosteroids are ineffective.[9,10,15] As reported in the literature, 16% to 34% of patients are nonresponders to corticosteroids.[11,16-18] Even though corticosteroids are effective in the induction phase, there is a drawback to corticosteroid use in the follow-up period. At 1 year, corticosteroid dependence or surgical intervention occurs in nearly 50% of such patients.[17] Because of this critical problem of corticosteroids, we replaced prednisolone (a glucocorticoid) with infliximab in 2010 when infliximab became available to use for UC in Japan. In Crohn disease (CD), early use of infliximab (top-down approach) is reported in the literature. The first-line use of infliximab for severe UC, however, has scarcely been reported.[19] Ochsenkühn et al.[19] demonstrated that infliximab and corticosteroids were equally effective for patients with severe UC who were not corticosteroid refractory, and

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Keywords: colectomy, dietary intervention, environmental factors, first-line therapy, infliximab, IPF, lifestyle medicine, plant-based diet, remission, severe ulcerative colitis, vegetarian diet

the authors indicated that infliximab could be an alternative in patients who cannot receive corticosteroids.

IBD is a polygenic disease triggered by environmental factors.[20] Among a variety of environmental factors, a westernized diet (high in fat, animal protein, and sugar; low in dietary fiber) is thought to be the most ubiquitous. A westernized diet, which tends to cause gut microbial dysbiosis followed by changes of microbial metabolites, is proinflammatory. On the contrary, a plant-based diet (PBD), which is low in fat, animal protein, and sugar and high in dietary fiber and which tends to increase microbial diversity, is antiinflammatory.[20] PBDs are listed as variations of US Department of Agriculture healthy eating patterns.[21] Epidemiologic studies have provided convincing evidence that individuals consuming PBDs experience greater longevity and are less affected by common chronic diseases compared with those eating omnivorous diets.[22,23]

We designed a semivegetarian diet, which is a type of PBD, as a therapeutic diet for patients with IBD.[24] From 2003, we have provided the PBD to all inpatients with IBD at our center. We achieved far better outcomes both in the induction and maintenance phases in patients with CD and for relapse prevention in patients with UC than those previously reported in the literature. On the basis of our recent reports on IBD therapy that replaced westernized diets with a PBD, we recommended PBD for patients with IBD.[25]

To our knowledge, no previous study has incorporated a PBD in the induction phase of treatment of severe UC. We designed infliximab and PBD as first-line (IPF) therapy not for corticosteroid-refractory patients but for new patients with severe UC without prior intensive intravenous corticosteroid use.[13] After induction of remission, patients were followed without scheduled infliximab maintenance therapy. We hypothesized that these modalities could enhance the induction rate in the short term and reduce the relapse rate in the medium term, as we experienced in patients with CD.[24,26] The aim of this study was to investigate the remission and colectomy rate in the induction phase and in the medium term with IPF therapy for severe UC.

METHODS

Design and Settings

We designed a prospective single-group, nonrandomized, open-label, uncontrolled trial, which was conducted at 2 hospitals in Akita, Japan (study ID no.: University Hospital Medical Information Network [UMIN] UMIN000019061 and UMIN000020402; registration: www.umin.ac.jp). Both Nakadori General Hospital and Akita City Hospital are tertiary care hospitals in Akita City. The first author (MC) worked for Nakadori General Hospital between 2003 and 2012 and has been working for Akita City Hospital since 2013.

This protocol was approved by the Ethical Committee of Nakadori General Hospital and by the Ethical Committee of Akita City Hospital (protocol no: 19-2003, 17-2014, 15-2015). Informed consent was obtained from all participants.

Patients

Infliximab, the first biologic agent for treatment of UC in Japan, was approved in 2010. All patients with severe UC were hospitalized for possible IPF therapy between August 2012 and April 2019. Severity was judged using the Truelove and Witts criteria.[9,27] There are 6 items in the Truelove and Witts criteria for severe UC[27]: diarrhea 6 or more times per day, bloody stool, and 4 systemic toxicity signs (pulse rate ≥ 90/min, temperature ≥ 37.5°C, hemoglobin < 10.5 g/dL, and erythrocyte sedimentation rate [ESR] ≥ 30 mm/h). Severe UC was defined as bloody diarrhea 6 or more times per day associated with 1 or more of the systemic signs.[27] Exclusion criteria were moderate severity of UC and previous treatment with biologics. A referred severe case already treated by intensive intravenous corticosteroids[13] also was excluded. Patients receiving 5-aminosalicylic acid, prednisolone, and azathioprine were included.

Protocol: Infliximab and PBD as first-line (IPF) Therapy

The IPF protocol was the same as that described for CD.[26] In summary, oral metronidazole (750 mg/d) was given after hospital admission, and any medication administered before admission was maintained. The following information was ascertained before the start of IPF therapy or simultaneously depending on the condition of the patients: 1) confirmation of diagnosis by pathologic findings; 2) an assessment of severity of disease by morphologic studies (ultrasonography, barium enema study), laboratory data, and clinical observation; 3) exclusion of other infectious colitis by stool culture or rapid membrane enzyme immunoassay for *Clostridium difficile* (C. Diff Quik Chek Complete, TechLab, Blacksburg, VA); 4) blood test for cytomegalovirus antigenemia[28]; 5) examinations for tuberculosis or hepatitis B infection[29]; and 6) presentation of application form, which includes diagnosis of UC and its severity to the city office for public aid.

Infliximab (Remicade, Janssen Biotech, Horsham, PA) was infused at weeks 0, 2, and 6.[30] The amount of infliximab was determined by body weight: 200 mg for those with a weight of 40 kg or less, 300 mg for more than 40 to less than or equal to 60 kg (≥ 5 mg/kg to < 7.5 mg/kg), and 400 mg for more than 60 to less than or equal to 80 kg (> 5 mg/kg to < 6.6 mg/kg).

The PBD was initiated on the same day as the infliximab infusion and comprised a lacto-ovo-vegetarian diet with fish

once a week and meat once every 2 weeks.[24] Whether to give rice gruel or regular rice and the amount of energy (initially 800 kcal/d or 1100 kcal/d) were decided according to each patient's condition. The energy was gradually increased to a maximum of about 30 kcal/kg of standard body weight.

After about 1 month, metronidazole was switched to 5-aminosalicylic acids. If azathioprine and/or prednisolone were administered by referral physicians, azathioprine was continued throughout the study while prednisolone was adequately tapered off. After the third infusion of infliximab, patients were discharged. Patients were morphologically studied by colonoscopy and/or contrast-enhanced barium enema before discharge. Patients who achieved clinical remission and could not be admitted for the entire induction phase were discharged after the second infliximab infusion and readmitted for the third infusion.[26]

Follow-up Studies

All patients excluding those who moved away and who underwent colectomy were followed. The medication used was oral 5-aminosalicylic acid. Azathioprine was continued if it had been administered. Scheduled infliximab maintenance therapy was indicated for some patients who achieved incomplete remission and who had been faced with an intractable clinical course. The interval between outpatient visits was 8 weeks.

Food-Frequency Questionnaire and PBD Score

A questionnaire of dietary habits and lifestyle behaviors before onset or relapse of the disease was obtained immediately after admission, as described in a previous report.[31] On the basis of the questionnaire, a table was generated that summarized the patient's current and future recommended lifestyle and dietary habits. This table was given to the patient during hospitalization and was used by the dietitian when giving dietary guidance. The questionnaire was repeated during short-term (≤ 2-y) or long-term (> 2-y) follow-up.[31]

A PBD score (PBDS) was calculated from the questionnaire. The method for how the PBDS was calculated has been described previously.[31] In brief summary, 8 items considered to be preventive factors for IBD (vegetables, fruits, pulses [beans, soybeans, peas, etc], potatoes, rice, miso soup, green tea, and plain yogurt) contributed to a positive score (PBDS+), whereas 8 items considered to be IBD risk factors (meat, minced or processed meat, cheese/butter/margarine, sweets, soft drinks, alcohol, bread, and fish) contributed to a negative score (PBDS−). Scores of 5, 3, and 1 were given according to the frequency of consumption: every day, 3 to 5 times per week, and 1 to 2 times per week, respectively. The PBDS was calculated as the sum of the positive and negative scores and ranged between −40 and +40. A higher PBDS indicated greater adherence to the PBD. The PBDS of a PBD during hospitalization was 35.[31]

Assessment of Efficacy of IPF Therapy

Short-term Period (Induction Phase)

In the induction phase, the remission rate, colectomy rate, and mortality were assessed. The primary endpoint was clinical remission, defined as the disappearance of bloody stool[27] at week 6 after commencement of the first infliximab infusion. Response without remission was defined as improvement without disappearance of bloody stool. Indication for colectomy or switching to another medication because of poor response before completion of the induction therapy was regarded as therapeutic failure. The secondary endpoints were change of C-reactive protein (CRP) level and ESR.

Medium-Term Period (Quiescent Phase)

In the follow-up studies, the remission rate, colectomy rate, relapse rate, and mortality were assessed at 3 months and 1 year after induction phase. A relapse was defined as a flare-up that required more aggressive medical treatment.[32-34] A reappearance of streak blood, a small volume of blood, or bloody stool was not counted as a relapse if the blood disappeared or was controlled with previous medication and/or modification of the diet or a lifestyle behavior. The secondary endpoint was change over time in PBDS. Short-term (≤ 2 y after discharge) and long-term (> 2 y) chronological changes in PBDS were studied.

Safety Evaluations

Safety assessments included vital signs, patient symptoms, findings during daily practitioner rounds, physical examination findings, and periodic laboratory data.

Statistical Analysis

Demographic parameters were expressed as mean (standard deviation) and/or median (interquartile range [IQR]), as appropriate. Kaplan-Meier survival analysis was used to calculate the cumulative proportion of patients who had a relapse. To evaluate the effect of treatment on CRP and ESR, differences were analyzed by analysis of variance. If the results of the analysis of variance were statistically significant, the data were analyzed using the post hoc Tukey-Kramer honestly significant difference test. Chronological changes in PBDS+, PBDS−, and scores in identical patients were compared using the paired *t*-test or

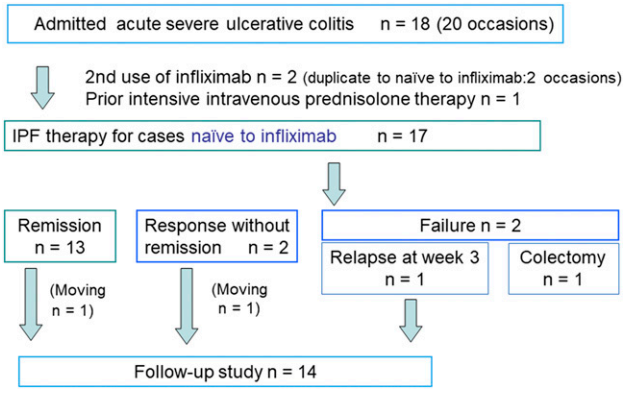

Figure 1. Enrollment of inpatients with severe ulcerative colitis for infliximab and plant-based diet as first-line (IPF) therapy.

Wilcoxon test. A p value of 0.05 or less was considered to indicate a statistically significant difference. Statistical analysis was performed using JMP 8 software (SAS Institute Inc, Cary, NC).

RESULTS

Patient Characteristics

Eighteen patients with severe UC were admitted 20 times; 2 patients were admitted twice and treated with infliximab and PBD twice (Figure 1). One patient was excluded from the study because of prior intensive intravenous corticosteroids treatment[13] by a referring physician. Therefore, IPF therapy for 17 patients naive to infliximab was included in this study. The demographics of the 17 patients are presented in Table 1. Mean (standard deviation) age was 43 (20) years. There were 11 initial episode cases, 4 relapsing-remitting cases, and 2 chronic continuous cases. There were 13 cases with extensive colitis and 4 cases with left-sided colitis. The median (IQR) disease duration was 36 (11-103) months. The median (IQR) CRP levels and ESRs were 4.5 (1.5-11.4) mg/dL and 54 (40-66) mm/h, respectively. No case had a positive result on the cytomegalovirus antigenemia test (n = 13) and the immunoassay for *C difficile* (n = 14; Table 1). Eight patients were discharged after the second infliximab infusion, and 7 of the 8 were readmitted for the third infusion.

Table 1. Demographic characteristics of 17 patients with severe ulcerative colitis

Characteristic	Total
Male/female sex, no. (%)	11/6 (65/35)
Age, y	
Range	18-78
Mean (SD)	43 (20)
Median (IQR)	38 (24-62)
Clinical type, no. (%)	
Initial episode	11 (65)
Relapsing-remitting	4 (24)
Chronic continuous	2 (12)
Extent of ulcerative colitis, no. (%)	
Proctitis	0 (0)
Left-sided colitis	4 (24)
Extensive colitis	13 (76)
Disease duration, mo	
Range	1-336
Mean (SD)	79 (103)
Median (IQR)	36 (11-103)
Case referral status, no. (%)	
Referred	9 (53)
Nonreferred	8 (47)
Previous status or treatment	
Steroid dependent, no. (%)	2 (12)
Previous proctocolectomy, no. (%)	0 (0)
Laboratory test results	
C-reactive protein, mg/dL (reference ≤ 0.3 mg/dL)	
Mean (SD)	7.1 (7.2)
Median (IQR)	4.5 (1.5-11.4)
Erythrocyte sedimentation rate, mm/h (reference ≤10 mm/h in men, ≤15 mm/h in women)	
Mean (SD)	54 (23)
Median (IQR)	54 (40-66)
Positive cytomegalovirus antigenemia, no. (%)	0/13 (0)
Positive immunoassay for *Clostridium difficile*,[a] no. (%)	0/14 (0)
Medication during hospitalization, no. (%)[b]	
Oral 5-aminosalicylic acids (5-ASA)	11 (65)
Immunomodulator	3 (18)
Prednisolone (PS) alone or combined with 5-ASA	2 (12)
PS, azathioprine, and 5-ASA	1 (6)
Follow-up period after discharge, y (n = 14)	
Mean (SD)	3.7 (2.8)
Median (IQR)	3.1 (1.3-6.1)

[a] C. Diff Quik Chek Complete, TechLab, Blacksburg, VA.
[b] Percentages do not total to 100 because of rounding.
IQR = interquartile range; SD = standard deviation.

Induction Phase

Primary Endpoint: Remission and Colectomy Rate

The remission rate in the intention-to-treat analyses, colectomy rate, response without remission, and therapeutic failure excluding colectomy was 76% (13/17), 6% (1/17), 12% (2/17), and 6% (1/17), respectively (Table 2 and Figure 1). One patient receiving total parenteral nutrition underwent proctocolectomy 12 days after the first infusion. In this case, intravenous prednisolone (60 mg/d) was initiated on the fourth day after the infusion because of a lack of improvement in symptoms. Prednisolone was also

Table 2. Outcomes of IPF therapy for severe ulcerative colitis, number (percentage)

	Induction phase	Medium-term period	
Outcome	At 6 weeks (n = 17)	At 3 months (n = 14)	At 1 year (n = 12)[a]
Remission	13 (76)	13 (93)[b]	9 (75)[b]
Response without remission	2 (12)	NA	NA
Colectomy	1 (6)	0 (0)	0 (0)
Failure	1 (6)	NA	NA
Relapse	NA	0 (0)	3 (25)
Corticosteroid treatment	NA	1 (7)	0 (0)
Corticosteroid dependence	NA	0 (0)	0 (0)
Death	0 (0)	0 (0)	0 (0)

[a] Two follow-up cases are not included because their follow-up periods were less than 1 y.
[b] Three cases of scheduled infliximab maintenance therapy in each subgroup are included.
IPF = infliximab and plant-based diet as first-line (therapy); NA = not applicable.

ineffective, and colectomy was indicated. The resected specimen was identified to be infected with cytomegalovirus. Two patients responded without remission. One patient was therapeutic failure who discharged in remission after the second infusion but relapsed 1 week later. This patient was treated with oral prednisolone (40 mg/d), resulting in remission. Seven patients who were discharged after the second infusion and readmitted during the third infusion achieved remission.

Secondary Endpoints

The mean concentration of CRP (reference ≤ 0.3 mg/dL) in 13 cases with clinical remission decreased from 9.42 mg/dL before IPF therapy to 0.61 mg/dL after the first infliximab infusion ($p < 0.0001$). The CRP concentration normalized (0.11 mg/dL) at week 2 and reached the lowest point (0.04 mg/dL) at week 4 but increased to 0.28 and 0.33 mg/dL at weeks 5 and 6, respectively (Figure 2 and Table 3). The mean ESR (reference ≤ 10 mm/h in men and ≤ 15 mm/h in women) decreased from 59 mm/h before IPF therapy to 17 mm/h at week 6 ($p < 0.0001$; Figure 2 and Table 3).

One patient among the 13 patients with clinical remission did not undergo morphologic study. Mucosal healing was achieved in 7 of 12 cases (58%). In the other 5 cases, there were still ulcers, although improvement was evident.

Quiescent Phase

Primary Endpoint

Excluding 1 patient who underwent colectomy and 2 patients who moved away immediately after discharge (1 patient with remission and 1 patient with response without remission), 14 patients were followed (Figure 1). Two patients were followed for less than 1 year, and the remaining 12 patients were followed for more than 1 year. Of these 14 patients, 12 had remission, 1 had a response

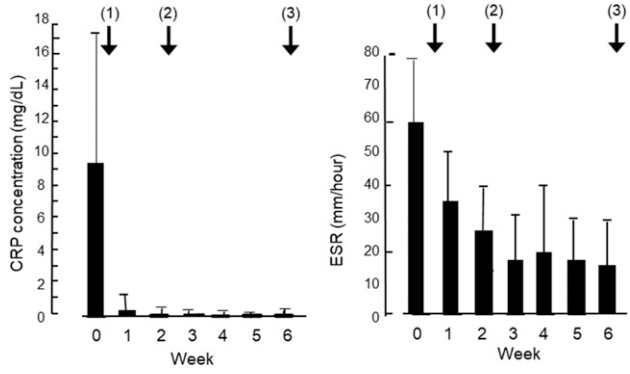

Figure 2. Change in C-reactive protein (CRP) concentration (left) and erythrocyte sedimentation rate (ESR; right) before and after infliximab and plant-based diet as first-line (IPF) therapy in 13 patients with severe ulcerative colitis who achieved clinical remission. Solid bar denotes mean, and error bar shows standard deviation. Arrows with a number in parentheses indicate 3 infliximab infusions at weeks 0, 2, and 6. CRP concentrations and ESRs are presented in Table 3. CRP concentrations and ESRs after IPF therapy were significantly decreased compared with before therapy (analysis of variance, $p < 0.0001$).

without remission, and 1 had treatment failure during the induction phase (Figure 1). The median follow-up was 3.1 years (IQR = 1.3-6.1 y; Table 1). Five patients received scheduled infliximab maintenance therapy: 1 patient achieved response without remission, 3 patients achieved clinical remission without endoscopic remission, and 1 patient had severe systemic complication (Takayasu arteritis). One patient with treatment failure was receiving prednisolone at month 3 and achieved remission without prednisolone at 1 year. There was no additional colectomy case through 1-year follow-up after discharge (Table 2). Three patients relapsed at 1 year. All 3 of these patients had achieved clinical remission in the induction phase. The cumulative relapse rate at 1 year of follow-up was 25% (Figure 3). There was no case of corticosteroid dependence at 1 year. There were no deaths during the study (Table 2).

Table 3. Change of C-reactive protein concentration and erythrocyte sedimentation rate during induction phase after IPF therapy

Parameter	Weeks after IPF therapy							p value (ANOVA)
	0	1	2	3	4	5	6	
Number of patients	13	13	13	10	7	8	13	
CRP, mg/dL, mean (SD)[a]	9.42 (8.29)	0.61 (0.67)	0.11 (0.17)	0.09 (0.16)	0.04 (0.04)	0.28 (0.54)	0.33 (0.65)	< 0.0001
Erythrocyte sedimentation rate, mm/h, mean (SD)[b]	59 (20)	37 (13)	25 (14)	17 (14)	26 (21)	18 (14)	17 (14)	< 0.0001

[a] Reference range ≤ 0.3 mg/dL.
[b] Reference range ≤ 10 mm/h for male patients; ≤ 15 mm/h for female patients.
ANOVA = analysis of variance; CRP = C-reactive protein; IPF therapy = infliximab and plant-based diet as the first-line therapy; SD = standard deviation.

Secondary Endpoints

Mean (standard deviation) baseline PBDS+, PBDS–, and PBDS in 17 patients were 19.9 (7.4), 11.1 (5.3), and 8.8 (7.4), respectively (Table 4). Short-term (≤ 2 y after discharge) and long-term (> 2 y) chronological changes in the PBDS were available in 10 and 8 patients, respectively. For 10 patients, at the median follow-up period of 1 year, respective scores were 30.2 (4.7), 2.5 (3.8), and 27.7 (7.0). These 3 values were significantly better than those at baseline ($p < 0.0001$, $p = 0.0028$, and $p < 0.0001$, respectively; Table 4). In 8 patients, at the median follow-up period of 4 years, PBDS+ was higher than that at baseline. The PBDS– and PBDS were significantly better than those at baseline ($p = 0.0167$ and $p = 0.0391$, respectively; Table 4).

Safety

In the induction phase, none of the 17 patients experienced infusion reactions to infliximab. Metronidazole was withdrawn in 2 cases: 1 case owing to hand paresthesia and 1 case to gastric distress. In an additional case, 5-aminosalicylic acid was withdrawn because of gastroenteritis. None of the patients experienced an adverse effect, such as gaseous distress, abdominal discomfort, or diarrhea, as a result of the PBD. Scheduled infliximab maintenance therapy was stopped in 2 cases: 13 months later because of an infusion reaction (respiratory distress) and 15 months later because of thrombocytopenia.

DISCUSSION

In this study, IPF therapy for severe UC achieved remission or response without remission in 88% of patients (n = 15 of 17). The colectomy rate was 6% during the induction phase. The cumulative relapse rate at 1 year was 25% without an additional case of colectomy. There were no deaths. There was no case of corticosteroid dependence at 1 year. These outcomes are clearly better than current intensive intravenous corticosteroid therapy or rescue therapy for patients unresponsive to corticosteroids. PBDSs in the short-term and long-term were significantly higher than the baseline PBDSs.

Severe UC is treated on an inpatient basis for intensive care. The first choice of treatment in the current guidelines is intravenous corticosteroids. Efficacy is judged on or around day 3 of corticosteroid therapy. If it is ineffective, either colectomy or rescue medical therapy is planned. The second-line rescue therapy in cases unresponsive to corticosteroids is either infliximab or cyclosporine. If rescue medical therapy is ineffective, colectomy is indicated. If patients respond to infliximab rescue therapy, scheduled infliximab therapy is recommended for maintenance of remission.[10,14,15]

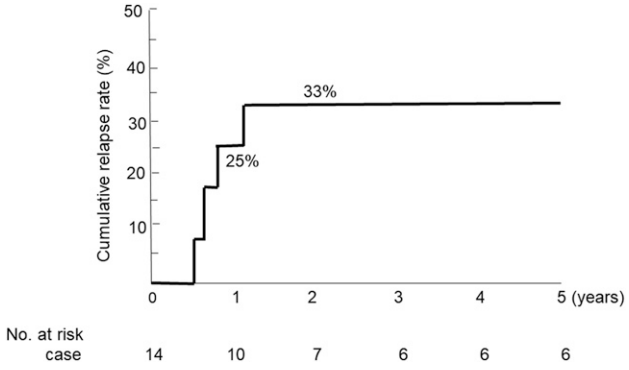

Figure 3. Cumulative relapse rates during follow-up after discharge for treatment of severe ulcerative colitis (n = 14).

When we evaluate the efficacy of therapy in severe UC, it is necessary to pay attention to heterogeneity in the degree of severity. There are 6 items in the Truelove and Witts criteria for severe UC[27]: diarrhea more than 6 times per day, bloody stool, and 4 systemic toxicity signs (tachycardia, fever, anemia, and elevated ESR). The definition of severe differs among reporters in the requirement of systemic signs, from strict requirement of all 4 signs to a liberal requirement of 1 sign.[11] Higher numbers of systemic signs translate into higher colectomy rates: 8.5% for 1 sign, 31% for 2 signs, and 48% for 3 or more signs.[8] The more common IBD becomes, the easier it is for patients to access physicians and receive early diagnosis and treatment. Physicians will not leave patients untreated. They will take adequate steps before patients deteriorate to the point of fulfilling all 4 criteria in current practice. Therefore, the current definition does not require all 4 systemic signs.[8-10] Ungar et al.[35] treated moderately severe cases of UC on an outpatient basis and acute severe cases on an inpatient basis. Outcomes of infliximab treatment in patients with UC are related to severity: higher induction rates and lower colectomy rates are seen in moderately severe UC compared with acute severe UC.[36] Currently, a CRP concentration of 3.0 mg/dL or greater is commonly used as a surrogate for an ESR at or above 30 mm/h, 1 of the original 4 systemic toxicity signs.[8] In our cases, the median CRP level and ESR were 4.5 mg/dL and 54 mm/h, respectively (Table 1).

Both infliximab and cyclosporine have been shown to be effective for rescue treatment in severe patients unresponsive to corticosteroids.[9,10] Nonrandomized studies suggested that infliximab was associated with better treatment response and lower risk of colectomy at 12 months.[12,37-39] Results of a recent review and meta-analysis showed that, in the case of induction with infliximab, the standard 3 infusions were more effective than a sole infusion.[14] There were contradictory results on accelerated infliximab induction therapy, and no superiority of the accelerated therapy to the standard induction therapy was confirmed.[14,40,41] It is noteworthy that chronological change in CRP values during the induction phase in patients with CD and those with UC were similar: the lowest value was at 3 to 5 weeks after therapy in CD[26] and at 4 weeks in UC. Then, CRP increased at 6 weeks to within the normal range in CD,[26] whereas it was above the normal range in UC (Table 3). The third infliximab infusion at week 6 seemed to suppress inflammation again. Although the standard induction schedule for infliximab in UC has been derived from studies in CD,[14] 3 infusions at weeks 0, 2, and 6 seem adequate.

Biologics are used in outpatients with moderate to severe UC and inpatients with severe UC. In both situations, they are indicated in patients refractory to corticosteroids.[1-5,8-10] In moderate to severe UC, remission rates are available for 4 biologics (infliximab, adalimumab, golimumab, and vedolizumab), whereas in severe UC only outcomes of infliximab are available. Despite the differences in study participants and in designs between these studies and our study, comparison of the outcomes in our study with those in other studies is merited. Remission rates in the induction phase in patients with moderate to severe UC who are naive to infliximab, adalimumab, vedolizumab, and golimumab are 38.8%, 49%, 19.2%, and 43.9%, respectively, in the literature.[1-4] The remission rates were scarcely described when infliximab was used as rescue therapy for severe UC because the main concern was to avoid colectomy.[8-10] A systematic review showed that overall colectomy rates at 1 month, 3 months, and 1 year in severe colitis treated with standard infliximab rescue therapy were 10.6%, 16.0%, and 26.2%, respectively.[14] In this study, the colectomy rate was 6% at 1 month, which is lower than the 10.6% just cited. In addition, there was no increase in the colectomy rate at 3 and 12 months. This finding indicates that incorporated PBD is beneficial in maintaining remission.

Rates of remission, incomplete remission, and colectomy with an intensive corticosteroid regimen for severe UC were 40% to 58%, 24% to 26%, and 18% to 34%, respectively.[11,16,18] Those in this study were 76%, 12%, and 6%, respectively, indicating a higher remission rate and lower colectomy rate (Table 2). At 1-year follow-up, corticosteroid dependence and additional colectomy accounted for approximately 50% of patients treated with corticosteroids.[17] There was no case of corticosteroid dependence or additional colectomy in our study (Table 2). Therefore, outcomes in the short term and medium term in IPF therapy could be concluded to be more effective for severe UC than in intensive corticosteroid therapy.

Although the patients with severe UC were different, in most patients without prior corticosteroid treatment in our study vs patients unresponsive to corticosteroids in the other

Table 4. Chronological change of plant-based diet score

Timeframe, n	Follow-up (months)		PBD score+		p value	PBD score-		p value	PBD score		p Value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		Mean (SD)	Median (IQR)		Mean (SD)	Median (IQR)	
Baseline, 17			19.9 (7.4)	20.0 (15.0-25.0)		11.1 (5.3)	11.0 (7.0-13.5)		8.8 (7.4)	8.0 (5.0-13.0)	
Follow-up											
Short-term, 10	14.3 (6.2)	12.5 (9.3-19.5)	30.2 (4.7)	30.5 (25.0-35.0)	< 0.0001	2.5 (3.8)	0.5 (0-4.8)	0.0028[a]	27.7 (7.0)	30.0 (22.3-34.3)	< 0.0001
Baseline, 10			18.9 (7.6)	20.5 (12.3-25.0)		10.6 (5.5)	11.5 (4.0-14.3)		8.3 (8.3)	10.5 (1.5-13.0)	
Long-term, 8	58.4 (31.9)	48.5 (38.3-64.8)	26.9 (6.2)	28.0 (24.8-31.8)	0.1484[a]	3.1 (2.6)	2.5 (1.3-5.3)	0.0167	23.8 (7.4)	25.5 (22.3-28.8)	0.0391[a]
Baseline, 8			19.9 (8.4)	23.5 (10.0-25.0)		10.0 (4.3)	11.0 (5.0-13.8)		9.9 (8.4)	10.5 (3.8-18.0)	

[a] p value obtained with paired *t*-test or Wilcoxon test.
IQR = interquartile range; PBD, plant-based diet; SD = standard deviation.

studies,[12,14,37] the induction regimen of infliximab and treatment on an inpatient basis were the same in both studies.[12,14,37] The difference was the incorporation of a PBD in our study. Approximately 10% to 40% of patients with UC, as well as patients with CD, have been found to be primary nonresponders to infliximab.[1,36,41-43] Rates of remission and primary nonresponse are related to each other in reverse fashion. By incorporating a PBD and first-line use of infliximab (IPF therapy) in CD, we showed that all patients achieved remission and that there were no primary nonresponders.[26,44,45] In the present study, a high remission rate (76%) and a low rate of primary nonresponders (6%) were observed (Table 2). In our previous studies, relapse prevention effects of PBD were shown in both CD and UC.[24,34,46] In this current study, no additional colectomy cases were observed at 1 year after IPF therapy, indicating favorable outcomes in the medium term (Table 2). Although sustained dietary modification is desired, a decrease in PBDS was observed over the long term (median duration = 4 years). Most patients tended to lose their determination once they had been in remission for a few years. However, they still consumed more of the recommended foods and consumed less of the foods that were discouraged compared with baseline (Table 4). Consequently, the PBDS was higher compared with baseline (p = 0.0391). We believe that a PBD and learning about healthy habits during hospitalization contributed to enhance self-management skill in maintaining remission.[34,46,47]

The described IPF therapy for severe UC has several advantages over an intensive corticosteroid regimen or infliximab alone. The rapid efficacy of infliximab enabled patients to ingest supper on the same day of the treatment in most patients. The standard induction therapy with infliximab alone without immunosuppressive agents is quite safe.[26] There is no worry about adverse events associated with the use of corticosteroids.[48] Most patients can maintain remission without scheduled infliximab maintenance therapy, which greatly reduces the cost of medical care. A PBD is useful to prevent various common diseases.[21-23] When IPF therapy is ineffective, corticosteroids can be used next, as in 2 patients in this study. Infliximab use in patients with UC does not increase the risk of postoperative complications.[49]

There was 1 colectomy case in this study. This patient was found to be infected with cytomegalovirus in a resected colonic specimen. Although patients are normally screened for cytomegalovirus infection at admission, screening was erroneously not performed in this patient. Cytomegalovirus infection within 3 months before infliximab treatment is shown to be a predictor of nonresponse to infliximab.[50]

The Ministry of Health, Labour and Welfare of Japan designated UC and CD as intractable diseases. Patients with intractable diseases are provided with public medical aid on registration at the public health office. Therefore, in Japan, physicians can provide therapy with less concern about medical expenses. In addition, biologics are currently approved only for patients unresponsive to conventional medications.[1–4,15] Thus, there might be limitations to providing the approach proposed herein in other countries and current practice. Considering various clinical situations, better short-term and medium-term outcomes than those reported in patients with severe UC were demonstrated in the present trial of IPF therapy.

Our study had some limitations. There was no control group, and the sample size was small. We hope that other larger, controlled studies will be conducted to validate our results.

CONCLUSION

Infliximab and a PBD as first-line (IPF) therapy induced remission in 13 (76%) of 17 patients with severe UC at week 6, and colectomy was performed in 1 patient (6%). There were no additional colectomy cases at 1 year. IPF therapy provided better short-term and medium-term outcomes for patients with severe UC than the outcomes reported in the literature. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Kathleen Louden, ELS, of Louden Health Communications performed a primary copy edit.

Authors' Contributions

Mitsuro Chiba, MD, PhD, designed and conducted the study and wrote the manuscript. Tsuyotoshi Tsuji, MD, PhD, Satoko Tsuda, MD, and Haruhiko Tozawa, MD, performed the colonoscopy. Hajime Ishii, MD, PhD, Hideo Ohno, MD, Yu Obara, MD, and Masafumi Komatsu, MD, PhD, contributed to the acquisition of cases. Mitsuro Chiba, MD, PhD and Kunio Nakane, MD, PhD, performed the statistical analysis. All authors approved the final version of the manuscript for submission.

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ORIGINAL RESEARCH ARTICLE

Refill Reminder Preference and Inhaled Corticosteroid Adherence Among Patients with Asthma

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ABSTRACT

Context: Refill reminders can help patients improve adherence to inhaled corticosteroid (ICS) therapy. However, little is known about patient preferences for reminder type or whether patients who express a preference differ from patients who do not.

Objectives: To describe patient preferences for ICS prescription refill reminder type and to compare baseline ICS therapy adherence, measured as proportion of days covered (PDC) 1 year before initiating preference-based reminders, between patients who did and did not express a preference.

Design: This substudy within a randomized multi-intervention study was conducted at Kaiser Permanente Colorado. Adults with asthma randomized to intervention were offered the opportunity to choose text, telephone, or email reminders. Patients who did and did not provide a preference were compared by baseline characteristics using log-binomial models.

Main Outcome Measure(s): The primary outcomes were reminder preference and type.

Results: A total of 1497 of 4545 patients (32.9%) expressed a preference; 789 (52.7%) chose text. The adjusted relative risk (aRR) of not providing a preference increased with decreasing PDC (PDC of 0.50 to < 0.80: aRR, 1.14; 95% confidence interval [CI], 1.04-1.25; PDC < 0.5: aRR, 1.76; 95% CI, 1.59-1.95) compared with patients with a PDC of 0.80 or greater.

Conclusion: Among patients who expressed a preference, text reminders were preferred. Patients who expressed a preference had higher baseline adherence. Further research is needed to determine whether expressing a preference for a refill reminder type is itself associated with adherence. Given that offering the opportunity to choose a reminder type only engaged a subset of patients, further work is needed to understand how best to leverage technology-enabled communication outreach to help patients optimize adherence.

INTRODUCTION

Health care professionals continue to seek evidence about how to help patients optimize adherence to medications for chronic conditions, such as asthma.[1-8] Technology-enabled communications using text, email, or automated call are useful for sending patients many types of health care reminders,[9-12] and some evidence suggests that technology-enabled communication reminders can improve adherence to inhaled corticosteroid (ICS) therapy among patients with asthma.[9,13] However, little is known about the preferences of patients with asthma for the modality (ie, type) of technology-enabled communication adherence reminders they receive.[9] Furthermore, little is known about whether or how patients who express a preference for a specific modality of adherence reminder differ from patients who do not express a preference.

The BreatheWell study is a pragmatic randomized clinical trial designed to test the effectiveness of multiple technology-enabled communication interventions. In the BreatheWell study, ambulatory patients with asthma were initially randomized into 3 groups: text or automated telephone call (intervention), email (intervention), or usual care. Each patient then received any of 3 applicable interventions. The interventions targeted the subsets of patients who 1) smoked (smoking intervention completed in 2017), 2) filled inhaled short-acting β-agonists (asthma relievers) prescriptions too frequently (β-agonist overfill intervention, completed in February 2018),[14] and/or 3) required refills of ICS prescriptions (asthma controllers; ICS prescription refill reminder preference intervention began in October 2018). Patients remained in their initially randomized group for the smoking and β-agonist prescription overfill interventions, which were completed before the start of the ICS intervention. For the ICS intervention, patients who had been initially randomized to either of the 2 intervention groups were combined into 1 intervention group and were offered the opportunity to choose a preferred modality of receiving ICS prescription refill reminders (ie, they could choose a reminder type that differed from their initially randomized group).

The ICS prescription refill reminder preference intervention is ongoing. When completed, the results will aid in answering questions about whether being able to choose a refill reminder type is associated with ICS therapy adherence. In addition, developing and implementing the ICS intervention provided the opportunity to better understand characteristics of patients who did or did not respond when given the opportunity to express a preference. Patients initially randomized to the usual care group were not offered

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the opportunity to provide a preference and therefore were not included in this study. The objectives of this study were to answer the following questions as a BreatheWell substudy. Among patients offered the opportunity to provide a preference for the type of ICS prescription refill reminders they receive, 1) what proportion expressed a preference and what modality of reminder did they prefer and 2) did patients who provided a preference have different baseline ICS therapy adherence than patients who did not provide a preference? For the second question, we hypothesized that patients who provided a preference would have higher ICS therapy adherence during the year before the ICS prescription refill reminder intervention compared with patients who did not provide a preference.

METHODS

Setting, Patients, and Eliciting Preference

This work was conducted at Kaiser Permanente Colorado (KPCO), an integrated health care system that had approximately 600,000 members in the Denver-Boulder metropolitan area in 2018. Patients were included in the BreatheWell study cohort if they were current KPCO members as of January 2017, were age 18 years or older (no upper age limit), and had persistent asthma (on the basis of a coded asthma diagnosis and an ICS prescription order within the previous year). Patients diagnosed with chronic obstructive pulmonary disease were excluded as were patients who died or disenrolled. The study cohort was refreshed in June 2018 (just before eliciting preference for the ICS prescription refill reminder preference intervention). The KPCO Institutional Review Board approved this study and waived the informed consent requirement.

Before the start of the ICS prescription refill preference intervention, in KPCO routine health care operations, all patients with asthma younger than age 65 years taking ICSs (ie, regardless of whether they were in the BreatheWell study cohort) received English or Spanish ICS prescription refill reminders by text or automated call when they were due (reminder sent 5-11 days before the refill due date) or overdue (reminder sent 30 days after refill due date) for an ICS prescription refill.[1] Patients did not choose the refill reminder type they received through routine health care operations; rather they received a text if their telephone was text enabled or an automated call if their telephone was not text enabled. Routine health care operations refill reminders were sent using the KPCO automated interactive voice response (IVR) system. In this IVR system, text messages are prioritized for text-enabled telephones, but patients can request not to receive texts. This IVR system has been used in multiple population-based interventions, including several that were subsequently incorporated into usual health care operations.[8,15-17] This IVR system is also being used for the BreatheWell ICS prescription refill reminder preference intervention.

For the ICS prescription refill preference intervention, all patients who had been initially randomized to either of the BreatheWell study intervention groups and who were taking ICSs were invited to choose whether they preferred to receive ICS prescription refill reminders by automated telephone call, text message, or email (see below). Patients who indicated a preference received ICS prescription refill reminders via that mode beginning with their first ICS prescription refill due after October 3, 2018. Patients of all ages who did not provide a preference received ICS prescription refill reminders as per routine health care operations detailed above. Patients originally randomized to the BreatheWell study usual care group were not invited to choose a modality of receiving ICS prescription refill reminders and are not included in this report.

To elicit a preference for type of ICS prescription refill reminders, patients were contacted by at least 2 of the following methods: mail, automated telephone call, and/or email. Contacts were continued until patients provided a preference or until they had been contacted at least 3 and no more than 5 times between June and August 2018. In these contacts, patients were directed to a website where they entered their names and dates of birth into an encrypted system to confirm that they were part of the BreatheWell study cohort. Once patients were verified as being in the study cohort, they could complete an online Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, TN) survey. The survey requested that participants indicate a preference for the modality by which they would receive ICS prescription refill reminders and provide the contact information they wanted used for reminders. Patients could select only 1 mode of refill reminder. As part of the contacts, patients were provided information about how to reach the BreatheWell study team if they had questions, to provide their preference (as an alternative to completing the online survey), or to opt out of participating in the intervention.

Data Sources

Patient demographic, administrative, utilization, and clinical data were extracted from the KPCO Virtual Data Warehouse (VDW). The VDW content areas used included demographics, enrollment, encounters, diagnoses, utilization, death, census, pharmacy, language preference, socioeconomic status, and benefits. The VDW data tables are linked by a common, unique patient identifier that differs from the patient's health record number. The crosswalk between the VDW unique patient identifier and the patient's health record number is maintained in a separate table. Patient email and telephone contact

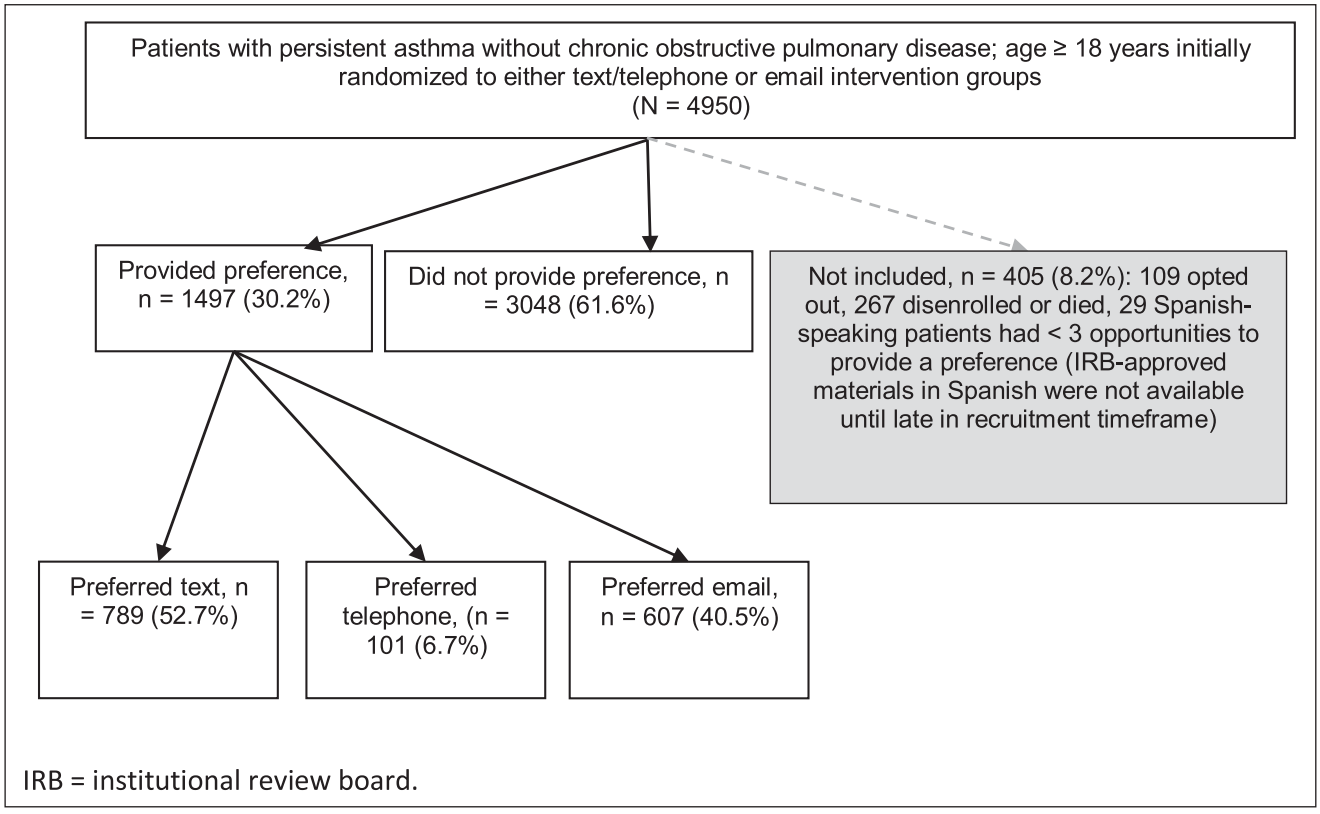

Figure 1. BreatheWell study intervention patients and preference for inhaled corticosteroid prescription refill reminders. Not included, n = 405 (8.2%): 109 opted out, 267 disenrolled or died, 29 Spanish-speaking patients had < 3 opportunities to provide a preference (IRB-approved materials in Spanish were not available until late in recruitment timeframe).

information was extracted from the electronic health record as well as the preference survey.

Statistical Analysis

Baseline characteristics of patients in the analytic cohort were examined using descriptive statistics. These characteristics included age, sex, race/ethnicity, socioeconomic status (educational level and income), insurance plan type, and enrollment history. In addition, for the year before the start of the ICS prescription refill reminder intervention (October 3, 2017, to October 2, 2018), the number of clinic appointments missed, adherence as the proportion of days covered (PDC),[18] and asthma exacerbations were determined. Asthma exacerbations were defined as oral corticosteroid bursts and asthma-related urgent care visits, Emergency Department visits, and hospitalizations. Patients who provided a preference were compared with those who did not on baseline characteristics, asthma exacerbations, and the PDC the year before the intervention. In univariable comparisons, the χ^2, *t*-test, or Wilcoxon rank-sum test was used to estimate the significance of comparisons between those who provided a preference and those who did not. For patients who chose 1 of the 3 reminder modes, the χ^2 test, analysis of variance, or Kruskal-Wallis test was used for comparisons.

Relative risks (RRs) and 95% confidence intervals (CIs) for the binary outcome of not providing a preference for refill reminder type were estimated using log-binomial models (ie, binomial distribution with a log link function).[19] Univariate RRs were estimated and a multivariable model of adjusted RR (aRR) was prepared to explore strengths of associations when all variables were modeled together. Characteristics in the multivariable model included age, sex, race/ethnicity, percentage of census block with less than a high school education, family income, insurance plan type, asthma exacerbations in the prior year, missed clinic appointments in the prior year, and ICS PDC. Statistical analyses used SAS Studio software, release 3.7 (Enterprise Edition) (SAS Institute Inc, Cary, NC).

RESULTS

The final analytic cohort included 4545 patients (Figure 1), including 1497 patients (32.9%) who provided a preference

Table 1. Characteristics of patients who did and did not provide a preference for the modality of receiving inhaled corticosteroid prescription refill reminders[a]

Characteristic	Offered preference, N = 4545		p value[b]
	Provided preference, n = 1497 (32.9%)	Did not provide preference, n = 3048 (67.1%)	
Age, mean (SD), y	57.5 (15.3)	48.9 (17.1)	< 0.001
Preference by age group, y			
< 65, n = 3394 (74.7%)	935 (62.5)	2459 (80.7)	< 0.001
> 65, n = 1151 (25.3%)	562 (37.5)	589 (19.3)	
Sex			
Female	1019 (68.0)	1812 (59.4)	< 0.001
Race/ethnicity			
Hispanic	163 (10.9)	530 (17.4)	< 0.001
Non-Hispanic white	1180 (78.8)	2064 (67.7)	
Non-Hispanic black	55 (3.7)	201 (6.6)	
Asian	38 (2.5)	72 (2.4)	
Other or unknown	61 (4.1)	181 (5.9)	
Education level			
Less than high school education, mean (SD), % of census block	7.2 (8.6)	9.2 (10.5)	< 0.001
Family income (per census block)			
< $50,000	143 (9.6)	453 (14.9)	< 0.001
$50,000-$100,0000	819 (54.7)	1,690 (55.4)	
> $100,000	535 (35.7)	905 (29.7)	
Insurance plan type			
Traditional HMO	723 (48.3)	1,179 (38.7)	< 0.001
Deductible HMO	550 (36.7)	1,226 (40.2)	
High deductible	130 (8.7)	311 (10.2)	
Medicaid	48 (3.2)	245 (8.0)	
Other	46 (3.1)	87 (2.9)	
Missed appointments in prior year			
≥ 1 Missed appointment(s)	501 (33.5)	1103 (36.2)	< 0.001
No missed appointments	957 (63.9)	1772 (58.1)	
No scheduled appointments	39 (2.6)	173 (5.7)	
ICS PDC[d,e]			
Mean (SD)	0.66 (0.26)	0.52 (0.28)	< 0.001
< 50%	434 (29.9)	1450 (51.5)	< 0.001
50%- < 80%	459 (31.6)	758 (26.9)	
≥ 80%	558 (38.5)	607 (21.6)	
Asthma exacerbations, mean (SD)[c,d]	0.33 (0.75)	0.31 (0.81)	0.189

[a] Data are presented as number (percentage) of patients unless otherwise indicated.
[b] The χ^2, *t*-test, or Wilcoxon rank sum test
[c] Includes asthma-related urgent care visits, Emergency Department visits and hospitalizations, or corticosteroid bursts.
[d] Year before intervention.
[e] n = 4266 for PDC (excludes 30 persons enrolled at < 6 months and 249 with no ICS days' supply in prior year).
HMO = health maintenance organization; ICS = inhaled corticosteroid; PDC = proportion of days covered; SD = standard deviation.

and 3048 patients (67.1%) who did not (Table 1). By age group, 562 of 1151 patients (48.8%) age 65 years or older provided a preference, whereas 935 of 3394 patients (27.5%) younger than age 65 years provided a preference. Patients who provided a preference differed from those who did not in most measured characteristics (Table 1). For example, they were older ($p < 0.001$) and had higher family income ($p < 0.001$). However, patients who provided a preference were like patients who did not provide a preference in asthma exacerbations (mean [standard deviation {SD}], 0.33 [0.75] vs 0.31 [0.81]; $p = 0.189$).

Table 2. Characteristics of patients who provided a preference by preferred type of ICS prescription refill reminder[a]

Characteristic	ICS prescription refill reminder preference type			p value[b]
	Text, n = 789 (52.7%)	Email, n = 607 (40.6%)	Telephone, n = 101 (6.8%)	
Age, mean (SD), y	53.5 (14.5)	60.4 (15.0)	71.2 (11.5)	< 0.001
Preference by age group, y				
< 65 (n = 935 [62.5%])	596 (75.5)	316 (52.1)	23 (22.8)	< 0.001
≥ 65 (n = 562 [37.5%])	193 (24.5)	291 (47.9)	78 (77.2)	
Sex				
Female	563 (71.4)	386 (63.6)	70 (69.3)	0.008
Race/ethnicity				
Hispanic	115 (14.6)	40 (6.6)	–[c]	< 0.001
Non-Hispanic white	586 (74.3)	516 (85.0)		
Non-Hispanic black	36 (4.6)	15 (2.5)		
Asian	16 (2.0)	17 (2.8)		
Other or unknown	36 (4.6)	19 (3.1)		
Education level				
Less than high school education mean (SD), % of census block	7.6 (9.1)	6.5 (7.8)	8.6 (9.4)	0.26
Family income (per census block)				
< $50,000	81 (10.3)	53 (8.7)	9 (8.9)	0.17
$50,000-$100,0000	432 (54.8)	322 (53.1)	65 (64.4)	
> $100,000	276 (35.0)	232 (38.2)	27 (26.7)	
Insurance plan type				
HMO	341 (43.2)	313 (51.6)	–[c]	<0.001
Deductible HMO	312 (39.5)	215 (35.4)		
High deductible	75 (9.5)	51 (8.4)		
Medicaid	36 (4.6)	10 (1.7)		
Other	25 (3.2)	18 (3.0)		
Missed appointments in prior year				
≥1 Missed appointment(s)	286 (36.3)	179 (29.5)	–[c]	0.08
No missed appointments	480 (60.3)	414 (68.2)		
No scheduled appointments	23 (2.9)	14 (2.3)		
ICS PDC[e,f]				
Mean (SD)	0.66 (0.26)	0.66 (0.27)	0.63 (0.28)	0.54
< 50%	218 (28.5)	178 (30.4)	38 (38.4)	0.31
50%- < 80%	246 (32.1)	188 (32.1)	25 (25.3)	
≥ 80%	302 (39.4)	220 (37.5)	36 (36.4)	
Asthma exacerbations, mean (SD)[d]	0.33 (0.72)	0.29 (0.74)	0.47 (0.97)	0.11

[a] Data are presented as number (percentage) of patients unless otherwise indicated.
[b] The χ^2, analysis of variance, or Kruskal-Wallis test.
[c] Actual numbers not given for entries with fewer than 6 patients to maintain Health Insurance Portability and Accountability Act compliance.
[d] Includes asthma-related urgent care visits, Emergency Department visits and hospitalization, or corticosteroid bursts.
[e] Year before intervention.
[f] n = 1451 for PDC (excludes 9 persons enrolled at < 6 months and 37 with no ICS days' supply in prior year).
HMO = health maintenance organization; ICS = inhaled corticosteroid; PDC = proportion of days covered; SD = standard deviation.

A total of 789 patients (52.7%) who provided a preference requested text reminders (Figure 1; Table 2); 596 (75.5%) of those who preferred text were younger than age 65 years (Table 2). Other than age, across patients who preferred a specific reminder type, there were far fewer differences in measured characteristics (Table 2) across patients who preferred text vs email vs telephone reminders than between patients who did vs did not express a preference.

The PDC the year before the intervention was higher in patients who provided a preference than in those who did not (mean [SD], 0.66 [0.26] vs 0.52 [0.28]; p < 0.001)

Table 3. Relative risks of not providing a preference for the modality of receiving ICS prescription refill reminders among patients with asthma

Characteristic	Unadjusted relative risk, n = 4545 (95% CI)	Adjusted relative risk n = 4212 (95% CI)[a]
Age (per 10 years)	0.91 (0.90-0.92)	0.87 (0.85-0.89)
Sex		
Female, reference	1.13 (1.08-1.17)	1.19 (1.10-1.30)
Race/ethnicity (reference: non-Hispanic white)		
Hispanic	1.20 (1.14-1.26)	1.20 (1.04-1.39)
Non-Hispanic black	1.23 (1.15-1.32)	1.30 (1.01-1.67)
Asian	1.03 (0.90-1.18)	0.99 (0.79-1.25)
Other or unknown	1.18 (1.09-1.27)	1.21 (0.99-1.49)
Education		
Less than high school education (per 10% increment), % of census block	1.06 (1.05-1.08)	1.08 (1.02-1.15)
Family income (reference: > $100,000)		
< $50,000	1.21 (1.14-1.28)	0.98 (0.81-1.18)
$50,000-$100,0000	1.07 (1.02-1.12)	1.03 (0.95-1.12)
Insurance plan type (reference: HMO)		
Deductible HMO	1.11 (1.06-1.17)	0.99 (0.91-1.09)
High deductible	1.14 (1.06-1.22)	0.96 (0.82-1.12)
Medicaid	1.35 (1.27-1.43)	1.53 (1.16-2.01)
Other	1.06 (0.93-1.20)	0.87 (0.69-1.10)
Missed appointments in prior year (reference: none)		
≥ 1	1.06 (1.01-1.11)	1.08 (0.99-1.17)
No scheduled appointments	1.26 (1.17-1.35)	1.54 (1.15-2.06)
ICS PDC in prior year (reference: ≥ 0.80)		
0.50- < 0.80	1.20 (1.14-1.28)[b]	1.14 (1.04-1.25)
< 0.50	1.48 (1.39-1.45)	1.76 (1.59-1.95)
Asthma exacerbations in prior year (reference: none)	0.97 (0.92-1.02)	0.97 (0.89-1.06)

[a] Adjusted for all characteristics listed. Excludes 30 persons enrolled at < 6 months and 303 persons with no asthma prescription dispensings in the prior year or no ICS days' supply in the prior year.

[b] n = 4266 for PDC (excludes 30 persons enrolled at < 6 months and 249 with no ICS days' supply in the prior year).

HMO = health maintenance organization; ICS = inhaled corticosteroid; PDC = proportion of days covered.

(Table 1). Across patients who preferred a specific reminder type, the PDC did not differ by preferred type of reminder (mean [SD], 0.66 [0.26] text, 0.66 [0.27] email, and 0.63 [0.28] telephone; p = 0.54) (Table 2).

The aRR of not providing a preference increased with decreasing PDC. Compared with patients with a PDC of 0.80 or greater, patients with a PDC of 0.50 to less than 0.80 had an aRR of 1.14 (95% CI, 1.04-1.25), and patients with a PDC less than 0.5 had an aRR of 1.76 (95% CI, 1.59-1.95) (Table 3). Two additional characteristics were associated with a moderate increase in aRR: having no scheduled clinic appointments in the prior year (aRR, 1.54; 95% CI, 1.15-2.06) and having Medicaid (aRR, 1.53; 95% CI, 1.16-2.01). As indicated in Table 3, several characteristics were associated with small increases in the aRR of not providing a preference. Increasing age was associated with a protective effect against not providing a preference (aRR, 0.87; 95% CI, 0.85-0.89).

DISCUSSION

In this evaluation of preferences of patients with asthma for the type of technology-enabled communication for ICS therapy adherence reminders they received, when offered the opportunity to choose a reminder type, only one-third of patients expressed a preference, and among those who provided a preference, more than half selected text messaging. Patients who provided a preference differed from those who did not in numerous ways, such as being older, having higher income, and more often being white. Importantly, we also found that patients who provided a preference had higher ICS therapy adherence the year before the ICS prescription refill reminder preference-based intervention than patients who did not provide a preference. Finally, we found that patients with the lowest ICS therapy adherence the year before the intervention had a 76% increase in the aRR of not providing a preference for ICS prescription refill reminder type, and patients who had no

scheduled clinic appointments in the prior year or who had Medicaid insurance had 54% and 53% increases, respectively, in the aRR of not providing a preference.

Across patients who expressed a preference, except for text reminders being preferred by younger patients, few characteristics differed on the basis of refill reminder type preferred. The PDC the year before initiating the ICS prescription refill reminder preference-based intervention did not differ across patients who preferred text, email, or telephone.

One factor that possibly contributed to the low proportion of patients who chose the type of ICS prescription refill reminders they preferred was that, in routine health care operations at KPCO, patients younger than age 65 years were already receiving ICS refill reminders by text or automated call. Although patients did not get to choose the type of refill reminders they received as part of routine health care operations, they could have been satisfied with these reminders and therefore did not feel it necessary to explicitly state a preference when asked to do so before the preference-based intervention. This theory is supported by our finding that 74.7% of patients were younger than age 65 years but accounted for 80.7% of patients who did not provide a preference (Table 1). We only surmise this, however, because our study did not examine the satisfaction of patients with refill reminders provided through routine health care operations.

Among patients who expressed a preference, more than half preferred to receive reminders by text. Our finding is consistent with at least 1 recent study that found that patients prefer text messaging for health-related reminders.[20] A difference in preferred prescription refill reminder type by age was noted. Although individuals age 65 years and older accounted for 37.5% of patients who provided a preference, they accounted for only 24.5% of patients who preferred text and 77.2% of the patients who preferred telephone call (Table 2). This finding is consistent with a study of cancer screening reminders that found younger individuals more commonly requested text or email reminders.[21]

A strength of this study is its large sample of demographically and socioeconomically diverse adults with persistent asthma. Our data sources were comprehensive and robust, with few missing data elements (eg, < 3% with unknown race/ethnicity) and contact information for essentially all patients in the cohort. Few patients opted out, maintaining the representativeness of the study sample.

As with any study, this work has limitations. It was not designed to assess preferences for reminder content, timing, or number. A high proportion of patients in this study were privately insured. It is unknown whether health care systems that serve predominantly publicly insured patients would have similar findings, particularly given that having Medicaid insurance was associated with not providing a preference. Finally, our health care system already had a nonpreference-based prescription refill reminder system in place for ICSs for patients younger than age 65 years; it is feasible that findings might differ in a patient population naïve to automated prescription refill reminders.

In view of the low proportion of patients who expressed a preference (less than half of patients whether age < 65 or ≥ 65 years), an important finding of this study is that further work is needed to understand how best to leverage technology-enabled communication outreach tools to help patients optimize adherence to ICS therapy. The proportion of patients in our study who did not express a preference for an ICS prescription refill reminder type suggests that offering the opportunity to choose a reminder type only engages a subset of patients. The fact that the subset of patients who expressed a preference had higher baseline ICS adherence potentially suggests that technology-enabled communication outreach may be perceived as more important by patients who are already focused on optimizing their asthma drug therapy management. Nonetheless, additional studies can help determine how and when to best use technology-enabled communication when reaching out to patients who are less engaged. Although we believe the results of our ongoing BreatheWell study that ICS prescription refill reminder preference intervention will shed light on whether preference-based technology-enabled communication outreach is effective in optimizing ICS therapy adherence compared with usual care, opportunities will remain to study how best to engage the many patients with suboptimal ICS adherence who do not express a preference for a specific type of refill reminder. Opportunities also exist to examine patient satisfaction with specific types of technology-enabled interventions and with timing and content of reminders.

CONCLUSION

Text messaging was preferred by more than half of patients who expressed a preference for a specific type of technology-enabled ICS prescription refill reminder; however, two-thirds of patients did not express a preference. Given that offering the opportunity to choose a reminder type only engaged a subset of patients, a key message for health care professionals is that further work is needed to understand how best to leverage technology-enabled communication outreach tools to help patients optimize adherence. Patients who chose a prescription refill reminder type had higher baseline ICS therapy adherence than patients who did not choose a reminder type, regardless of whether they chose text, email, or telephone call reminders, suggesting they were already more engaged in optimizing adherence to their asthma therapy than patients who did not choose a reminder type. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Authors' Contributions

Raebel led study design, participated in data analysis and interpretation, and led manuscript preparation. Shetterly participated in study design, participated in data analysis and interpretation, and reviewed and edited the manuscript. Goodrich participated in study design, led data collection, participated in data analysis and interpretation, and reviewed and edited the manuscript. Anderson participated in data collection, data interpretation, and reviewed and edited the manuscript. Bender participated in study design, data interpretation, and reviewed and edited the manuscript. Wagner participated in study design, data interpretation, and reviewed and edited the manuscript.

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ORIGINAL RESEARCH ARTICLE

Clinical Implications of the Association of Race With Body Satisfaction and Perceived Control Over Eating in Women Initiating a Behavioral Obesity Treatment

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ABSTRACT

Objective: An improved understanding of the implications of race on body satisfaction might optimize the weight loss process and quality of life in women with obesity.

Methods: Women with obesity (mean [standard deviation] age, 33.0 [13.8] years) of black (n = 32) and white (n = 38) racial groups volunteered for a cognitive-behavioral weight management program.

Results: Body satisfaction scores at baseline and month 3 were significantly higher in the black group; however, the significant within-group improvements in that variable and on weight, physical activity, fruit and vegetable consumption, sweets intake, perceived ability to control eating, and emotional eating did not significantly differ by racial group. Neither weight nor age significantly added to the strength of the association between race and body satisfaction. Perceived ability to control eating mediated the associations between race and body satisfaction as well as change in weight and change in body satisfaction. In post hoc analyses, inverse associations between body satisfaction and emotional eating were detected regardless of race.

Conclusion: The findings of this study increased understanding of body satisfaction in women with obesity and have implications for addressing psychosocial factors within weight loss treatments across racial and at-risk groups.

Introduction

In the US, 32% of white women and 55% of black women have obesity (body mass index ≥ 30 [calculated as weight in kilograms divided by square of height in meters]).[1] Of those with an unhealthy weight, approximately 60% are actively trying to lose weight.[1] A poor understanding of psychosocial factors associated with weight and weight loss has rendered almost all behavioral (nonsurgical and nonpharmacologic) treatments ineffective beyond their initial weeks.[2] Psychosocial factors, such as body satisfaction, emotional eating, and perceived ability to control eating, can have important implications in early months of treatment that could vary by ethnicity/race and age in women.[3] For example, black women tend to have a more favorable body image and less disordered eating than white women.[4,5] However, these findings are less clear for those participating in treatments for obesity and across age groups.[3,4] Notably, more women who have a healthy weight seek weight loss because of a poor body image than those with overweight or obesity.[6] Body satisfaction is an important quality-of-life variable that might be affected by cultural factors, including pressures for thinness in women.

On the basis of social cognitive and self-efficacy theories,[7,8] perceptions of one's ability to control eating might affect body satisfaction, disordered eating, and weight loss behaviors.[3] Thus, theory-based, behavioral weight management treatments have emphasized the use of self-regulatory skills (eg, relapse prevention) to overcome barriers to behavioral changes and foster feelings of perceived ability to sustain desired changes. Although analyses of possible psychosocial factors of typical treatment outcome measures (eg, weight and body composition) have long been advocated, minimal research attention has been focused on these factors to help inform treatment architectures.[2] An increased understanding of the aforementioned associations could also be useful for interactions between medical professionals and patients.

Thus, this study assessed white and black women with obesity participating in a theoretically driven, behavioral weight management program intended to induce both sustained physical activity and eating changes. It assessed 3-month changes in body satisfaction and other psychological and behavioral factors relevant to weight and the weight loss process, accounting for race, age, and initial weight.

Our hypotheses were as follows. First, significant 3-month improvements would be seen in weight, physical activity, fruit and vegetable consumption, sweets intake, body satisfaction, perceived ability to control eating, and emotional eating across racial groups. Second, black race would be associated with higher body satisfaction. (It was set as a research question, without hypotheses, whether the addition of weight and age would significantly affect that association.) Third, perceived ability to control eating would mediate the association between race and body satisfaction

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and the association between changes in weight and body satisfaction.

Methods

Participants

Women in the Southeast US volunteered for a weight management program that emphasized physical activity and healthy eating. Inclusion criteria were obesity, no known health issues that precluded safe participation, no regular exercise (≤ 1 exercise session per week during the previous year), and not currently participating in any weight loss program. The present data set was part of a larger and longer-term research project and included only black (n = 32) and white (n = 38) women. There were no significant group differences in age (mean [standard deviation], 33.0 [13.8] years) and weight (mean [standard deviation], 95.5 [12.7] kg). Almost all the women were in the middle socioeconomic stratum. Approval of the study protocol and of the written informed consent form required for participation was obtained from Kennesaw State University institutional review board.

Measures

Body satisfaction was measured using the body areas satisfaction scale of the Multidimensional Body-Self Relations Questionnaire.[9] Happiness or unhappiness with 9 areas of a respondent's body (eg, lower torso [buttocks, hips, thighs, legs]) was self-reported, with possible responses ranging from 1 (very dissatisfied) to 5 (very satisfied). Item scores were summed and then divided by 9. The internal consistency was Cronbach α = 0.73, and test-retest reliability during 4 weeks was 0.74. Strong correspondences with other well-validated body image scales were found.[9] For the present sample, Cronbach α = 0.75.

Perceived ability to control eating was measured using the Weight Efficacy Lifestyle Questionnaire.[10] Items included feelings of control over eating under conditions of negative emotions, social pressures, physical discomforts, high food availabilities, and positive activities (eg, television watching). Possible responses to the 20 items, such as "I can resist eating when I am anxious (nervous)" and "I can resist eating even when others are pressuring me to eat," ranged from 0 (not confident) to 9 (very confident) and were summed. Internal consistencies ranged from Cronbach α = 0.70 to 0.90,[10] and for the present sample was Cronbach α = 0.74 to 0.82.

Emotional eating was measured using the Emotional Eating Scale.[11] Fifteen items addressed how feelings related to anxiety (eg, on edge), depression (eg, sad), and anger (eg, irritated) led a respondent to a desire or urge to eat. Possible responses ranged from 0 (no desire to eat) to 4 (an overwhelming urge to eat) and were summed. Internal consistency was Cronbach α = 0.76, and test-retest reliability during 2 weeks was 0.79. Strong correspondences with binge eating disorder scales were found.[11] In the present sample, Cronbach α = 0.73.

Physical activity outputs of 15 minutes or longer during the previous week were measured by the Leisure-Time Physical Activity Questionnaire.[12] Frequencies of bouts of mild exercise or minimal exertion (eg, easy walking) through strenuous exercise or heart beats rapidly (eg, running) were coded as 3-9 metabolic equivalents (a physiologic measure of exertion) and summed. Previous research indicated significant associations between accelerometer and physiologically based energy expenditure results, and the test-retest reliability during 2 weeks was 0.74.[12,13]

On the basis of portion sizes indicated by the US Department of Agriculture,[14] portions of fruits (eg, 118 mL of canned pears), vegetables (eg, 118 mL of peas), and sweets (eg, 118 mL [small piece of] cake) consumed in a typical day were recalled. Strong correspondences were found with comprehensive food frequency recalls and energy consumption. Test-retest reliabilities during 2 weeks averaged 0.81.[15] Consumption of fruits and vegetables was summed.

Body weight was measured in kilograms using a recently calibrated digital scale after removing heavy outerwear and shoes. The mean of 2 consecutive measurements was recorded.

Procedure

Health educators with national certifications were trained in the administration of the physical activity and eating behavior-change components that were based on tenets of social cognitive theory,[7] self-efficacy theory,[8] and self-regulation theory.[16] Their instruction to participants was further supported by retained manuals and videos. The physical activity support component consisted of 4 educator-to-participant sessions of 45 minutes each during the 3-month study, starting at baseline. The protocol was intended to counter common barriers to regular exercise, such as slow progress, discomfort, and boredom, through the use of self-regulatory skills, such as relapse prevention, cognitive restructuring, and stimulus control, which were addressed during each session. Individualized proximal goals were also discussed, revised, and documented during each session. Physical activity types were based on participant preference, and their durations and intensities were adjusted so that they were associated with reinforcing feelings of revitalization.[17]

Six weeks after treatment start, participants were required to log their foods and kilocalorie intake. Soon after, a daily limit of 1500 kcal was established, and group nutrition sessions of 10 to 15 participants were held every 2 weeks. During each of these 60-minute sessions, the self-regulatory

Table 1. Within-group changes in study variables during 3 months[a]

Variable	Baseline		Month 3		Score change[b]		t	p	d[c]	95% CI
	Mean	SD	Mean	SD	Mean	SD				
Weight, kg										
White	96.32	13.72	93.61	13.79	−2.71	3.39	4.92	< .001	0.20	−3.82 to −1.59
Black	94.43	11.56	91.46	10.81	−2.96	4.04	4.42	< .001	0.26	−4.42 to −1.51
Aggregated	95.45	12.72	92.63	12.48	−2.82	3.68	6.43	< .001	0.22	−3.70 to −1.95
Physical activity, METs per week										
White	10.70	8.76	29.65	13.24	18.95	15.05	7.76	< .001	2.16	14.00-23.90
Black	13.16	9.28	34.86	17.06	21.70	16.56	7.41	< .001	2.34	15.73-27.67
Aggregated	11.82	9.02	32.03	15.22	20.21	15.70	10.77	< .001	2.24	16.46-23.95
Fruits and vegetables, portions per day										
White	3.49	2.12	5.21	2.73	1.72	2.23	4.76	< .001	0.81	0.99-2.46
Black	3.30	1.96	4.97	2.14	1.67	1.77	5.34	< .001	0.85	1.03-2.31
Aggregated	3.40	2.04	5.10	2.46	1.70	2.02	7.04	< .001	0.83	1.22-2.18
Sweets, portions per day										
White	2.05	1.45	1.28	0.91	−0.78	1.24	3.86	< .001	0.54	−1.18 to −0.37
Black	2.70	2.15	1.25	1.09	−1.45	1.96	4.20	< .001	0.67	−2.16 to −0.75
Aggregated	2.35	1.82	1.26	0.98	−1.09	1.63	5.57	< .001	0.60	−1.47 to −0.70
Body satisfaction										
White	1.04	0.42	1.34	0.58	0.30	0.53	3.47	.001	0.71	0.12-0.47
Black	1.33	0.53	1.70	0.70	0.37	0.65	3.22	.003	0.70	0.13-0.60
Aggregated	1.18	0.49	1.51	0.66	0.33	0.58	4.73	< .001	0.67	0.19-0.47
Perceived ability to control eating										
White	88.61	27.41	113.21	28.27	24.61	29.03	5.22	< .001	0.90	15.06-34.15
Black	101.28	30.17	125.88	28.51	24.59	24.20	5.75	< .001	0.82	15.87-33.32
Aggregated	94.40	29.20	119.00	28.88	24.60	26.74	7.70	< .001	0.84	18.22-30.98
Emotional eating										
White	26.36	10.19	20.33	9.82	−6.03	10.21	3.64	.001	0.59	−9.38 to −2.67
Black	24.88	11.45	18.00	10.03	−6.91	9.67	4.04	< .001	0.60	−10.39 to −3.42
Aggregated	25.68	10.73	19.25	9.92	−6.43	9.90	5.43	< .001	0.60	−8.79 to −4.07

[a] n = 38 white women (*df* = 37) and n = 32 black women (*df* = 31). N = 70 (*df* = 69) for aggregated data.
[b] Score change was calculated as the month 3 score minus the baseline score.
[c] Cohen's measure of within-group change (mean at month 3 minus mean at baseline divided by SD at baseline).
CI = confidence interval; METs = metabolic equivalents; SD = standard deviation.

skills learned for adhering to regular physical activity were adapted and applied to healthy eating, with emphases on increasing fruit and vegetable consumption and reducing sweets intake. Thus, feelings of the ability to control eating were targeted. Instructions in observing satiety levels in the context of when to eat were also included.

Identical measures were administered to participants in a private area at treatment start and month 3. Fidelity checks on approximately 15% of treatment sessions were structured to identify protocol delivery compromises. Study staff were able to easily correct the few minor protocol violations.

Statistical Analysis

Because there was no systematic bias in the 11% of missing cases, the expectation maximization algorithm was used for imputation and to facilitate an intention-to-treat format. For the planned regression analyses, 67 participants or more were required to detect a moderate effect ($f^2 = 0.15$) at the statistical power of 0.80 ($\alpha \leq 0.05$).[18] SPSS statistical software, version 22 (IBM Corporation, Armonk, NY), was used for the statistical analyses, incorporating the Process macroinstruction application Model 4 (mediation analysis, with 20,000 bias-corrected and accelerated bootstrap resamples).[19] Tolerance values > 0.90 indicated acceptable collinearity. Statistical significance was set at $\alpha \leq 0.05$ (2-tailed for group differences and 1-tailed in regression analyses where directionality of relationships was previously established[3]).

Independent *t*-tests were performed to assess the significance of group differences at baseline and month 3.

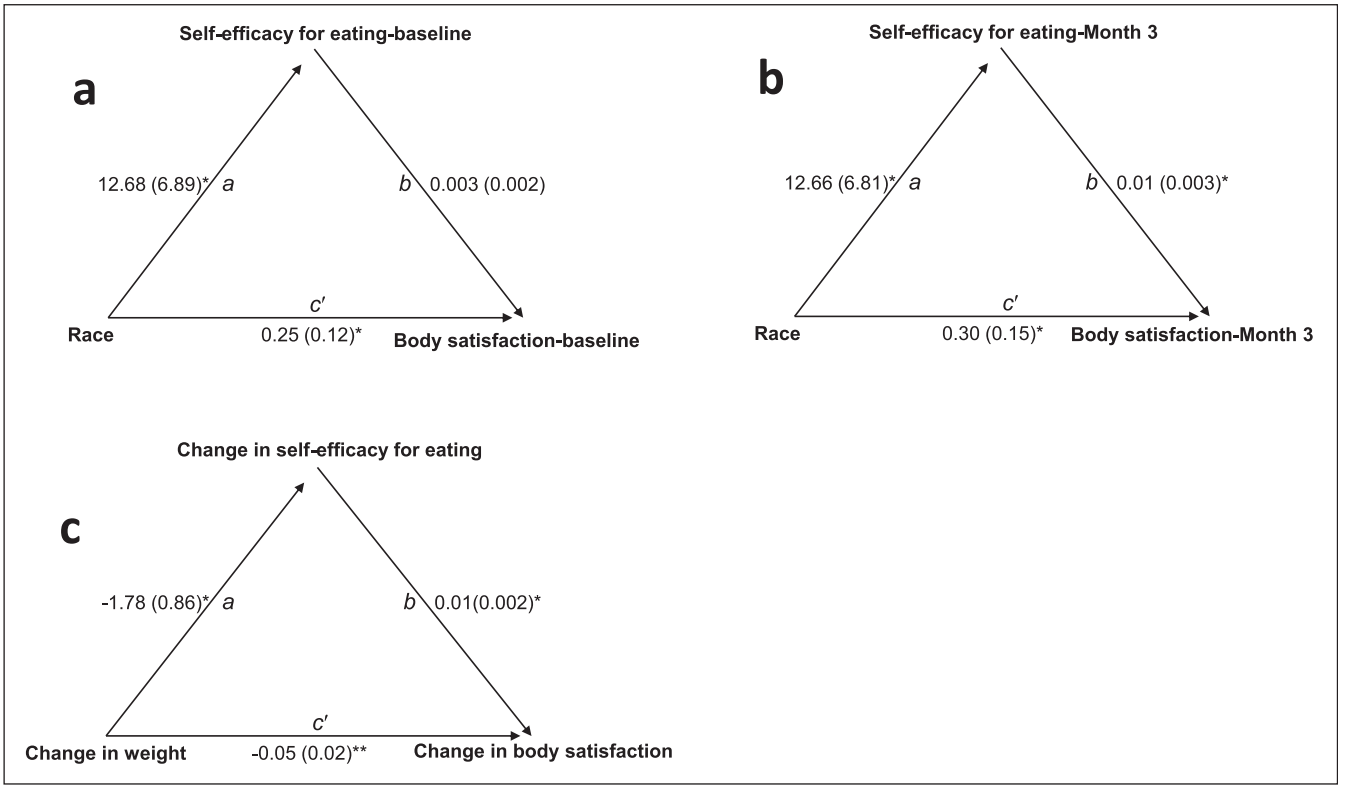

Figure 1. Mediation of the association of race and body satisfaction by perceived ability to control eating at baseline (A) and month 3 (B) and mediation of the association of changes in weight and body satisfaction by change in perceived ability to control eating (C). Paths a, b, and c′ are labeled in italics. *p ≤ 0.05 and **p ≤ 0.01 (1-tailed tests).

Dependent *t*-tests and mixed-model repeated measures analyses of variance were then performed to evaluate within-group score changes from baseline to month 3 and between-group differences in those changes. Small, moderate, and large effect sizes were defined, respectively, as a Cohen's d of 0.20, 0.50, and 0.80 for the *t*-tests and $\eta^2_{partial}$ of 0.06, 0.14, and 0.20 for the analyses of variance.

Multiple regression analyses assessed the associations of race (coded as 1 for white and 2 for black) with body satisfaction. Weight and age were next entered as additional indicators in step 2 of those equations. Scores were appraised at baseline, month 3, and change from baseline to month 3. Mediation effects of perceived ability to control eating on associations between race and body satisfaction as well as changes in weight and body satisfaction were evaluated.

Results

Baseline and month 3 scores on body satisfaction were significantly greater in the black group (t_{68} = 2.53, p = 0.014, d = 0.60, 95% confidence interval [CI] = 0.06-0.51, and t_{68} = 2.35, p = 0.022, d = 0.56, 95% CI = 0.05-0.66, respectively). No other significant group difference was found (Table 1). For both racial groups, weight, emotional eating, and sweets intake significantly decreased, whereas and physical activity, fruit and vegetable consumption, body satisfaction, and perceived ability to control eating significantly increased during 3 months (Table 1). No significant between-group difference was found in those improvements.

At baseline and month 3, neither weight (β = −0.003 and −0.19, respectively; p > 0.100) nor age (β = −0.18 and −0.01, respectively; p > 0.130) significantly added to the strength of a significant association of race with body satisfaction at both baseline (R^2 = 0.09, $F_{1,68}$ = 6.40, p = 0.014) and month 3 (R^2 = 0.08, $F_{1,68}$ = 5.53, p = 0.022). The nonsignificant changes in the R^2 values were 0.03 and 0.04.

Perceived ability to control eating significantly mediated the association between race and body satisfaction at baseline (B = 0.04, standard error [SE] = 0.03, 95% CI = 0.003-0.104) and month 3 (B = 0.06, SE] = 0.05, 95% CI = 0.006-0.181) (Figure 1A and B). Change in perceived ability to control eating significantly mediated the association between changes in weight and body satisfaction (B = −0.01, SE = 0.01, 95% CI = −0.031 to −0.001) (Figure 1C).

In exploratory post hoc regression analyses that assessed the associations between body satisfaction and emotional eating, no significant association was found between those

variables when baseline scores were entered (R^2 = 0.03, B = −3.88; SE = 2.61, 95% CI = −8.234 to 0.485), but significant associations were found when scores at month 3 (R^2 = 0.05, B = −3.49, SE_B = 1.78, 95% CI = −6.456 to −0.515) and score changes from baseline to month 3 (R^2 = 0.04, B = −3.47, SE = 2.05, 95% CI = −6.893 to −0.052) were entered. Entering racial group in step 2 of those equations did not significantly add to the strength of the associations (95% CIs = −4.892 to 4.082, −5.267 to 2.870, and −4.452 to 3.562, respectively). The nonsignificant changes in *R2* values were < 0.004.

Discussion

As expected, the self-regulation-based weight loss treatment was associated with 3-month improvements in all tested behavioral and psychosocial variables, regardless of racial group. In addition, as hypothesized, the black group had a significantly greater initial body satisfaction score than the white group. That moderate effect size was somewhat larger than the mean of 93 such contrasts of US women (d = 0.29),[4] which included 13 contrasts that incorporated the currently used body areas satisfaction scale. Because the treatment-targeted construct of perceived ability to control eating mediated the race-body satisfaction and weight change-body satisfaction change associations, its estimated utility supported theory[7,8] and related research.[3]

Although body satisfaction is an important quality-of-life factor, its identified negative association with weight change further justifies intervention-based attention. The detected association between body satisfaction and emotional eating warrants further research and might have implications for treating the problem of disordered eating that have not yet been identified.[5,6] This could enhance relationships between medical professionals and patients in areas that are rarely considered.

Because the various subgroups of the participants who self-classified as black (eg, African immigrant, Caribbean origin) were not accounted for, extensions of this research should evaluate other racial groups to determine cultural implications.

Conclusion

Although limitations inherent in field studies, such as effects of social support, experimenters, and expectations, were likely present, extensions and replications of this research across sample types have potentials for addressing psychosocial indicators of weight loss and thus improving the success of behavioral treatments across at-risk groups. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Laura King, ELS, performed a primary copyedit.

Author Contributions

JJA conceptualized the study, supervised the data collection, conducted the data analyses, and wrote the report. PHJ contributed to the data collection and the writing of the report. Both authors approved the final version of the report.

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ORIGINAL RESEARCH ARTICLE

Physicians' Views on a Wellbeing Course Gifted to Them: A Qualitative Study

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ABSTRACT

Introduction: Given concerns about staff burnout and distress, the Chief of the Department of Medicine sponsored the Physician Wellbeing program making it cost-free for doctors at a large academic medical setting. Ninety doctors registered within the 1-year pilot project time frame. Following a Mind-Body Medicine online and Mindful Medical Practice workshop a qualitative study was conducted to identify physicians' views about the initiative. Physicians who agreed to take part following the workshops were the participants in the study.

Methods: Focus groups and individual interviews were conducted following 4 workshops. Participants (N = 15) were queried about helpful and unhelpful aspects of the program. Thematic framework analysis was employed for data analysis.

Results: Four themes regarding participants' views on the well-being course were identified. These were: 1) online curriculum (from engaging to disengaging); 2) intimate sharing amongst physicians in the workshop; 3) reflecting on and practicing wellness; and 4) a valuable "gift" from the Department of Medicine. Workshops were highly valued as they provided an opportunity to practice what was learned online as well as engage in fruitful exchanges amongst colleagues.

Conclusions: Physicians supported the integration of wellness programs into medical settings where stress is an inherent aspect of the work environment. They were grateful for the "gift" of being valued and supported by the administration.

INTRODUCTION

Health care systems are constantly undergoing rapid changes to better serve and care for an aging population while simultaneously seeking to reduce costs and introduce technological advances to streamline processes.[1] These changes may lead to unintended negative consequences, especially if the ailing aspects of health care systems are not recognized, addressed, and transformed. First, no matter whether the health care system is universal, provided by health maintenance organizations or veterans' administrations, costs are skyrocketing. Second, people are living longer with chronic conditions. More palliative care, whether it is provided in hospital, residences, or via hospice in patients' homes, is essential. Third, health care systems are changing at a pace that may be detrimental to health care providers and their patients. Change is inherently stressful and can result in suboptimal patient care (eg, medication errors).

Facing these changes and challenges are physicians and allied health care professionals (HCPs) (eg, nurses and social workers) who are essential for the optimal functioning of health care systems. In 2017, the Canadian Medical Association (CMA) conducted the CMA National Physician Health Survey to assess the state of physician health in Canada. Of the 2547 physicians and 400 residents who responded, 30% reported burnout, 34% met criteria for depression, and 8% experienced suicidal ideation in the past year.[2] Moreover, West found that for house staff (USA), up to half of physicians, a third of nurses and as many as two-thirds of other HCPs were experiencing symptoms of burnout.[3]

It is well documented that an increase in distress and decline in empathy begins in medical school and worsens dramatically during residency.[4,5] This is a clear call for action because unwell providers commit more medical errors, their patients are dissatisfied, and the likelihood for litigation is higher.[6,7] Furthermore, burnout is associated with job dissatisfaction, reduction in work effort, and attrition from medical practice.[8] Importantly, burnout compromises the well-being of the physician and is associated with a host of negative outcomes including substance abuse/dependence, suicidal ideation, and decreased quality of life.[9,10]

As stated by the CMA's Policy on Physician Health, physician well-being is critical to "the long-term sustainability of the physician workforce and health systems."[11] Addressing and fostering physicians' well-being and resilience is a shared responsibility of individual physicians and the health care systems and institutions in which they work.

West and colleagues conducted a systematic review and meta-analysis of interventions aimed at prevention or treatment of physician burnout.[12] "Bottom up" strategies (ie, focus on the individual) included mindfulness-based programs, stress management training, and small group curricula. "Top down" (ie, organizational changes) included duty hour limitation and modifications in clinical processes. Randomized clinical trials and cohort study results concurred in that two components of burnout were reduced: emotional exhaustion and depersonalization for both approaches. The authors stated, "Although the magnitude of the reductions in burnout domain scores appears modest, evidence has linked 1-point changes in burnout scores with meaningful differences in important adverse outcomes."

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Notably, a few adverse events were cited when duty hours were reduced (eg, residents' satisfaction with training decreased). Yet, only 3 randomized trials examined system changes.

Another way to view "top down" is focus on leadership in an organization. Shanafelt and colleagues studied the relationship between physician supervisors' leadership qualities with burnout and work-related satisfaction for 2183 doctors.[13] For each 1-point, increase in a composite leadership score was associated with a 3.3% decrease in the likelihood of burnout ($p < 0.001$) and a 9.0% increase in the likelihood of satisfaction ($p < 0.001$) of the physicians supervised.

When the Chief of the Department of Medicine at the McGill University Heath Center (MUHC) agreed to sponsor the University of Arizona Physician Wellbeing course (ie, pay licensing fees) for all medical doctors in the department, including "cost-free" CME credits, it was with the agreement that 3-hour workshops would complement the online self-study methodology. The online work preceded the workshop—providing the opportunity to learn about mind-body medicine first and practice one of three exercises (eg, journaling) for 2 weeks (as prescribed in 1 of the modules). Given the pilot project nature of the endeavor, a qualitative study was conducted to learn about participants' views of the course. The fact that the project was approved and funded within a large medical center reflects the "top-down" aspect of the project.

METHODS

The McGill University Faculty of Medicine IRB approval was secured prior to the focus groups and individual interviews. Participants signed an informed consent form. To ensure that participants felt "safe" to take the PWB program (given that their email addresses include their names), no data were collected on demographics, other than specialty (eg, internal medicine, gastroenterology, palliative medicine). CME approval and certificates for 4.5 Section 1 and 3 Section 3 credits were secured prior to beginning the course.

Recruitment

An introduction video (made by PLD) was posted online to help doctors decide if they wanted to register for the entire course. A description was of it included in the department newsletter (1 month before the program began) and an announcement was posted on the hospital website. Finally, emails from the department head's office were sent inviting participation of up to 100 doctors (out of a cohort of about 400). Once registered, participants were given full access to the online program.

Interventions

Physician Wellbeing Online Modules

1. Self-Assessment (burnout, wellness, resiliency, stress response)
2. Introduction to Wellness
3. Wellness Inventory
4. Burnout
5. Resiliency
6. Mind and Spirit
7. Resiliency Practice
8. Personal and Professional "time-out" ie, 2-week practice period (gratitude journal or meditation practice, or finding meaning at work)
9. Personal Development Plan
10. Self-Assessment (post-tests from module 1)

Mindful Medical Practice (MMP) Workshop[14,15]

Epstein published the seminal paper *Mindful Practice*[16] and more recently a book, reviewing decades of research and clinical experiences pertaining to being mindful and relationship-based care.[17] Our faculty have been offering MMP courses for 13 years, including medical students,[18] residents, and physicians.[19] An 8-week program modeled on Mindfulness-Based Stress Reduction (MBSR), half-day, full-day, and weekend workshops have been provided—each modified to suit the needs of health care professionals.[20] Characteristics of a mindful clinician (eg, attentive, curious, beginner's mind, and being fully present with their patients), effective communication, and deep-listening skills are emphasized.[21,22] All are offered in a small group setting with the intention to end professional isolation and provide a safe forum to share clinical experiences.

The 3-hour MMP workshop covered topics such as resilience, finding meaning at work, and MMP. Groups of 10-16 were conducted in a conference room at the hospital either during early evening hours or on Saturday. Healthy snacks were served. Given that participants were from various departments and in different phases of their careers, most did not know other group members. The facilitator (PLD) is a clinical psychologist, trained in group dynamics, and is certified as a MBSR instructor. She emailed participants 1 month (several times) prior to the workshop to encourage completion of the online work. During the workshop, a narrative medicine exercise, body scan meditation, and discussions pertaining to online learning and relevant experiences occurred. For example, subgroups of 3 doctors were formed to discuss their 2-week practices (eg, meditation and journaling). As required for CME credits, an evaluation form was completed at the end of the workshop and an invitation to participate in a focus group was extended.

RESULTS

Recruitment took place twice. The first cohort (Fall) included 57 doctors. Of the 57, 6 never logged in, 38 (66.7%) completed the online work, and 45 attended 1 of 4 workshops. The second cohort (Summer) took place

Table 1. PWB Online & On-site CME Course Evaluation
(Summary of four workshops)

1. How useful were the online self-assessment questionnaires?

Definitely useful	Moderately	Somewhat	Slightly	Not at all
5	4	3	2	1
16	**16**	**8**	**2**	

MEAN: 4.14

2. How helpful was it to be able to read the online responses to reflections written by peers?

Definitely helpful	Moderately	Somewhat	Slightly	Not at all
5	4	3	2	1
9	**7**	**15**	**7**	**3**

MEAN: 3.29

3. Please comment on how successfully the following learning objectives were met:
Increase physician resiliency and hardiness: □ Yes □ No □ Not Sure
28 2 13
Provide strategies for coping with stress: □ Yes □ No □ Not Sure
38 5
Provide strategies on decreasing physician burnout: □ Yes □ No □ Not Sure
35 1 7
Practice mindfulness: □ Yes □ No □ Not Sure
39 4

4. The course content (online and workshop) has enhanced my knowledge:

Strongly Agree	Moderately	Neutral	Slightly	Strongly Disagree
5	4	3	2	1
15	**23**	**3**		

MEAN: 4.29

5. Indicate which CanMEDS roles you felt were addressed during this educational activity.
Collaborator: **22**
Communicator: **36**
Medical Expert: **8**
Health Advocate: **23**
Manager: **11**
Professional: **37**
Scholar: **12**

10 months following the first launch; 33 registered, 8 never went online, 6 (18.2%) completed the online work, and 10 attended the final workshop. Across both cohorts, the number of times logged in varied across participants (1-29 times) as did the number of hours online per person (< 1 hour-7 hours).

Table 1 summarizes the results of the CME evaluation forms completed only by physicians who attended workshops.

Qualitative Data Collection

Participants' views were collected from May to July 2019 by the second author; she was independent of all other aspects of the program. Data collection was performed in 2 phases, first via focus groups, and second via individual interviews. For each focus group, we attempted to schedule 6 individuals, a number recommended in the literature for group size.[23] Even though 30/45 (66.6%) from the first cohort agreed to attend a focus group and responded to online scheduling, attendance was poor. Nonetheless, 3 focus groups were completed, including 2-5 participants each, ranging from 60-75 minutes in duration (n = 10). To address recruitment barriers and further contextualize the phenomenon, 5 single individual phone interviews were completed; these ranged from 15-30 minutes in duration. An experienced master's level qualitative data collector (CV) conducted all focus groups and individual interviews. A research assistant (RA) was present during the focus group to obtain informed consent, help with logistics, and take notes during the interview.[23]

To enhance consistency of data collection, the same semi-structured interview protocol comprised of 9 open-ended questions was used to guide the focus group and individual interviews. Each interview addressed participant experiences of the course particularly related to helpful and unhelpful aspects. All interviews were audio-recorded and transcribed verbatim by the RA without any identifying participant details.

Data Analysis

Thematic framework analysis was employed for data analysis, because this approach is appropriate for both individual and focus group interviews. [24,25] This process involves 5 interconnected stages: familiarization, identifying a thematic framework, indexing, charting, mapping, and interpretation. It started with familiarization with the data by reading each interview transcript multiple times, while often listening to the accompanying recording to garner an overall sense of the transcript. Subsequently, a line-by-line analysis of each transcript was performed, highlighting quotes that pertained to the PWB experience (both online and during the workshop) and writing notes at the margin of the transcript to facilitate the development of a thematic framework. The stages of indexing and charting involved sorting the highlighted quotes and making comparisons both within and between participant cases. Highlighted quotes that reflected similar concepts were then grouped into themes for each transcript. Sub-themes within each theme were further organized.

Once each transcript was analyzed, themes and sub-themes were compared across all interviews. The process of interpretation involved movement between understanding individual quotes, seeing relationships between participant quotes, and establishing links between all data.[26] Interpretation of quotes was facilitated by considering the frequency, emotion, context, and specificity of the coded data. Ultimately, a detailed description that captures participants' PWB course experiences was developed, emphasizing commonalities and differences in their experiences.

To enhance rigor (trustworthiness) an operationalized set of criteria was used.[26,27] To ensure credibility, this study used: 1) member checking by soliciting feedback from the participants about the representativeness of emerging findings; 2) team debriefing after each focus group; and 3) multiple sources of data (ie, focus group transcripts, individual interview transcripts, and field notes and reflections) to explore and contextualize phenomenon. To facilitate transferability of the study findings to similar setting, we offer a detailed description of the context surrounding the findings, such as the setting of the study. To enhance dependability and allow for replication, we provide a comprehensive account of all research procedures (eg, recruitment challenges). Last, for confirmability, we maintained a detailed audit trail of all the steps taken during the study.

Thematic Structure

Participants spoke about their experiences of the program at length, addressing both helpful and unhelpful aspects of the course. The 4 themes that emerged are presented below, along with supporting verbatim excerpts from participant interview transcripts.

Online Curriculum—From Engaging to Disengaging

Participants' description of the online curriculum is conceptualized on a continuum, ranging from highly engaging to highly disengaging experiences. When talking about the online curriculum, participants concentrated on three major aspects, namely its content, approach, and format. Eleven participants found the online content to be stimulating, with some participants describing the whole curriculum as "particularly good," "useful," and "really interesting." Four participants mentioned enjoying the "varying techniques" and "many different aspects of well-being that were covered" in the curriculum. Additionally, 6 participants appreciated how the audio-visual materials, specifically, the TED talks, heightened their experience of the course. For instance, Dr B noted: "I thought the

audio-visual content was well balanced. I thought that it enhanced the experience, whether it be a TED talk or other things … It helped make things get through."

A few participants also commented on the experiential component of the course and how it allowed them to not only learn the material in a cognitive way, but also to practice it. Dr S explained: "I thought it was a good thing that you had to do a 2-week practice of one tool … because it was an occasion to try something out, it was also forcing us to do it, in a sense, instead of just describing it."

Additionally, 4 participants indicated that they appreciated the evidence-based approach of the course, as wellness is often presented in ways that lack scientific rigor and is associated with "artsy," "goody stuff," and "symbolic interaction." Dr B explained:

"Reading referenced information was good stabilizers … I wanted to get some kind of footing that were indisputable. There are data where you can dispute them, but at least you know there was some verified information referenced, which I was looking forward to seeing some of that."

Seven participants emphasized how the online format was convenient, flexible, and accessible, which facilitated their engagement with the course. Dr T commented on the value of the online format: "having the ability to access things online anytime from home was really helpful … I can do it at the end of the day … after the kids are asleep." A few participants also highlighted the website as user-friendly, labeling it as efficient and straightforward.

Participants also addressed aspects of the online curriculum that they deemed unhelpful and which contributed to some disengagement from the course. Four participants experienced the online curriculum content as tedious, with some describing it as repetitive, elementary, too theoretical, and not particularly exciting. For example, Dr H seemed to have experienced the online modules as a chore, which led to some impatience:

"The modules were long. You know I was thinking, 'Am I finished yet?' … But then it wasn't the last one yet … that was just impatience on my part. That wasn't very negative. It was just I think a normal human kind of thinking 'Oh, there's work to do'. I like live things. [The online] I found it a little dead."

Three participants questioned the applicability of the online curriculum to their realities as experienced physicians, given that the curriculum was designed for residents. For example, in Dr G's case, this perceived lack of relevance contributed to the experience of the course as a burden, which resulted in unmindful engagement at times:

"The program was designed for residents just starting on a career. And the problem with that, is that it's not transferrable [to people at my stage] … It was a burden to continue doing the exercises because the relevance was not apparent. In many cases, I just clicked without thinking, especially near the end of a very long series of questions, just to get to the next page."

While 2 participants appreciated the efforts of the course to be evidence-based, they described the scientific background of the course as "superficial." For example, Dr J noted that the scientific content was over-emphasized in the course, as many generalizations that were not directly linked to wellness or performance were made:

"It became a bit of sort of a sore point as I was going through it, that the these phrases and [physiological] stuff were being brought in to sort of justify this is why you should be doing it, rather than saying 'Look, there is some evidence about this, there is some physiological stuff that we know about, but a lot of this is behavioral' … That lost me after a while, and I got a little frustrated."

Intimate Sharing Among Physicians in the Workshop

Most participants identified discussions with other physicians at the workshop as the most helpful and impactful component of the course. These participants revealed that it was important and meaningful to have an open conversation about personal stories with other physicians from different practices and stages in their career. For example, Dr H reflected on the authenticity, openness, and positive impact of the workshop:

"The part that worked best for me was in the in person … I really liked [that it] was very real because people were there at different phases of their career … I mean it was so authentic … [There was a] huge amount of openness … So that was very powerful and really made me think, 'We're doing a good thing here. This is really good to hear other people's experiences.'"

Four of the participants further highlighted the strengths of the in-person workshop compared to learning about physician well-being online or through theoretical methods. Dr M explained the importance of this interactive and experiential component for physicians:

"Having an open discussion about real-life techniques to encourage well-being. That's what I found the most interesting with regards to the course. We are given opportunities to read about information online and articles about physician well-being, but it doesn't compare to being in a classroom with other attendings and hearing personal stories of which I think helped the most."

Some participants spoke about factors that influenced group dynamics at the workshop. Four participants expressed their appreciation toward the facilitator's approach during the workshop, because the facilitator made participants feel safe and engaged. Dr M explained: "[I felt very open to share my experiences. [The facilitator] made it a comfortable atmosphere for everyone, so it was very enjoyable." A few participants mentioned that they would have liked more space for exploring participant's journeys and

experiences within the workshop. Dr J expressed this desire, "I thought the workshop was going to be a little bit more of a space to explore some issues, because people come to this from very different angles and so understanding why people are pursuing this, I think is important." Last, 3 participants spoke about the detrimental impact of participants who displayed a negative attitude during the workshop. Dr C commented on how this influenced her experience, "Unfortunately, one of the things I remember the most was a person who clearly did not want to be there. It became so distracting … eye rolls and snapping and sighs and this and that." Similarly, Dr J addressed the impact of such behavior on group dynamics: "I had the sense that a number of people resented being there. They got there a bit late and were just like "Ugh, I just want to go to sleep" … That didn't help the atmosphere of the sharing."

Reflecting on and Practicing Wellness

Most participants described how the course afforded them an opportunity to reflect on their own well-being and partake in practices to promote their wellness. The reflective journey started with the completion of the self-assessment questionnaires on burnout and resilience. Seven participants described the results as illuminating and revealing. For example, Dr S commented: "It was enlightening in a sense … To see it in numbers, in a language that you could kind of relate to … To know where you are on the spectrum of certain aspect or trait, it can be a wake-up call." Indeed, 6 participants explained how the self-assessment results served as an impetus for change and to work on their wellness. Dr E described how the burnout inventory results reaffirmed her commitment towards her wellness: "[The results] made me realize that it is time to sort of take a step back and assess the situation and try and gain a little bit of control." Of note, 3 participants found the results to be valid but not necessarily motivating for change, 3 participants could not recall this experience, and 1 participant challenged the validity of the test results.

Additionally, most of the participants addressed how they appreciated the opportunity to practice diverse wellness exercises and reflect on their progress throughout the course. The exercises that were most frequently identified as helpful by the participants were the gratitude journal (ie, noting three things they were grateful for each day) and mindfulness. For example, Dr M stated, "I feel my outlook was more positive … Waking up in the morning, starting off on a positive note and thinking of things I'm grateful for. All these has allowed me to be more mindful and in the moment." Additionally, Dr M explained how the course helped her to become more fully connect with her patients, because she was more mindful about the whole person and deriving pleasure from the encounter:

"The course stated to try to find pleasure with each patient and try to make more of a connection with each patient … It was something I was taking for granted … I feel like I'm able to be more in the moment with my patients. I feel I understand more what it is exactly that they're going through more than just medical. So, if anything, [the course has] improved, the empathy aspect of the doctor-patient relationship."

Furthermore, 3 participants specifically addressed how the program helped them to reflect on and deconstruct negative messages regarding well-being and self-care that they had internalized during training and that are sustained by the culture of medicine. For instance, Dr N explained, "I was actively trained in the 1970s to not look after myself … It's a huge statement to say I'm more self-aware and looking for ways to integrate these techniques … into one's daily life." In a similar vein, Dr J noted how the course highlighted the potential relevance of physician self-care to sustainability and patient care, which runs counter to cultural messages of how physicians must operate:

"I was intrigued by … this idea that … physician well-being translates into better care because that's somewhat counter to the general thread of medical student training etc., which is that you run yourself into the wall because you're trying to do everything that you can … You're trying to get this idea across that what you are doing is not only not gonna be sustainable long-term, but it's probably meaning that you're not delivering the best care. But we don't have enough evidence yet to really back the argument, but hopefully that will come."

Last, 2 participants reflected on how the program's approach lacked resonance with their personal style of wellness, and as such, they did not benefit from it. For example, Dr G identified the course's mostly solitary approach as the issue, noting he would benefit more from interpersonal interactions with other physicians:

"The problem is that it's not a personal journey that needs to be validated by others. By doing it alone in a room with a computer, you can make the same mistakes … If that were a consistent, collegial, cooperative, relationship-based endeavor, that would go a much longer way."

A Valuable "Gift" from the MUHC Department of Medicine

All participants expressed their appreciation and gratitude for the Department of Medicine's active involvement and sponsorship of the PWB. Participants described the Department's support as "powerful," "valuable," and an "important shift," as it affirmed that the Department cares about its physicians, recognizes the challenges that physicians are currently facing, and is taking important steps to improve the staff's well-being. Dr D addressed the significance of the Department's decision to fund and sponsor this initiative:

"Symbolically it was actually very important that it was sponsored by the department of medicine [and] that it was free

… I'm sure all of us could have afforded to pay for it, but the fact that the department of medicine thought that it was important enough, that they were offering it to us a gift was … very valuable. I thought that it implied that the Department of Medicine was concerned about its faculty, which was very nice."

Furthermore, Dr V mentioned how the Department's support made her feel seen and understood: "[The Department's support meant that] people care about us … there was recognition that there's a whole human element to our work and I was very touched actually. I thought 'Oh good, the faculty, they just so get me.'" Additionally, some participants hinted at how the Department's support represented a cultural shift regarding physician wellness. Dr L illustrated this premise: "What usually comes out of the department of medicine from my perspective is academics, research, and to have something come out that was about you and helping you as a person and to cope … I thought was a major shift actually." Dr H perceived that the Department's novel approach was not only healthy, but also acted as a facilitator to physician engagement in the course:

"I think in the distant past the Department of Medicine wouldn't have supported anything like this or put energy into anything like this. They would've assumed this is not their issue. That was very healthy that they did, and I think that the fact that the Department supported it made people more likely to do it."

Last, even the 2 participants who did not particularly benefit from the course conveyed the relevance and helpfulness of this initiative. For example, Dr J explained: "For me [the course] was superficial and didn't quite do the things I was hoping it would, but I don't want to take away from the fact that I still think it's a very important step in the right direction."

DISCUSSION

The two-part PWB course offered one step towards physician well-being, supported from the "top" while carried out by the "bottom." The physicians who agreed to speak with us acknowledged the importance of providing concrete means to maintain wellness in the context of hospital service to patients across specialties and years of practice. The fact that the workshops were provided onsite may have encouraged them to register. Yet, time is perceived as a taxing stressor;[28] thus, asking physicians to "do more" to take care of themselves may seem paradoxical. Nonetheless, when framed as "well doctors promote wellness in their patients," many allowed themselves to participate. For some, online access provided the flexibility needed to learn where and when they could.

We observed an openness to learning new strategies for personal, educational, and professional development. Not surprisingly, engagement online varied—as seen in the first theme as well as the numbers and hours of online work and attendance at workshops. To date, there is no published literature on the PWB online course. Preliminary analyses of 617 residents' reports were sent [to PLD] when negotiating the contract. At 2 UAZ sites, junior doctors rated the online program technology as "smooth to use" (mean = 4.6). This was replicated in our study. Reading peer online reflections was rated as somewhat helpful by our group (mean = 3.3) and by UAZ respondents (mean = 3.2). Here, more detailed comments, such as positive experiences with audio-visual tools and negative views (eg, redundancy of material), were chronicled.

The workshop aspect of the course was valued as it provided an opportunity to share experiences in person with other doctors. Our findings concur with Brown and colleagues' conclusions for wellness workshops that were integrated into faculty development for new faculty members in another academic Canadian medical setting.[29]

The culture of medicine can be callous (eg, the expectation to work despite illness) or worse (eg, bullying and harassment from colleagues and patients).[5] There has been a call for a shift in how institutions address self-care and how it is viewed by staff (see CanMEDS). [30] This was reflected in our results. As expected, for some MDs, self-assessment served as a motivator to discover pathways towards resilience. Being offered an opportunity to practice, both online and during the workshop was viewed as helpful. Gratitude was expressed for the "gift" from the Chief of Medicine. This served as encouragement and the sense of "being seen and cared for" ie, recognized and appreciated. It should be noted, however, that during workshops the issue of "systemic" problems was raised. That is, if the work environment and regulatory demands (eg, EMRs) [31] do not change, expecting the "bottom" to do the "heavy lifting" seemed unjust. Stanford University Medical Center's approach can serve as a model to deal with this legitimate concern. [32]

When the first author presented the proposal to the MUHC executive committee one skeptical member asked it made sense to ask burned out doctors to do more. We emphasized that the program could be viewed as primary (or secondary) prevention, with an emphasis on maintaining resilience. Unsympathetic views towards "weakness" reflects a darker side of the medical culture. Thus, one must tread with care when inviting participation. Rather than dealing with "what is wrong with you," it is better to suggest how to strengthen what is "right." Presenting the course as part of faculty development is recommended.

What about "top down" changes? Doctors want their ideas heard and their initiatives to improve quality of patient care to be understood.[28] Junior Australian doctors described "workplace issues" that were stressful, such as meal breaks cut or disrupted and discouragement to claim overtime.[5] Managers may need to address these problems. When senior doctors are capable role models who mentor trainees with empathy, they

can ease transitions for junior doctors. Their presence in designing and offering wellness initiatives is encouraged.

Given that registering for the online course and attending the workshop were voluntary, our results cannot be generalized. Even though the ethics committee chair advised us that we could use the online self-assessment results if they were anonymized, we chose not to for several reasons. First, it varied when the questionnaires were completed (this was also found in the UAZ data). For example, 1 person could finish all modules in 1 month whereas another did so in 3. Second, change takes time and thus it was unlikely to find significant and meaningful transformation over a short testing period. Moreover, costs for analyses seemed to be higher than the potential usefulness of pre-program data only. Although the sample size was small, this is common in qualitative research. For example, Baathe and colleagues interviewed 7 Norwegian surgeons (one-third of the MDs in the department) who described "stretching themselves" to handle the tensions between quantity and quality, to overcome organizational shortcomings (eg, unforeseen scheduling changes).[28] The information gained through this methodology appears richer than the simple responses to the questions found on the evaluation forms. The results suggest that on-site programs for physicians are feasible and when offered by management, viewed positively. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Authors' Contributions

Patricia Lynn Dobkin designed and provided the Physcians Wellness Program and co-wrote the manuscript with Camila Valez. Camila Velez designed the qualitative study, conducted the analyses and co-wrote the manuscript with Patricia Lynn Dobkin.

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Abbreviations:

PWB = Physician Wellbeing.

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ORIGINAL RESEARCH ARTICLE

Evaluation of Dipeptidyl Peptidase-4 Inhibitors versus Thiazolidinediones or Insulin in Patients with Type 2 Diabetes Uncontrolled with Metformin and a Sulfonylurea in a Real-World Setting

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ABSTRACT

Background: Guidelines do not make clear recommendations for third add-on agents to metformin plus a sulfonylurea. This study compared the effectiveness and safety of dipeptidyl peptidase-4 inhibitors (DPP4is) to thiazolidinedione (TZD) or insulin as a third add-on agent to metformin plus a sulfonylurea in an integrated health care setting.

Methods: This retrospective database cohort study included adults with type 2 diabetes not at goal hemoglobin A_{1C} (HbA_{1C}) who initiated DPP4i, TZD, or insulin as a third add-on agent to metformin plus a sulfonylurea from January 2006 to June 2016. Primary outcomes were the proportion of patients who achieved goal HbA_{1C} after starting the third add-on agent and change in HbA_{1C}. Subgroup analysis was performed for patients with baseline HbA_{1C} greater than 9%.

Results: In this study, 2080 patients started on a DPP4i were matched to 8320 patients started on TZD and to 8320 patients taking insulin. A significantly higher percentage of patients taking TZD reached goal HbA_{1C} (31.0% versus 23.6%; $p < 0.05$) and had a significantly larger HbA_{1C} reduction (−0.94% ± 1.34% versus −0.79% ± 1.23%; $p < 0.01$) compared to patients taking a DPP4i. No difference in the percentage of patients meeting goal HbA_{1C} nor in change in HbA_{1C} was demonstrated between insulin versus DPP4i regimens. For patients with baseline HbA_{1C} greater than 9%, insulin or TZD resulted in a significantly higher proportion of patients achieving goal HbA_{1C} compared to DPP4i (17.3% and 19.0% versus 12.4%, respectively; $p < 0.01$).

Conclusion: TZD was more effective than DPP4i but DPP4i was as effective as insulin as a third add-on agent in the overall study population. Insulin was more effective than DPP4i only in the subgroup analysis of patients with baseline HbA_{1C} greater than 9%.

INTRODUCTION

Type 2 diabetes (T2D) is a metabolic disorder that affects the body's ability to produce or use insulin efficiently, leading to chronic hyperglycemia and long-term microvascular and macrovascular complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. Several studies suggest that lowering hemoglobin A_{1C} (HbA_{1C}) to 7% can reduce these long-term complications.[1]

Metformin has long been recommended as a first-line treatment for the management of T2D in adults unless contraindications or adverse effects preclude its use, but add-on glucose-lowering drugs may be required to help patients meet their glycemic goals.[2,3] Sulfonylureas were commonly prescribed as add-ons to metformin because they are available as inexpensive generics and can lower HbA_{1C} by 1% to 2%.[4] A study by Cook et al[5] concluded that glycemic control is improved after the addition of sulfonylureas to metformin. However, a worsening of glycemic control is seen as early as 6 months for some patients, which suggests that insulin therapy or the addition of a third agent is necessary.[5] Clinical studies have evaluated the safety and efficacy of triple-combination antidiabetic therapy, showing that triple therapy is superior or comparable to dual therapy.[6-8]

There are limited studies that evaluate the newer glucose-lowering agents as a third-line add-on agent after metformin and a sulfonylurea. A retrospective study by Levin et al[9] evaluated outcomes for 51,771 adult patients with T2D previously treated with 2 oral antidiabetic agents and then treated with a third antidiabetic agent (any oral diabetic agent versus a glucagon-like peptide-1 receptor agonist [GLP1RA] versus insulin). The potential oral agents included metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitors (DPP4is), thiazolidinedione (TZD), meglitinide, or α-glucosidase inhibitors. After a 2-year follow-up, the change in HbA_{1C} from baseline was −0.88% for the insulin group, −0.33% for the GLP1RA group, and −0.64% for the oral diabetic agent group. However, the authors did not compare the outcomes among these groups for

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statistical significance. In addition, there was no evaluation performed for specific oral antidiabetic agents.

Two network meta-analyses have evaluated the effect of adding a third antidiabetic agent for adult patients with T2D who did not achieve glycemic control with metformin and a sulfonylurea.[10,11] Using data from 9 trials, Gross et al[10] concluded that there were notably higher HbA_{1C} reductions for patients receiving acarbose, TZD, GLP1RA, DPP4i, or insulin when added as a third agent to metformin and a sulfonylurea compared to placebo. McIntosh et al[11] evaluated 33 randomized controlled trials with a minimum 4-week duration. This analysis, which included more active comparison trials, found that insulin, DPP4i, GLP1RA, and TZD led to significant reductions in HbA_{1C} in combination with metformin and a sulfonylurea, whereas meglitinides and α-glucosidase inhibitors did not.[11] Since these meta-analyses used studies that compared active drugs to placebo, the investigators relied on many indirect comparisons and extrapolation of data. There is limited evidence to help clinicians determine a preferred third-line agent.

In an open-label study by Hsia et al,[12] 108 patients who had uncontrolled T2D and were taking metformin and a sulfonylurea were treated with add-on sitagliptin, a DPP4i, and compared to a historical control of similar patients treated with an add-on TZD. Patients in the TZD group achieved a larger mean HbA_{1C} reduction compared to that of patients in the sitagliptin group (−2.0% versus −1.3%; $p = 0.006$). In a similar open-label study by Liu et al,[13] the mean change in HbA_{1C} from baseline was −0.94% ± 0.12% for 59 patients treated with pioglitazone and −0.71% ± 0.12% for 60 patients treated with sitagliptin, but these results were not statistically significant due to the small sample size ($p = 0.16$). Mean weight gain was significantly higher in the pioglitazone group ($p < 0.01$).

At the time this study was conducted, guidelines available to aid clinicians in the decision-making process for selecting the third agent were lacking. Prior to 2018, both the American Diabetes Association (ADA)[2] Standards of Medical Care in Diabetes as well as the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)[3] Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan did not provide recommendations for when to use a specific drug or class of drugs as a second or third add-on agent to metformin due to the lack of comparative efficacy. Instead, they recommended a stepwise approach to managing treatment for patients with T2D, emphasizing a patient-centered approach to care by considering patient preferences, needs, and values.[2,3] The guidelines suggested that if patients did not attain glycemic control after 3 months of metformin monotherapy, then the addition of another glucose-lowering drug is recommended. The appropriate drug to add on could be selected after consideration of several factors, including the HbA_{1C} reduction needed to reach goal, risk of hypoglycemia, effects on weight, adverse effect profile, and cost.[3]

The National Committee for Quality Assurance developed a standardized performance Healthcare Effectiveness Data and Information Set for managed care organizations. Under the comprehensive diabetes care measure, poor HbA_{1C} control has been listed as one of the quality indicators since 2000.[7,8] In efforts to improve the quality of diabetes care and achieve Healthcare Effectiveness Data and Information Set measures, there has been a growing interest in the role of newer antidiabetic agents, such as DPP4is, as a third-line add-on agent after metformin and a sulfonylurea. However, these agents may have varying levels of HbA_{1C} reduction, unclear long-term safety, and high costs compared to traditional third-line add-on agents such as insulin and TZD.

Studies evaluating triple-therapy combinations are limited and are needed to help clinicians determine optimal therapeutic options. This study evaluates the comparative effectiveness and safety of DPP4i versus TZD or insulin as a third-line add-on option to metformin and a sulfonylurea in an integrated health care system.

METHODS

Data Source

This retrospective cohort study was conducted within the Kaiser Permanente Northern and Southern California Regions, which are large not-for-profit integrated health care systems covering more than 8 million patients. A comprehensive electronic medical record system captured all interactions and aspects of care within the health care delivery system since 2006. This included demographics, membership and benefits, inpatient and outpatient encounters, laboratory test results, and prescription records. Institutional review boards in the Kaiser Permanente Northern and Southern California Regions reviewed and approved this study. Informed consent was waived due to the retrospective nature of the study.

Patient Selection

This study included all patients who were not at goal HbA_{1C} after receiving dual therapy with metformin and a sulfonylurea for at least 90 days and initiated triple therapy with DPP4i, insulin, or TZD during January 2006 to June 2016. The date of initiation was defined as the index date. The definition of goal HbA_{1C} depended on each patient's age. Goal HbA_{1C} was defined as less than 7% for patients younger than 65 years or less than 8% for patients age

65 years or older.[2,3] Patients must have had a diagnosis of T2D, which was defined as having at least one International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification diagnosis code (ICD-9-CM 250.0x and 250.2x or ICD-10-CM E11.x, respectively) within 12 months prior to the index date. Only patients aged 18 years or older on the index date were included. In addition, patients must have had continuous medical and pharmacy benefits for at least 6 months before initiation of triple therapy, a baseline HbA_{1C} measured within 6 months prior to the index date, and a follow-up HbA_{1C} measured within 3 to 7 months after the index date. Dose changes were allowed during the follow-up period. Patients must have had evidence of picking up prescriptions for all 3 agents for at least the first 90 days from the index date. Patients were followed until the end of membership, the end of their triple-therapy regimen, death, or the study end date of December 31, 2016, whichever occurred first.

The study group was defined as patients taking metformin and a sulfonylurea who started on DPP4i as a third-line add-on agent (+DPP4i), whereas the 2 control groups included patients taking metformin and a sulfonylurea who started on TZD or insulin as a third-line add-on agent (+TZD or +insulin, respectively).

To minimize the differences in baseline demographics, each study group patient was matched to 4 patients from each control group using propensity score matching without replacement to adjust for treatment selection bias.[14] The conditional probability propensity score of receiving DPP4i was estimated using logistic regression with the following covariates: demographics (age, sex, race), baseline HbA_{1C}, duration of T2D, a diagnosis of hypertension or hyperlipidemia, metformin at maximum dose (2 g/d), and health status defined by the Charlson comorbidity index (CCI).[15] The matched patients in the control groups were selected by using the nearest neighbor matching method.

Study Outcomes

The primary outcomes were the proportion of patients who achieved goal HbA_{1C} within 3 to 7 months and change in HbA_{1C}. Secondary outcomes included mean change in body weight and proportion of patients with a hospital encounter or emergency department (ED) visit due to a hypoglycemic event. Follow-up HbA_{1C} results were measured within 3 to 7 months after the index date. If patients had multiple HbA_{1C} measurements within the allotted time frame, then the latest HbA_{1C} was used. Hypoglycemia was defined as an ED visit or hospitalization encounter with a primary diagnosis of ICD-9-CM (251.X) or ICD-10-CM (E16.X, E09.64X, E11.64X, E13.64X) codes during the time when patients were receiving the triple-therapy regimen.

In addition, a subgroup analysis was performed on the primary outcome for patients with an HbA_{1C} greater than 9% at baseline. This analysis was performed due to interest regarding how these third-line add-on therapies performed for this subset of patients with uncontrolled T2D.

Statistical Analysis

Assuming that 20% of patients would attain goal HbA_{1C}, 695 patients were needed in the study group and 2780 matched patients at a ratio of 1:4 were needed in the control group based on an α of 0.05 and 80% power in order to detect an absolute 5% difference in the proportion of patients who met this goal. Descriptive statistics were used to evaluate differences in baseline patient demographics and clinical characteristics between the cohorts before and after propensity score matching. Student *t*-tests were used to analyze continuous variables, chi-squared tests were used to analyze categorical variables, and Kruskal-Wallis tests were used for nonparametric ordinal variables. A logistic regression was performed to calculate the odds ratio (OR) of achieving goal HbA_{1C}. This regression was controlled for age (as a continuous variable), sex, baseline HbA_{1C} greater than 9%, race, CCI, metformin at maximum dose, and a history of hyperlipidemia or hypertension. Maximum dose for metformin was defined as a dose of 2 g/d or greater. All data were analyzed using SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

A total of 225,816 members were identified as starting a triple-therapy glucose-lowering regimen during the study period from January 2006 to June 2016. A total of 167,504 patients were excluded for the following reasons: not being a Kaiser Permanente member for 6 months or longer prior to the initiation of triple therapy (15%); were at goal HbA_{1C} (15%) at baseline; initiated triple therapy with agents other than insulin, TZD, or DPP4i (17%) or did not continue their triple-therapy regimen for at least 90 days (20%); or missing baseline or follow-up HbA_{1C} measurements (22%). Some patients were excluded because they met more than 1 criterion. The remaining 60,118 patients met all of the inclusion criteria, with 37,831 patients in the +insulin treatment group, 20,207 in the +TZD treatment group, and 2080 patients in the +DPP4i treatment group (Figure 1).

There were significant differences in baseline demographic and clinical characteristics among the 2 cohorts before propensity score matching. Patients in the +insulin group had a higher baseline HbA_{1C} compared with the +DPP4i or +TZD groups. In addition, patients in the +insulin group had a higher CCI score, and there were

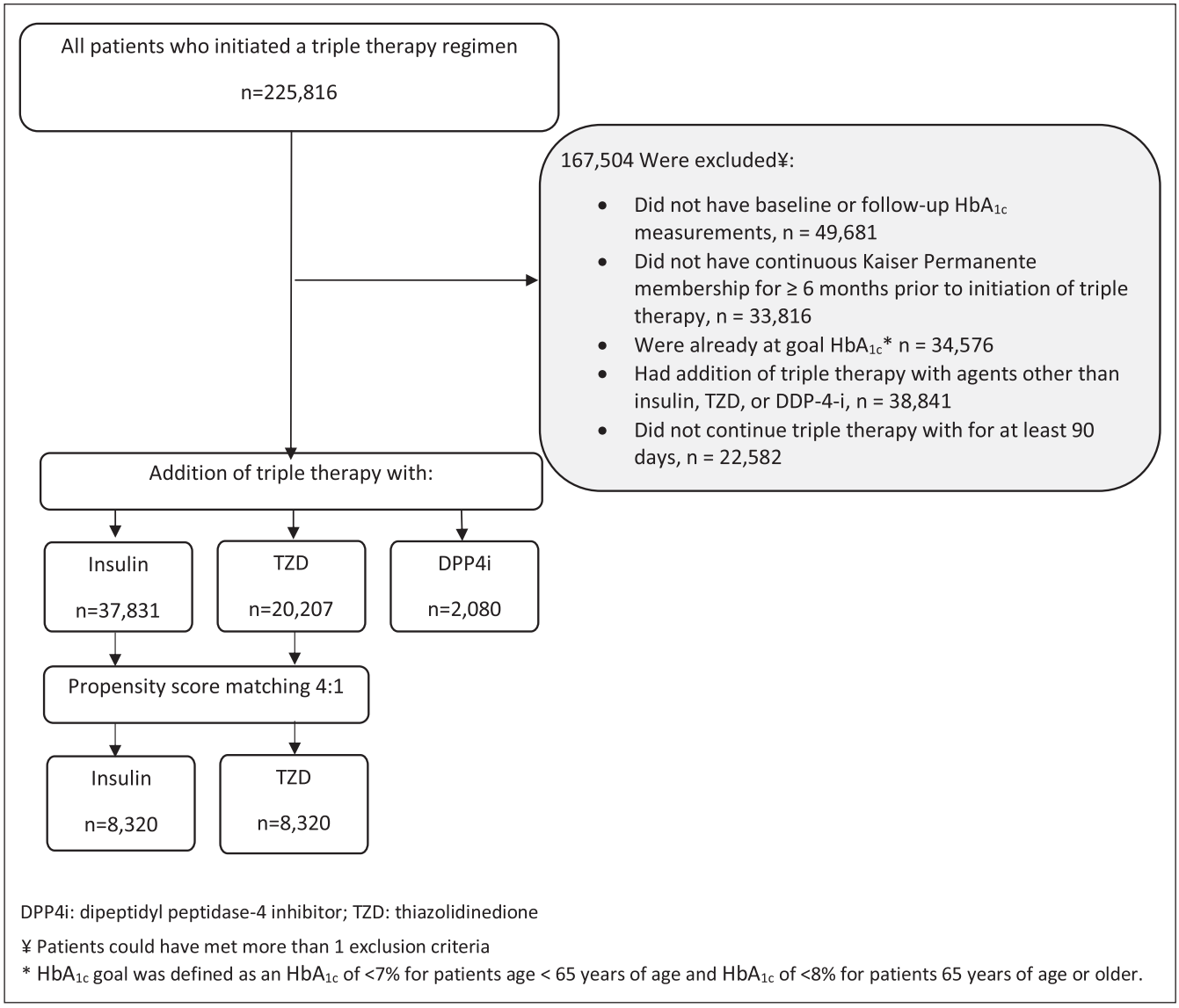

Figure 1. Patient selection cohort flow chart. ¥ Patients could have met more than 1 exclusion criterion. *HbA_{1C} goal was defined as less than 7% for patients younger than age 65 years and less than 8% for patients aged 65 years or older. DPP4i = dipeptidyl peptidase-4 inhibitor; HbA_{1C} = hemoglobin A_{1C}; TZD = thiazolidinedione.

more patients taking metformin at maximum dose in the +TZD group (Table 1).

After propensity score matching, the cohorts were well matched in all observed baseline variables. There were 2080 patients in the +DPP4i group, which was matched to 8320 patients in the +insulin group and 8320 patients in the +TZD group. For the overall population, the mean age was 58.0 ± 9.9 years, 42.8% of patients were women, 33.8% of patients reported as white, and the mean baseline HbA_{1C} was 8.9% ± 1.3% (Table 1). Patients reporting Hispanic ethnicity were not significantly different among the study groups (33.0%, 34.3%, and 33.2% for the +insulin, +TZD, and +DPP4i groups, respectively; p = 0.55).

Proportion at Goal

The results for the proportion of patients who attained goal are presented in Table 2. When comparing the +DPP4i group to the +insulin group, there was no difference in the percentage of patients who achieved goal HbA_{1C} (24.2% versus 23.6%, respectively; p = 0.58). However, +TZD use resulted in a significantly higher percentage of patients who achieved goal HbA_{1C} compared to +DPP4i use (31.0% versus 23.6%, respectively; p < 0.01).

Table 1. Baseline characteristics[a]

Characteristic	DPP4i (n = 2080)	Insulin				TZD			
		Before propensity score matching (n = 37,831)		After propensity score matching (n = 8320)		Before propensity score matching (n = 20,207)		After propensity score matching (n = 8320)	
		Value	p value	Value	p value	Value	p value	Value	p value
Mean age, y	58.0 ± 9.9	57.4 ± 10.8	<0.01	57.6 ± 10.3	0.99	56.8 ± 10.0	<0.01	57.6 ± 10.3	0.11
Men	58.17	51.83	<0.01	57.87	0.80	55.27	0.01	56.39	0.14
White race	34.04	37.59	<0.01	34.36	0.95	33.34	0.01	33.17	0.80
Mean baseline HbA_{1C} (range)	8.87 ± 1.3 (8.0-9.5)	9.60 ± 1.6 (8.4-10.5)	<0.01	8.9, 1.2	0.99	8.9 ± 1.3 (8.0-9.6)	0.06	8.9 ± 1.3	0.64
Mean duration of T2D, y (range)	8.2 ± 4.7 (4.4-11.7)	7.8, 4.5	0.03	8.2, 4.6	0.89	6.4 ± 3.7 (3.8-8.6)	<0.01	7.7 ± 3.8	<0.01
Median CCI (IQR 25th, 75th)	2.0 (2, 4)	3.0 (2, 4)	<0.01	2.0 (2, 4)	0.98	2.0 (1, 4)	<0.01	3.0 (1, 4)	0.06
HTN diagnosis	66.35	71.69	<0.01	66.57	0.84	74.95	<0.01	67.87	0.18
HLD diagnosis	68.03	70.87	0.01	67.10	0.42	63.94	0.02	67.82	0.89
Maximum metformin dose	53.80	52.82	0.39	54.07	0.82	56.64	0.01	53.85	0.97

[a] Values are given as means ± SD or percentages unless indicated otherwise.
CCI = Charlson Comorbidity Index; DPP4i = dipeptidyl peptidase-4 inhibitor; HbA_{1C} = hemoglobin A_{1C}; HLD = hyperlipidemia; HTN = hypertension; IQR = interquartile range; SD = standard deviation; T2D = type 2 diabetes mellitus; TZD = thiazolidinedione.
Men, White race, HTN diagnosis, HLD diagnosis, and Maximum metformin dose.

Change in HbA_{1C}

The mean change in HbA_{1C} is shown in Table 2. When comparing the +DPP4i group to the +insulin group, there was no significant difference in the reduction of HbA_{1C} (−0.79% ± 1.23% versus −0.79% ± 1.31%, respectively; p = 0.97) between the 2 groups. However, the +TZD group had a significantly larger mean HbA_{1C} reduction compared to the +DPP4i group (−0.94% ± 1.34% versus −0.79% ± 1.31%, respectively; p < 0.01).

Hypoglycemia

There was no significant difference in the rate of hospital or ED hypoglycemic events when evaluating the +insulin group (0.41%; p = 0.07) and +TZD group (0.31%; p = 0.19) compared to the +DPP4i group (0.14%) (Table 2).

Weight

In terms of weight, the +insulin and +TZD groups had a significantly larger mean change in weight compared to the DPP4i group, which had a decrease in weight (0.49 ± 4.05 kg and 1.22 ± 3.59 kg versus −0.15 ± 3.33 kg, respectively; p < 0.01) (Table 2).

Patient Population HbA_{1C} Greater than 9%

Results of the subgroup analysis for the patient population with HbA_{1C} greater than 9% at baseline (n = 6597; mean HbA_{1C} = 10.2% ± 1.1%) are summarized in Table 2. The +insulin group had a higher proportion of patients who achieved goal HbA_{1C} compared to the +DPP4i group (17.3% versus 12.4%, respectively; p < 0.01). The +insulin group had a larger mean HbA_{1C} reduction compared to the addition of +DPP4i (−1.66 versus −1.45, respectively; p = 0.02). Similarly, the +TZD group also had a higher proportion of patients who achieved goal HbA_{1C} compared to the +DPP4i group (19.0% versus 12.4%, respectively; p < 0.01) and had a larger mean HbA_{1C} reduction compared to the addition of +DPP4i (−1.71 versus −1.45, respectively; p < 0.01).

Factors Affecting the Odds of Achieving HbA_{1C} Goal

A logistic regression was performed to predict the odds of achieving goal HbA_{1C} among the +DPP4i and +TZD groups. The use of +DPP4i was less likely to help patients attain goal HbA_{1C} (OR = 0.63; 95% CI = 0.56-0.71; p < 0.01) compared to +TZD (Table 3).

There were no statistically significant differences in the odds of achieving goal HbA_{1C} when evaluating +DPP4i compared to insulin (OR = 0.98; 95% CI = 0.87-1.10; p = 0.68) using logistic regression (Table 4).

Patients with a baseline HbA_{1C} greater than 9% were less likely to achieve goal HbA_{1C} when evaluating +DPP4i

Table 2. Unadjusted primary and secondary outcomes by study groups[a]

Characteristic	DPP4i	Insulin		TZD	
		Value	p value	Value	p value
Patients, n	2080	8320		8320	
Proportion achieving HbA_{1C} goal	23.6	24.2	0.58	31.0	< 0.01
Change in HbA_{1C}	−0.79 ± 1.23	−0.79 ± 1.31	0.97	−0.94 ± 1.34	< 0.01
Frequency of hypoglycemia, n (%)	3 (0.14)	34 (0.41)	0.07	26 (0.31)	0.19
Patients, n	758	2351		1829	
Mean change in weight	−0.15 ± 3.33	0.49 ± 4.05	< 0.01	1.22 ± 3.59	< 0.01
Patients, n	696	2974		2927	
Proportion achieving HbA_{1C} goal: baseline HbA_{1C} > 9%	12.4	17.3	< 0.01	19.0	< 0.01
Percent change in baseline HbA_{1C} > 9%	−1.45 ± 1.46	−1.66 ± 1.45	0.02	−1.71 ± 1.55	< 0.01

[a] Values are given as means ± SD or percentages unless indicated otherwise. p values reflect comparison with the DPP4i group.
DPP4i = dipeptidyl peptidase-4 inhibitor; HbA_{1C} = hemoglobin A_{1C}; TZD = thiazolidinedione.
Proportion achieving HbA1c goal and Proportion achieving HbA1c goal: baseline HbA1c >9%.

compared to +TZD (OR = 0.67; 95% CI = 0.52-0.86; p < 0.01; Table 3) and +DPP4i compared to insulin (OR = 0.55; 95% CI = 0.42-0.71; p < 0.01; Table 4).

DISCUSSION

In this real-world study, we assessed the comparative effectiveness and safety of third-line add-on options to metformin and sulfonylurea therapy for patients treated from January 2006 to June 2016. Our study demonstrated that there was no difference in the percentage of patients who achieved their goal HbA_{1C} or in the mean HbA_{1C} reduction between the +DPP4i and +insulin groups. However, for patients with a baseline HbA_{1C} greater than 9%, the addition of insulin had a substantially larger mean HbA_{1C} reduction compared to the addition of DPP4i. Theoretically, the absolute decrease in HbA_{1C} is larger with higher baseline HbA_{1C} values and smaller for lower HbA_{1C} values. When appropriately adjusted, insulin has no limit on HbA_{1C} reduction and may be beneficial for patients with a higher baseline HbA_{1C}.

In regard to the comparison of DPP4i to TZD, our findings are similar to that of controlled trials. In an open-label study by Hsia et al,[12] patients in the TZD group achieved a larger mean HbA_{1C} reduction compared to that of the sitagliptin group (−2.0% versus −1.3%; p = 0.006). Our study adds to the literature because it draws from an ethnically diverse cohort.

A notably higher percentage of patients achieved their goal HbA_{1C} and a larger mean HbA_{1C} reduction was achieved in the +TZD group versus the +DPP4i group. A potential reason for this difference is that patients with insulin resistance may benefit more from an insulin sensitizer than a drug that acts as a secretagogue. In our study, the majority of TZD prescriptions were prescribed during the first year of the study period (2006). After 2006, TZDs

Table 3. Multivariate logistic regression of achieving goal hemoglobin A_{1C} when comparing dipeptidyl peptidase-4 inhibitors and thiazolidinedione as the third-line triple-therapy agent[a]

Characteristic	Odds ratio (95% CI)	p value
DPP4i vs TZD	0.63 (0.56-0.71)	<0.01
HbA_{1C} > 9%	0.55 (0.42-0.71)	<0.01
Age, y	1.07 (1.06-1.07)	<0.01
Race		
Black vs white	0.84 (0.70-1.00)	0.52
Hispanic vs white	0.74 (0.66-0.83)	<0.01
CCI score		
1-2 vs ≥ 5	0.90 (0.79-1.02)	0.10
3-4 vs ≥ 5	0.85 (0.75-0.97)	0.01

[a] c-index = 0.724.
CCI = Charlson comorbidity index; CI = confidence interval; DPP4i= dipeptidyl peptidase-4 inhibitor; HbA_{1C} = hemoglobin A_{1C}; TZD = thiazolidinedione.

Table 4. Multivariate logistic regression of achieving goal hemoglobin A_{1C} when comparing dipeptidyl peptidase-4 inhibitors and insulin as the third-line triple-therapy agent[a]

Characteristic	Odds ratio (95% CI)	p value
DPP4i vs insulin	0.98 (0.87-1.10)	0.68
HbA_{1C} > 9%	0.67 (0.52-0.86)	<0.01
Age, y	1.07 (1.06-1.0)	<0.01
Race		
Black vs white	0.77 (0.64-0.93)	0.01
Hispanic vs white	0.64 (0.57-0.72)	<0.01
CCI score		
1-2 vs ≥ 5	0.84 (0.73-0.95)	0.01
3-4 vs ≥ 5	0.88 (0.77-1.01)	0.06

[a] c-index = 0.725.
CCI = Charlson comorbidity index; CI = confidence interval; DPP4i= dipeptidyl peptidase-4 inhibitor; HbA_{1C} = hemoglobin A_{1C}; TZD = thiazolidinedione.

had fallen out of favor likely due to the US Food and Drug Administration Drug Safety Communication regarding rosiglitazone and heart failure as well as other safety risks.[16] More recently, an updated 2016 US Food and Drug Administration review concluded that the use of pioglitazone may be linked to an increased risk of bladder cancer.[17] Although +TZD use was more effective than +DPP4i in this study, it is important for providers to properly screen patients and only treat appropriate patients in order to minimize the risk of adverse effects such as edema, fractures, heart failure, and bladder cancer, which were not evaluated in this study.[18,19]

In terms of safety outcomes, there was no statistically significant difference in the frequency of composite hypoglycemic events, including ED visits or hospitalizations, when evaluating the +insulin and +TZD groups compared to the +DPP4i group (Table 2). In terms of weight, the +insulin and +TZD groups had a larger mean change in weight compared to the +DPP4i group.

Systematic reviews and network meta-analyses have previously attempted to determine the most optimal add-on agent to metformin and a sulfonylurea. Gross et al[10] concluded that there was no clear difference in benefit compared to placebo when adding a third agent for patients who had not achieved glycemic goals while taking metformin and a sulfonylurea. McIntosh et al[11] concluded that third-line agents for treatment of T2D have similar glycemic control but vary in their tendency to cause weight gain or hypoglycemia. Our study had a larger sample size, and it focused on the comparative effectiveness and safety of specific drug classes (DPP4i, TZD, insulin) and was able to detect a difference.

Major recommendation changes were made to the ADA Standards of Medical Care in Diabetes in 2018 and 2019, notably for patients with established atherosclerotic cardiovascular disease or chronic kidney disease who may benefit from treatment with a sodium-glucose cotransporter 2 inhibitor or GLP1RA. However, for patients without these comorbidities and for whom cost is a major issue, a sulfonylurea or TZD can still be used as second or third add-on agents to metformin per the 2019 ADA Standards of Medical Care in Diabetes. This recommendation is in line with one of the treatment arms of our study. Considering that cost of therapy is a true concern for patients with diabetes, there is value in the applicability of the results of this study for these patients.[20,21]

This study has several strengths. This real-world study evaluated a large sample size population, accounting for real-world practice and variations in diet, lifestyle, and medication compliance. Multiple variables with significant clinical impact were taken into consideration, and several methods of data analyses were utilized with similar results, which adds to the robustness of the outcomes. Propensity score matching was used to match the control and treatment groups, adjusting for confounding factors and reducing the risk for bias. Since Kaiser Permanente is an integrated health care system that allows collaboration between health care members, the system can easily collect and analyze patient outcomes, laboratory data, and prescription information for all patients.

This study has some limitations. Since this is a retrospective analysis, covariates such as medication adherence, optimization of sulfonylurea and TZD therapy, and insulin titration were not controlled. This assumed that the clinician intensified therapy following the different guidelines available during the study period from 2006 to 2016. However, we did not expect a difference among study groups, since education regarding diet and lifestyle modifications is standardized within the organization. Selection bias also cannot be ruled out because there may be additional considerations or unobserved variables when selecting the appropriate third-line agent. For example, we did not examine the renal function of patients evaluated in the study. However, the third-line agents evaluated in this study (insulin, TZD, and DPP-4i) can be used for patients with renal impairment. The use of propensity score matching minimized differences using observable variables.

Chart reviews were not performed to validate hypoglycemic events for both the study and control groups; hence, hypoglycemic events were only counted if they were the primary diagnosis. Mild cases of hypoglycemia may not be well documented in the electronic medical record; thus, our study was not able to capture these results. Moreover, patients are usually able to self-manage mild cases of hypoglycemia without incurring additional health care resources. In addition, the goal HbA_{1C} cutoff was based solely on age, not comorbidities. To remedy this, the CCI was evaluated, which predicts the 1-year mortality for a patient who may have a range of comorbid conditions such as heart disease and cancer. For this analysis, the +DPP4i, +insulin, and +TZD groups had a similar CCI score.

Another limitation is that the primary outcomes were surrogate markers, which lack information on long-term outcomes such as microvascular or cardiovascular events. Furthermore, this study was conducted in a large managed care setting, which may limit the applicability of these results to other practice settings. Despite these limitations, given the large sample size, this study reflects real-world practice and can help guide clinicians in decision making.

In the future, additional studies to evaluate the impact of race or ethnicity may be helpful to address the diverse T2D population. Studies with longer follow-up periods may show the long-term effectiveness of these drugs as third-line agents in the treatment of T2D.

CONCLUSION

Although the previous ADA and AACE/ACE guidelines prior to 2018 recommended metformin as first-line therapy, no specific recommendations for second- and third-line agents were made at that time. Not only did clinicians need to consider expected HbA_{1C} reduction and risk of hypoglycemia associated with treatment, but they also had to weigh other factors such as weight gain, adverse effects, cost, and patient preferences when selecting glucose-lowering therapy.[1] The 2019 ADA guidelines make recommendations for second- and third-line agents based on patient characteristics such as comorbidities, hypoglycemic risk, impact on weight, risk for side effects, and cost.[20] The 2019 AACE/ACE guidelines suggest a hierarchy of therapeutic options, considering the medication's properties and patient characteristics.[21]

The use of DPP4i was as effective as insulin as a third-line add-on option in the overall population in terms of HbA_{1C} reduction and the proportion of patients achieving goal HbA_{1C}. Insulin may be more effective in patients with a baseline HbA_{1C} greater than 9% when evaluating HbA_{1C} reduction. TZD was more effective than DPP4i as a third-line oral agent when evaluating both HbA_{1C} reduction and proportion achieving goal HbA_{1C}. Clinicians should consider the effectiveness and safety of glucose-lowering medications when determining the most optimal triple-therapy regimen. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Authors' Contributions

Vittoria Marie Ledesma, PharmD, BCPS, Rita L Hui, PharmD, MS, and Fang Niu, MS, contributed the study concept and design, with assistance from Natalie Aboubechara, PharmD, BCPS, and Mirta Millares, PharmD, FCSHP, FASHP. Rita L Hui and Fang Niu were responsible for data collection. Vittoria Marie Ledesma, Rita L Hui, and Fang Niu, along with Natalie Aboubechara, interpreted the data. Natalie Aboubechara, Vittoria Marie Ledesma, and Rita L Hui wrote the manuscript, with assistance from Susan M Lee, PharmD, BCPS, Fang Niu, Yesha A Patel, PharmD, BCPS, and Mirta Millares. All authors reviewed and edited the final manuscript. All authors have given final approval to the manuscript.

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ORIGINAL RESEARCH ARTICLE

Knowledge, Attitudes, and Perceptions About Medicolegal Education: A Survey of OB/GYN Residents

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ABSTRACT

Introduction: Medicolegal concerns affect the career decisions of obstetrics/gynecology (OB/GYN) residents; however, their exposure to medicolegal education during residency training is virtually unknown.

Objective: To assess the knowledge, attitudes, and perceptions of medicolegal concepts among OB/GYN residents.

Methods: All residents in an accredited residency training program in OB/GYN in the United States during the 2017-2018 academic year were invited to complete an anonymous online survey.

Results: Of the 5152 OB/GYN residents invited to complete the survey; nearly 17% (n = 866) responded. Basic medicolegal knowledge was poor. Almost 60% of respondents (n = 500) could not identify malpractice as a form of tort liability. Among respondents, 44% (n = 378) reported receiving no medicolegal education during residency, 21% (n = 181) were unsure, and 34% (n = 293) reported receiving some education. Of those who reported receiving medicolegal education, the majority, 66% (n = 549), received it informally: by "word of mouth" or by "observing colleagues." Most (67%, n = 571) of the residents did not believe they had adequate exposure to medicolegal topics, and 19% (n = 163) were unsure. Ninety-two percent of residents (n = 782) reported concerns about being sued, and 67% (n = 571) believed that formal instruction during residency training may prevent lawsuits.

Conclusion: Exposure to medicolegal topics during OB/GYN residency training is very limited and unstructured. This study showed that residents desire a more formalized medicolegal curriculum during postgraduate training and that implementation may have several benefits.

INTRODUCTION

Medical malpractice influences practice patterns and affects health care delivery in the United States. It is especially relevant in OB/GYN, a medical subspecialty with one of the highest incidences of malpractice suits.[1] A recent Medscape survey suggests that 85% of all OB/GYN physicians have been sued.[2] In fact, *The New England Journal of Medicine* reported that by the age of 65 years, 99% of physicians in high-risk specialties will face a malpractice claim.[1] As a result, approximately 50% of OB/GYNs have altered the scope of their clinical practice because of the real or perceived risk of malpractice litigation, and 40% report making changes to their clinical practice because of the availability and affordability of professional liability insurance.[3] A survey of fourth-year OB/GYN residents identified Pennsylvania and New York as states most likely to be avoided for postresidency practice based on medicolegal risk.[4] Historically, resident physicians were safeguarded from malpractice suits, but this same study revealed that 1 in 5 fourth-year OB/GYN residents has been involved in a lawsuit during residency.[4]

Medicolegal issues are important for any field of medicine, but especially for those in high-risk specialties such as OB/GYN. Arguably, residency is one of the best times to expose physicians to these concepts so they can integrate them into the practice of medicine while they learn the craft unique to their specialty. Despite this noted salience, little is known about the baseline knowledge of all OB/GYN residents and the extent and type of medicolegal education they receive. A survey of OB/GYN residency program directors conducted in 2005 by Hunt-Moreno and Gilbert[5] found that 86% of program directors believed they provided formal and informal medicolegal instruction to their residents. Despite this, 88% believed that the curriculum was inadequate and too informal.[5] Another study by Blanchard et al[4] showed that approximately 50% of fourth-year residents believed they received some education in medical liability risk management in residency, but 80% reported they did not receive training in "next steps" after being named in a lawsuit. Of note, the way the education was delivered was not specified.[4] When looking to other medical specialties for some guidance, surveys of internal medicine and family medicine residents illustrate a low level of medicolegal knowledge.[6] One study reported that 96% of residents found medicolegal issues to be important, but only 28% believed that these issues were adequately addressed in their residency training.[7]

When formal medicolegal curricula were piloted in select emergency medicine and pediatric residency programs, residents demonstrated improved communication skills, expanded knowledge base, and increased recognition of documentation pitfalls.[8-10] Despite data and dialogue

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suggesting benefits to implementation of formal medicolegal education during residency training, current medical education is lacking in this regard.[11] The Accreditation Council for Graduate Medical Education (ACGME) does not have specific learning objectives or requirements for formal medicolegal curricula.[12] There is a dearth of information about what OB/GYN residents know and how they are being exposed to these topics during training. The aim of our study was to describe the medicolegal training experience of OB/GYN residents in ACGME-accredited training programs and to investigate the knowledge, attitudes, and perceptions of medicolegal concepts among OB/GYN residents.

METHODS

All residents undergoing ACGME-accredited residency training in OB/GYN in the United States during the 2017-2018 academic year were invited to complete a voluntary, anonymous 16-question survey. The survey was developed by first identifying topics that were relevant to residents, drafting questions, and then reviewing them. The questions were then pretested on study team members. The team members reviewed the choice options, how the options were described, and the order of the options, and then provided feedback. The knowledge questions were reviewed by a member of the institution's medicolegal department. The final set of questions was then modified on the basis of this feedback. An online survey (SurveyMonkey) link[13] was emailed to OB/GYN residency program directors, program coordinators, or residents, who were asked to forward the survey to the program residents. The survey queried residents regarding their demographics (n = 4), their medicolegal knowledge (n = 4), the type of medicolegal education received during residency (n = 4), and the impact of potential litigation on their clinical practice and career plans (n = 4).

This study received exemption status by the Kaiser Permanente Northern California institutional review board. The primary outcome was the proportion of residents who felt their program's medicolegal curriculum was insufficient. Secondary outcomes included the basic medicolegal knowledge of the residents, an inventory of current medicolegal curricula, and resident-reported perceptions of the impact of the medicolegal climate on their future practice and career trajectory.

Data were analyzed using descriptive statistics for demographics and survey constructs as well as bivariate analyses to assess demographic variations according to specific survey responses. Chi-squared and Fisher exact tests were used for categorical variables, and the Kruskal-Wallis test was used for continuous variables. The p values for overall comparisons were considered significant at less than 0.05.

Table 1. Survey respondents' demographic characteristics and baseline knowledge.

Characteristic	Number (%)
Demographic	
Sex (n = 864)	
Male	122 (14.12)
Female	738 (85.42)
Other	4 (0.46)
Race (n = 866)	
Asian	106 (12.24)
Black	49 (5.66)
White	604 (69.75)
Hispanic/Latino	65 (7.51)
Native American	2 (0.23)
Other	40 (4.62)
Region (n = 865)	
Northeast	255 (29.48)
Midwest	242 (27.98)
South	182 (21.04)
West	186 (21.5)
Year of residency (n = 865)	
First	246 (28.44)
Second	208 (24.05)
Third	216 (24.97)
Fourth	195 (22.54)
Baseline knowledge	
Malpractice cap question (n = 836)	
Yes	162 (19.38)
No/unsure	674 (80.62)
Body of law question (n = 837)	
Correct (torts law)	337 (40.31)
Wrong/unsure	499 (59.69)
Alternative dispute question (n = 832)	
Yes	75 (9.01)
No/unsure	757 (88.99)
Malpractice claim question (n = 837)	
Yes	63 (7.53)
No/unsure	774 (92.47)

All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Of 5152 possible respondents, 866 (17%) completed the survey. The respondents were equally geographically distributed among the 4 regions of the continental US (Table 1), as defined by the US Census Bureau. A similar number of residents from each training level responded to the survey: first year, 28.4% (n = 246); second year, 24.1% (n = 208); third year, 24.9% (n = 216); and fourth year,

Table 2. Body of law for medical malpractice				
Year of residency	Correct (torts law), number (%)	Wrong/unsure, number (%)	Total, number	p value[a]
First	84 (35.4)	153 (64.5)	237	0.004
Second	69 (34.3)	132 (65.6)	201	
Third	90 (42.8)	120 (57.1)	210	
Fourth	94 (50.0)	94 (50.0)	188	
Total	337 (40.3)	499 (59.6)	836	

[a] Chi-squared test.

22.5% (n = 195). Of the respondents, 86% (n = 738) identified as female, and 14% (n = 122) identified as male. Most respondents (70%, n = 604) were white. Almost 12% (n = 106) were Asian, 6% (n = 49) were black, 8% (n = 65) were Hispanic/Latino, and nearly 5% (n = 40) identified as other.

Residents' baseline medicolegal knowledge was poor. Most respondents (80%, n = 674) were not aware of whether their state law included a cap on medical malpractice damages, although respondents from the South and West regions were more familiar with damage caps in their states. Sixty percent (n = 500) could not name the body of law that encompasses medical malpractice. Only 9% of residents (n = 75) were familiar with the process of alternative dispute resolution, and 91% (n = 757) were unfamiliar or unsure. Only 8% (n = 63) of the respondents could name all 4 elements that plaintiffs must prove to make a successful medical malpractice claim (Table 1). The correct answer to the body of law question for medical malpractice was significantly different by year of residency (p = 0.004). Those who did know the correct answer were more likely to be third-year or fourth-year residents (Table 2).

Only about one third of respondents (35%, n = 293) reported receiving at least some formal medicolegal training. When asked about whether the training included formal lectures, 81% (n = 693) reported fewer than 3 hours of didactics, and 19% (n = 158) reported 3 or more hours of education, with little difference in response to this question by region. When asked to further describe the type of training offered by their residency programs, 29% of residents (n = 258) reported it was conveyed by physician faculty in formal lecture, and 30% (n = 262) reported that medicolegal attorneys or other experts gave formal lectures. However, 46% (n = 556) reported that education was delivered informally by "word of mouth" or by observing colleagues or mentors, and 15% (n = 131) reported no education at all. Most study participants (87%, n = 734) were either unsure or did not believe they received an appropriate level of exposure to medicolegal issues in their residency training, and 67% (n = 571) believed that education on medicolegal issues during residency would help prevent lawsuits during their medical career (Table 3).

Table 3. Training characteristics	
Question or topic	Number (%)
Formal training question (n = 852)	
Yes	293 (34.39)
No/unsure	559 (65.61)
Hours of training question (n = 851), hours	
< 3	693 (81.43)
≥ 3	158 (18.57)
Training provided believed sufficient question (n =847)	
Yes	113 (13.34)
No/unsure	734 (86.66)
Source of medical training[a] (n = 1207)	
Attending physicians via formal lectures	258 (29.79)
Medicolegal attorneys or other experts via formal lectures	262 (30.25)
Word of mouth and observing colleagues or mentors	556 (64.2)
No education about medicolegal issues	131 (15.12)
Impact of training on career	
Prevent getting sued question (n = 849)	
Yes	571 (67.26)
No/unsure	278 (32.74)
Worry about being sued question (n = 852)	
Yes	782 (91.78)
No/unsure	70 (8.22)

[a] Respondent could make multiple choices.

Of the respondents, 92% (n = 782) expressed concern over being sued during their OB/GYN career (Table 3). This rate was similar across the geographic regions (p = 0.41) and increased with each year of residency (Table 4). When asked their opinions on what inspired the most lawsuits in the field of OB/GYN, 66% of respondents (n = 556) listed poor communication, 14% (n = 115) named poor documentation, 11% (n = 92) identified failure of early intervention by risk management or an ombudsman during an adverse outcome, 7% (n = 56) believed it was due to a systems-based practice failure, 4% (n = 31) believed it was the result of medical error or negligence, and 0.23% (n = 2) believed suits were caused by other reasons (Figure 1). Almost 60% (59%, n = 491) of OB/GYN residents either believed medical malpractice trends might influence their

Table 4. Residents' concern over being sued		
By demographic characteristic	**Number (%)**	**p value[a]**
Geographic region		0.41
Northeast[b]		
Yes	228 (90.12)	
No	12 (4.74)	
Unsure	13 (5.14)	
Midwest		
Yes	216 (92.31)	
No	13 (5.56)	
Unsure	5 (2.14)	
South		
Yes	165 (92.18)	
No	7 (3.91)	
Unsure	7 (3.91)	
West		
Yes	173 (92.97)	
No	10 (5.41)	
Unsure	3 (1.67)	
Year of residency		0.01
First		
Yes	214 (88.8)	
No	13 (5.39)	
Unsure	14 (5.81)	
Second		
Yes	186 (90.29)	
No	17 (8.25)	
Unsure	3 (1.46)	
Third		
Yes	196 (92.89)	
No	8 (3.79)	
Unsure	7 (3.32)	
Fourth		
Yes	186 (95.9)	
No	4 (2.07)	
Unsure	4 (2.07)	

[a] Chi-squared test.
[b] A few of the northeasterners did not respond to this question.

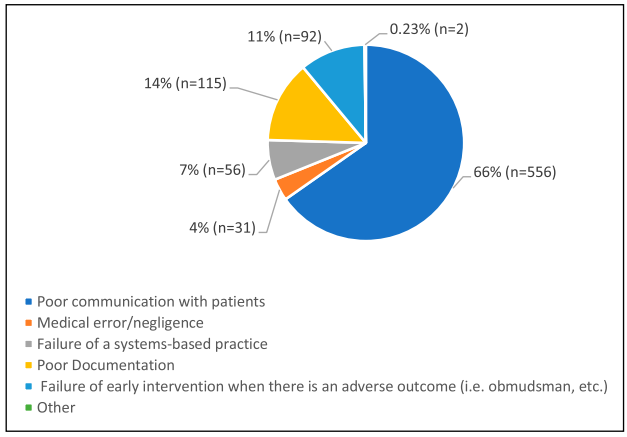

Figure 1. Respondents' opinions on causes of lawsuits.

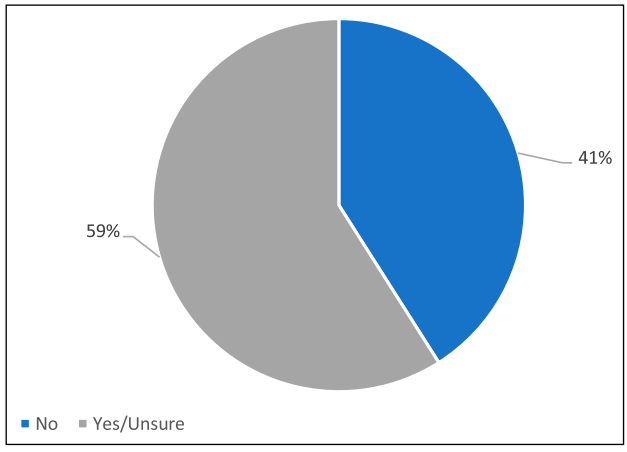

Figure 2. Impact of litigation on future geographic location of practice.

choice of geographic location for their clinical practice or were unsure (Figure 2). The bivariate analysis showed that this response did not statistically differ by region (p = 0.19). There was no significant difference in response to the questions regarding the presence of formal medicolegal training (p = 0.76), hours of instruction, and exposure (p = 0.37) to education by region, but senior residents felt less hopeful that education may help prevent lawsuits (Table 5).

DISCUSSION

Our study found that OB/GYN residents are unfamiliar with basic medicolegal concepts. This supported the findings of Blanchard et al[4] but provided a more in-depth analysis by quantifying and qualifying the deficit in knowledge previously identified. Although that prior study assessed only chief residents, this one studied all years of residency, quantified hours of training, qualified how the training was delivered, and examined differences by training level and location. Most residents were unaware of the body of law that malpractice falls under and the elements that constitute liability in a malpractice suit. Most residents were uninformed about caps on malpractice damage claims, although this varied by region, with respondents from the South and West regions exhibiting more knowledge about caps than those from the Northeast and Midwest. Despite the use of processes such as arbitration by health systems to settle malpractice claims, most residents were not familiar with alternative dispute resolution. Our study results show that OB/GYN residents are highly unprepared from a knowledge standpoint for potential lawsuits in the litigious climate in which they work.

Table 5. Medicolegal issues in curriculum by geography

	n	%	p value[a]
Medicolegal issues present Northeast			0.76
Yes	88	34.78	
No/unsure	165	65.22	
Midwest			
Yes	86	36.75	
No/unsure	148	63.25	
South			
Yes	60	33.52	
No/unsure	119	66.48	
West			
Yes	59	31.89	
No/unsure	126	68.11	
Number of hours of instruction in curriculum Northeast, hours			0.37
< 3	206	81.42	
≥ 3	47	18.58	
Midwest			
< 3	195	83.33	
≥ 3	39	16.67	
South			
< 3	138	77.09	
≥ 3	41	22.91	
West			
< 3	153	83.15	
≥ 3	32	16.85	

[a] Chi-squared test.

Among those residents who reported receiving some medicolegal education, the minority reported that it was formal. The percentage of residents reporting exposure to medicolegal topics increased by year of training, suggesting they are more likely to be exposed in the latter part of residency training. When asked the quantity of time dedicated to medicolegal training, most residents reported 3 or fewer hours of instruction, and many specified it was by "word of mouth." This corroborates the results of the studies by Blanchard et al[4] and Hunt-Moreno and Gilbert,[5] showing that even if instruction was given, it was inadequate. The bivariate analyses indicated that there was no statistically significant difference by region either in exposure to medicolegal topics or number of hours spent in teaching, suggesting that the deficiency in medicolegal training during OB/GYN residency may be nationwide.

Residents in OB/GYN across the United States do not believe they have adequate medicolegal education during residency and fear being sued in the course of their careers. Based on practitioner data about the prevalence of lawsuits, that fear is well founded. Although most survey respondents believed that education in residency may help in preventing lawsuits, the proportion of those answering "yes" was more likely to be junior residents. However, more senior residents expressed concern over being sued at some point during their careers, suggesting that as physicians progress in training, they have more exposure to a climate of lawsuits or feel more susceptible.

When asked about the most likely cause of lawsuits, most residents indicated poor communication or poor documentation. A smaller proportion believed that lawsuits are provoked by failure of a systems-based practice or failure of the hospital/medical group to provide a mediator when there are adverse outcomes. Respondents were given the option of an open-ended reply in naming other reasons for suits. The most commonly entered response was that the United States has a litigious society. Only 4% of OB/GYN residents thought lawsuits *actually* involved medical malpractice and erroneous physician-directed care. The 2017 Medscape study suggests that when all medical specialties are considered, the most common reasons for suits are a failure to diagnose a condition and a delay in diagnosis of a condition.[2] However, when surgical specialties are considered independently, the most lawsuits originate from complications from surgery or treatment. Poor outcomes or disease progression was the next most common reply.[2] Interestingly, for those sued, 22% wished they had better chart documentation, and 16% wished they had some improvement in communication or spent more time with the patient. Many wished they had known more about the overall processes and procedures involved in litigation. This shows that although the residents' perceptions of what ultimately leads to suits may be misplaced, they are still accurate in identifying important contributing factors such as documentation and communication. Additionally, only 5% of the physicians in the Medscape study thought the lawsuit was warranted.[2] This finding was similar to what the residents in the present study thought.

Our study found that medicolegal issues can affect resident career trajectories, a finding consistent with the studies by the American College of Obstetricians and Gynecologists[3] and Blanchard et al.[4] Forty percent of those surveyed reported that malpractice considerations may influence where they practice after residency, and 20% were unsure. Our study supports the previously identified notion that the medicolegal climate and state-specific medical malpractice laws will continue to have an impact on health care access, as providers continue to choose to work in states and system locations with more protections for health care providers. These results may be generalizable. Although our study examined only the

OB/GYN specialty, it is reasonable to conclude that similar trends may be seen in other high-risk fields, such as neurosurgery or emergency medicine.

In addition to showing the effects of malpractice on career choices, these data also highlight the toll that litigation may take on practitioners individually. An older 2015 Medscape survey reported that approximately 50% of physicians (in all specialties) stated that being sued was a either a "horrible" experience or the "worst" experience of their lives.[14] Other studies suggest that litigation may also lead physicians to leave the practice of medicine.[15] Moreover, data suggest that women are more likely to be negatively affected by litigation than men.[2] This is a concerning statistic because the OB/GYN field is becoming increasingly dominated by women, which implies that litigation may have a magnified effect on the OB/GYN provider population. The physician shortage is a well-known phenomenon facing the United States, and it limits patient access to care, especially in underserved areas. Our study findings support the idea that litigation may be one of the contributing factors to this shortage and highlight the need for education and the increasing importance of malpractice reform.

Recommendations

This conclusion then begs the question of what that curriculum should contain. Although some litigation may be unavoidable as the result of poor health outcomes or surgical complications, suits that originate from poor clinician documentation or communication may be remediable. A graduate medical education curriculum that focuses on communication and documentation would be an excellent place to start because it would likely serve to mitigate these risks and simultaneously assist with better delivery of patient care. Additionally, because most OB/GYN physicians find themselves involved in a lawsuit at some point in their careers, preparing OB/GYN residents with sufficient medicolegal knowledge and giving them exposure to the medicolegal process may make the process more familiar and less traumatic. As such, in addition to addressing documentation and communication, a good curriculum might also include legal basics and an overview of the litigation process from filing suit to judgment. The findings of Drukteinis et al[8] and Harrison et al[9] showed that exposing residents to a mock trial and a workshop on deposition preparation, respectively, were well received. A study by Evans and Refrow-Rutala[16] implemented a more thorough, multiday intensive course, which included didactics covering legal basics, a practice case in a mock trial, a trip to the county courthouse, and question-and-answer panels with experts. The surgical residents who participated believed it was "essential" for graduating residents.[16] If a national curriculum is put in place, future studies could then evaluate the short-term and long-term effects of the instituted curriculum such as determining whether the intervention of education does reduce the incidence of malpractice suits brought against those educated or whether they are able to cope better with the process as a result of their exposure to the curriculum.

Study Limitations and Strengths

Our study is not without limitations. Our response rate was 17%, which was not unexpected, given the study population and inherent difficulty with survey response. Of note, this response rate is typical for an external survey. However, the net number of respondents neared 1000, which allowed us to achieve statistical significance when comparing some of our subgroups and to provide precise estimates of the statistics. Additionally, all geographic regions and year of residency were well represented, and the makeup of the study population by sex mirrored national OB/GYN residency statistics.[17] It was difficult to find national statistics on the complete, racial composition of the OB/GYN residency population, but the study population resembled the racial composition of OB/GYNs in practice.[18]

CONCLUSION

Residents in OB/GYN lack basic medicolegal knowledge, and they report inadequate exposure to medicolegal topics during training. Overwhelmingly, the results of this study show that residents desire more formal medicolegal instruction during residency. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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ORIGINAL RESEARCH ARTICLE

Characteristics Associated with Participation in ENGAGED 2 – A Web-based Breast Cancer Risk Communication and Decision Support Trial

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ABSTRACT

Purpose: We evaluated demographic and clinical characteristics associated with participation in a clinical trial testing the efficacy of an online tool to support breast cancer risk communication and decision support for risk mitigation to determine the generalizability of trial results.

Methods: Eligible women were members of Kaiser Permanente Washington aged 40-69 years with a recent normal screening mammogram, heterogeneously or extremely dense breasts and a calculated risk of > 1.67% based on the Breast Cancer Surveillance Consortium 5-year breast cancer risk model. Trial outcomes were chemoprevention and breast magnetic resonance imaging by 12-months post-baseline. Women were recruited via mail with phone follow-up using plain language materials notifying them of their density status and higher than average breast cancer risk. Multivariable logistic regression calculated independent odds ratios (ORs) for associations between demographic and clinical characteristics with trial participation.

Results: Of 2,569 eligible women contacted, 995 (38.7%) participated. Women with some college (OR = 1.99, 95% confidence interval [CI] 1.34-2.96) or college degree (OR = 3.35, 95% CI 2.29-4.90) were more likely to participate than high school-educated women. Race/ethnicity also was associated with participation (African-American OR = 0.50, 95% CI 0.29-0.87; Asian OR = 0.22, 95% CI 0.12-0.41). Multivariate adjusted ORs for family history of breast/ovarian cancer were not associated with trial participation.

Discussion: Use of plain language and potential access to a website providing personal breast cancer risk information and education were insufficient in achieving representative participation in a breast cancer prevention trial. Additional methods of targeting and tailoring, potentially facilitated by clinical and community outreach, are needed to facilitate equitable engagement for all women.

INTRODUCTION

Breast density is one of the strongest risk factors for breast cancer, after age and family history, with dense breast tissue conferring a 3- to 6-fold increased risk of breast cancer.[1-5] Most women, however, are not aware of their breast density status or that breast density is an independent breast cancer risk factor.[6] In an effort to increase women's awareness of breast density, 37 states have enacted legislation requiring breast density notification after mammography,[7] and in 2019 federal law now requires that the Food and Drug Administration develop reporting language about breast density.[8] To some extent, notification laws have led to improved knowledge of breast density status and motivating women towards clinical follow-up relative to states without notification.[6] However, results are mixed as to whether density legislation leads to appropriate clinical translation, in terms of breast cancer risk assessment and supplemental screening,[9] or serves as a source of confusion for both women and clinicians.[10-13]

The addition of breast density in breast cancer risk prediction tools more accurately discriminates cancer risk[14,15] and provides an opportunity to share with women a highly relevant and underappreciated risk factor. Hence, effective interventions that support women in breast health with risk assessment, clinical education, targeted screening recommendations, and shared decision-making should be evaluated for alignment within clinical care. Haas et al. randomized 459 women with recent normal mammograms to receive either a brief video personalized to a woman's density (high vs low) and breast cancer risk status (high vs average) or usual care (ie, a form letter).[16] The personal video significantly improved women's knowledge of their density status and breast cancer risk compared to usual care. Further, women who viewed the video were more likely to discuss their mammogram results with their primary care provider. These promising results are tempered by the fact that the predominantly white and highly educated participants in this trial were not representative of the underlying population of women at risk for breast cancer. Further, with only 9% of participants having clinically elevated breast cancer risk,[17,18] those most likely to benefit from the intervention were also underrepresented in the trial.

In this study, we describe participation in a randomized trial that targeted women at clinically elevated breast cancer risk based on their breast density and additional breast cancer risk factors. The purpose of the randomized trial was to test a web-based breast cancer risk communication and

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decision-making tool compared with usual care. We describe overall participation rates in the trial and variation in participation based on demographic and clinical characteristics.

METHODS

Study Population and Setting

Eligible women were aged 40-69 years with a recent normal mammogram and members of Kaiser Permanente Washington, an integrated care delivery system. At the time of the research study (2017-2018), state law did not mandate reporting of breast density. However, as a practice, Kaiser Permanente Washington included the Breast Imaging Reporting and Data System (BI-RADS)[19] breast density assessments in the radiology mammography report, which was available in the online patient portal.

Women self-reported breast cancer risk factors at the time of a screening mammogram, including age, race/ethnicity, first-degree family history of breast cancer, history of breast procedures, and other risk factors. BI-RADS breast density was determined by the reading radiologist of the mammogram.

Five-year breast cancer risk was calculated using the Breast Cancer Surveillance Consortium (BCSC) Five Year Risk Calculator.[17] To be eligible for the trial, women had to be at elevated risk based on a combination of their BCSC risk and their BI-RADS breast density assessment. Thus, women were eligible for the study if they had either: 1) an intermediate 5-year risk of invasive breast cancer (1.67%-2.49%) and extremely dense breasts; or 2) a high 5-year cancer risk (≥ 2.50%) and either heterogeneously dense or extremely dense breasts. Primary clinical outcomes of the trial were chemoprevention prescriptions and receipt of breast magnetic resonance imaging by 12 months after the baseline interview. Additional outcomes were self-reported cancer-related distress, clinician conversations about chemoprevention and breast MRI, and mammography maintenance. Notably, the study outcomes were not noted in our recruitment materials.

We excluded women with a personal history of lobular carcinoma in situ, any cancer diagnosis excluding nonmelanoma skin cancer, and a previous referral for cancer genetic counseling and/or prior genetic testing. Additional details of the trial methods are available.[20,21]

Recruitment

Study recruitment materials (see Appendix at www.thepermanentejournal.org/files/2020/19.205supp.pdf), including letters and telephone scripts, developed by the study team and edited by a plain language consultant at Kaiser Permanente Washington Health Research Institute.[22] Materials were drafted with a literacy level at the 6th grade. Women were invited to participate in a research study "*because their recent mammogram showed that (they) had dense breast tissue. Having dense breast tissue, along with other risk factors (such as age, family history, or prior breast biopsy) means (their) risk of developing breast cancer is higher than average for a woman of (their) age and race.*" Women who were assigned to the intervention were told they would "*learn about breast density, their personal breast cancer risk, options for screening and prevention and steps they can take to manage their risk.*" (see Appendix)

From February 2017 to May 2018, all eligible participants were mailed a study recruitment letter within 6 months of their most recent normal mammogram (median = 4.5 months). A survey team member followed-up by phone within a few days to assess eligibility and willingness to participate. Women were contacted up to 10 times by telephone. Eligible women who enrolled in the trial completed a baseline interview by telephone. Women were then emailed a link to the study website where they provided informed consent. Consented participants were then directed to either the intervention website (intervention group) or general content about breast health (control group). The intervention group received personalized 5- and 10-year breast cancer risk estimates online; information about chemoprevention and breast magnetic resonance imaging; and were able to complete a values clarification and question prompt list to share with their primary care provider. All participants were encouraged to talk to their primary care provider about their breast cancer risk.

Statistical Analysis

We describe trial enrollment and reasons for nonparticipation in a Consolidated Standards of Reporting Trials diagram (Figure 1). Participants included women who completed a baseline interview and provided informed consent. Non-participants included all other eligible women, who did not consent to participate in the trial. Women ineligible at the time of telephone contact were excluded from the study population. We also examined recruitment yield from each step of our enrollment procedures.

Patient characteristics were self-reported at the time of the most recent mammogram to assess relationship with participation. Women's current addresses were linked to census data to impute household income. We calculated descriptive frequencies of baseline characteristics by participation status. We used multivariable logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for demographic and clinical characteristics independently associated with trial participation. Given that the BCSC model accounts only for the presence of an affected first-degree relative and not specific aspects of family history that are clinically relevant, we also examined specific components of cancer family history available from self-reported

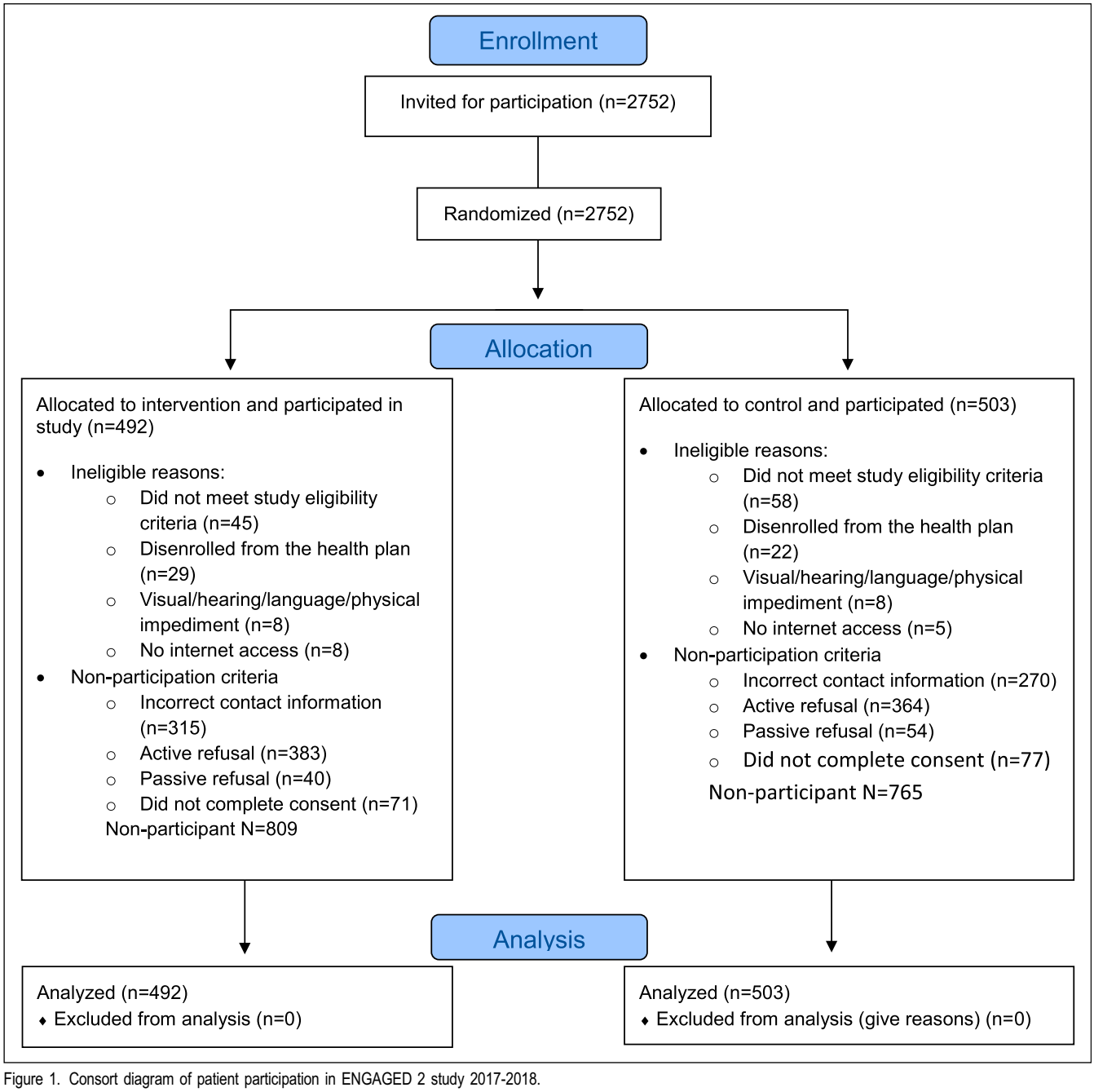

Figure 1. Consort diagram of patient participation in ENGAGED 2 study 2017-2018.

questionnaires in a separate multivariate model. Analysis was conducted using Stata version 15 by StatCorp, College Station, TX.[23]

RESULTS

We contacted 2,569 eligible women with 995 (38.7%) who participated, with similar proportions by intervention and control group (Figure 1).

We examined the number of contacts required for study enrollment (data not shown). Among women who enrolled in the study, 71% enrolled by the 4th call attempt (12.4% in call 1, 26.4% in call 2, 19.2% in call 3, and 12.9% in call 4). Similarly, among women who actively refused, 68% refused by 4th telephone attempt (30.2% in call 1, 16.6% in call 2, 11.2% in call 3, and 10.2% in call 4). For each phone attempt, the proportion of women who enrolled in the study

Table 1. Characteristics of eligible participants by enrollment and consent in the ENGAGED 2 study in Kaiser Permanente Washington women members, 2017-2018

	Non-Participant		Participant	
Characteristic	**No.**	**(%)**	**No.**	**(%)**
Number of women (row%)	1,574 (61.3)		995 (38.7)	
Age at baseline				
40-49	47	3.0	19	1.9
50-59	532	33.8	280	28.1
60-69	994	63.2	696	70.0
Mean age (SD)	60.8 (5.5)		61.9 (5.1)	
Race/ethnicity				
White, non-Hispanic	1,385	88.0	943	94.8
Asian/Pacific Islander	96	6.1	14	1.4
Black, non-Hispanic	56	3.6	19	1.9
Hispanic	33	2.1	16	1.6
Mixed or other	4	0.3	3	0.3
Education				
HS/GED or less	147	9.3	38	3.8
Some college	443	28.1	218	21.9
College graduate	919	58.4	722	72.6
Missing	65	4.1	17	1.7
BCSC[a] risk level				
1.67-2.49	502	31.9	250	25.1
> 2.50	1,072	68.1	745	74.9
First degree family history of breast cancer				
No	763	48.5	480	48.2
Yes	657	41.7	447	44.9
Unknown	154	9.8	68	6.8
Prior breast biopsy				
No	783	49.8	486	48.8
Yes	699	44.4	452	45.4
Unknown	92	5.8	57	5.7
Median family income				
< $70,000	366	23.3	221	22.2
$70,000-$89,999	334	21.2	227	22.8
$90,000-$109,999	332	21.1	239	24.0
$110,000-$129,999	216	13.7	128	12.9
> $130,000	233	14.8	130	13.1
Unknown	93	5.9	50	5.0
Menopausal status				
Postmenopause	165	10.5	75	7.5
Premenopause	1,409	89.5	920	92.5
Breast density				
Heterogeneously dense	737	46.8	554	55.7
Dense	837	53.2	441	44.3

[a] Five-year BCSC risk based on https://tools.bcsc-scc.org/BC5yearRisk/intro.htm.
HS/GED = high school/General Education Development certificate,

Table 2. Detailed family history of breast and ovarian cancer among participants by enrollment and consent

	Non-Participant		Participant	
Characteristic	**No.**	**(%)**	**No.**	**(%)**
Number women with known family history data	1,420		927	
Breast cancer				
FDR	657	46.3	447	48.2
FDR age < 50	241	17.0	125	13.5
FDR, bilateral	105	7.4	49	5.3
2+ relatives ages < 50	81	5.7	31	3.3
3+ relatives	32	2.3	18	1.9
Any male relative	11	0.8	1	0.1
Any other relative (aunt, grandmother)	459	32.3	328	35.4
Ovarian cancer				
Any family history	141	9.9	89	9.6
2+ relatives on same side	18	1.3	9	1.0
FDR with breast AND ovarian cancer	48	3.4	18	1.9
Ashkenazi Jewish relative with breast OR ovarian cancer	37	2.6	32	3.5
One relative with breast and 1 relative with ovarian cancer on same side of family	75	5.3	38	4.1

FDR = first degree relative.

increased from 5.2% at call 1 to 13.3% enrolled in call 2 (highest) and then diminished slowly to 5-7% enrollment by the 6th call attempt.

Women who participated were more likely to be age 60 or older, White, and have some college education or college degree compared with non-participants (Table 1). Further, a higher proportion of women who participated had BCSC 5-year risk > 2.5% and heterogeneously dense breasts. Self-report of detailed family history of breast and ovarian cancer was similar among participants and non-participants, across measures of cancer type, number of relatives, and age at diagnosis (Table 2). Among participants, 48.2% reported a first degree relative with breast cancer; and 9.6% reported any family history of ovarian cancer (Table 2). Non-participants reported similar prevalence (46.3% and 9.9%, respectively).

In multivariate models, study participation was independently associated with age, race/ethnicity, and education (Table 3). For every 1-year increase in age, women were 4% more likely to participate in the trial (OR = 1.04, 95% CI 1.02-1.06). Women who identified as Black (OR = 0.50, 95% CI 0.29-0.87) or Asian/Pacific Islander (OR = 0.22, 95% CI 0.12-0.41) were significantly less likely to participate than White women. Women with some college (OR = 1.99, 95% CI 1.34-2.96) or a college degree (OR = 3.35, 95% CI 2.29-4.90) were more likely to participate than women with a high school education. No other factors were

Table 3. Univariate and multivariate ORs of participant characteristics associated with enrollment in the ENGAGED 2 study

Characteristic	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Age (continuous)	1.04 (1.02-1.05)	1.04 (1.02-1.06)
Age group		
40-49	1.0	N/A
50-59	1.30 (0.75-2.26)	
60-69	1.73 (1.01-2.97)	
Race		
White, non-Hispanic	1.0	1.0
Black, non-Hispanic	0.50 (0.29-0.84)	0.50 (0.29-0.87)
Hispanic	0.71 (0.39-1.30)	0.77 (0.41-1.45)
Asian/Pacific Islander	0.21 (0.12-0.38)	0.22 (0.12-0.41)
Mixed/other	1.10 (0.25-4.93)	0.96 (0.21-4.40)
Education		
HS/GED or less	1.0	1.0
Some college	1.90 (1.29-2.82)	1.99 (1.34-2.96)
College graduate	3.04 (2.10-4.40)	3.35 (2.29-4.90)
Missing	1.01 (0.53-1.92)	1.29 (0.67-2.48)
Menopausal status		
Postmenopausal	1.0	1.0
Premenopausal	0.70 (0.52-0.93)	1.03 (0.73-1.47)
Breast density		
Heterogeneously dense	1.0	1.0
Extremely dense	0.70 (0.60-0.82)	0.86 (0.68-1.07)
Family history		
No	1.0	1.0
Yes	1.08 (0.92-1.28)	1.20 (0.94-1.53)
Unknown	0.70 (0.52-0.95)	0.74 (0.54-1.03)
Prior biopsy result		
No	1.0	1.0
Yes	1.04 (0.88-1.23)	1.18 (0.93-1.50)
Unknown	1.00 (0.70-1.42)	1.18 (0.81-1.73)
Income		
< $70,000	1.0	1.0
$70,000 to < $90,000	1.12 (0.89-1.43)	1.06 (0.83-1.36)
$90,000 to < $110,000	1.19 (0.94-1.51)	1.13 (0.88-1.45)
$110,000 to < $130,000	0.98 (0.75-1.29)	0.90 (0.67-1.21)
$130,000+	0.92 (0.70-1.21)	0.91 (0.67-1.23)
Unknown	0.89 (0.61-1.30)	0.86 (0.58-1.28)
Five-year risk		
1.67-2.49	1.0	1.0
> 2.50	1.40 (1.17-1.67)	0.78 (0.56-1.09)

[a] Adjusted for age (continuous), race, family history, biopsy history, income, 5-year risk, facility, education, menopausal status, and density.

significantly associated with study participation in multivariate analysis, including menopausal status, breast density, prior biopsy, income or BCSC 5-year breast cancer risk.

Women's self-reported family history of breast or ovarian cancer did not influence their participation in the trial, except among two key family features (Table 4). Women with a first-degree relative with bilateral breast cancer (OR = 0.69, 95% CI 0.48-0.99) or with 2 or more first degree relatives with breast cancer diagnosed under age 50 (OR = 0.63, 95% CI 0.41-0.97) were less likely to participate than women without this family history, adjusted for age, race/ethnicity, mammographic facility, and education.

TABLE 4. Multivariate adjusted ORs of ENGAGED 2 participation compared to non-participation by breast and ovarian cancer family history characteristics

Characteristic	Adjusted OR[a] (95% CI)
Breast cancer	
First degree relative	1.09 (0.92-1.30)
First degree relative age < 50	0.82 (0.64-1.04)
First degree relative, bilateral	**0.69 (0.48-0.99)**
Two or more relatives ages < 50	**0.63 (0.41-0.97)**
Three or more relatives	1.07 (0.57-2.02)
Any male relative	0.26 (0.06-1.17)
Any other relative (aunt, grandmother)	1.08 (0.90-1.30)
Ovarian cancer	
Any family history	0.92 (0.69-1.22)
Two or more relatives on same side	0.97 (0.43-2.21)
Breast or ovarian cancer	
First degree relative with breast AND ovarian cancer	0.66 (0.37-1.17)
Ashkenazi Jewish relative with breast OR ovarian cancer	1.05 (0.64-1.71)
One relative with breast and 1 relative with ovarian cancer on same side of family	0.88 (0.58-1.33)

[a] Adjusted for age (continuous), race, facility, and education.

DISCUSSION

Participation in a breast health risk communication and decision support trial varied by women's demographic characteristics, specifically by age, race/ethnicity, and education. Despite study efforts to improve recruitment through plain language,[24,25] which supports readability of the study materials, accessible materials might be necessary, but not sufficient to achieve a representative sample. Hence, the results from our ongoing trial will reflect the underlying population who participated but might not reflect the behavior patterns observed if all women eligible had participated.

Our study population only included women with at least 1.67% 5-year risk of breast cancer, an elevated risk compared with average risk women. While the study population from Haas et al. included < 10% of women at clinically elevated risk,[16] our two populations were similar in participant demographics. Despite differences in breast cancer risk, the similar study demographics suggests that the offer of tailored breast cancer risk information is not sufficient to compel broad and representative participation. Further, these observed patterns of research participation mirror participation statistics from other studies aimed to increase women's attendance at high-risk breast clinics, where attendance remained low (< 15%) even after targeted invitations following screening mammography.[26] Similar to our participation factors, attendance rates increase based on women's demographics (older, white),[27] higher breast cancer risk, or a family history of the disease, and in some studies, moderate levels of anxiety.[28]

Further, women also need to see the topic and clinical services as personally relevant to them. Lived experience[29] and perceived personal relevance[2] are associated with higher research participation and clinic attendance rates, suggesting that supporting women's knowledge of their own current breast cancer risk could be motivational in adoption of preventive health strategies. In our study, eligible participants were told their density status and comparative breast cancer risk (i.e., higher than average) when randomized to the intervention, but not told their numeric breast cancer risk as part of the recruitment process. Without this knowledge of personal risk, neither women's clinical history nor their family history impacted their participation in the study, which suggests that these factors alone are not sufficiently motivational for participation.

Our intention of studying women at elevated risk of breast cancer was to exclude women potentially at risk of hereditary breast and ovarian cancer (HBOC), based on genetic counseling referrals and genetic testing. Women at risk of HBOC experience different clinical management than for women at elevated risk but without a risk of HBOC.[33] While we did not observe an association between the number of relatives diagnosed with breast or ovarian cancer with study participation, we did find that participants with other potential indicators of HBOC risk were less likely to participate. Representing only a handful of women in our analysis, these women might have recognized their own personal risk and appropriately did not identify the study as relevant to them. We did not specifically exclude eligible participants based on self-reported family history alone, as additional information through genetic counseling would be needed to assess for HBOC risk. Clear documentation of complete family history is important to ensure women receive appropriate risk management for their family history background.

Study recruitment might have created unforeseen barriers to participation for some women. We utilized the risk factor questionnaire, which women complete at the time of their mammogram, to efficiently identify risk factors calculate 5- and 10-year risk of breast cancer. From this information, we recruited women on average 4.5 months after a normal screening mammogram. However, a delay in initial recruitment contact created a disconnect in timing and potentially reduced any motivation derived from screening mammography. Further, our survey department needed at least four call attempts to reach about 70% of the eligible sample. In both the intervention and usual care groups, women were excluded from the final study population if they completed a telephone baseline survey but did not

complete the consent process online. More educated or resourced women may be more likely to participate, given these barriers of timing, telephone recruitment, and motivation. Future work should consider aligning the timing of participation and create a more seamless experience for the participant from recruitment to delivery of the intervention.

Unfortunately, our study continues a history of breast cancer prevention and control research that disproportionally recruits White, educated women.[34] Dean et al. emphasizes the need for incorporating social factors like race/ethnicity into clinical cancer care studies, specifically in breast cancer.[35] As an example, the Gail Breast Cancer Risk Assessment Tool[36] originally underestimated the risk of breast cancer in Black women. With a revised model now validated in Black women, the Breast Cancer Risk Assessment Tool better discriminates breast cancer risk, and the proportion of Black women now considered at elevated breast cancer risk tripled.[37] Due to this historical inaccuracy, women of color, particularly Black women, might be less aware of their potential breast cancer risk.[35] Given that women of color have denser breast tissue compared with White women,[38,39] the relevance of future tools to support breast health requires considering the potentially unique needs of this population and working harder to ensure that they are represented in ongoing research. This general difference in awareness of breast cancer risk aligns with what has been demonstrated to date regarding breast density awareness. Prior surveys have found lower levels of awareness among women of color compared with White women, as well as those with less education and lower income.[40-42] Given that our recruitment materials included density-specific information, this information could have more salience among women who had some awareness of the topic.[43]

Bringing important health information to all women, regardless of demographic factors, is important to consider in scalability within clinical care. Implementation of breast health education tools like ours might require additional supporting activities to actively engage all women. Several methods have been successful in increasing attendance of breast cancer screening, which could be further refined for this context. Methods to evaluate in future research and scalability include community health advisors or peer counselors,[44,45] the use of targeted, tailored, and linguistically appropriate materials,[46-48] and research and clinical staff who can support the linguistic and cultural needs of the patients.

While our ongoing trial will have several strengths in supporting women's breast health, our results will remain limited in generalizability. All women in the study were insured and cared for within an integrated care delivery system, providing care from primary care to specialty including genetics. Our study population does not reflect all US healthcare settings, or women uninsured or publicly insured by Medicaid. Further studies should evaluate the use of breast health information, particularly in underserved communities.

In conclusion, the use of plain language and provision of density status and comparative breast cancer risk information were insufficient in engaging a representative sample of women in a breast cancer prevention trial, particularly across race/ethnicity, age, and educational backgrounds. Additional methods of targeting and tailoring, facilitated by clinical and community outreach, are needed to equitably scale breast health interventions within clinical care.

Ethics Approval

All study activities were approved by the Georgetown University Institutional Review Board Committee as the Institutional Review Board of record with a partial waiver of informed consent for recruitment activities. The Kaiser Washington State ceded to the Georgetown University Institutional Review Board.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available, as they are still in process for analysis for our main results but are available from the corresponding author on reasonable request. ❖

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Authors' Contributions

Substantial contributions to the conception or design of the work were made by KJW, KAL, MDS, and SCO; the acquisition, analysis, or interpretation of data for the work was done by KJW, EAB, SK, KAL, HG, MDS, and SCO; drafting the work or revising it critically for important intellectual content was done by KJW, EAB, SK, KAL, HG, MDS, and SCO; and final approval of the version to be published was provided by KJW, EAB, SK, KAL, HG, MDS, and SCO.

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ORIGINAL RESEARCH ARTICLE

Patients' Experiences with Refilling their HIV Medicines: Facilitators and Barriers to On-Time Refills

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ABSTRACT

Background: Adherence to antiretroviral therapy (ART) is particularly important for patients with HIV. Prior research on ART adherence has focused primarily on behavioral interventions targeting patients and providers. No study has focused on the pharmacy refill experience as a potential target for improving adherence to HIV medicines. Informed by patients' experiences, this study aimed to assess patients' experiences with refilling their HIV medicines and to explore facilitators and barriers to refilling medicines on time.

Methods: We interviewed patients at three time points during their first year of care at an HIV clinic in Houston, TX. We analyzed interviews using directed and conventional content analysis.

Results: Analyses revealed individual, interpersonal, and system-level barriers that affect patients' ability to pick up their HIV medicines on time. Many patients perceived the refill process as being difficult. For some patients, picking up their HIV medicines each month triggered anxiety. Positive interactions with pharmacists and pharmacy staff, as well as clear and consistent messaging, played a key role in augmenting patients' refill experience. Self-efficacy, social support, and workarounds to resolve issues were also key facilitators. Many patients said changing ART-dispensing protocols from 30- to 90-day refills could mitigate the anxiety experienced with picking up HIV medicines and decrease opportunities for missing a refill.

Conclusion: Offering 90-day refills for HIV medicines may decrease anxiety concerning missed doses and improve medication adherence. Providing pharmacy staff with communication skills training is another strategy that may improve the patients' refill experience.

INTRODUCTION

Adherence to antiretroviral therapy (ART) is critical to optimizing outcomes in HIV infection. Patients who take their ART as prescribed are more likely to achieve viral suppression, stay out of the hospital, and live longer.[1-3] Prior research on ART adherence has focused primarily on behavioral interventions targeting patients (eg, use of pill boxes and alarms) and providers (eg, communication skills training, adherence counseling).[4] Few studies have focused on the pharmacy refill experience as a potential target for improving adherence to HIV medicines.

Pharmacists and pharmacy staff have frequent contact with patients and are well positioned to play a key role in improving adherence to medicines.[5,6] Studies in other chronic diseases show the important role of clinical pharmacists in educating patients about their medicines and working closely with health care providers to monitor and identify problems.[4, 7-10] Chrisholm et al showed that a pharmacy intervention to provide counseling and clear instructions to patients improved adherence to immunosuppressive medications in renal transplant patients.[7] Patients with HIV infection are a particularly vulnerable population, and, given their experiences with stigma, pharmacists and the pharmacy itself may play an even more important role in providing a safe place to refill medicines and ensuring a positive patient experience.

Beyond positive interactions with pharmacists and pharmacy staff, studies in other chronic conditions indicate that changing pharmacy dispensing protocols can affect adherence. These findings have proven true across a wide variety of medical conditions, including diabetes, hypertension, hyperlipidemia, and coronary artery diseases.[11,12] Specifically, they indicate that patients given a 90-day supply are significantly more likely to have a higher proportion of prescriptions filled than those given a 30-day supply.[11,13] With a 90-day supply, patients have fewer opportunities to miss a refill. This likely contributes to better adherence. Khandewal et al. showed that adherence rates in patients who filled 90-day prescriptions remained high, whether or not they filled their prescriptions through a retail pharmacy or via mail order.[14] Beyond pharmacy-dispensing outcomes, studies indicate that 90-day supplies can result in improved health outcomes. For example, a landmark study shows that women given a 90-day supply of oral contraceptives had significantly less unplanned pregnancies and abortions. In fact, the 2013 CDC guidelines on oral contraceptives recommend dispensing a 90-day supply to all women.[15]

In HIV care, medication adherence is particularly important because nonadherence has serious consequences.

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In contrast to other chronic conditions, nonadherence in patients with HIV infection can result in resistance to an entire class of medication.[16] A large body of literature on barriers and facilitators of adherence to ART point to transportation, lack of knowledge, difficulty with motivation/self-efficacy, lack of social support, depression/anxiety, and stigma as barriers to on-time medication refills.[4,17,18] Beyond individual factors, studies show the importance of the health care team and positive patient care experiences in optimizing adherence.[19-21] Herein, we explore the pharmacy refill experience as a potential target for improving adherence to HIV medicines. Although much of the literature on pharmacy-based interventions in HIV has focused on pharmacist-directed patient education and adherence counseling, this study is unique in focusing on the patient's pharmacy refill experience.[22,23] Such data can contribute to the literature and provide a nuanced understanding on how patients' experiences refilling their medication can affect adherence. Informed by patients' experiences, this study assesses patients' experiences with refilling their HIV medicines and explores facilitators and barriers to refilling medicines on time. It also identifies what patients see as critical elements to a positive pharmacy refill experience.

METHODS

This study was part of a larger study to understand how new patients experience and evaluate their overall HIV care.[24] We recruited new patients from August 2014 to November 2014 at Thomas Street Health Center (TSHC) in Houston, TX. We then followed participants over their first year of care at TSHC (Table 1).

Table 1. Baseline characteristics of participants (N = 35) at Thomas Street Health Center in Houston, Texas

Characteristics	Value
Age, y (mean SD)	39±12
Gender, n (%)	
Male	25 (71)
Female	10 (29)
Race ethnicity, n (%)	
Non-Hispanic black	23 (65)
Hispanic	10 (29)
Non-Hispanic white	2 (6)
Education, n (%)	
Some high school or less	9 (26)
High school graduate or equivalent	11 (31)
Some college or higher	15 (43)
Income, per year, n (%)	
≤ $10,000	19 (54)
> $10,000 and ≤ $30,000	13 (37)
> $30,000	3 (9)
HIV risk factor, n (%)	
Injection drug use	3 (9)
Male/male sex, no injection drug use	14 (40)
Heterosexual sex, no injection drug use	18 (51)
Time from HIV diagnosis, n (%)	
≤ 3 mo	8 (23)
3 mo-1 yr	4 (11)
1-5 yr	10 (29)
5-10 yr	6 (17)
> 10 yr	7 (20)
CD4 cell count > 200 cells/mm^3	24 (69)
HIV RNA < 20 copies/mL – (%)	11 (31%)

Study Population

Informed consent was obtained from all participants. Eligible patients were older than 18 years of age, had been diagnosed with HIV infection, and had not completed their first visit with the HIV clinic. Exclusion criteria included those who were mentally unable to complete interviews or give informed consent, non-English speaking, or incarcerated. A research coordinator approached consecutive patients new to the clinic and enrolled them prior to their first visit with the HIV provider.

Setting

Harris Health System is a safety net health system that provides health care for poor and uninsured residents of Harris County, TX. It operates TSHC, an urban, community-based HIV clinic serving about 6000 patients with HIV infection yearly. The pharmacy is located on the first floor of the clinic. Five pharmacists and six technicians work in the clinic pharmacy. Each month, the pharmacy processes approximately 7000 to 8000 prescriptions. Approximately 30% of patients use the Texas AIDS Drug Assistance Program (ADAP), funded by the Ryan White HIV/AIDS program, to receive their medications; 30% use Medicare/Medicaid; and 40% use private insurance. The pharmacy provides adherence counseling on all new prescriptions, and patients can request counseling on refills. When questions about dosing or drug-drug interactions arise, pharmacy staff are able to send messages or directly call providers in the clinic. At the time of the study, the pharmacy used Epic Willow software.

Development and pre-testing of the interview guide

We developed an interview guide based on our prior work and a review of the literature. We pilot-tested the guide with 15 patients at TSHC to ensure that questions and prompts were easy to understand and elicited relevant data. We conducted cognitive interviews using the Think Aloud method.[25] Think Aloud is a cognitive interviewing method that asks the participant to tell the interviewer what goes through his or her mind when given an interview question

Table 2. Key interview questions
Now let's talk about all the other pieces of the HIV clinic visit you had today/on <date>, everything except the time spent with doctor. How do you feel about the pharmacy?
Tell me about the last time you refilled your HIV medicines. Walk me through the steps of refilling your HIV medicines.
How often do you refill your HIV medicines?
How do you feel about refilling your HIV medicines every ____days?
Have you missed any HIV medicine because you had trouble refilling them on time?

(eg, "Tell me what you think when you hear this sentence"). This ensures comprehension of the question as intended by the researcher. Participants in the pre-testing phase received $20. Revisions to content and wording were made prior to the main study (Table 2).

Main Study

We interviewed patients three times over their first year of HIV care. The first interview occurred prior to the patient's initial visit with the HIV provider (T1). We aimed to understand expectations about the pharmacy. We anticipated longitudinal dropout by increasing the number of interviews by 25% at the first time point. The second interview occurred 2 weeks after the initial visit with the HIV provider (T2). We aimed to see what their early experiences with the pharmacy were like. The third interview occurred 6 to 12 months after the initial visit with the HIV provider (T3). We aimed to see how their experiences evolved and if they were able to solve any barriers they encountered. Interviews took place in private rooms at TSHC. Interviews were audio-recorded and professionally transcribed verbatim. Participants received $10 for completion of the first interview, $15 for the second interview, and $25 for the third interview. Recruitment and interviewing continued until we reached data saturation (ie, no new themes emerged).

The Institutional Review Board at Baylor College of Medicine approved this study. All participants gave written informed consent. All names in the text are pseudonyms to protect patient confidentiality.

Data Analysis

The research team consisted of two HIV primary care physicians and health services researchers (BND and TPG), a PhD-level behavioral scientist with expertise in behavioral health promotion and intervention mapping (CM), and two Masters-level public health professionals (SNM and SRJ). BND, CM, SNM, and SRJ have formal training in qualitative methods.

The principal investigator (BND) developed a list of themes patients identified as important to their care experience based on her prior work, a literature review, and notes taken during and shortly after each interview.[24,26] ATLAS.ti software was used to evaluate interview data via conventional and directed content analysis.[27] BND and SN listened to each interview and identified quotes related to themes, including those related to the pharmacy, refills, anxiety, and treatment factors. BND and SN wrote memos regarding emerging themes related to patients' experiences refilling their HIV medicines and noted memorable quotes.

SRJ then consolidated all quotes into a query report. SRJ summarized the data using 2 methods. She first created a matrix grouping quotes from each patient according to the different time points (ie, T1, T2, and T3) to understand the overall pharmacy experience for all patients at each time point. She then created another matrix displaying the quotes in chronologic order for each patient to understand how each patient's story changed over time [28]. SRJ reviewed these structured matrices and, through an iterative process, identified emergent themes of different things patients said they experienced at the pharmacy and facilitators and barriers to refilling medicines on time. SRJ and BND met frequently to discuss the emergent themes and to develop the conceptual model within the context of the patient's overall HIV care experience.

RESULTS

Thirty-five patients from TSHC participated in this study. The mean age was 39 years, and most patients were male (71%). More than half of the participants were non-Hispanic black (n = 23), 29% were Hispanic (n = 10), and 6% were non-Hispanic white (n = 2). A total of 23% were diagnosed with HIV within the last 3 months, and 26% had a CD4 cell count less than 200. Less than a quarter (20%) were diagnosed with HIV infection for greater than 10 years. Less than half (31%) had an undetectable HIV viral load (< 20 copies) at entry to the clinic. All completed the first interview, 28 (80%) completed the second interview, and 17 (49%) completed the third interview. Interviews averaged 60 minutes each.

Individual Barriers to Refilling HIV Medicines on Time

Our analyses of the patients' pharmacy refill experiences revealed individual factors that influence their ability to refill medication on time. Individual factors affecting patients' experience when refilling their medication include transportation, conflicts with work schedule, travel time, and cognitive barriers.

Transportation

Many patients expressed that lack of transportation was a major barrier to refilling HIV medication on time. Lee

described the hassle of having to navigate getting to the clinic without his own transportation:

And like I was telling you before, the place that used to pick me up and bring me here doesn't do that anymore. And I'm taking a big risk using my job's car to come here and then I have to come here two times [to drop off prescription and pick up the medicine] instead of just the one.

Conflicts with Work Schedule

Some patients do not have flexible work schedules that allow them to pick their medication up during pharmacy operating hours (ie, Monday through Friday). Navigating a demanding work schedule and finding time to refill medication is difficult, but, ultimately, patients would do their best to pick up their medication on time. Jean shared:

I just take that day off but my job uh put points against you when you don't come to work. So if I get over 10 points or something they'll write me up you know. Then if I get over 12 points then they then they suspend me for 2 days. But I don't miss work so for a miss for a point against me to come to see about my health; I don't mind.

Travel Time

Patients shared that travel time could deter them from frequently visiting the pharmacy to pick medication up. Sam said:

It's too far out to come for doctor visits or to pick up medicine. Umhm well now it's an hour because we have so much construction. Usually it's like maybe 30 to 45 minutes but since it's so much construction it takes about an hour, hour and 15 minutes to get here.

Cognitive

Having to call in a refill (as opposed to automatic refills) also posed a threat to on-time medication refills. Patients reported their struggles with monitoring when it was time to refill their HIV medications. Casey said: Well it's kind of a hassle because if you don't pay attention to how many pills are left you get screwed. You know you either have to skip a couple of days without medication because they will not provide you with any medication.

Anxiety and Stigma

For some patients, picking up their HIV medicines each month triggers anxiety. Rob described his first time visiting the pharmacy: When I said uh shook up; I was scared. I didn't know what was going to happen. I didn't know what was going on within the pharmacy and once- once I uh- once I talked to the- just like I said earlier; once I talked to the lady downstairs and she explained to me what was going on then I felt at ease. But when you first walk through that door you don't know what's going on; you're shook up.

Patients also talked about the fear of being recognized at the clinic pharmacy and dealing with the stigma associated with HIV. Both dispositions exemplify the deeply rooted anxiety experienced with picking up their HIV medicines.

Systems-level Barriers to Refilling Medication on Time

Refill Process

Our analyses revealed system-level barriers that make it hard to refill HIV medicines. Many patients perceive the refill process as being difficult or frustrating. These difficulties generate negative emotions and increase the risk of not refilling HIV medicines on time, which can lead to missed doses. Blake said: So that's frustrating too. Because then to get my meds, my HIV meds filled I have to come in at least twice; one to tell them I need it filled and then to get it filled. And then half the time they don't have it filled or I'll come in and they'll tell me, "We sent it back; you need to come in another day." So usually it takes about 3 or 4 [days].

While sharing her opinion on medication refills, Jordan shared how increasing the dispensing interval to 90-day supply would alleviate some of her frustration.

I might actually ask my doctor if I can have him do it like every 90 days or something instead ..... I just- I'm so sick of coming in here three times to get it filled.

Interpersonal Barriers to Refilling Medication on Time

Lack of Helpfulness of the Pharmacy Staff

The clinic pharmacy plays an integral role in helping patients navigate the refill process and addressing their frustrations. Lack of information or unclear directions from the pharmacy staff can lead to missed doses of medication. Taylor said: I missed a day one time…So they told me my meds the one time that I came in early and then they didn't have them on time and I had to- I would've gone a week without them. And they were like, "Okay you can come back in Tuesday." And they didn't listen to like the time of day that I take them; I told them I needed six [pills] not five because I take it at night and I needed one for that day still. And so they still only gave me five. Like, they just don't listen…Like most of them just like they're very frustrating.

Facilitators of Refilling Medication on Time

Ways Patients Coped with Negative Experiences

Patients had different ways of coping with negative experiences regarding refilling their ART medications. Patients who were able to overcome barriers in refilling their medications reported positive experiences at subsequent interviews. Our analyses of longitudinal data revealed several patient-level factors that affect their refill experience.

Key factors include 1) self-efficacy, 2) social support, and 3) workarounds. Each factor is detailed below.

Self-Efficacy During the first interview, Chris talked about his indifference toward following up with the clinic about his eligibility for subsidized care.

Yeah, I didn't hear back. You know as soon as my mama, my mother said that she heard back, and she said they approved them right then and there, I was like well, I have things to do, so I'm not going to sit and wait.

A year later, after talking with his mother, he decided to take his health more seriously and reapply for eligibility so he could begin receiving HIV treatment. He now felt empowered to take responsibility for his health and knew it was something he was capable of.

I feel confident that I can call in and make an appointment. Very confident. I've always been that person. When there's a will, there's a way. If I can make a way, I'm going to make a way, and there are numerous ways.

During his second interview, he reflected on how his mindset toward his health had changed.

The first time I was supposed to come here for a screening [nurse intake], I did not come. Partially, I was nervous, scared, just wanted to act like I didn't know what I just found out…I knew I was supposed to go. I had time to go. It was at 11:00. I'm up at 6 am every morning. I could have easily gotten dressed, came here, did the screen, and everything. I just did not do it…like I said last time I'm coming back here to see you, if I make an appointment with somebody, I like to keep the appointment.

This new sense of self efficacy carried over into him coping with the anxiety of visiting the pharmacy and picking up his medications.

It's just that last step of going to the pharmacy and getting the medicine was just like okay, you know what, I can do this.

During his third interview, his self-efficacy was more evident than ever.

As far as involvement, it's you doing your part. It's you taking your meds. Can't nobody. You're grown. Everyone that's come into this clinic that I've seen so far is grown. They're all adults. You do what you're supposed to do. You can take it, or you cannot take it. You can decide if you want to live or not to live. Me personally, I want to live, so I'm going to do my part and take my medicine, keep my appointments, you know.

Visiting the pharmacy to pick up his medication became a part of his routine, and he became more familiar with the system, making his medication pickups even easier.

Like for the medicine at first I had to like come up here and sit and wait because I couldn't call it in. But now I call it in; I just learned how to call it in on the phone too; I didn't know how to do that. So I learned how to call it in on the phone; then it's a good thing because you ain't got to worry about, "Okay I wonder if my prescription ready."

Social Support Visiting the pharmacy can trigger anxiety for patients with HIV. Patients discussed how intimidating their first visit to the pharmacy was and the realization that this would be part of their routine for the rest of their lives. Ashton talked about how meaningful it was to have her boyfriend with her during her first visit to the pharmacy.

After I got out the doctor's, I still wasn't in a laughing mood, and I forgot what he did, but he, I think he started poking me on my side because you know I'm ticklish right there, and I was like stop it because I'm really not trying to laugh right now, but I started laughing anyway…So yeah, I find it's really important if you feel that you need someone to be there with you for moral support, ask that person to come there [to the pharmacy].

Workarounds During the second interview, Reese discussed his difficulty with getting through to the pharmacy by phone and getting the answers he needed.

Calling the pharmacy is a different subject um. If you like really need…because like I said, the first 3 months I actually had to talk to someone um [at the pharmacy] to see what was going on um and I know a lot of the times when I call. I don't know if it be a over-log of calls, the number just be shut down or busy.

He also detailed his frustrations that stemmed from inconsistent messaging from the pharmacy staff.

I almost went off on the- on the- on the pharmacist that was there because he was trying to tell me that I did not call to pick up medicine ever and I'm like, "Well that's not true and look in your computer again." I called my medicine in that day; it said it was ready. That's why I came here, otherwise I wouldn't've just showed up and when I got here you're telling me that it wasn't ready. But they had to reorder it and- and that- and that just frustrated me that day. It's frustrating me right now talking about it.

After his experience with calling in his medication refill and it not being ready for pickup, he persisted. During his third interview, he shared that his experience with the pharmacy was much better due to his persistence and that he learned how to navigate the pharmacy system to ensure he did not miss any doses of medicine.

I will call in like they say. They say call it in advance because it takes 5 to 10 days. Like I said, it'll just have to go down into my calendar to call in my medicine a week before I run out or 2 weeks before I run out.

Patient Identified Solutions Several patients mentioned increasing the dispensing interval to 2 to 3 months would minimize a lot of the hassle by spreading it over a longer period of time. Sidney shared:

Coming here from where I live and usually from where I'm primarily working is a hassle. And I've got to fight traffic on the way back if I come after 2 o'clock. That means I'm probably going to sit down there at the pharmacy till about 4. Uh-huh and now I've got to fight traffic. I wish it could be like a 2- or 3-month supply.

DISCUSSION

This qualitative study provides insight into the pharmacy refill experience for patients with HIV infection. It identifies facilitators and barriers to refilling medications on time and points to steps the pharmacy can take to address these barriers.

Figure 1 illustrates a conceptual model of the barriers and facilitators to on-time medication refills, developed from our analyses of the qualitative interviews. Analyses revealed individual, interpersonal, and system-level barriers that affect patients' ability to pick up their HIV medications on time. In addition to missed refills, based on our interviews, these barriers directly evoked negative emotional responses from patients. Self-efficacy, social support, and work-arounds served as facilitators to on-time refills. Patients noted how vital these factors were in increasing their on-time medication refills.

At the time of these interviews, many of the patients in our study received HIV medications through ADAP. In Texas, the ART medications are mailed from Austin and delivered to contract pharmacies. Several steps need to align perfectly in the refill process so patients can receive their medication on time each month. Patients using the pharmacy at TSHC need to call the pharmacy refill line when they have 7 days of medication left.[29] This provides a buffer in case there is a delay in one of the steps. At the time of the study, the only two options to request a refill were via phone or in person. Several patients in our study reported difficulty calling the pharmacy and getting through. Since the interviews have taken place, Texas ADAP has moved to allowing patients to receive a 90-day supply,[30] and patients at TSHC can request refills through a patient portal in the electronic medical record or enroll in an automated refill

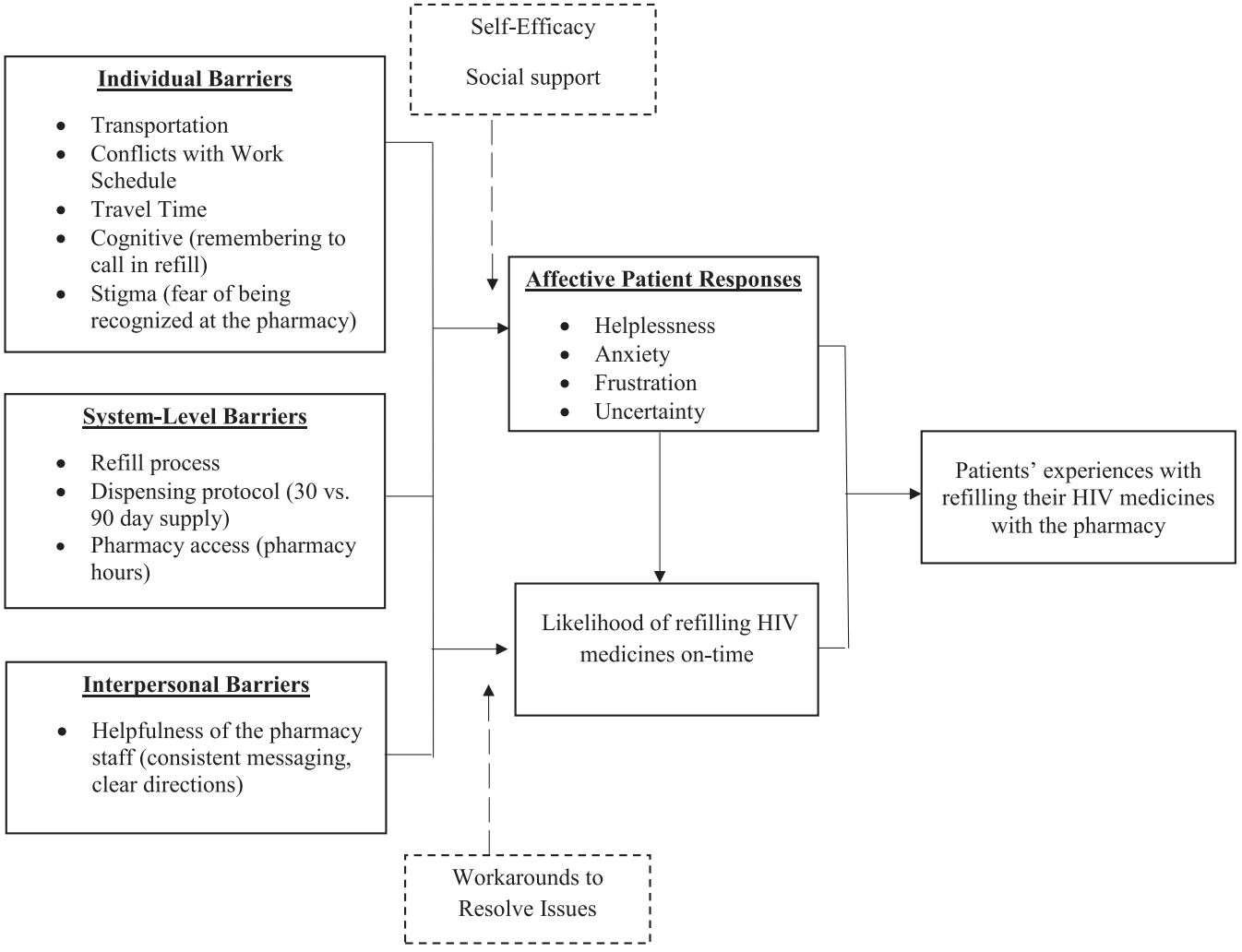

Figure 1. This figure details the barriers and facilitators experienced by patients in our study that affect their ability to pick up their medication on time. The dotted lines represent facilitators that can help patients overcome barriers.

program. This change in pharmacy dispensing protocol was mandated by the state and is not directly related to findings from this study.

Since the interviews of this study have been completed, another study has focused on the benefits of multi-monthly ART prescription schedules. In a study conducted among children and adolescents with HIV in six African countries, participants who began receiving multi-monthly ART prescription schedules had favorable health outcomes regarding immunologic status, ART adherence, viral suppression, retention, and mortality.[45]

In addition to the intervention being feasible, the analysis showed less frequent clinical visits and extending ART refills contributed to the favorable health outcomes.

Patients refilling their HIV medicines can experience negative emotions, such as heightened feelings of helplessness, anxiety, frustration, and uncertainty/confusion, especially because HIV is a life-altering condition. Physicians and pharmacists should be mindful of how getting refills can trigger anxiety for patients with HIV. A 30-day supply of ART medication requires more opportunities to feel those negative emotions, and a 90-day refill might therefore reduce anxiety.

Although the patients in our study had favorable responses to a 90-day supply, there may be unintended consequences. For some patients, frequent visits to the pharmacy every 30 days could be a positive thing, particularly if they find the pharmacy safe, inviting, and a source of social support. Frequent visits could also provide greater opportunities for pharmacy staff to remind patients of ADAP renewal deadlines and things they need to do to maintain eligibility. In other conditions, interventions resulting in more frequent contact with the pharmacy yielded favorable patient experiences.[31,32] When pharmacy staff are well trained and have the time to interact with patients, they are part of a health intervention. Stigma is also a prevalent issue, particularly for patients new to HIV and likely still grappling with stigma associated with HIV. People with HIV have stated that fears related to stigma, including fears of being judged and fears of being seen picking up HIV medicines, can provoke anxiety. In our study, positive interactions at the pharmacy and feelings of support were important to patients feeling accepted.

Our qualitative findings show that the pharmacy staff plays a key role in shaping the patients' refill experience. Patients depend on the pharmacy for the information regarding medication refills. Our patients share that inconsistent messaging from the pharmacy causes frustration and anxiety that deters them from refilling their ART medications on time. Staff have opportunities to make the refilling process smoother by explaining how refills work and involving the patient in managing these steps. Kamei et al found that, among other things, good information management, which is how information regarding the medications is given to patients, is vital for a pharmacy.[5] Themes that emerged from patient interviews align with the findings of Kamei's study, which reinforces the importance of communication. Our patients said communication is important not only in imparting knowledge and education but also with dealing with anxiety related to medication refills.

A strategy to improve lines of communication in the pharmacy is to train pharmacy staff to increase their awareness of patient barriers and improve customer service. A study showed that patients care more about how pharmacy services are delivered (eg, fast, friendly, functional) than what they receive (eg, counseling on how to take medication, medication brochures).[6] A qualitative study exploring pharmacy staff's perception of service quality indicates that pharmacy staff want specific and more frequent feedback from upper management and more clarity in their roles as it relates to service quality.[33] No rigorous studies testing the impact of different feedback interventions for pharmacy staff exist.

Patients in our study say some of the greatest barriers of refilling medication involve travel and time. Commercial pharmacies have implemented several technology-based interventions to decrease the number of trips to the pharmacy and to increase on-time medication refills. One pharmacy in Iowa revamped its process to synchronize patients' medication refills so that patients have 1 medication pick up instead of multiple pickups[34]. TSHC now gives patients the option to synchronize their medications as well. In another study, patients preferred to refill their medications online because it was faster than calling in a refill. [35] The pharmacy in this study has subsequently added an online portal for refills.

Allowing prescriptions to be filled online is favorable for many patients and can improve medication adherence.[35] In a qualitative study conducted at a pharmacy in Pittsburgh, patients preferred e-prescribing and liked the convenience of not having to drop off a prescription and then return to pick up the medication. These patients also said this convenience made it more likely for them to pick up their medications.[36] Another study of patients picking up their asthma, high blood pressure, diabetes, or high cholesterol medication for the first time also showed that patients with e-prescriptions had higher first-fill rates.[37] Refills at TSHC pharmacy can be requested online via MyHealth, and refill prescriptions are e-prescribed unless a patient requests a hard copy prescription.

Dispensing literature on other common chronic medical conditions provides a lens to understand the potential value of 90-day vs 30-day prescriptions as it relates to medication

adherence and clinical outcomes.[38-41] In a study conducted with among patients high cholesterol, hypertension, or diabetes, patients with a 90-day supply of medication had more improved adherence than patients with a 30-day supply.[12] Adherence was measured by medication possession ratio. Beyond medication possession ratio, several studies have looked at clinical outcomes. A study conducted among patients with acute myocardial infarctions demonstrated favorable patient health outcomes among patients surviving 1 year; when looking at 1-year survivors, compared with patients who did not survive, a higher percentage had a 90-day prescription of statins.[42] The most compelling data come from the women's health literature with oral contraceptives.[15] Patients with 90-day oral contraceptive prescriptions had fewer missed doses and unintended pregnancies.[43] Given this, the Department of Human Health Services national guidelines now recommend 90-day refills for oral contraception. As noted above, Texas ADAP now allows a 90-day supply to be dispensed.

Although some privately insured patients can access 90-day supplies of ART, HIV medicines are expensive, and many insurance plans limit supplies to 30 days at a time.[44] Our data support shifting stable patients to 90-day supplies when feasible and suggest policies supporting 90-day supplies should be considered. We expect patients with HIV filling 90-day supplies to have improved adherence and pharmacy refill experiences. We hope our study points to potential benefits of increasing dispensing protocols to 90 days, including the potential for mitigating structural and psychosocial barriers (ie, by decreasing the number of pharmacy trips needed).

limitations

This study took place at one clinic. Our study participants represent an underserved population, and results may not generalize to other populations. This is a qualitative study, and the findings are exploratory; the levels of anxiety and measures of medication adherence could not be quantified or correlated with missed doses. However, qualitative findings are necessary to provide context and to understand the patient's perspectives. As anticipated, we had longitudinal dropout. Still, we retained a reasonable number of patients at T2/T3 and were able to see how their experiences changed over time.

CONCLUSION

This study identified several individual, intrapersonal, and system-level barriers affecting patients' ability to refill their ART medication on time. Analyses revealed patient-centered solutions to address these barriers: 1) providers and pharmacy staff should be mindful how getting refills can trigger anxiety for patients, 2) proactive communication and consistent messaging from pharmacy staff is vital, and 3) dispensing protocols should be increased from 30 days to 90 days. Patients in our study said they would prefer to receive 90-day prescription refills of their ART medications. Changing dispensing protocols of ART medication from 30-day prescription refills to 90-day prescription refills is a patient-centered solution that, based on our interviews, may decrease anxiety concerning missed doses and improve medication adherence.

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Ethics Approval

All procedures performed in studies involving human participants were in accordance with the Baylor College of Medicine Institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Authors' Contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by Sarah Njue-Marendes, MPH, and Bich N Dang, MD. Analysis was performed by Bich N Dang, MD, and Syundai R Johnson, MPH. The first draft of the manuscript was written by Syundai R Johnson, MPH, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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ORIGINAL RESEARCH ARTICLE

Demographic, Clinical, and Prescribing Characteristics Associated with Future Opioid Use in an Opioid-Naive Population in an Integrated Health System

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ABSTRACT

Introduction: Health systems and prescribers need additional tools to reduce the risk of opioid dependence, abuse, and overdose. Identifying opioid-naive individuals who are at risk of opioid dependence could allow for the development of needed interventions.

Methods: We conducted a retrospective cohort analysis of 23,804 adults in an integrated health system who had received a first opioid prescription between 2010 and 2015. We compared the demographic, clinical, and prescribing characteristics of individuals who later received a third opioid dispense at least 27 days later, indicating long-term opioid use, with those who did not.

Results: The strongest predictors of continued opioid use were an initial prescription dosage of 90 morphine milligram equivalence or more; prescription of extended-release opioids, rather than short-release; and being prescribed outside of a hospital setting. Patients with a third prescription were also more likely to be older than 45 years, white, and non-Hispanic and to have physical comorbidities or prior substance abuse or mental health diagnoses.

Discussion: Our findings are largely consistent with prior research but provide new insight into differences in continued opioid use by opioid type, prescribing location, ethnicity, and comorbidities. Together with previous research, our data support a pattern of higher opioid use among older adults but higher rates of diagnosed opioid abuse among younger adults.

Conclusions: By identifying population characteristics associated with continued opioid use following a first prescription, our data pave the way for quality improvement interventions that target individuals who are at higher risk of opioid dependence.

BACKGROUND

Over the past 30 years, opioid prescribing in the US has increased substantially. The number of prescriptions nearly tripled from 76 million in 1991 to more than 210 million in 2010.[1] Since 2012, the number of opioid prescriptions has slowly declined; the number stood at about 191 million in 2017.[2] Although the prescribing decline is good news, opioid abuse and addiction continue to take a heavy toll. Between 1999 and 2017, overdose deaths in the US due to prescription opioids increased 6-fold.[3] Nearly 218,000 people died in the US from overdoses related to prescription opioids over that time period.[1] Overdoses involving opioids caused more than 47,000 deaths in 2017, and 36% of those deaths (about 17,000) involved prescription opioids.[4,5]

These statistics document a crisis that has destroyed individual lives and damaged families and communities. In 2016, the CDC released a Guideline for Prescribing Opioids for Chronic Pain, which recommended that prescribers limit the use, duration, and potency of prescribed opioids for adults seen in primary care.[6] In 2017, the US Department of Health and Human Services declared the opioid crisis a public health emergency.[7] As federal agencies have moved to curb the crisis, health care systems have come under increased pressure to more tightly control opioid prescribing.

To prevent future opioid addiction among those who are not currently using opioids (ie, naive populations), health systems need to identify patient characteristics associated with future opioid use disorder. Such information can help systems develop interventions to provide additional support and outreach to those who are most at risk of addiction. Several previous studies have identified individual patient demographics (eg, male gender,[8,9] younger age,[8-10] receiving public insurance[11,12]), clinical conditions (eg, previous mental health diagnoses,[8,9,13,14] previous substance abuse), and prescribing characteristics (eg, more days of supply,[8,9,15] higher daily dose[10,15], extended duration of opioid release[16-18]) associated with future opioid use or with diagnosis of opioid use disorder. However, analyses that use a population-based approach examining an entire cohort of patients over time to identify patient-level characteristics associated with future use are limited. Moreover, limited studies of this kind have been conducted within integrated health care systems where more comprehensive clinical information is available (eg, clinical comorbidities). Also, few studies have looked at a third prescription of opioids shortly after an index prescription, which can be a "leading indicator" and have strong predictive power for long-term use.

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In this study, we examined the independent associations of demographic, clinical, and prescribing characteristics with future opioid use among all naive (first-time) users in Kaiser Permanente Northwest (KPNW), an integrated group model health maintenance organization serving more than 626,000 members in Oregon and southwestern Washington. By studying the characteristics associated with continued opioid use using a cohort-based approach within an integrated health system, we will be able to better identify characteristics associated with long-term use that can be used to create new predictive models. These models can help health systems identify individuals who are most likely to be at risk for future long-term opioid use and dependence and target additional support and resources toward these individuals.

METHODS

We conducted a retrospective cohort analysis of 23,804 patients who meet the following inclusion criteria: 1) adults (age 18 and older) with at least one opioid prescription (eg, oxycodone, hydrocodone, tramadol) between January 1, 2010 and September 30, 2015 (index prescription) who 2) did not have an opioid prescription 6 months prior to the index prescription (opioid naive). Patients with cancer diagnoses (any type) or who were receiving hospice care were excluded. These criteria were based on previous research defining opioid-naive populations.[19] Data needed for the analyses were identified through KPNW's electronic health record. Opioid medications included only those filled at KPNW pharmacies. The quality lead for specialty care for Northwest Permanente, KPNW's physician group, was closely involved with the development and execution of this analysis. The primary intent of the analysis was quality improvement oriented, with the results used to inform future initiatives by identifying factors that predict risk for future opioid use among the naive population. The analysis was reviewed and approved by the KPNW Institutional Review Board.

Measures and analyses

The primary outcome measure was whether a patient received a third prescription of opioids at least 27 days after index prescription (yes vs no). The rationale for the outcome was 2-fold. First, previous research has demonstrated that each additional opioid prescription has predictive power for future opioid dependence,[20] but few studies have examined factors associated with a third prescription, which may have strong predictive power for future use. Second, the rationale for at least 27 days to third dispense was that it is a reasonable time period in which to consume the index and second opioid prescriptions for patients filling a third prescription and that the majority of third dispenses occurred 27 or more days after the index prescription.

Predictor Measures: Demographic, Clinical, and Prescribing Characteristics

Predictor measures in this analysis included demographic, clinical, and prescribing characteristics available from KPNW's electronic health record. The selection of these measures was based on previous published research.[8-10, 15-18]

Demographic measures included age category (< 45, > 45 and < 65, > 65), sex (male, female), race (white, non-white), and Hispanic ethnicity (Hispanic, non-Hispanic). We also examined whether individuals had Medicaid insurance (yes vs no) and Medicare insurance (yes vs no).

Clinical characteristics included the Charlson Co-morbidity Index (CCI, 0 vs 1+), a measure of clinical comorbidities in the year prior to index prescription,[21,22] any prior substance abuse diagnosis (yes vs no), and any prior mental health diagnosis (yes vs no). The look-back period to assess substance abuse and prior mental health diagnosis was a far as KPNW membership existed.

Prescribing characteristics included prescribing location (hospital, outpatient, other location [eg, specialty care]), type of opioid (extended/long release vs short release), and total morphine milligram equivalents (MME) dosage for index prescription (MME > 90 vs MME < 90). This was one of the first studies we are aware of that compared prescribing location of opioids for index fill as a predictor for long-term use of opioid medications.

Statistical Analysis

We conducted univariate descriptive analyses comparing the population who received a third prescription with those who did not on each of the characteristics listed above using γ^2 analyses at baseline. Next, we conducted multivariable logistic regression to determine which characteristics best predicted receiving a third prescription when controlling for the other characteristics. The final model was estimated using logistic regression with stepwise variable selection, from those variables compared at baseline, to develop the most parsimonious statistical model.

RESULTS

Of the 23,804 patients who received a first opioid prescription during our study period, 8,762 (36.8%) received a third prescription at least 27 days later. Table 1 presents univariate descriptive characteristics among those who did and did not receive a third prescription. Except for sex and Medicaid insurance status, all demographic, clinical, and prescribing characteristics were associated with whether a patient received a third prescription.

Table 1. Population Characteristics. Opioid Naïve Population by Prescription Status.

Variables	No 3rd prescription N=15,042 (63.2%)	3rd prescription N=8,762 (36.8%)	p-value
Demographic measures			<0.0001
Age categories N (%)*			
Age ≤ 45	5,243 (34.9%)	2,313 (26.4%)	
Age > 45 and Age ≤ 65	6,290 (41.8%)	4,149 (47.4%)	
Age > 65	3,509 (23.3%)	2,300 (26.3%)	
Sex N (%)			
Male (vs. female)	5,710 (38.0%)	3,260 (37.2%)	0.25
Race			
White (vs. non-White)*	13,742 (91.4%)	8,188 (93.5%)	<0.0001
Ethnicity			
Hispanic (vs. non-Hispanic)*	899 (6.0%)	278 (3.2%)	<0.0001
Medicaid/Medicare status			
Had Medicaid insurance (vs. none)	585 (3.9%)	348 (4.0%)	0.75
Had Medicare insurance (vs. none)*	4,179 (27.8%)	2,912 (33.2%)	<0.0001
Clinical measures			
CCI (≥ 1 vs. 0)*	5,602 (37.2%)	3,928 (44.8%)	<0.0001
Prior substance abuse diagnosis (vs. none)*	3,286 (21.9%)	2,423 (27.7%)	<0.0001
Prior mental health diagnosis (vs. none)*	4,794 (31.9%)	3,448 (39.4%)	<0.0001
Prescribing characteristics			
Prescribing location			
Hospital*	1,572 (10.5%)	302 (3.5%)	<0.0001
Outpatient*	8,372 (55.7%)	5,108 (58.3)	<0.0001
Other location*	5,098 (33.9%)	3,352 (38.3%)	<0.0001
Opioid type: extended (vs. short release)*	4,368 (29.0%)	4,288 (48.9%)	<0.0001
Morphine milligram equivalency (MME)*			
MME ≥ 90 (vs. < 90)	7,152 (47.6%)	6,744 (77.0%)	<0.0001

*p < .05.

Table 2 presents the final multivariable logistic model of predictor measures associated with having a third prescription of opioid medications, after stepwise variable selection. Those who received a third prescription were significantly more likely to be in the older age categories, white, and non-Hispanic. They were also significantly more likely to have a CCI score of 1 or higher, including prior substance abuse and mental health diagnoses. Patients prescribed in the hospital were significantly less likely to receive a third prescription than those prescribed in other settings (eg, specialty care). Last, there was no difference between rates of receiving a third prescription in outpatient as compared with other settings. Those receiving extended-release prescriptions and dosages above 90 MME were significantly more likely to receive a third prescription than those who received short-release prescriptions or lower dosages.

DISCUSSION

In one of the first studies examining predictors of opioid use in a population-based cohort from an integrated health system, we identified several demographic, clinical, and prescribing characteristics that were associated with a third opioid prescription within 27 or more days of a patient's first opioid prescription. These findings provide new insights about characteristics that could contribute to chronic opioid use. These data can be used to develop innovative provider-based interventions for individuals at high risk of developing a pattern of chronic opioid use.

The strongest predictors of receiving a third prescription were characteristics of the initial prescription. Consistent with many previous studies that found associations between opioid dosage and chronic use or abuse/dependence,[10,12,15] we found that patients who received doses above 90 MME were three times more likely to have a third prescription than those who were prescribed lower doses. We also found that those prescribed extended-release opioids were 1.53 times more likely to receive a third prescription than those prescribed short-release opioids. Although few previous studies have examined differences in long-term use based on type of opioid prescription, one previous study based on a large commercial claims database found a

Table 2. Multivariable Logistic Regression Results: Association of Demographic, Clinical and Prescribing characteristics with Opioid 3rd Prescription.

Variables	Odds Ratio (OR)	95 % Confidence Interval (CI)	p-value
Demographic measures			
Age ≤ 45	1.00	–	–
Age > 45 and Age ≤ 65	1.34	1.25-1.44	<0.0001
Age > 65	1.23	1.13-1.33	<0.0001
Race			
White (vs. non-White)	1.24	1.11-1.39	<0.0001
Ethnicity			
Hispanic (vs. non-Hispanic)	0.60	0.52-0.69	<0.0001
Clinical measures			
CCI (≥ 1 vs. 0)	1.14	1.07-1.21	<0.0001
Prior substance abuse diagnosis (vs. none)	1.19	1.11-1.27	<0.0001
Prior mental health diagnosis (vs. none)	1.25	1.18-1.33	<0.0001
Prescribing characteristics			
Prescribing location			
Hospital	0.20	0.17-0.22	<0.0001
Outpatient	0.98	0.92-1.04	0.49
Other	1.00	–	–
Opioid type: extended (vs. short release)	1.53	1.43-1.64	<0.0001
Morphine milligram equivalency (MME)			
MME ≥ 90 (vs. < 90)	3.00	2.80-3.21	<0.0001

stronger relationship between short-acting opioids and later opioid misuse than between long-acting opioids and later opioid misuse. This difference may be due to different outcome variables: Short-acting opioids may put patients at a higher risk of misuse, whereas long-acting opioids may be more associated with prolonged use.

Our study was also the first to show a lower rate of continued use among patients prescribed opioids in a hospital setting compared with other prescribing settings. This may be because of high awareness among hospital providers of the need to prescribe low opioid pill counts following inpatient surgical procedures; lower pill counts have been associated with lower long-term opioid use.[23]

In our cohort, older age was associated with higher likelihood of a third prescription. At first glance, this finding may appear to be in conflict with previous reports of lower risk of opioid abuse and dependence among older age groups.[8-10, 13] However, 2 other studies that have focused on prolonged opioid use, rather than misuse or abuse, also found higher rates of continued use among older adults.[12,15] Together, these data paint a picture in which younger adults who are prescribed opioids may be more at risk of misuse, whereas older adults are more likely to become chronic prescription users under the guidance of their doctors.[14]

Our study also adds to the sound body of literature demonstrating that individuals with a past history of substance abuse or mental health diagnoses are more at risk for long-term use of opioids.[10,12,13] Additionally, we found that patients with a CCI score of 1 or higher were significantly more likely to get a third prescription. This is consistent with another study that found a relationship between CCI and chronic opioid therapy.[12] In contrast, the few studies examining the relationship between CCI and opioid abuse or dependence have reported mixed results.[10,13]

Although studies have consistently found that white race is associated with higher risk of chronic opioid use or dependence, findings about the relationship with Hispanic ethnicity have been more mixed. Whereas some studies have found higher rates of misuse among Hispanic populations,[13,14] we found that Hispanic patients were less likely to receive a third prescription. This is consistent with a previous study that showed that Hispanic ethnicity was associated with lower likelihood of filling an opioid prescription,[11] possibly due to problems with cost and access among lower-income Hispanic populations. We also found no differences by sex in patients' likelihood to continue using opioids, whereas some past studies have found higher rates of chronic use or reported misuse among women.[14,15]

These results provide preliminary evidence of the characteristics associated with continued opioid use among naive users. This evidence can be used to develop more refined predictive risk models that could identify patients most in

need of additional resources and support, including quality improvement interventions, to reduce their likelihood of chronic opioid use or misuse. Future research could also examine whether tailoring interventions to individuals with specific demographic, clinical, or prescribing characteristics could prevent future opioid dependence. For example, individuals with a past history of substance abuse may benefit from different interventions than older adults with multiple physical comorbidities. Similarly, prescribing location and prescribing characteristics could be used to tailor interventions appropriately for individuals with different medical histories and reasons for using opioids.

More research is needed to develop and evaluate effective provider-based interventions with a focus on naive opioid users with the goal of reducing future opioid dependence. These interventions should use predictive models and other tools, such as identifying outliers, to maximize the effectiveness of limited resources and improve outcomes for patients who are most at risk. Our results suggest that KPNW pharmacists could be a key component of such interventions, using this information to select alternate medications to opioids and to connect with patients' primary care clinicians to better manage and coordinate care.

One limitation of this study was that it only includes data from patients first dispensed opioids between 2010 and 2015. Opioid use was declining during this period and continues to decline through the present day. However, the factors associated with long-term opioid use are likely similar between this time frame and the present. A second limitation is that this analysis occurred in an integrated health system in the Pacific Northwest; therefore, results may not be generalizable to the larger US population. Last, this analysis only included opioid prescriptions filled in KPNW pharmacies; the associations of patient characteristics with the third prescription of opioids may not be the same in prescribing locations outside of KPNW.

CONCLUSION

In a population-based cohort of 23,804 naive opioid users, prescribing characteristics (dosage, extended vs short release, and prescribing location) most strongly predicted continued opioid use, as measured by a third prescription at least 27 days after the initial prescription. We also identified key clinical and demographic factors associated with continued use. These findings could be used to inform quality improvement interventions for preventing opioid dependence. Such innovative quality improvement approaches should involve collaboration with KPNW pharmacists and primary care physicians to prescribe alternate medications to opioids and better manage and coordinate care. ❖

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ORIGINAL RESEARCH ARTICLE

Evaluation of a Motivation-Based Intervention to Reduce Health Risk Behaviors among Black Primary Care Patients with Adverse Childhood Experiences

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ABSTRACT

Background: Considerable evidence suggests that greater attention should be paid to the impact of trauma among low-income, racial/ethnic minority patients living in urban communities. The goal of this article is to evaluate a 2-session, motivational intervention designed to motivate a change in health risk behaviors among low-income, self-identified Black/African American patients with adverse childhood experiences (ACEs).

Methods: Qualitative self-reported data described helpful aspects of the intervention and those that could be improved. Eligible participants with 1 or more ACEs being seen in a community-based clinic were interviewed by a mental health clinician researcher for 2 in-person sessions scheduled 1 month apart. Content analysis was performed using a general inductive approach to identify core themes.

Results: In total, 36 of 40 participants completed both sessions, with the majority reporting a high rate of satisfaction. Participants emphasized the importance of talking with a trained professional who could listen without judgment, understand patient challenges, clarify patient goals, and facilitate behavior change plans. Suggestions for improvement included modifying structure and content, enhancing clinic environment, improving linkages to behavioral health, and increasing communication and collaboration with clinicians.

Conclusion: Participant evaluation data gathered for this study suggest that through the practice of asking, listening, and accepting, clinicians can help patients who have been exposed to childhood adversity better understand themselves and promote healthy coping behaviors. This study provides preliminary data on the needs of underserved patients that can be utilized to develop and deliver health promotion interventions using a trauma-informed approach in community-based clinics.

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Keywords: adverse childhood experiences, African American, health promotion, medically underserved, primary care, trauma-informed care

INTRODUCTION

Black Americans are disproportionately exposed to major stressful events, including discrimination, community violence, and poverty, all of which contribute to increased risk of poor health.[1,2] The impact of trauma on health often goes unaddressed among Black Americans due to poor access to care, stigma, and mistrust in health care.[3,4] Racial biases in health care indicate the need for facilitating greater health equity in underserved communities.[5,6] Health disparities can be more broadly addressed with a trauma-informed approach to health care that recognizes trauma prevalence and its impact on mental and physical health.[7,8] There is considerable evidence that greater attention should be paid to trauma screening and intervention in primary care, particularly for low-income, racial/ethnic minority patients living in urban communities.[9,10] To that end, we implemented a strengths-based, trauma-informed, motivational intervention within a primary care clinic primarily serving low-income, Black American patients designed to motivate a change in health risk behaviors. This article assesses participant perceptions of what helped and what could be improved about the intervention.

Adverse Childhood Experiences

Drs Felitti and Anda uncovered a strong association between early childhood adversity and adult chronic health conditions in their landmark Adverse Childhood Experiences study in 1998.[11] Adverse childhood experiences (ACEs) include abuse, neglect, and household dysfunction prior to age 18 years. Since the initial findings of the ACE study, the dose-response relationship between childhood adversity and a number of health risk indicators, including alcohol misuse,[12,13] drug abuse,[14] obesity,[15] risky sex,[16] and smoking,[17,18] has been replicated in more than 80 publications.[19] Decades later, Dr Felitti incorporated ACE questions into a comprehensive medical assessment, which led to substantial reductions in physician office visits and emergency room visits. Although this was a retrospective observational finding that did not control for confounding factors that may have contributed to the finding of fewer office and emergency room visits, Dr Felitti attributed outcomes to 3 basic characteristics of human interactions: "We realized that asking … coupled with listening and implicitly accepting the person who had just shared his or her dark secrets, is a powerful form of doing."[19] This study

seeks to translate Felitti's insights of asking, listening, and accepting into clinical practice.

Trauma-Informed Care

Trauma-informed care (TIC) is a systems approach to health care that conveys an awareness of the impact of trauma on health by incorporating an understanding of trauma and resilience throughout all aspects of care.[20-22] The Substance Abuse and Mental Health Services Administration (SAMHSA) outlined 4 key assumptions of a trauma-informed approach: 1) realize trauma prevalence, 2) recognize signs of trauma, 3) respond using trauma-informed principles, and 4) resist retraumatization.[23] The 6 principles of TIC defined by SAMHSA include the following: 1) safety; 2) trustworthiness and transparency; 3) peer support; 4) collaboration and mutuality; 5) empowerment, voice, and control; and 6) cultural, historical, and gender acknowledgment. These principles constitute an approach to enhancing patient engagement through relationship-building[7] that can guide clinical practice and inform clinical decision-making with trauma survivors.[24] They work in unison to effectively address the consequences of trauma while enhancing resilience and preventing retraumatization.[25] An emphasis on physical and psychological safety is the basis for clear expectations, roles, and boundaries that are navigated by clinicians and patients alike.[22] TIC is governed by strengths-based care, which makes use of every opportunity to provide choice, rebuild control, and promote self-efficacy. Patients' strengths and resilience are highlighted, rather than focusing on symptoms and pathology. TIC principles can help medical practice become trauma informed by providing a basis for high-quality relationship-based care. The state of the science on trauma-informed health care suggests that TIC can improve clinician and patient satisfaction, reduce health care costs, and lower no-show rates.[26]

Motivational Interviewing

Motivational interviewing (MI), a collaborative, evidence-based technique, features a set of 5 guiding principles including 1) expressing empathy, 2) developing discrepancy, 3) dealing with resistance, 4) supporting self-efficacy, and 5) developing autonomy.[27] MI encompasses a trauma-informed approach that can enhance motivation in changing behavior within an atmosphere of acceptance and compassion.[28] Previous research shows that people who express commitment for change are more likely to make behavioral changes such as reducing drinking.[29-31] Clinicians can promote coping self-efficacy, which is predictive of better health outcomes, by reflecting change-talk to patients.[29,32] Together, TIC and MI principles and strategies form the basis for the novel intervention featured in this study.

Objectives

A previously published study of this intervention indicated that it was feasible to implement a brief, motivation-based intervention within primary care that could help to develop healthier ways of coping with stress among trauma-affected low-income patients of color.[33] A second manuscript describes the patient experience of changing a health risk behavior. The current study expands on the previous publications by evaluating the qualitative data of what helped and what could be improved about the intervention from the patient/participant perspective. This study provides preliminary data that can be utilized to develop and deliver resilience-promoting interventions, increase trauma competence for clinicians, and enhance engagement in care for low-income Black Americans with childhood trauma exposure. The intervention has the potential to help participants connect with what happened to them in childhood and how those experiences may be affecting them today.

METHODS

The intervention was administered at an urban community care clinic to Black American patients who endorsed exposure to childhood trauma. It was implemented to help participants reduce stress and health risk behaviors by making improvements in coping self-efficacy[34,35] and to encourage behavioral health referral acceptance.[36,37] The intervention assisted participants to explore ambivalence in making behavior changes and to create a change plan that included a measurable goal, strategies to mitigate triggers, social supports, and rewards of progress.

Clinic Setting

This study was conducted in a Federally Qualified Health Center located in the center of a large metropolitan area. The clinic predominantly serves low-income, racial/ethnic minority patients. The patient population comprises predominately Black (76%), Medicaid-insured (76%) women (60%) who are aged between 18 and 49 (44%) or 50 years or older (25%) and have a diagnosable mental health or substance use disorder (27%). All participants were recruited from a family/internal medicine setting offering primary care services. The study protocol was approved by the University of Wisconsin Health Sciences Institutional Review Board.

Participants

Eligible participants of the clinic were adults, English speaking, and self-identified as Black/African American with 1 or more ACEs. Patients were excluded if they had noticeable signs of mental instability or intoxication or if they were physically too sick to participate. Data were collected from July 2017 through January 2018. Patients in

the waiting room of the clinic were invited to participate in a research study about Black/African American adult primary care patients whose lives are affected by stressful events that occurred when they were children or teenagers. Potential participants were told that the goal of the research was to learn whether a certain kind of counseling would help individuals to feel less stress, to be better able to cope with stress, and to do some things that might improve their health. The data could assist providers to better understand the stressful childhood experiences that affect the lives of their patients. Patients who agreed to the initial screening were advised that some of the questions were sensitive and that they could skip any question that they preferred not to answer. An eligibility screen was administered by either the principal investigator or a trained research assistant using the 10-item ACE study questionnaire,[11] which was scored upon completion by the person administering it. Patients with 1 or more ACEs were invited to participate in the intervention study and scheduled within 2 weeks for an initial session with the principal investigator.

Of the 188 patients who were assessed for eligibility in the clinic waiting room, 162 patients had 1 or more ACEs, reinforcing the suitability of implementing a trauma-informed intervention for this clinic population with substantial trauma exposure. Of those patients who met the eligibility requirement, 55 patients declined to participate for the following reasons: not interested in research, not having enough time, not feeling well, questions were too personal and sensitive, and other (eg, does not live near the clinic, not brought up in the United States, not stressed, in good health, busy filling out paperwork). Of the 107 patients that had scheduled a first session, 67 did not show for unknown reasons. Forty patients with 1 or more ACEs participated in the study.

Intervention Procedure

After having participants read and sign the informed consent, the intervention was completed by the first author (EG), a licensed professional counselor and primary care researcher. Two sessions, offered 1 month apart, were privately conducted in a patient room. The first session lasted approximately 45 to 60 minutes. The session began with a probing question to elicit resilience and resource survival skills—for example, "How has early life adversity affected you today and what has helped you the most?" In this session, the interviewer used MI techniques to support participants to identify healthy and unhealthy coping skills, explore ambivalence of changing a health risk behavior (eg, pros/cons about the behavior and worst/best things about changing), and create a written behavior change plan to generate actionable steps in changing a health behavior. The interviewer asked guiding questions to help participants create an action plan that encompassed specifying a measurable goal, identifying anything that could possibly get in the way of following through with their goal, strategizing ways to mitigate triggers, choosing specific support people to hold them accountable, as well as thinking of several ways that they could acknowledge and reward progress toward their goal. Reinforcements of participant self-efficacies and strengths whenever possible were woven throughout the conversation, elicited by questions such as, "What have you successfully changed or accomplished in the past and what personal strengths helped you to achieve your goal?" The second session lasted 20 minutes and was an opportunity to report progress and troubleshoot barriers to their goal. The interviewer inquired about coping mechanisms that the participant had tried and not tried since the prior session, what worked and what was not as helpful about what they tried, how barriers to trying new coping were addressed, and any changes in the plan going forward. A trained research assistant conducted all the participant satisfaction surveys by phone a few days after the completion of sessions 1 and 2 and then 2 months postentry. Participant evaluation responses were simultaneously typed verbatim into a protected database.

Data Collection

To determine participant eligibility, the 10-item ACE study questionnaire was used to screen for ACE exposures prior to age 18, including emotional, physical, and sexual abuse; emotional and physical neglect; and household dysfunction such as witnessing domestic violence, growing up with mentally ill, substance abusing, or criminal household members, and parental separation or divorce.[38]

Participants' perceptions of the most helpful aspects of the intervention and how it could be improved from sessions 1 and 2 were addressed by asking the following questions: "What was most helpful about the session?" and "What do you think could be improved about the session?" At follow-up, participants were asked about the program as a whole—for example, "What was most helpful about the program?" and "What do you think could be improved about the overall program?"

Thematic Analysis

Participant responses describing what was helpful and what could be improved about the intervention were extracted from the database in a deidentified format. Content analysis was performed using a general inductive approach to identify core themes. Two researchers (EG and SFB) independently performed an analysis to identify emergent themes and met to resolve discrepancies. Several procedures were used to analyze the manifest content of participant responses.[39,40] Initially, responses were distributed into content analytic units by

entering individual meaning units into an Excel spreadsheet beneath each corresponding question. Each analytic unit was coded based on the content of the response. The data were reduced by grouping similar responses into categories and assigning them to thematic domains. A third author (JT) performed an audit of the coding. The analytic team discussed and refined themes. Exemplar quotes of participant responses were selected to illustrate identified themes.

RESULTS

Demographics

Table 1 displays baseline characteristics of Black American patients being seen in a Federally Qualified Health Center within a city in the Upper Midwest. The 40 study participants had a mean age of 44 ± 13 years (range = 20-64). The majority of participants were female (27; 67.5%) with some college or higher (25; 62.5%), and they earned a household yearly income of $30,000 or less (39; 90%). Twenty-six participants (65%) reported 4 or more ACEs and 23 (57.5%) reported 3 or more PTSD symptoms. While 15 participants (37.5%) were currently receiving behavioral health services, 31 (77.5%) reported receiving past mental health counseling.

Participants identified health risk behaviors that they wanted to change, including poor nutrition (13 participants), smoking (8 participants), anger (6 participants), physical inactivity (4 participants), drug use (3 participants), risky sexual behaviors (3 participants), unhealthy alcohol use (2 participants), and stress (1 participants). In total, 36 of 40 participants completed both sessions. Two participants were unable to be contacted and 2 discontinued participation. By the 2-month follow-up, 35 of 40 participants had completed assessments. One participant was unable to be contacted for the follow-up survey. Figure 1 exhibits the participant flow diagram.

Table 1. Baseline characteristics of 40 Black American primary care patients being seen in a Federally Qualified Health Center within a city in the Upper Midwest

Characteristic	Total, n (%)[a]
Age, y	
Mean ± SD	43.83 ± 13.05
Range	20-64
Sex	
Women	27 (67.5)
Education	
Less than high school	5 (12.5)
High school complete	10 (25.0)
Some college or more	25 (62.5)
Income, USD	
<10,000	19 (47.5)
10,000-30,000	17 (42.5)
>30,000	3 (7.5)
ACE score	
1-3	14 (35.0)
≥4	26 (65.0)
PTSD score, symptoms (n)	
1-2	12 (30.0)
>3	23 (57.5)

[a]Column percentages may not add up to 100% due to missing values.
ACE = adverse childhood experience; PTSD = posttraumatic stress disorder.

Participant Evaluation

Satisfaction with the program was high, with 94% of participants endorsing that they were "moderately" or "extremely" satisfied. Participants described what they found most helpful about the 2 individual sessions and the program as a whole. Key themes that reflected participants' experience of the program included connection with other, personal development, connection with self, and professional resources.

Connection with Other

This theme demonstrates how much participants highly valued talking with, being listened to, and feeling understood and accepted by another person. They reported that talking with someone was one of the most helpful aspects of the program.

Just to talk to someone, that's what I wanted to do. I wanted to put plans into perspective, you know what I mean? Some people don't have people to talk to. I have people to talk to. But you know, your family may have heard it all before; they may say, "You already said that before" or things like that, so I find it's just talking to somebody. That's what I needed.

Participants found it helpful to have someone to listen to them and felt understood and accepted as they shared their personal stories.

It wasn't just her just talking at me and me listening, or me talking about or filling out some list and her writing something down. We communicated together and that went well for me. A lot of times, you just need to listen to people. You don't even need to or mean to ask, you don't need to. You just need to listen.

Many participants echoed similar sentiments of feeling heard and understood and appreciated being able to express themselves freely: "She didn't try to dig into stuff. She just allowed me to explain and talk about what it was I wanted to talk about and come to conclusions on my own." Another participant spoke of "being able to talk about my feelings with no judgment or feelings of judgment."

Personal Development

Perceived benefits related to personal development noted by participants included creating a behavior change plan, managing stress, and focusing on themselves. It was helpful to have reflection and input to clarify personal health goals.

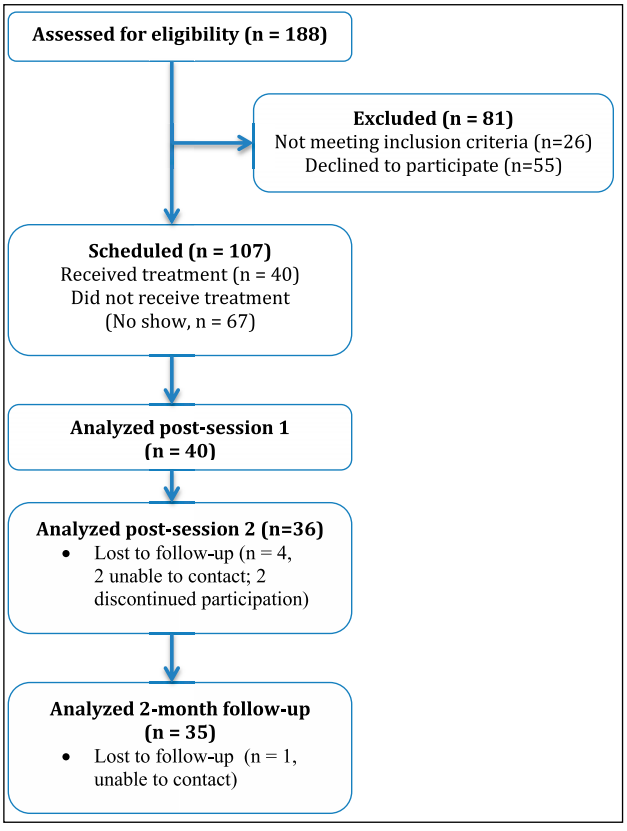

Figure 1. Participant flow diagram.

She listened [and] gave helpful, unique techniques to cope with stress and help maintain whatever my goals were. Sometimes you have goals, but they're not specific or written down, but she made them more solid and crystal clear.

Participants recognized how the sessions allowed more time to focus on the issues in their lives that might be underlying their stress.

It was the time to actually talk to acknowledge and give a voice to some of the trauma that might possibly impact what's going on now and not to stress, but [the] biggest was to look at outcomes and ways to change and spend time focusing.

Others shared about how the session helped them to manage stress better.

It was a real nice talk to see different perspectives, and the conversation that we did have, it brought me to realize that everything I was stressing over. She showed me how to ease myself and stay relaxed and not think about it while putting my best effort doing something to accomplish my goals and to ease stress and relax.

Connection with Self

A third fundamental theme describes how the intervention helped participants better understand themselves through self-awareness and recognizing their own strengths.

Managing my stress is my own weakness, but learning that I'm strong within myself and that I have the characteristics within myself … that I do have these characteristics, and that I do have the abilities to strengthen myself, and that I do have a way to overcome all the things I am focusing on helps me.

Self-understanding and self-expression are critical to the integration of the whole self. One participant commented that the intervention was, "Bringing out some feelings in me that I didn't know I had." Another participant shared, "That made me understand that I stress out all the time." And a third stated, "That it brought things to my understanding. It helped me put into perspective how I can get myself back together." This theme further illustrates helping participants to recognize their struggle and to feel empowered to take action: "It helped me plan out areas I was not doing too well, and it also helped point out all the messages or ways I can go about getting help and approaching my problems head-on."

Professional Resources

Informational resources (eg, free online resources and self-help and communication books) and the connection to professional supports (eg, counselors and mindfulness practice and substance abuse groups) were reported as being helpful and provided a sense of hope for some participants.

Suggestions for Improvement

Participants described suggestions for improvement for the 2 individual sessions and the program as a whole. Key themes that reflected participants' experience of the program include intervention structure and content, clinic environment, behavioral health referrals and collaborative care, and the working alliance between counselor and participant. Participants mentioned increasing the length of the first session, which would allow for more time to respond to questions and delve into specific issues. Some participants suggested increasing the number of sessions, stating that they would prefer "being able to talk to her more often instead of just month to month." Participants commented on aspects of the intervention content that could be improved such as changing the style of the questions, clarifying goals and expectations, distinguishing between research and therapy, and emphasizing the impact of ACEs on health. For example, some questions seemed limiting for some participants who may have preferred open-ended questions that allowed them to speak more freely. In addition, taking time to clarify personal goals and expectations at the onset of the meeting can be helpful to match what the session had to offer with the needs of the individual. For some participants, it was not clear how the intervention differed from a therapy session. Others expressed wanting a better understanding of the link between childhood events and how those experiences affected them today. Participants commented on wanting to talk about sensitive topics in an

environment that was more comfortable and private as opposed to a medical setting. They also expressed the importance of increasing collaboration and communication between the counselor and clinician to support the goal of improving patient health. Several participants commented on the working alliance between themselves and the counselor. One participant observed the differences in perspectives and styles between themselves and the interviewer by stating, "It's just a different way of seeing things. Some of the things she suggested were different than the things I suggested."

DISCUSSION

Participant responses on perceived benefits and limitations reflected the aspects that they found most satisfying and identified what could be improved about the intervention. As a result, these findings can contribute to improving engagement in care for low-income, Black Americans with childhood trauma exposure. The intervention elements described below provide a method for the translation of TIC principles into direct and effective practice by guiding clinicians on how to ask about trauma and to respond sensitively to patient disclosures. Operating within these principles can ensure that clinicians are practicing within a trauma-informed framework and assist to protect against unintentionally revictimizing patients.

According to participants, connection with the counselor was the most helpful aspect of each session and the program as a whole. Talking with a trained professional who can listen without judgment and is able to understand the experience of another creates a sense of safety. Feeling genuinely heard and therefore valued is healing in itself and, in some cases, may be the most effective intervention a clinician has to offer. Feeling accepted when talking about difficult and sensitive topics builds trusting relationships that create the opportunity to share more. Broaching the topic of childhood trauma is more likely to be successful with an accepting and compassionate approach. A clinician's attitude of acceptance reduces patients' likelihood of feeling stigmatized, shamed, or blamed for what happened to them and reinforces patient stress responses as a normal reaction to abnormal and overwhelming events or circumstances.

Forming a healthy, secure attachment is the basis for healing trauma and increasing one's capacity to cope with stress.[41,42] A person's ACE history can help to create a coherent narrative of what happened, eliciting empathetic support from clinicians rather than labeling what is wrong with an individual. With sensitive practice using the ACE questionnaire and other tools, the whole person is being treated and not just the problem or symptom. Operating within these principles will ensure and protect against unintentionally revictimizing patients by giving permission and offering choice before administering procedures and protocols that may potentially be retraumatizing to trauma-exposed patients. It is not possible to know in advance the profile of every person in a clinical setting who has been trauma exposed; therefore, it is beneficial to practice universal precautions and to apply TIC principles with all patients.[43]

Collaboration was illustrated through the opportunity to clarify and work on realistic and achievable health goals by creating a behavior change plan with a trained professional. The counselor worked collaboratively with participants to create their behavior change plan, taking into account the best scientific evidence available as well as the individual's values and preferences. The plan helped participants to identify triggers of using health risk coping, create proactive strategies to mitigate triggers, and establish accountability with a trusted individual.[44,45] The process of developing a plan provided opportunities to point out patient strengths and competence. Emphasizing inherent resilience promoted self-efficacy among participants and notably enhanced the positive connection with the counselor. Additionally, describing the impact of trauma on adult health and consequent use of health risk behaviors as coping with stressful life events helped participants to better understand the connection between their ACEs and their health risk behaviors. Furthermore, garnering insight from talking with the counselor enhanced participants' understanding of themselves, which bolstered confidence to make different choices. The intervention has the potential to help participants connect with what happened to them in childhood and how those experiences may be affecting them today.

Participants reported developing increased self-understanding as a result of the intervention while also learning about resources that inspired new ways of coping. Many participants arrived at the sessions with a variety of coping skills; through talking with the counselor, they were able to explore new coping strategies and to connect with additional helpful resources. For example, mindfulness-based practices such as breath awareness and relaxation and grounding techniques were introduced to participants as alternatives to respond to difficult situations in new ways. Clinicians and clinic staff can reinforce TIC principles by being aware of dysregulation cues and by introducing regulation skills to counteract distress in their patients. Trauma-related symptoms can provide the impetus to resolve underlying affect dysregulation resulting from past traumas, particularly when clinicians have a trauma-informed approach to health care.[46]

Learning new skills can help to rewire the brain, which is imperative for trauma recovery and healing.[47] As a result,

skills practiced on a regular basis such as mindfulness-based techniques can strengthen cortical functioning and emotional regulation as well as deactivate the fear response stimulated by the amygdala's survival response to perceived or actual threat, all of which can increase one's capacity to cope with stress.[48-52] Mindfulness practices can be incorporated into a patient visit as a 3- to 5-minute exercise that can assist patients with a direct experience of its benefits.[53] Working collaboratively to identify coping resources that are accessible, affordable, and in accordance with one's preferences increases chances of sustaining new practices.

Gathering feedback from participant responses provided useful information that can be used to refine and tailor the intervention structure and content, clinic environment, linkages to behavioral health services, and collaboration with clinicians, in addition to the working alliance between the counselor and participant. For example, increasing the number and frequency of sessions would grant additional support and time for participants to adopt new strategies to cope with stressful life experiences. It could also enhance the experience of being heard and listened to, which appeared to make a lasting impression on participants.

Other critical areas of feedback highlighted initially creating a clear understanding of goals and expectations with participants, while inquiring about how the session is working at regular intervals to ensure that their needs are being adequately met during the session. In addition, distinguishing counseling from research would clarify the work to be accomplished and the timeframe in which to do it. A few additional comments underscored the need to provide a comfortable and soothing atmosphere conducive to discussing sensitive topics. It is likely that people attribute these types of conversations to having a therapy session. Incorporating assessments more routinely about ACEs and other sensitive topics into the medical encounter will help to normalize and familiarize patients with having these conversations on a regular basis with their clinician. An additional point was made by participants regarding the need to increase linkages with behavioral health services and improve communication between counselors and clinicians. The facilitation of linkages among diverse clinicians would ensure that connections are made by establishing a system of warm hand-offs with behavioral health providers who are embedded within the clinic or located elsewhere. Finally, increasing the counselor's awareness and sensitivity to any differences between the counselor and the participant could enhance the therapeutic relationship.

Several limitations qualify the study. First, results emerged from a relatively small convenience sample of patients motivated to make changes in their health behaviors. There were a number of patients who did not attend a scheduled first session, resulting in a 63% no-show rate. Along with the knowledge that the majority of participants had already received mental health counseling, the no-show limitation reinforces the motivated nature of the final sample of participants and recommends potential modifications to the intervention protocol such as outreach to scheduled patients with the assistance of the host clinic and reminder calls. Any potential barriers such as childcare, work schedules, and transportation should be discussed and resolved with participants at recruitment. Adding the session to a medical encounter and having the clinician introduce and recommend the program to their patients may also increase the number of people whom this intervention can potentially reach. It is possible that the high retention rate for those attending a first session may be attributed to the particular nature of the intervention (eg, a strengths-based motivational approach that facilitated counselor-patient rapport). Participant evaluation interviews were performed by a research assistant to minimize social desirability and to maintain participant anonymity. Nonetheless, researchers collected some data through on-site surveys, which may have potentially increased social desirability. The 10-item ACE study questionnaire was normed in a sample of white, middle class, health maintenance organization-insured patients, which would likely underestimate the number of adversities to which a low-income, racially and ethnically diverse patient sample may have been exposed. Future studies testing the efficacy of this intervention should use a more ecologically valid screener that includes the myriad community stressors that underserved patients may encounter.

Future work should assess the efficacy of such interventions. If, as we expect, positive results emerge from randomized field trials, then we would recommend wider uptake of trauma-based screening and brief intervention protocols across primary care settings. Stakeholders will pose questions about how to integrate these services into the clinic workflows. To address such issues, research can explore best practices related to intervention timing, location, and personnel, and insights gleaned can inform local implementation efforts akin to widespread brief intervention implementation initiatives for alcohol and drug misuse. With accumulation of research support and policy advocacy, trauma-related screening and referral services should become reimbursable under similar codes that cover similar substance misuse services.

CONCLUSION

The participant evaluation data gathered for this study suggest that through the practice of asking, listening, and accepting, clinicians can help patients who have been exposed to ACEs better understand themselves and their behaviors and ultimately foster resilience-promoting behaviors. It is essential that clinicians listen to patient stories,

since what happened is at the core of trauma healing and relationships are at the core of good health care. The therapeutic qualities of relating are powerful forms of doing that confer relief for patients. The motivation-based intervention featured in this study has clinical utility to help patients change unhealthy behaviors and assist health care clinicians to become more adept at meeting the health care needs of underserved patients with childhood trauma exposure. When implemented within clinics serving low-income patients, the intervention can potentially promote health equity. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Authors' Contributions

As Principal Investigator and lead author, EG, conceptualized and designed the study, and conducted participant interviews, the qualitative analysis, and interpretation of the results. As the subject matter expert, JT contributed to the conception and design of the study and interpretation of the results. SFB contributed to the analysis and interpretation of the results. As the research assistant, KS collected participant evaluation data. All authors contributed to writing and editing the manuscript in addition to reading and approving the final manuscript.

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ORIGINAL RESEARCH ARTICLE

The Potential Protective Effect of Hope on Students' Experience of Perceived Stress and Burnout during Medical School

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ABSTRACT

Background: A major problem facing today's physicians and medical students is burnout. Christina Maslach and fellow researchers have described burnout as a product of chronic stress and a lack of protective psychological factors like hope. The purpose of this study was to explore the relationships between hope, stress, and burnout among medical students.

Methods: This study involved an online survey of 329 first- through fourth-year allopathic and osteopathic medical students. Validated psychometric scales were used to measure the primary variables. We conducted Pearson correlation, hierarchical regression, and mediation analyses to test the relationships between hope, stress, and burnout and to determine whether hope directly impacts stress and burnout.

Results: We found significant correlations between hope, stress, and burnout. Hierarchical regression revealed that hope accounted for significant variance in burnout over and above psychological stress and that stress and hope together accounted for 48% of this variance. We discovered that hope may be partially mediating the relationship between stress and burnout.

Conclusion: Hope may play a significant protective role in the stress-burnout relationship in the context of medical students: higher levels of hope are associated with lower levels of stress and burnout. Our study supports the idea of using hope-based interventions in medical student populations and investing more resources into this area of research.

INTRODUCTION

A major problem facing today's physicians and medical trainees is burnout, a phenomenon described by Christina Maslach, PhD, psychology professor at the University of California, Berkeley, as a combination of exhaustion, depersonalization, and diminished professional efficacy.[1,2] The progression of burnout symptoms in professional settings often leads to dissatisfaction with one's profession and an overall feeling of disillusionment.[2-5] Aside from professional detachment, burnout also has the potential to produce a number of other negative outcomes for those experiencing it, including absenteeism from work and deterioration of social support systems; within medical settings, burnout can contribute to a marked decrease in patients' perception of health care quality and safety.[1,6,7]

Medical provider burnout follows a pattern of increasing symptomatic severity that begins in medical school.[3,8,9] Research has shown that many medical students in their third year of training experience high levels of distress and, in some cases, fail to cope effectively, which can lead to chronic, unresolved negative stress.[10] The cyclical nature of chronic stress can ultimately lead to negative behavioral patterns that promote progression to burnout, which may have physical health implications like elevated stress-related biomarkers.[11,12] Moreover, prolonged stress and burnout are associated with lower academic performance among medical students.[13] A number of different protective factors, such as workplace support and job control, have been identified that are associated with significantly lower rates and levels of chronic stress and burnout.[14] Early exposures to chronic professional stress left unchecked by protective psychological factors may further exacerbate the burnout epidemic.

Certain protective psychological factors have been recognized as being potentially beneficial in the stress-burnout relationship.[2,10,15] One such factor is hope, a measurable trait related to upstream factors like goal attainment and motivation to pursue goals that can affect the manifestation of psychological stress.[15] Originally described by a research team led by Charles "Rick" Snyder, hope theory is a form of positive psychology that defines the interaction of 2 cognitive processes: pathways thinking and agency thinking.[16,17] Pathways thinking refers to the appraisal of available resources and options when pursuing a desired goal, and agency thinking refers to the perceived capability and motivation to achieve the goal.[16,17]

These 2 manners of thinking about a goal are inextricable: deficient levels of agency with sufficient pathways identification, or vice versa, result in overall decreased levels of hope.[17,18] Moreover, people often exhibit a pattern of "grief" related to the inability to achieve a desired goal according to this theory: as pathways to goals become blocked and alternative pathways cannot be identified, people may experience intense frustration referred to as rage followed by despair and apathy.[17] The more significant a goal is, the more likely that barriers may lead to this process.[17,18] Theoretically, people with fewer and larger goals are more susceptible to

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decreased hope levels and possible despair and apathy should major challenges arise that are not easily overcome.[15-18]

Research demonstrates the negative relationship between hope and burnout: high hope correlates with a lower rate of burnout.[19] Hopeful individuals are more likely to experience confidence in their ability to achieve new goals, which, in the context of burnout symptomology, means those individuals are less likely to struggle with chronic stress and downstream burnout symptoms.[20,21] In addition, high levels of hope have been reported as being associated with improved academic performance, notably among law and undergraduate students.[22,23]

The aim of this study was to document the levels of burnout, stress, and hope in a sample of medical students enrolled in an allopathic medicine program and an osteopathic medicine program. We hypothesize that there would be negative correlations between hope and stress and between hope and burnout and that there would be a positive correlation between burnout and stress. This hypothesis is based on the observation that high levels of hope enhance one's ability to cope more effectively with novel and more intense stressors and that burnout arises from chronic stress. We further hypothesize that hope may be mediating the relationship between perceived stress and burnout in medical students.

METHODS

Target Population

We recruited participants from the first- through fourth-year classes of 2 medical schools in a Midwestern state of the United States. One of these schools provides allopathic medical training, and the other provides osteopathic medical training. In total, 1101 students from the 2 medical schools were sent email requests to complete an anonymous Qualtrics survey over a 4-week period. All study recruitment occurred between January and April 2018.

Ethical Approval

This study was initially approved following expedited review by the University of Oklahoma Health Sciences Center Institutional Review Board (IRB) on January 13, 2018 (IRB number 8778; reference number 674302). Modifications to the study that expanded the sample population were approved by the same review board on March 11, 2018 (IRB number 8778; reference number 675576).

Study Measures

The majority of the survey consisted of validated psychometric instruments designed to measure dispositional hope, perceived stress, and burnout. We measured hope using the Adult Dispositional Hope Scale (range = 8-64), which was created and validated by Snyder and fellow researchers.[16,24] We measured burnout using the English version of the Oldenburg Burnout Inventory (range = 16-80). This validated measure was selected because of its utility in measuring burnout in academic and work environments, which is theorized to apply to clinical training environments.[25,26] We assessed stress using the Perceived Stress Scale (range = 10-50).[27]

Demographics

Demographic questions were included to collect information about each respondent's biological sex, age, marital status, employment status, race, and classification by year in medical school.

Statistical Analysis

All data were analyzed using the Statistical Package for Social Sciences (version 24).[28] The 2 schools' individual data sets were maintained and analyzed separately and then were consolidated for aggregate analysis. Descriptive and inferential statistics were generated for each group and then for both groups combined. Before the data were analyzed in aggregate, analysis of variance was performed to ensure that the medical students did not differ significantly in terms of their psychometric scale scores based on year in school, biological sex, or school attended. Pearson correlation and hierarchical regression analyses were performed to describe the relationships among the variables of interest.

RESULTS

Number of Respondents and Response Rates

Of the 1101 students asked to participate in the study, 329 respondents successfully completed the survey (overall response rate = 29.9%). For the allopathic medical school, 236 of 652 eligible participants completed the survey (response rate = 36.2%). For the osteopathic medical school, 93 of 449 eligible participants completed the survey (response rate = 20.7%).

Demographic Characteristics of Study Participants

Table 1 details the demographic characteristics of the study participants, showing each program's numbers and the total participant numbers. The distribution of respondents captured in the study sample was similar to the characteristics of the student population at the 2 medical schools. The overall distribution of the respondents based on biological sex was fairly evenly split between men (48.6%) and women (51.1%). The median age of the respondents was the same for the 2 programs (median = 25 years). When asked about their relationship status, the majority of respondents identified as single (71.1%), with the next most represented group identifying as married (26.1%). In terms

Table 1. Sociodemographic characterisitcs of allopathic and osteopathic medical students[a]

Characteristic	MD students(n = 236)	DO students(n = 93)	All students(N = 329)
Biological sex			
Men	111 (47.0)	49 (52.7)	160 (48.6)
Women	124 (52.5)	44 (47.3)	168 (51.1)
Other	1 (0.4)	0 (0.0)	1 (0.3)
Median age, y	25	25	25
Relationship status			
Married	55 (23.3)	31 (33.3)	86 (26.1)
Common-law	2 (0.8)	1 (1.1)	3 (0.9)
Separated	0 (0.0)	1 (1.1)	1 (0.3)
Divorced	2 (0.8)	2 (2.1)	4 (1.2)
Single	177 (75.0)	57 (61.3)	234 (71.1)
Widowed	0 (0.0)	1 (1.1)	1 (0.3)
Employment status			
Yes	14 (5.9)	11 (11.8)	25 (7.6)
No	222 (94.1)	82 (88.2)	304 (92.4)
Race[b]			
American Indian	17 (7.2)	11 (11.8)	28 (8.5)
Asian	39 (16.5)	5 (5.4)	44 (13.4)
African American	3 (1.3)	3 (3.2)	6 (1.8)
Caucasian	197 (83.5)	82 (88.2)	279 (84.8)
Hispanic	7 (3.0)	5 (5.4)	12 (3.6)
Other	5 (2.1)	2 (2.2)	7 (2.1)
Year in school			
First	52 (22.0)	32 (34.4)	84 (25.5)
Second	100 (42.4)	23 (24.7)	123 (37.4)
Third	48 (20.3)	17 (18.3)	65 (19.8)
Fourth	36 (15.3)	21 (22.6)	57 (17.3)

[a]Data are presented as n (%) unless indicated otherwise.
[b]Percentages for race are based on the number of responses for a particular choice over the total number of responses for the column because respondents were allowed to select more than 1 race if applicable.

of racial characteristics, the majority of respondents identified as being Caucasian (84.8%), followed by Asian (13.4%) and American Indian (8.5%). There were more second-year medical students (37.4 %) represented in this study than any other year in school, followed by first-year students (25.5%). Third- (19.8%) and fourth-year (17.3%) medical students were underrepresented in the sample.

Distributions of Primary Variables of Interest

Analysis of variance testing showed that the scale scores did not differ significantly when comparing students from each program based on their demographic characteristics, psychometric scale scores, and year in school. Cronbach's alpha testing of the validated psychometric scales used in this study showed appropriate levels of internal consistency for both data sets. This outcome prompted the analysis of the 2 data sets in aggregate. The average scale scores for all 329 student responses were as follows: hope (53.0 ± 6.6), perceived stress (26.6 ± 7.3), and burnout (43.3 ± 9.7); these results indicate that on average, the sample experienced high levels of hope, moderate levels of perceived stress, and moderate levels of burnout.[16,25,27]

Table 2. Correlation matrix for hope, perceived stress, and burnout[a]

Variable	Hope	Perceived stress	Burnout
Hope	1		
Perceived stress	–0.571[b]	1	
Burnout	–0.504[b]	0.663[b]	1

[a]Data are presented as Pearson correlation coefficients (N = 329).
[b]$p < 0.001$ (2-tailed).

Relationships Between Stress, Burnout, and Hope

Table 2 presents the Pearson correlation results: the analysis demonstrated a significant positive relationship (r = 0.663;

$p < 0.001$) between stress and burnout, a significant negative relationship ($r = -0.504$; $p < 0.001$) between hope and burnout, and a significant negative relationship ($r = -0.571$; $p < 0.001$) between hope and stress. The data were further investigated using hierarchical regression analysis. Tests for multicollinearity indicated that no significant level of multicollinearity was present. As shown in Table 3, hierarchical regression revealed that stress accounted for about 46% of the variance in burnout ($\triangle R^2 = 0.46$; $F_{(1, 321)} = 267.076$; $p < 0.001$) and that hope accounted for a small yet significant amount of variance in burnout over and above stress ($\triangle R^2 = 0.02$; $F_{(1, 320)} = 15.111$; $p < 0.001$). In addition, the analysis revealed a significant negative relationship between hope and medical student burnout. In the final model, hope and stress accounted for approximately 48% of the variance in medical student burnout.

Table 3. Hierarchical regression analysis of medical student burnout

Hierarchical model and results	B	SE	Beta	p-Value
(Constant)	24.866	4.678		0.000
Perceived stress	0.925	0.057	0.695	0.000
Step 1				
$R^2 = 0.46$				
$F_{(1, 321)} = 267.076$[a]				
(Constant)	42.925	6.523		0.000
Perceived stress	0.770	0.068	0.578	0.000
Hope	–0.286	0.073	–0.194	0.000
Step 2				
$\triangle R2 = 0.02$				
$F_{(1, 320)} = 15.111$[a]				

[a]$p < 0.001$. Final $R^2 = 0.48$.

Mediation Analysis of Stress, Burnout, and Hope

Figure 1 provides the details regarding the relationships among the 3 variables of interest wherein we hypothesized that hope was mediating the relationship between stress and burnout. This model was predicated on the assumption that chronic stress leads to burnout. The simple mediation model showed that the relationship between stress and hope was significantly negative ($B = -0.52$; $t_{(325)} = -12.54$; $p < 0.001$), hope predicting burnout was significant ($B = -0.29$; $t_{(324)} = -3.95$; $p < 0.001$), and the direct relationship between stress and burnout was significant ($B = 0.88$; $t_{(324)} = 15.94$; $p < 0.001$). Furthermore, the model demonstrated that the relationship between stress and burnout with hope removed was significantly decreased ($B = 0.73$; $t_{(324)} = 11.12$; $p < 0.001$). The mediation analysis revealed that hope may be partially mediating the relationship between stress and burnout and that this indirect effect was significant ($B = 0.15$; $Z_{Sobel} = 3.76$; $p < 0.001$). In other words, this model showed that stress reduces hope and that reduced hope leads to increased burnout.

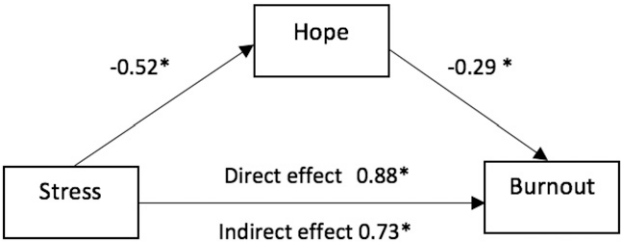

Figure 1. Mediation for hope, perceived stress, and burnout.

DISCUSSION

This study explored the relationships between perceived stress, burnout, and hope among a sample of medical students. Our alternative hypotheses were as follows: 1) there will be negative correlations between hope and stress and between hope and burnout; 2) there will be positive correlations between burnout and stress; and 3) hope may be mediating the relationship between perceived stress and burnout in medical student populations. The findings from the Pearson correlation analysis are of sufficient statistical significance to reject the null hypotheses associated with the first 2 alternative hypotheses. These relationships were explored further using hierarchical regression analysis, which showed that higher levels of hope have a statistically significant association with lower levels of burnout among medical students over and above the influences of stress. The null hypothesis associated with the third alternative hypothesis was rejected on the grounds that mediation analysis showed that hope may be partially mediating the relationship between stress and burnout.

We found that while hope is high among medical trainees, there is room for improvement for many students. Given that increasing hope could lead to better academic performance in addition to improved well-being indicators in medical student populations,[17,22,23] we argue that building foundations of hope should be a focus of modern student wellness programs. One example of how this could be accomplished involves active self-reflection activities in which students can map out how their daily activities feed into larger goals that are connected to the ultimate goal of practicing medicine. The results reinforce the relationships between stress, hope, and burnout and suggest possible relationships hope may have with other positive psychological factors reported in different studies.[29-31] Furthermore, these findings suggest that leveraging hope has the potential to decrease the impact of chronic stress on medical students as well as mitigate the impact of burnout.

These findings are consistent with other studies that revealed higher-than-normal levels of stress and burnout

among medical trainees relative to the general population.[8-10] To our knowledge, no other study to date has attempted to measure dispositional hope in medical students and then explore how hope is related to stress and burnout. What this study contributes to the literature is evidence that hope helps to explain more of what is occurring in medical student burnout, especially when considering students' levels of perceived stress. One possible explanation for this is that, according to hope theory, hope levels decrease when pathways to goals become blocked and alternative pathways cannot be identified.[17] When this occurs, demands begin to exceed the perceived availability of resources to get through to the next step along the goal pursuit sequence, leading to increased psychological stress and, eventually, symptoms of burnout.[32] The main implication of this explanation is that students can better manage their stress if the pathways leading to success as a future physician are perceived as being more available, which could entail showing how one can make contributions to medicine outside of the competencies directly assessed by standardized examinations. These contributions may consist of activities like patient advocacy, critical or creative writing on topics related to health and health care, and interdisciplinary collaboration to address important community health problems.

According to the current literature on hope theory, there are many possible applications of hope, even in academic contexts.[33,34] For example, hope therapy and similar strategies consisting of guided discussions related to the primary constructs in the hope theory framework (ie, pathways, agency, goals, and barriers) have been effective at increasing hope in different populations.[35] In addition, there is evidence from a study involving children who were exposed to domestic violence that offering activities that are productive and promote self-worth might be able to increase dispositional hope in adults.[36] Given that high levels of both agency thinking and pathways thinking are needed for high levels of hope,[16,17] we argue that finding ways to make incremental changes to medical school culture surrounding the value of life outside of school might be beneficial for increasing dispositional hope and decreasing the burden of chronic stress and burnout on trainees. These changes could involve slightly restructuring the preclinical and clinical curricula to build in more time for quality improvement or research projects that are of deep personal interest and formative for physicians in training. Regardless of which approach is used, the relationships demonstrated in this study are promising for future medical education environments if appropriate interventions can be adopted by medical school administrations.

The limitations of the study included the fact that the data are cross-sectional in nature, are all self-report from students, and were collected from a geographically limited sample (ie, all from 1 state). Although the majority of respondents were about 25 years of age and Caucasian, these characteristics were expected based on national demographic data of medical students.[37] People from underrepresented groups generally suffer more social stressors, and this fact may contribute to possible sample bias since most of the respondents were Caucasian.[38] There was a sampling bias in the responses toward first- and second-year students who were completing preclinical coursework (62.9%) compared to those completing their clinical training (37.1%). The competing priorities of students involved in clinical rotations may help to explain this bias. However, no differences were found for the variables of interest among the respondents based on their year in school.

The strengths of this study include the use of validated measures and inclusion of both allopathic and osteopathic medical students. This study's findings help bring attention to the potential utility of hope among health care professionals in training, especially given the United States' struggle to combat burnout in different industries, including health care.[39] Our results show that there may be empirically based hope interventions for medical schools working to combat and prevent burnout that are inexpensive to implement on an institution-wide level.

These data were collected with the intention of better understanding the association between hope and burnout in medical students. A follow-up study focused on different hope- and burnout-related modifying factors would benefit this area of research. For example, research could improve our understanding of how systems-level factors, such as standardized examination cutoffs for certain residency training programs, might be contributing to hope, burnout, and stress because our findings suggest that, if we can address those systems, we may be able to improve hope and students' overall well-being. Moreover, further research on this topic could build on this knowledge by studying specific applications of hope-based interventions in medical student education. An increasing number of studies have explored such interventions in certain populations, such as in patients with cancer and those diagnosed with mental illnesses.[40-44] There appears to be a need to expand the literature in the area of hope-based interventions and medical education.[45]

CONCLUSION

The data collected in this study provide a promising avenue for future research in the areas of hope-based interventions, positive psychology overall, and the relationship between certain protective psychological factors and burnout in medical student populations. We found that hope is significantly associated with stress and burnout and that this protective psychological factor may be partially mediating the stress-burnout relationship. Our findings

suggest that medical school administrations can leverage hope to approach the issue of burnout in medical education in a more focused, less resource-intensive fashion. They also suggest that systems-level factors are likely important targets for intervention. The growing body of research supports hope as an important protective factor in one's ability to cope with stress. Hope also reflects a cognitive process that can be learned and sustained through targeted interventions. Our study supports the use of hope-based interventions in medical student populations. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Authors' Contributions

Ashten R Duncan, MPH, developed the idea for this project, designed the study survey, prepared the IRB protocol and application, administered the survey to the participating medical schools, communicated with prospective participants via email, directly managed the data collection, performed data analyses, drafted the majority of the contents of the manuscript, and submitted the manuscript for consideration in this journal. Chan M Hellman, PhD, provided expert guidance throughout the entire project, offered constructive feedback during the idea development phase, revised and submitted the IRB application, met regularly with the lead author to assess progress, led the data analyses presented in the manuscript, and assisted with revising the manuscript based on feedback from reviewers. All authors have given final approval to the manuscript.

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ORIGINAL RESEARCH ARTICLE

Routine Screening for Sepsis in an Obstetric Population: Evaluation of an Improvement Project

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ABSTRACT

Introduction: Our objectives were to calculate the timeliness of treatment following implementation of routine sepsis screening in an inpatient obstetric population using obstetric-adjusted systemic inflammatory response syndrome (SIRS) criteria, evaluate the performance of obstetric-specific screening criteria in the identification of sepsis, and to better characterize the frequency of end-organ dysfunction associated with those who met the definition of sepsis.

Methods: Electronic medical record data were collected from all pregnant or newly delivered women admitted for observation, admission, or postpartum readmission in the hospital maternity unit from March 1 through December 31, 2017 (n = 5075). Combinations of SIRS criteria were collected and compared with clinical indicators of end-organ dysfunction in those who met the definition of sepsis. Maternal conditions and neonatal outcomes were evaluated.

Results: In the study period, 204 cases of sepsis were identified among 201 women, 2 of whom experienced multiple episodes of sepsis, resulting in an incidence of sepsis of 4.0 per 100 livebirths. There were 92 (45.2%) with sepsis and 112 (54.9%) with end-organ dysfunction. Two women were admitted to the intensive care unit and no women died from sepsis.

Discussion: Use of a standardized, obstetric-specific sepsis screening process provided for early identification and treatment of sepsis in this population. Fourteen unique combinations of SIRS criteria were noted among those with sepsis; no combination was uniquely associated with the severity of sepsis.

Conclusion: Pregnant and newly delivered women benefitted from implementation of routine sepsis screening; this resulted in timely initiation of treatment.

INTRODUCTION

There is growing attention to the morbidity and mortality associated with sepsis, which remains the second leading cause of maternal death in the United States.[1] The rate of severe maternal sepsis morbidity and mortality in the United States rose between 1998 and 2008.[2] The Surviving Sepsis Campaign guidelines resulted in significant decreases in sepsis-related mortality in the adult nonpregnant population.[3] However, these guidelines fail to account for the normal physiologic changes of pregnancy. Although evidence-based standardization of preeclampsia and obstetric hemorrhage care has decreased mortality for women with those conditions,[4] sepsis in the maternity population has not yet received the same national attention.

Routine sepsis screening and treatment in the adult, nonobstetric population was a standardized practice in our facility's emergency department and intensive care units (ICUs) before the initiation of this project. The inpatient obstetric units lacked a standardized screening process because of multiple factors. There is no nationally accepted standard for sepsis screening in the maternity population; therefore, there was no established process to screen patients for sepsis in the maternity units. There was a lack of consensus among the clinical staff about the applicability of standardized sepsis treatment bundles in the obstetric patients. In particular, there were concerns about providing a large intravenous fluid bolus to a woman with preeclampsia and lack of agreement on the utility of lactic acid as a marker of end-organ dysfunction. The lack of a systematic method to identify and treat sepsis in this population was recognized as a potential threat to patient safety by facility interdisciplinary perinatal and sepsis quality improvement.

The third International Consensus definitions for sepsis and septic shock (Sepsis-3) recommend the use of a quick Sequential (Sepsis-related) Organ Failure Assessment score (qSOFA) as a prompt to begin evaluation for end-organ dysfunction.[5] However, it lacks diagnostic utility in the obstetric population, with a 50% sensitivity.[6] Although recent literature has indicated that there are potential modifications of qSOFA for use in the obstetric population,[7,8] those recommendations were published after the initiation of this project.

The Centers for Medicare & Medicaid Services Early Management Bundle, Severe Sepsis/Septic Shock core measure (SEP-1), uses the presence of 2 or more systemic inflammatory response system (SIRS) values as a component of the definition of severe sepsis.[9] SIRS criteria have been used in past screening tools to prompt evaluation for the presence of infection. Clinicians caring for adults at the study site rely on SIRS criteria to screen for sepsis per facility guidelines. In the nonobstetric adult population, there are widely accepted clinical criteria to define SIRS.[10]

A challenge with applying adult SIRS criteria to pregnant women stems from the normal physiologic changes that

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occur in pregnancy. Physiologic changes of pregnancy mimic those seen with sepsis in a nonpregnant population. Maternal heart rate, respiratory rate, and white blood cell (WBC) count are usually elevated during pregnancy.[11] Modifications of the standard adult SIRS screening criteria have recently been proposed to account for the normal changes of pregnancy to identify triggers for sepsis evaluation.[11-15] Fetal tachycardia is an additional marker of systemic response and is variably used as a sign of maternal sepsis.[15-18] Given there is no single presentation of sepsis in the obstetric population,[19] clinical suspicion and a combination of clinical signs must be used for early detection.

In an effort to improve the identification and treatment of sepsis in our inpatient obstetric population, we instituted routine use of a Maternal Sepsis Screening Pathway in February 2017. A second objective was to meet the SEP-1 requirements. The process implemented was designed to meet requirements put forth by this measure. The purpose of this paper is to report on the timeliness of treatment provided as a result of this program, the frequency of obstetric sepsis identified using the Maternal Sepsis Screening Pathway guidelines, and to evaluate the performance of obstetric-specific screening criteria following program implementation. Maternal and neonatal complications and the type and frequency of end-organ dysfunction present in this population will also be described.

METHODS

Guidelines for treatment of sepsis were created in association with the facility's committees related to sepsis and to perinatal patient safety and obstetric and maternal-fetal medicine specialists. Care was provided per the clinical judgment of the individual provider. Patient data were collected and abstracted from the electronic medical record and facility reports. Data were deidentified and stored in a confidential manner.

Approximately 6000 births occur annually at the study site, which is a tertiary care center located in a suburban setting in the western United States. Training of the obstetric physicians, certified nurse midwives, and nursing staff caring for patients in the ante-, intra-, and postpartum units took place before implementation of the Maternal Sepsis Screening Pathway program. Program leaders were visible champions of the initiative and included a maternal-fetal medicine physician, obstetric unit nurse managers, and endorsement by facility sepsis and perinatal patient safety committees.

The Maternal Sepsis Screening Pathway program uses obstetric-adjusted SIRS criteria to prompt evaluation for sepsis in the obstetric inpatient population. The obstetric SIRS criteria used in this study included a higher maternal heart rate, respiratory rate, and WBC count than are used with standard adult sepsis SIRS criteria. Two other California health care systems use obstetric-adjusted values in their maternal sepsis screening criteria.[15,20] Our criteria are consistent with those health care systems and with Barton & Sibai.[13] Fetal tachycardia was included as a marker for fetal response to infection. The remaining standard adult SIRS criteria were used without modification (Table 1).

Routine screening was completed by the obstetric nurse at the time of the patient's presentation to triage, upon admission, and once per shift. Women with an antepartum admission or postpartum readmission were also routinely screened. The presence of altered mental status, or 2 or more SIRS criteria, act as a trigger for the nurse to confer with the obstetric provider (either an obstetrician or certified nurse midwife). Clinical evidence of SIRS prompted further assessment for infection by the obstetric provider.

The SEP-1 guidelines define severe sepsis as the presence of a source of infection, 2 SIRS criteria, and end-organ dysfunction.[9] The working definition of sepsis for the Maternal Sepsis Screening Pathway was modified from the institutional adult sepsis protocol and based on SEP-1 and the 2016 Surviving Sepsis Campaign guidelines.[21] In this pathway, sepsis was defined as a positive SIRS screen and a suspected source of infection.

Initial evaluation included clinical assessment and laboratory assessment (complete blood count, lactic acid, bilirubin, activated partial thromboplastin time [APTT], blood culture, urinalysis, chemistry panel). Cases of sepsis were further categorized as: 1) sepsis, if there was no evidence of end-organ dysfunction; 2) severe sepsis, with evidence of end-organ dysfunction; or 3) septic shock in the presence of a markedly elevated lactic acid level or if hypotension was present and persisted despite volume resuscitation (Table 2). Evaluation and stratification of severity of sepsis and treatment guidelines were determined in collaboration with the facility committee on sepsis, the facility perinatal patient safety committee, and in keeping with the treatment guidelines included in the SEP-1 initiative. In the Maternal Sepsis Screening Pathway, assessment of end-organ dysfunction largely mirrors that used in the adult nonobstetric population (Table 2). Creatinine values were adjusted to reflect the lower values that are present in the obstetric population as a result of the physiologic changes of pregnancy.

Initial management included administration of intravenous fluids and administration of antibiotic or antiviral medication, as indicated by the specific suspected infection. Evidence-based recommendations for patient care were provided, but individual care was left to the discretion of the obstetric provider. Intravenous fluid resuscitation, either 2 L of normal saline or 30 mL/kg of body weight, was indicated for the diagnosis of severe sepsis or septic shock.

Table 1. Systemic Inflammatory Response Syndrome values adjusted for an obstetric population

Variable	Adult, nonobstetric population[a]	Adjusted for obstetric population
Altered mental status	Present	Same value
Temperature		
Low	> 100.4°F (38°C)	Same value
High	< 96.8°F (36°C)	Same value
Heart rate	> 90 bpm	> 110 bpm
Respiratory rate	> 20 breaths per minute	> 24 breaths per minute
White blood cell count (mL)		
Low	< 4000	Same value
High	> 12,000	> 15,000
Bands	> 10% bands	Same value
Fetal heart rate	Not included	> 160 bpm for 10 min

Comparison to adult, nonobstetric population values.
bpm = beats per minute.
[a] Adult, nonobstetric Systemic Inflammatory Response Syndrome values from previous work.[7]

Documentation of the nurse's sepsis screen was contained in a note in the patient's electronic medical record (EMR), During the study period, 2 spot checks were performed to ensure that the sepsis screens were taking place. Checks were completed 1 and 7 months following implementation. All inpatient obstetric patient EMRs were checked for presence of screening documentation. In both sets of checks, every patient had a record of a screen performed, with greater than 80% having a screen documented during each shift the patient was an inpatient.

Audits of patient EMRs were determined to be the best method to evaluate for frequency of the presence of sepsis, which SIRS criteria were present at the time of the diagnosis, and which markers of end-organ dysfunction were present. During implementation, it was noted that there was a preponderance of sepsis cases identified during the active phase of labor, and that the most common source of infection was chorioamnionitis. Stage of labor, the source of infection, and placenta pathology results were evaluated to better describe the patterns of sepsis occurring in our population.

Data reports were run from the facility EMRs to evaluate the medical records of all inpatient women who were pregnant, postpartum, or who experienced a postpartum readmission. Administrative reports identified those who had a lactic acid level drawn and those who had a diagnosis of infection or sepsis during the study period. Three women who had received interventions for sepsis and then transferred to our unit from another facility were excluded. For women with multiple hospitalizations for sepsis, each event was considered independently. Neonatal data were linked to the intrapartum event for all sepsis cases.

Data were abstracted from the EMR (H.C.) during the study period, March 1 through December 31, 2017. The obstetric-adjusted SIRS criteria and a suspected source of infection were identified through record review. Neonates born to women with intrapartum sepsis during labor were identified. Maternal and neonatal data were linked. The EMR of each neonate was reviewed, and data were abstracted. Demographics of women who screened positive were compared against the total delivery population. Additionally, Apgar scores were compared against hospital-wide data from all newborns delivered during the study period.

Manual chart review was performed to determine diagnosis, maternal clinical findings, and neonatal outcomes. Altered mental status was defined as a reported or noted change in her baseline cognitive state or level of consciousness. Maternal temperature; WBC count, including bands; respiratory rate; heart rate; and fetal heart rate (FHR), blood pressure, and mean arterial pressure (MAP)

Table 2. Severity of sepsis criteria with defined end-organ dysfunction categories used in the Maternal Sepsis Screening Pathway

End-organ dysfunction	Sepsis	Severe sepsis	Septic shock
Systolic blood pressure (mmHg)		< 90[a]	< 90[b]
Mean arterial pressure		< 65	< 65 [b]
Urine output		≤ 30 mL/h for 2 h	
APTT		> 60 s	
Creatinine		≥ 1.5 mg/dL	
Bilirubin		> 2 mg/dL	
Lactic acid (mmol/L)	< 2.0	2.0-3.9	> 3.9
Platelet count (10^9/L)		< 100,000	

APTT = activated partial thromboplastin time.
[a] Must be at least 5 mmHg lower than patient's baseline rate.
[b] Following fluid resuscitation.

were evaluated for the presence of SIRS criteria. When the MAP was not noted, it was calculated from the recorded blood pressure closest to the time the 2 SIRS criteria were present. Those who met the SIRS inclusion criteria had their records evaluated for a documented presence of infection. Once the individual met the diagnosis of sepsis (ie, 2 SIRS criteria and a suspected source of infection were present), data were abstracted for that individual.

Vital sign data were those obtained within 30 minutes of the time when a positive SIRS screen was identified. The WBC count value used as a SIRS criterion was antecedent to the diagnosis of sepsis and not the one drawn in response to a positive sepsis screen. The laboratory values for end-organ dysfunction were those recorded at the time of SIRS criteria being met, or within 1 hour before that time.

Laboratory testing was deferred until after birth for those who screened positive in the second stage of labor. Sepsis was determined to occur in the postpartum period if orders for laboratory tests and antibiotics were placed at least 2 hours following delivery. Facility guidelines recommend obtaining placental pathology for a variety of clinical indications, including all cases of sepsis that occur before or immediately following birth. Histologic evidence of chorioamnionitis included placentas with a diagnosis of funisitis and fetal surface vasculitis. Placental culture was not routinely requested, but performed at clinician's request.

Descriptive statistics were used for demographic and clinical characteristics data. Chi-squared testing was used to measure association with categorical variables. Odds ratios and 95% confidence intervals (95% CIs) were calculated for dichotomous variables.

RESULTS

During the 10-month study period, 5075 women gave birth at the site. In total, 204 cases of sepsis were identified in 201 women (2 women had multiple incidents of sepsis). The observed incidence rate of obstetric sepsis was calculated at 4.0 per 100 births. All inpatient obstetric patients who were antepartum, intrapartum, postpartum, or experienced a postpartum readmission for sepsis were included in the calculation of the incidence of sepsis because all would have received routine screening.

Antibiotics were administered to those with a diagnosed bacterial source of infection (n = 202, 99%). Of those, 145 women (72%) received antibiotics within 1 hour of a sepsis diagnosis and 186 (92%), within 3 hours. Adequate fluid resuscitation was provided to 69% of the women with severe sepsis or septic shock. An additional 12 women (6%) received a 1-L intravenous fluid bolus.

No maternal deaths from sepsis occurred during the study period. Neither admission to the ICU (n = 2, 1.0%) nor development of pulmonary edema (n = 3, 1.5%) was common among women with sepsis. No pulmonary edema resulted from administration of fluid resuscitation ordered for treatment of severe sepsis or septic shock.

Most women (n = 146, 71.6%) developed sepsis during the intrapartum phase of pregnancy; of the others, 35 (10.2%) during postpartum, 13 (6.4%) as antepartum admissions, and 10 (4.9%) during a postpartum readmission. Twenty women (10.2%) developed SIRS-positive criteria immediately before delivery, or up to 3 hours postdelivery. Of all women with sepsis, most (n = 181, 88.7%), developed SIRS-positive criteria during the hospitalization, the rest were septic at the time of admission to the triage observation area (n = 23, 11.3).

Out of the 204 cases of sepsis, 92 (45.1%) met sepsis criteria, 87 (42.6%) met severe sepsis criteria, and 25 (12.3%) met septic shock criteria. In most cases (n = 189, 92.6%), the lactic acid result defined the severity of sepsis. Of the 15 women who met severe sepsis or septic shock criteria for a reason other than an elevated lactic acid level, 7 (46.7%) had decreased urine output, 4 (26.7%) had a creatinine level >1.5 mg/dL, 3 (20%) had a systolic blood pressure of 90 mmHg or less, and 1 (6.7%) had a MAP < 65 mmHg. Three women (20%) with a mean arterial pressure < 65 mmHg also met the initial low blood pressure criteria with systolic blood pressures < 90 mmHg (Table 3).

Not all of the laboratory tests listed on the Maternal Sepsis Screening Pathway were ordered; notably, APTT was ordered in 56 (27.4%) of cases and bilirubin in 93 (45.6%) of cases. No women met the severity criteria for elevated bilirubin level, platelet count less than 100,000 10^9/L, elevated APTT, nor systolic blood pressure decrease of less than 40 mmHg from her baseline blood pressure. No woman met septic shock criteria by having persistent hypotension following fluid resuscitation.

Women with sepsis were more likely to have a history of prior cesarean delivery (p = .01), or be primigravid (p = .01). Those with sepsis were more likely to have anemia when compared with women with severe sepsis or septic shock (p = .01) (Table 4). There were no statistical differences of other maternal characteristics for women when stratified by the severity of sepsis. Obstetric provider documentation supplied information as to the suspected source of infection. Chorioamnionitis was the most frequently diagnosed infection (n = 128, 62.7%). Of those cases of chorioamnionitis, 24 (15.8%) were not confirmed on placental pathology. Endomyometritis was the second most frequent diagnosis (n = 21, 10.3%), followed by urinary tract infection or pyelonephritis (n = 12, 5.9%). Six (2.9%) individuals had 2 diagnoses: 2 with pyelonephritis and pneumonia (1%), 3 (1.5%) with chorioamnionitis and a urinary tract infection, and 1 (0.5%) with a pelvic abscess and endomyometritis. Two women (1%) had upper

Table 3. Clinical values present which determined the severity of sepsis in women with a diagnosis of sepsis (N = 204)

Values present	n (%)	Sepsis severity
Lactic acid < 2.0 mmol/L	92 (45.1)	Sepsis
and serum creatinine ≥ 1.5 mg/dL	2 (1.0)	Severe sepsis
and urine output ≤ 30 mL/h for 2 h	4 (2.0)	Severe sepsis
and MAP < 60 mmHg	1 (0.5)	Severe sepsis
Lactic acid 2.0-3.9 mmol/L	75 (36.8)	Severe sepsis
and serum creatinine ≥ 1.5 mg/dL	2 (1.0)	Severe sepsis
and urine output ≤ 30 mL/h for 2 h	2 (1.0)	Severe sepsis
and systolic blood pressure < 90 mmHg and MAP < 65 mmHg	1 (0.5)	Severe sepsis
Lactic acid > 3.9 mmol/L	22 (10.8)	Septic shock
and urine output ≤ 30 mL/h for 2 h	1 (0.5)	Septic shock
and systolic blood pressure < 90 mm and MAP < 65 mmHg	2 (1.0)	Septic shock

MAP = mean arterial pressure.

respiratory infections. Three (1.5%) had no documented source of infection and received antibiotics and fluids per the pathway guidelines. The remaining infections were 1 each of the following: abdominal source, fever of unknown origin, influenza, mastitis, pneumonia, vulvar cellulitis, and a viral gastrointestinal disorder.

Of the women in labor, 36 (17.6%), developed positive SIRS criteria when they were dilated between 0 and < 6 cm, 58 (28.4%), between 6 cm and < 10 cm, and 52 (25.5%) at complete dilatation. The length of time for rupture of membranes for those in labor (n = 146) ranged from women with intact membranes (n = 13) to 1 who had membranes ruptured greater than 9 days. The remaining 132 women had lengths of time of ruptured membranes ranging from 1 minute to 79 hours, with a mean of 14.5 hours, 95% CI (12.5-16.5), median of 12.1 hours, and standard deviation (SD) = 11.8 hours. There was no association noted between lactic acid levels and the length of time of ruptured membranes. There were 14 unique combinations of SIRS criteria associated with the women with the diagnosis of sepsis (Table 5). None had altered mental status at the time of the SIRS positive screen. No women had a temperature < 36°C, or a WBC count < 4000 × 10^9 /L, or > 10% bands concurrent with another SIRS criterion. Most women (n = 147, 72%) met the definition of sepsis with 2 positive screening criteria; however, 48 women (23.5%) had 3 positive criteria and 9 (4.4%) had 4 positive criteria at diagnosis. The most frequent combinations of SIRS criteria were maternal fever in combination with elevated maternal heart rate (n = 124, 60.8%), fetal tachycardia (n = 74, 36.3%), or elevated maternal WBC count (n = 45, 22.1%). There was no statistical difference noted among the 14 SIRS combinations and the severity of sepsis, regardless of the number of positive screening criteria. Fifty-one women who were pregnant (32.3%) were identified as SIRS-positive with FHR tachycardia, in association with 1 other SIRS criterion. Of these, 24 (15.2%) had a significantly elevated lactic acid level.

There were occasions in which the obstetric provider ordered lactic acid values when the patient had fewer than 2 SIRS criteria present at the time of sepsis screening. Data review revealed that women who did not initially meet SIRS criteria, but who had lactic acid levels ≥ 2.0 mmol/L, developed 2 SIRS criteria within 3 hours of the initial lactate collection, with 1 exception. One woman (0.5%) with an initial temperature of 39.3°C, with a diagnosis of endomyometritis, and positive blood cultures for *Pseudomonas putida*, never developed a second SIRS criterion.

Blood cultures were collected on 153 (75%) of the women identified with sepsis. Five of the blood cultures collected had positive results. There were 69 urine cultures collected. Of those 69, 18 (26.1%), were positive. Four women (2.0%) diagnosed with pyelonephritis or urinary tract infections had negative urine cultures. Six women (2.9%) with positive urine cultures had nonurinary tract sources of infection listed: 5 with chorioamnionitis or endomyometritis (4.9%) and 1 without a listed source of infection (0.5%).

Placental examination by a pathologist occurred in 144 (79.6%) cases of those diagnosed with sepsis during labor or postpartum (n = 181). Of the 144 placentas sent for examination, 109 had histological evidence of chorioamnionitis, and 2 were positive for bacterial growth. Positive placental findings were associated with a diagnosis of chorioamnionitis (n = 102, 93.6%), endomyometritis (n = 4, 3.7%), and pyelonephritis or urinary tract infection (n = 2, 1.8%).

In the women with all forms of sepsis, 161 (79.0%) women had creatinine values recorded at the time of the diagnosis of sepsis. Of these, 52 (32.3%) had a creatinine ≥ 0.8 mg/dL. There was statistical significance noted in the

Table 4. Demographic, obstetric factors, and co-morbidities in women with sepsis diagnosis compared to those who met severe sepsis or septic shock criteria (N =204)

Demographic, delivery, and risk factors	Sepsis n (%)	Severe sepsis or septic shock n (%)	p
Age (y)			0.08
< 20	7 (3.4)	1 (0.5)	
20-30	48 (23.5)	57 (27.9)	
30-39	34 (16.7)	51 (25.0)	
≥ 40	3 (1.5)	3 (1.5)	
Race			0.22
Asian/Pacific Islander	16 (7.8)	33 (16.2)	
Black/African American	10 (4.9)	8 (3.9)	
Hispanic	16 (7.8)	23 (11.3)	
White	48 (23.5)	45 (22.1)	
Other/decline to state	2 (1.0)	3 (1.5)	
Parity			0.01
0	56 (27.5)	87 (42.6)	
≥ 1	36 (17.6)	25 (12.3)	
Cesarean delivery history			
Yes	12 (5.9)	4 (2.0)	0.02[a]
No	80 (39.2)	108 (52.9)	
Fetal death			0.59 [a]
Yes	2 (1.0)	1 (0.5)	
No	90 (44.1)	111 (54.4)	
Gestational age (n = 181)			0.18
< 37 weeks	12 (6.6)	10 (5.5)	
≥ 37 weeks	63 (34.8)	96 (53.0)	
Twin gestation			0.84
Yes	2 (1.0)	2 (1.0)	
No	90 (44.1)	110 (53.9)	
Delivery type (n = 190)			0.24
Vaginal	50 (26.3)	58 (30.5)	
Cesarean section	31 (16.3)	37 (.19.5)	
VAVD	3 (1.6)	7 (3.7)	
Forceps	0 (0)	4 (2.1)	
Anemia[b]			0.01
Yes	26 (12.7)	16 (7.8)	
No	66 (32.4)	96 (47.1)	
Asthma			0.53
Yes	6 (2.9)	10 (4.9)	
No	86 (42.2)	102 (50.0)	
Body mass index (n = 203)			0.78
Normal (18.5-24.9)	8 (3.9)	6 (3.0)	
Overweight (25.0-29.9)	29 (14.3)	33 (16.3)	
Class 1 (30.0-34.9)	29 (14.3)	44 (21.7)	
Class 2 (35.0-39.9)	16 (7.9)	19 (9.4)	
Class 3 (≥ 40.0)	9 (4.4)	10 (4.9)	
Diabetes			0.45
Yes	7 (3.4)	12 (5.9)	
No	85 (41.7)	100 (49.0)	

(continued on following page)

Table 4. Demographic, obstetric factors, and co-morbidities in women with sepsis diagnosis compared to those who met severe sepsis or septic shock criteria (N =204) (continued)

Demographic, delivery, and risk factors	Sepsis n (%)	Severe sepsis or septic shock n (%)	p
Hypertension			0.25
Yes	27 (13.2)	25 (12.3)	
No	65 (31.9)	87 (42.6)	
Preeclampsia			0.78
Yes	8 (3.9)	11 (5.4)	
No	84 (41.2)	101 (49.5)	
Group B streptococcus culture (n = 184)[c]			0.28
Positive	14 (7.6)	13 (7.1)	
Negative	64 (34.8)	93 (50.5)	

χ^2 value for cells with values > 5.
VAVD = vacuum-assisted vaginal delivery.
[a] Fisher's exact test.
[b] Hemoglobin < 11 g/dL or less at time of admission.
[c] n = status documented at time SIRS positive.

women with elevated creatinine who developed severe sepsis or septic shock when compared with those without elevated creatinine levels (p < .05). There was a positive correlation between lactic acid and creatinine levels recorded in the women at the time laboratory tests were drawn following a sepsis diagnosis (p < .05).

The mean lactic acid level for all women was 2.4 ± 1.3 mmol/L. Mean (M) lactic acid values were calculated for antepartum patients (n = 12, M = 2.0, SD = 0.8*)*, postpartum (n = 15, M = 2.0, SD = 1.0), and those with postpartum readmissions (n = 10, M = 1.2, SD = 0.5). A positive correlation was noted for lactic acid levels and cervical dilatation recorded at the time of the diagnosis of sepsis (p < .05).

Lactic acid values were also calculated based on stages of labor, defined as early, less than 6 cm of cervical dilation (n = 35, M = 1.9, SD = 0.9), 6 to 10 cm of dilation (n = 61, M = 2.4, SD = 1.2), and complete dilation (n = 50, M = 3.0, SD = 1.4). Several notes in the clinical record indicated a patient met SIRS criteria while pushing, but there was a decision to delay blood collection until the immediate postdelivery period. A time period for the first 3 hours postdelivery was created in acknowledgment that the time of sepsis was often associated with the time of delivery. The mean lactic acid values for this period resembles that of complete dilation (n = 20, M = 3.1, SD = 1.5).

There were 145 infants born to women who developed intrapartum sepsis. Most (n = 140, 96.6%) had a gestational age greater than 35 weeks. At the study site, infants with a gestational age less than 35 weeks are admitted to the neonatal intensive care unit (NICU). Data related to NICU admission for was available for 141 (97.2%) infants; of these, 27 (19.1%) required a NICU admission for a reason other than gestational age (13.7%, p = .43). One infant, born to a mother who developed septic shock, required whole body cooling.

Table 5. Combinations of obstetric-adjusted SIRS present at time of diagnosis of sepsis (N =204)

Obstetric-adjusted SIRS Present	Frequency n (%)
T + MHR	70 (34.3)
T + FHR	41 (20.1)
T/MHR/FHR	22 (5.5)
T + WBC	18 (8.8)
T/MHR/WBC	17 (8.3)
MHR/FHR	9 (4.4)
T/MHR/WBC/FHR	8 (3.9)
MHR + WBC	6 (2.9)
T/MHR/RR	5 (2.4)
MHR/WBC/FHR	3 (1.5)
T/WBC/FHR	2 (1.0)
RR + FHR	1 (0.5)
T/MHR/RR/FHR	1 (0.5)
WBC + FHR	1 (0.5)

FHR = fetal heart rate tachycardia > 160 bpm for > 10 minutes; MHR = maternal heart rate > 110 bpm; RR = maternal respiratory rate > 24 bpm; T = maternal temperature ≥ 38.0°C; WBC = maternal white blood cell count > 15,000 × 10^9 L.

Neonatal Apgar scores at 1 and 5 minutes of age were compared against the distribution of Apgar scores of all deliveries during the study period. An Apgar score ≤ 6 at 1 and 5 minutes was more likely with intrapartum sepsis, odds ratio 12.1 (95% CI = 7.9-18.6) for the 1-minute Apgar, and 3.1 (95% CI = 1.4-6.8) for the 5-minute Apgar score. Infant Apgar scores ≤ 6 at 1 minute were associated with the presence of funisitis or vasculitis in the placenta when compared to solely the presence of chorioamnionitis $\chi 2$ (1, N = 96) = 4.68, p < .05. No statistical significance was

noted between the unique SIRS combinations and the presence of vasculitis or funisitis in the placenta.

DISCUSSION

There was no established standard of care for identification of possible sepsis in this population at the study site before the implementation of this routine standard screening process. Thus, we could not compare results with any previous process. However, per the SEP-1 criteria, there are established time frames for the administration of antibiotics and a fluid bolus when sepsis is identified. We found that use of routine screening for sepsis using obstetric-adjusted SIRS criteria resulted in timely assessment for end-organ dysfunction and administration of antibiotics. Fluid bolus administration of at least 1 L of fluid was provided to 75% of the women, whereas in the past there was no standard for treatment with an intravenous fluid bolus in this population. We observed few cases of severe morbidity and no maternal deaths related to sepsis.

Strengths of this study include the delivery volume at the study site, the standardized approach used to assess for the presence of sepsis, and the information related to neonates born to women who developed sepsis during labor. Individual chart review ensured the accuracy of diagnoses and an assessment of the completeness of data. Upon review of the administrative data set, only 1 case of severe sepsis was not identified by the presence of SIRS criteria. Although our study did not allow us to directly assess the sensitivity and specificity of our screening criteria, in this population these criteria performed well as a screening tool for sepsis in gravidae.

In our study, there was insufficient information to identify any specific pattern of obstetric-adjusted SIRS criteria that predicted ICU admission. This was in contrast to a prospective study using the Sepsis in Obstetrics Score, which reliably demonstrated a scoring system that identified women at high risk for ICU admission.[22,23] The Sepsis in Obstetrics Score included vital signs (temperature, systolic blood pressure, heart rate, respiratory rate, blood oxygen saturation), and lactic acid, WBC, and immature neutrophils.[22]

The 2017 Society of Obstetric Medicine Australia and New Zealand guidelines outline use of an obstetrically modified quick Sequential Organ Failure Assessment score called omqSOFA.[8] The omqSOFA uses the concept of a quick assessment, similar to the qSOFA established in Sepsis-3.[5] There are 3 parameters in the omqSOFA assessment that earn a score of 1; respiratory rate > 25 breaths per minute, systolic blood pressure < 90 mmHg, and altered mentation.[8] A score meeting 2 or more may then require an assessment for sepsis.[8] This guideline was not published before the beginning of our initiative and was not considered for adoption at our site. However, when the score was calculated as part of data analysis, no women in our population achieved an omqSOFA score of 2 or more.

The observed incidence of sepsis in this study, 4%, is consistent with the reported incidence of chorioamnionitis of between 3% and 5%.[24] Chorioamnionitis was the predominant source of infection in the study population (62.7%). Before the start of this initiative, the clinical suspicion of chorioamnionitis would trigger the bedside nurse to notify the obstetric provider of the abnormal findings, which subsequently led to a very similar treatment workflow. Although our criteria may not be specific for sepsis-related morbidity, it performs well as an initial screen as a good screening tool may sacrifice specificity to achieve a high sensitivity.

Chorioamnionitis may first present with fetal response, identified by fetal tachycardia. As such, we included fetal tachycardia as a screening criterion, consistent with that used by Shields et al.[15] and the National Sepsis Programme.[18] The use of fetal tachycardia as an obstetric-adjusted SIRS criterion resulted in the identification of women who would not otherwise have been assessed for end-organ dysfunction, as roughly 1/3 were found to have significantly elevated lactate levels. Elevation of lactic acid is associated with maternal morbidity. The exclusion of fetal tachycardia in our screening criteria would have resulted in a missed opportunity for early recognition and timely treatment for these women. Although other authors have not incorporated fetal tachycardia in their screening criteria, we feel that it is an important predictor of morbidity and warrants consideration.

The use of lactic acid as a marker of severity of sepsis has not been well-studied in the obstetric population. Although research is limited, the progress of labor may affect lactic acid level in the absence of concerns of sepsis or infection.[25,26] We observed a correlation, with higher values in active labor and the second stage of labor. These findings may reflect a tendency for lactic acid levels to be higher during active labor, consistent with Bauer et al.[25] At the study site, most obstetric patients with lactic acid values > 3.9 are managed in labor and delivery and not transferred to the ICU. This limits the ability to compare ICU admissions as a marker of severity of illness. Further research on the relationship between labor and lactic acid is needed to better improve the recognition and management of sepsis in the obstetric population. [25]

Our data demonstrated a correlation between elevated lactate levels and the likelihood of depressed Apgar scores. The Neonatal Resuscitation Program guidelines[27] recommend that there be 2 Neonatal Resuscitation Program-trained individuals assigned to care for the neonate at the time of delivery when the mother has chorioamnionitis. Our findings suggest the presence of a full complement of pediatric providers at the delivery of a woman who, while in labor, develops sepsis from any source.

The results of this study may not be generalizable to other centers as the sample was limited to 1 site, where most women experience care as part of an integrated health system. Not all who met the criteria for sepsis may have been identified because of limitations of the methods selected. However, administrative data failed to show missed cases. Urine output data were missing in 104 of 181 (57.4%) of the records. These missing data may have resulted in the lack of identification of cases of severe sepsis through data review.

Challenges related to maintenance of routine screening at the study site include the lack of a sepsis-specific documentation flowsheet in the EMR. This type of flowsheet would act as a prompt for the nurse to document the sepsis screen results. Although all newly hired clinicians are instructed in the use of the Maternal Sepsis Screening Pathway, there is not a routine process in place to ensure that new and experienced staff are continuing to routinely screen for sepsis and treat patients per the maternal sepsis pathway. Factors that contribute to the development of chorioamnionitis, such as frequent vaginal examinations, were not specifically addressed in the design of this study. Future quality improvement work related to sepsis in this population would benefit from the establishment of safety guidelines limiting practices which may contribute to the development of chorioamnionitis.

We suspect that inclusion of fetal tachycardia, at least as we have defined it, to be overly sensitive. Although we feel we missed no cases of sepsis, many women with chorioamnionitis underwent a complete sepsis workup that may be unwarranted. Further research is needed to better understand how the fetal response to maternal infection relates to significant morbidity.

Difficulties in implementation of routine screening for sepsis in the obstetric population include creating a shared mental model about which clinical symptoms require a timely assessment for sepsis, which laboratory tests provide relevant information, the relation of lactic acid results to severity of sepsis, and the need for intravenous fluid administration. Some of these challenges were evident in this study as inconsistent ordering of certain laboratory tests, fluid boluses, and documentation of urine output by nurses. Sharing this information with the clinical teams, and monitoring for improvement in these areas, are some steps that could improve future performance of this initiative.

CONCLUSION

Adult sepsis screening tools were not designed to adequately assess for sepsis in the maternal population. The normal physiologic changes of pregnancy necessitate the adoption of SIRS criteria that are specific to the obstetric population. The criteria proposed here accurately identified all but 1 case of sepsis and were easily implemented. Our findings support the practice of routine, ongoing screening with obstetric-adjusted SIRS criteria, including FHR tachycardia. Standardized, ongoing assessment for sepsis, paired with timely administration of antibiotics and fluid resuscitation, may reduce maternal morbidity by prompting early identification and treatment. Routine measurement and documentation of urine output is critically important to aid in the assessment for sepsis. Using the criteria we have proposed, we have better defined sepsis characteristics in the obstetric population. However, a better understanding of the role of lactic acid levels and fetal tachycardia in the intrapartum population are still needed to better understand obstetric sepsis. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Authors' Contributions

Holly Champagne, DNP, RN, participated in project design, data abstraction and analysis, and drafting and submission of the final manuscript. Matthew Garabedian, MD, participated in study design, data analysis, and drafting of the final manuscript.

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ORIGINAL RESEARCH ARTICLE

A Reconceptualization of the Negative Self-Stereotyping of the Patient-Partner to the Introduction of the Patient Perspective Consultant

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ABSTRACT

The label of "patient-partner" is widely used when referring to a person living with a specific health condition that participates in research teams or consults on clinical practice guidelines. However, being a patient-partner says nothing about one's potential role outside a biomedical context. Labeling a person as such can be detrimental to their perception of themselves. The intention of this paper is to provide a philosophical conceptual framework to understand the complexities and consequences of labeling people as patients outside of direct healthcare. A philosophical hermeneutic approach was used to explore how labeling and self-stereotyping can affect the patient-partner, leading to the possible erosion of their personhood. The authors suggest that research teams instead employ the more accurate and dignified term, "patient perspective consultant." Accurate titles allow team members to relate to each other, leaving room for everyone to contribute meaningfully. The shift from patient-partner to patient perspective consultant does not change the nature of the role. It clarifies the context through increased accuracy, and adds dignity and purpose.

INTRODUCTION

Integrated within a graduate course on the philosophy of health for Master's and PhD students, we explore a variety of related topics through our own experiences, interpretations and perspectives. Among course activities of learning how to interview, process data, and interpret and analyze data, we write a paper of common interest. This educational experience provides students with opportunities to explore their own and other people's health situations using personal experiences, conversations, and transformative learning approaches.

The purpose of writing this manuscript is to provide a philosophical conceptual framework for a topic of common interest and perspectives reflective of current research topics: the meaning of being a patient outside of healthcare[1]. Currently, the title "patient-partner" is widely used when referring to a person living with a specific health condition, such as chronic pain, who participates in research or consults on clinical practice guidelines and practices. Rarely do researchers and clinicians read outside of their discipline despite a growing amount of qualitative patient perspective research, which would allow them to learn from the other such as the patient-partner. Consequently, taking up a topic about the possible negative effects of the self-stereotyping patient-partner with the potential for the erosion of personhood requires input from disciplines other than medicine, such as philosophy, psychology, disability studies and education.

BACKGROUND

We as human beings are always observing, reflecting and interpreting the world around us and always from the perspective of our unique ever-evolving experiences that form our lifeworld. As a person who is living with chronic low back pain from bicycling accident, a recent diagnosis of psoriatic arthritis, and even more recent diagnosis of advanced metastatic prostate cancer, I am frequently a patient. As the teacher of this course, my medical conditions are revealed openly for discussion that include both as an academic researcher as well as from a patient perspective. Through these diverse experiences and evolving perspective, my medical conditions provide a unique viewpoint that can be of value to researchers and clinicians. One viewpoint is to realize that being a patient-partner says nothing about my potential role in this non-medical context. It is limiting in so much as it leaves everyone at a loss of how to interact with each other. Researchers and clinicians have a much better sense of how to work together because of their related backgrounds, language, and understandings of the topic of interest. How do we even begin to describe the participation of the patient-partner other than knowing from their label that they are patients (that, outside of direct healthcare, they are not), and they are partners? This ambiguity may promote further negative self-stereotyping

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for the patient-partner as the divide between "them and us" remains perpetuated.[1]

The Role of the Consultant

If we think about the role of the patient-partner and the potential they can bring to research, we discover that their experiences, reflections, and perspectives can make valuable contributions to research and clinical practice because of the conditions in which they are continuing to learning to live with adversity and ambiguity. Over time, people living with chronic health conditions accumulate knowledge, experience, and skills to self-manage their specific condition, hence, they have accumulated a knowledge base to an extent even more than a medical student can be taught didactically or perhaps even imagined. This is the work of qualitative research: to provide insight into human conditions not yet experienced by others.

These appear as real-life examples or cases to learn from people who have first-hand experiences. There is certainly a positive trend to increase involvement of people with chronic health conditions in the health education sector as stated by the following: "The active involvement of patients in health professional education is increasing partly due to the recognition that patients have unique expertise derived from their experience of illness, disability or the effects of the social determinants of health."[2]. The word "consultant" seems a better fit as it describes in general terms how they can meaningfully participate with others. As a "patient perspective consultant," the person living with their health condition, the researchers and the clinicians now have a common ground of understanding to how to work together. In this light, the word "patient" now has context as it refers to a perspective based on their experiences while in healthcare and explains that their role in this context is that of a consultant.[3] This makes way for the development of positive self-stereotyping, because being a consultant is positive and can be supported by others on the research team. When we adopt the label of patient-partner into our sense of self, we may be negatively influencing the totality of our personhood.

Personhood in Context

Our personhood represents who we have come to believe we are based on all of our experiences, relationships and projections past and future. Personhood is understood to mean the totality of how someone perceives themselves, through their lived experiences and within the lifeworld they have created throughout their lives. Metaphorically, we can see this as the interweaving of fabrics of our lives based on experiences, family, culture, society, education, health as a multi-dimensional influencer, as well as the numinous relational encounters we have with other people within a diversity of life contexts. Our identity is, therefore, not a singular aspect representing self but a complex one that ebbs and flows as we find our place in the world. We can be a mother, a father, a sister or brother, a student, a teacher, a doctor, and a researcher as well a multitude of other combinations. Who are we, one could ask; our answer is complex because it is contextual? At times, we are students, professors, researchers, athletes, educators, or artists, but most of all caring, empathetic and compassionate human beings, however, unfinished works in progress. As explored by White[4]: "In existential thought, characteristics of human personhood are innate and are to be discovered" (p. 83).

Exploring one's personhood means to look inward into one's self, reflectively and interpretatively. Students explore their sense of personhood at first by situating themselves in many different ways. Marie (a MSc. student) writes of her exploration into this activity. "The contextual nature of our identity means that seemingly contradictory aspects shine through in different situations. I might feel old in a room filled with undergraduates, but quite young at a retirement information meeting. I might feel very French in a room filled with Québécois, and very Québécoise in a room filled with French nationals. Yet, this does not make me partially French and partially Québécoise; my whole being is both French and Québécoise. This modularity, where bits and pieces are added and removed depending on our environment is a testament to the complexity of human identity. This may at first seem to be unrelated to our topic at hand, however, this is necessary to help ground oneself within their own life context, their personhood."

Kristina (a MSc. Student) responds with a reflection provoked by a paper she read. "We are all people figuring out the meaning of our own personhood through experiences, self-discovery, and self-reflection. We have the right to define our own personhood thus mislabeling one's personhood is simply inacceptable. Is the concept of personhood even articulated in the healthcare system? An article by Speraw,[5] entitled "Talk to Me—I'm Human": The Story of a Girl, Her Personhood, and the Failures of Health Care," points out the moral failure occurring from health providers that focus solely on one's disease rather than one's personhood."

Veeresh's (a PhD student) reflections of being a patient are profoundly relevant, because he has lived his whole life requiring scheduled monthly visits for blood transfusions in healthcare. "Ever since the earliest years, I have grown up as "patient." In India, I got diagnosed at the age of 6 months old with a genetic blood disorder known as "beta thalassemia major." This condition requires regular blood transfusions to survive as well as it entails a poor prognosis.

My parents were bluntly told that I would not survive beyond my first birthday. After visiting an expert hematologist in the city of Bombay, I became a baby trapped in the healthcare system; I received a better prognosis of living to 7–8 years of age. Fortunately, today in the high-income countries, the lifespan is nearly "normal." On this ongoing journey of parents' concerns, doctor visits, and treatment centers, one's personhood goes out the window, and labels such as "sick baby," "sick child," and "patient" begin to creep in. Hence, the "gnawing" at the personhood gets a head start from early childhood. Persons with genetic health conditions start seeing themselves and believing that he/she is a patient first and a person second. My question to all is, "Who is responsible for this?" Seeing one's self as a person and making people see you as a person has tremendous positive impact on ones' personality to achieve and realize dreams like anybody else in society. For that to happen is a process. If I need to respond to the question about how I took control of my personhood, I would say moving to Canada from India was the best thing for me, because first, the management of my treatment was regularized and that gave me hope to pursue my dreams of attaining a good education by attending college and university. After completion of my undergraduate degree, I was thrilled to work full-time for nearly 15 years, after which, I decided to return to school for my graduate degree and continued to pursue my PhD at McGill. These accomplishments give a person who faces health challenges a degree of normalcy with respect to the contribution one makes to the society, which in turn gives confidence and sense of purpose to life. Thus, helping to gain ones' personhood defines us as well as completes us to face the world head-on."

Ongoing Personhood

In life, we experience many encounters; some events are mundane while others can be extraordinary. We then reflect and interpret on how our lived experiences (sometimes with help) become interwoven into the fabric of our life and how they fit, or not, in our historical effective consciousness.[6] This process of experience and reflection adds to our unique perspective on our life and identity. As such, we are the product of all our collective experiences, from childhood through to adolescence, to young adulthood, in middle age and older age. All these interactions within our life-worlds constitute our historical effective consciousness.[6] These are the foundations of our personal narratives and stories, uniquely different than others but always adding to the greater narratives shared by many. Hence, the purpose of qualitative research is to offer insight into experiences that others may have not yet personally or professionally encountered. This hermeneutic approach to research and education offers the opportunity to explore meaning and context through conversation with metaphors as a useful way to make sense of complex ideas.[7]

"To be historically means that knowledge of oneself can never be complete. All self-knowledge arises from what is historically pregiven, our personal substance, because it underlies all subjective intentions and actions, and hence both subscribes and limits every possibility for understanding any tradition whatsoever in historical alterity" (p. 302).[6]

Understanding with the Use of Metaphors

The following from Marie demonstrated how she interpretively used a familiar metaphor to help explore new lived experiences. In this context, the metaphor of fabric and weaving is incredibly accurate for her understanding. Marie writes, "Natural fibers come from an animal, be it a sheep, alpaca of silkworm and have different properties depending on the breed, nutrition and environment of the animal. This fiber is entirely unique and cannot be exactly replicated. The fiber is then carded and spun into yarn and woven into fabric. The fabric that comes from that fiber is therefore also unique not only due to the fibers used, but the person doing the weaving." Our experiences and identities are just as unique as hand-woven fabric from natural fiber. By ascribing generic traits to ourselves, we move away from our unique identity and toward self-stereotyping.

Historical Effective Consciousness

Every experience we have then becomes woven into our historical effective consciousness,[6] meaning that our identities are vulnerable to the influence of others who may even unknowingly be eroding our personhood. For example, to diminish a person's historical effective consciousness with being the label of patient-partner although they are members of a research team, along with academic researchers and clinicians may erode their personal attributes and accomplishments. Being an academic or clinical researcher or healthcare provider carries substantially more status than being a patient, partner, or otherwise. To be a patient-partner while in healthcare makes sense when a person with a health condition in direct contact with healthcare seeks to work closely with a healthcare provider. However, extending the label of "patient" beyond direct healthcare applications for a person who frequently must access healthcare, when participating on research teams or as a consultant for clinical practice, for example, is inaccurate.

Another way to understand the uniqueness of personhood is to view it as a horizon of understanding, expanding with each new experience. Our personal horizon refers to the depth and breadth of understanding we accumulate over a lifetime. For example, a young person begins life with a

limited horizon of self and world but with time, events, reflection, experience and perspective, evolves an historical effective consciousness over time, wisdom of sorts. This horizon is a metaphor for the range of vision that includes everything that can be seen from a particular vantage point.

A person without a personal horizon of understanding is unable see far enough from what is close at hand and consequently over values that which is nearest to her. On the other hand, "to have a horizon" (p.302)[6] means not being limited to what is only perceived as immediate but being able to see beyond it. This is a case of challenging the label of patient-partner. At first glance, we may not see a problem with this label because it is catchy and informs others that a different kind of partner is present. However, looking beyond this horizon (our discipline-specific horizon) of understanding, we learn that such labeling can be detrimental to how the patient-partner understands their own historical effective consciousness as experienced through their ever-evolving horizon.

Labels Matter

Being labeled a patient outside the context of healthcare is simply inaccurate. While sitting in on a research meeting, I am a patient perspective consultant, but not a patient. Given the importance of context in defining human identity as discussed above, ignoring context with the use of the "patient" label lacks the sensitivity, respect, and title-accuracy that should be afforded to any member of a research team. On the other hand, the word "consultant" comes from Latin *consultare*, which means "to take the advice of/to deliberate." Essentially, people living with a condition are providing their advice and their own personal definition of that condition to the "experts" that adds value that no quantitative scale can ever measure. This perspective will help the research team and its individual members broaden their horizons of understanding of the condition and thus come up with better rounded solutions to the issues at hand. The term patient perspective consultant leads to questions. Questions are a result of interest and curiosity.

We have learned from other disciplines such as community rehabilitation and disability studies a label is akin to stereotyping as it dissolves personhood to accommodate who? Patients are patients, not of their own volition, but due to external circumstances. Patient-partners, on the other hand, although they are part of the research project voluntarily, did not choose to become patients and certainly did not decide to make a career out of "patient-hood." To them, the research group is not solely about a research project, but about a condition that they know intimately and that affects every aspect of their lives. To label patient-partners as such is to strip them of their life's identity, complexity, and accomplishments and to only retain a single fact: that they are a patient. As Hovey et al.[6] explains, "These narratives add meaning to the person as a stay against only having a clinical-pathological understanding of what is happening to our body and as a person." (p. 95).

Self-Stereotyping Personal Reflections

Veeresh offers his experience of being labeled a patient throughout his life. "Being born directly into the healthcare world, I am constantly referred to as a "patient" everywhere I go—hospital, school, work even in the comfort of my own home surrounded by my family and friends—I have this label woven into me. This leaves an imprint, a stamp on ones' mind. Am I this "sickly" person? Can I dream to have a life like others? The narrative needs to change and become context specific from a "patient" to a "person" to help diminish the possibility of a negative self-stereotyping."

Marie adds her reflections on the effects of labeling on her experiences with PTSD. "I live with post-traumatic stress disorder. I have for over 13 years now, and it went undiagnosed for 12 years specifically because physicians I had seen didn't want to label me as a "psych patient." Two separate physicians diagnosed me with "highly situational depressive mood and anxiety" during those 12 years, both giving me a different version of "you know, so you don't get labeled." Both these physicians at least unconsciously understood the potential harm in labeling and self-stereotyping and tried to avoid it happening to me."

Historically, self-stereotyping has been important in social psychology because prominent theorists thought that it was an unavoidable consequence of group membership. Conceptualizing self-stereotyping more broadly than is done today, they argued that being viewed a certain way because of one's group membership undoubtedly should affect how individual group members see themselves. The modern importance of self-stereotyping stems from the functions it is thought to serve. Some researchers argue that self-stereotyping can translate into beliefs and behaviors that help support existing inequalities between groups in society. Other researchers argue that self-stereotyping fulfills the need to feel close to other group members. From this perspective, self-stereotyping is beneficial in that it creates a sense of group unity and solidarity. Research documenting other functions of self-stereotyping needs to be done.[13,14,15]

Belonging versus Fitting In

Self-stereotyping occurs when someone's belief about their own characteristics correspond to common beliefs of a group they belong to. One belongs to a group by identifying themselves with people with similar interests or

similar characteristics. One can belong to many groups.[13,14,15] However, labeling and placing people into groups leads to self-stereotyping. Self-stereotyping can influence how we think about other people and how we think about ourselves. Self-stereotyping may lead to judgement and misguidedness. In the healthcare domain, people living with a condition are placed into categories and are often referred to as "patients." What connotation do you get from "patient"? What synonym can you derive from "patient"? Is it healthy for one to belief that they are a "patient"? Is someone a "patient" because they had an experience with the healthcare domain?[1] Do I become a "patient" because I need stitches from cutting my finger by accident when making a salad?

Self-stereotyping in its most positive sense tends toward creating a sense of belonging, or as Gadamer would say "feeling at home."[6] This is shown in studies looking at self-stereotyping for sororities and fraternities.[8] This perspective, although truthful and valid, is not accurate in the case of patient-partners, because association with such groups is voluntary, unlike living with a chronic condition. A sports team fan or a fraternity member associates with a sports team or fraternity by choice and can shed the emblems (clothes, jerseys, hats, etc.) associating them with those groups should they wish to disassociate from them. A chronically ill person cannot shed their chronic condition.

A recent personal observation from Richard (teacher) explores positive/negative self-stereotyping while attending one of his recent frequent visits to a hospital observed positive reinforced self-stereotyping with a group of surgeons. "During a medical appointment [Pre-COVID19], I was waiting in the hospital's cafeteria. I watched as a group of three people arrived for lunch wearing scrubs, surgical hats, with face masks dangling below their chins. Over the next 15 minutes, several others appeared, all wearing more or less the same uniform. Not one person in this group took off their hat or masks (these were turned to one side) while they ate their lunch. This was a positive display of a group identity, an example of positive self-stereotyping, because being a surgeon is a socially constructed positive stereotype with status and prestige."

Another observation on the same day was from a (my personal) patient's perspective. In this case, I was a patient because I was there for medical examinations and/or treatments. In a waiting room, where men and women sit patiently in their underwear covered by a robe that never seems to fit properly, risking the exposure of some random body part, we endure. I realize it is a necessary indignation to facilitate the medical examinations that follow. The self-stereotypical patient accepts this temporary ignominy for a greater cause, their health. However, once I leave the hospital, I am no longer a patient. This does not mean that I forget about my experience because it adds to my sense of personhood, however, it should never replace it.

The experiences described above touch on a phenomenon described by Latrofa et al.[9]: when individuals belong to an ingroup that is stigmatized or threatened within a larger group, they are more likely not only to identify with the characteristics of this ingroup, but also act in ways that showcase these characteristics. For patient-partners within research teams, to be labeled as patients is likely to both have them describe themselves as patients outside of healthcare more often and adopt stereotypical behaviors and characteristics of patients, even outside of direct healthcare.

Usually, where a large group of similarities are involved, stereotyping is an easy way to label the group (e.g., in a hospital setting). When persons with a certain condition, such as "thalassemia," get labeled as a "thal patient" instead of "persons with thalassemia," we begin to see ourselves first as a patient than a person. This negative self-stereotyping happens in a sub-conscious way, and we start seeing ourselves first as a "sick person" than just as a "person."

Erosion of Personhood

The patient-partner title remains obscure, inaccurate, and potentially harmful to the people who have been given this label.[10] "The loss of personhood happens within medical sciences when the individual patient is objectified in terms of a mere multiplicity of data. In a clinical investigation all the information about a person is treated as if it could be adequately collated on a card index. If this is done correctly, then the relevant data will all uniquely apply to the person involved. But the question is whether the unique value of the individual is properly recognized in the process. In other words, are we treating the patient partner as a member of the research team with insights just as valuable as the researchers, or as a subject to be studied to generate data?" (p. 81).

Gadamer[10] speaks to the incongruity of referring to individuals as "patients" outside of the healthcare context. He speaks to the push and pull of, on the one hand, wanting to fit in and in doing so, flattening our individual identity, and on the other hand, knowing and affirming who we are and our unicity as individuals to identify what we need to feel at home. He explains that to "sustain our internal balance" (p.81) between fitting in and feeling at home, we must find our place and purpose in the world and our community. In other words, patient-partners may accept this label as an attempt to fit into the research team, but in doing so, shrink their identity to fit into what is expected of them and forgo any hope of feeling at home and purposeful within this very team. Without a clear definition of one's role in unfamiliar situations, one might feel unsure of expectations of

themselves and others, creating a kind of participation paralysis.

In the context of health research in which recruitment of patient-partners is deemed necessary for a specific project, the label patient-partner becomes affixed to the person holding that title. To be given access to the research group, the patient-partner must accept the label and integrate it into their own identity. In this context, they are no longer a person offering insight into a patient perspective (a consultant); they are a patient, even outside of healthcare. They are altering their personal identity to fit the requirement of patient-partner and thus, according to Gadamer, moving away from "feeling at home" and closer to "fitting in."[12] Without a title that names their role, like researcher or healthcare provider as clinicians, the patient-partner title remains vague, not only to the patient-partner, but to all the other team members.

CONCLUSION

We took up the challenge of confronting the label of "patient-partner" outside the context of healthcare to prevent negative stereotyping and the erosion of personhood through offering a straightforward suggestion of a title change to "patient perspective consultant" within research teams. We believe it is important for researchers, clinicians, and everyone else to widen their horizon of understanding by being aware of the work done in other disciplines regarding the harmfulness of labels. This work is the result of decades of research and serves as a building block for allowing people to belong:

"Research has shown that when people become engulfed in the client or patient role, it is difficult for them to see their own capacities and strengths. People are robbed of their power and trapped in their passive roles. The focus on needs within a deficit framework is one of the ways our society constructs vulnerability."[11]

Consciousness of being affected by history is primarily consciousness of a hermeneutical "situation." To acquire an awareness of a situation is, however, always a task of particular difficulty. The very idea of a situation means we are not standing outside it and hence are unable to have objective knowledge of it. We always find ourselves within a situation and throwing light on it is a task that is never entirely finished.

The shift from patient-partner to patient perspective consultant does not change the nature of the role, it clarifies the context through increased accuracy. It also affords patient perspective consultants the respect and dignity that is afforded to the other members of the research team. The steps involved in materializing this change will help foster awareness and thoughtfulness of working with people from outside our discipline. ❖

Authors' Contributions

Richard B. Hovey, BEd, MA, PhD, conceptualized the content of the manuscript, provided original content writing, drafting, editing and participated in the critical review, and submission of the final manuscript. Veeresh Pavate MEd, Kristina Amja BSc and Marie Vigouroux BA participated in the development of this manuscript by providing original content writing contributions, researching and reviewing relevant literature, actively edited and drafted the final form of the manuscript for submission. All authors have given final approval to the manuscript. No funding was provided for this study. All authors declare that they had no competing interests.

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ORIGINAL RESEARCH ARTICLE

Prevalence and Characteristics of Chronic Cough in Adults Identified by Administrative Data

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ABSTRACT

Context: International Classification of Diseases-9/10 codes for chronic cough (CC) do not exist, limiting investigation.

Objective: To develop a computerized algorithm to determine CC prevalence and its characteristics.

Design: This observational study using administrative data identified hierarchically patients aged 18 to 85 years with CC from 2013 to 2016. First, a specialist-diagnosed CC group was identified using an internal CC encounter code during an outpatient visit to a pulmonologist, allergist, otolaryngologist, or gastroenterologist. Subsequently, an event-diagnosed CC group was identified based on clinical notes through natural language processing, ICD-9/ICD-10 cough codes, and dispensed antitussives.

Main Outcome Measures: Prevalence of CC and comparison of clinical characteristics between specialist-diagnosed and event-diagnosed CC subgroups.

Results: A total of 50,163 patients with CC of more than 8 weeks were identified. Of these, 11,290 (22.5%) were specialist diagnosed, and 38,873 (77.5%) were event diagnosed. The CC cohort was 57.4 ± 16.5 years of age; 67.6% were female. The overall prevalence was 1.04% (95% confidence interval = 1.03-1.06) in 2016. Prevalence in 2016 was higher in female patients (1.21%) than in male patients (0.81%), higher in patients aged 65 to 85 years (2.2%) than in patients aged 18 to 44 years (0.43%), and higher in Blacks (1.38%) than in Whites (1.21%). Compared with patients with event-diagnosed CC, patients with specialist-diagnosed CC exhibited significantly higher frequencies of laboratory tests and respiratory and nonrespiratory comorbidities and dispensed medication and lower frequency of pneumonia, all-cause and respiratory-cause emergency department visits and hospitalizations, and dispensed antitussives.

Conclusions: We identified a CC cohort using electronic data in a managed care organization. Prevalences varied by sex, age, and ethnicity. Clinical characteristics varied between specialist-diagnosed and event-diagnosed CC.

INTRODUCTION

Chronic cough (CC) is defined as a cough that lasts more than 8 weeks.[1-4] Estimates of CC prevalence range from 2.5% to 12%, varying by study design and type of data collection (eg, survey, patient report, or physician diagnosis).[1,3,5,6] Systematic approaches to the assessment[7] and management of CC are highlighted in guidelines developed by professional organizations.[3,4, 8-12] Studies report the substantial clinical and healthcare burden of CC.[13-15] However, real-world studies of CC based on administrative health care data are challenged by the lack of specific ICD-9 or ICD-10 diagnostic codes to identify CC. To address this limitation, we identified a subgroup of CC patients seen by specialists using an internal Kaiser Permanente Southern California (KPSC)-specific CC encounter code. Burden of disease was greater in these specialist-diagnosed CC patients compared with a matched noncough cohort.[16]

The present study sought to determine the overall prevalence of CC at KPSC. To accomplish this objective, we needed to identify CC patients other than those who were specialist diagnosed. We used a combination of cough-related keywords or concepts in clinical notes extracted by natural language processing (NLP), ICD-9 or ICD-10 cough diagnosis codes, and dispensed antitussive medications to identify an event-diagnosed CC cohort with CC of more than 8 weeks using a prespecified algorithm. The combination of specialist-diagnosed and event-diagnosed CC patients was used to determine CC prevalence. The burden of CC was determined in the entire cohort and compared between specialist-diagnosed CC and event-diagnosed CC during the baseline and follow-up years. Given the chronicity of CC, its persistence was determined in the follow-up year.

METHODS

Study Design

This observational study used the KPSC Research Data Warehouse to capture administrative pharmacy and healthcare resource utilization (HCRU) data from 4.6 million enrollees across the Southern California region whose demographics are comparable to residents in the region.[17,18] Details of HCRU data capture capabilities at KPSC have been reported.[17] The study was approved with waiver of written consent by the KPSC Institutional Review Board.

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Cohort Identification

Using administrative pharmacy and HCRU data, we identified hierarchically patients aged 18 to 85 years with CC in 2013 to 2016 as specialist-diagnosed CC and event-diagnosed CC (Figure 1). Patients in both groups were required 1) to have continuous health plan enrollment (no enrollment gap of >45 days) and pharmacy benefit in the 12-month period prior to and the 12-month period after the CC index date (see the definition of index date below) and 2) no angiotensin-converting enzyme inhibitor (ACE-I) use in the year prior to and at the index date because up to 20% of ACE-I users experience cough.[19] For both specialist-diagnosed and event-diagnosed CC patients, the baseline period was the 12 months prior to and including the index date, and the follow-up year was the 12-month period after the index date.

Specialist-diagnosed CC

A specialist-diagnosed CC group was identified using a KPSC-specific CC encounter code (#529563) during a clinic visit to a pulmonologist, allergist, otolaryngologist, or gastroenterologist as reported previously (Figure 1).[16] ICD-9 and ICD-10 codes are not specific enough to identify CC; therefore, only the internal CC encounter code was used. The index date for the specialist-diagnosed CC cohort was the earliest date of the specialist visit with the CC-specific encounter code. A manual chart review based on a random sample of 200 specialist-diagnosed CC patients revealed that 90.5% had evidence of CC of more than 8 weeks.[16]

Event-diagnosed CC

An event-diagnosed CC group was identified based on any 3 of the following clinical events that occurred within 120 days: 1) mentioning of cough or related keywords or concepts in qualified clinical notes extracted by NLP (Table 1); 2) physician diagnosis of cough (ICD-9: 786.2 or ICD-10: R05); the patients who were coded with the internal CC-specific encounter code were also coded with either 786.2 (ICD-9) or R05 (ICD-10) for the same encounter; and 3) dispensed antitussive medication.

The first and the last of the 3 events were required to be at least 56 days (8 wk) apart, and any 2 of the 3 events were required to be at least 21 days (3 wk) apart. If more than 3 events during the study period were found, the first 3 qualifying events were used. The third event was defined as the index event for the event-diagnosed CC cohort.

The process of information extraction from clinical notes through NLP is described in Table 1. Cough-related keywords were based on the list in the Merck/Regenstrief Institute collaboration study,[20] ontologies in the Unified Medical Language System,[21] and possible linguistic variations and misspelling or mistyping (Table 1). An internal validation of the NLP algorithm based on a sample of 200 clinical notes revealed a positive predictive value of 96.7% and sensitivity of 96.7%. Of the 5,219,820 NLP-identified cough events, 5,210,284 (99.82%) were for cough only, 5939 were for cough and expectorant use (0.11 %), and 3597 (0.07%) were for expectorant use only.

Patient Characteristics

Measures on median household income and highest education level at the census block group-level were derived from geocoded addresses of KPSC health plan enrollees. All patient characteristics were captured electronically. Smoking status was the last measure at or before index date. All comorbidities were defined by ICD-9 and ICD-10 codes as described previously.[22] The Charlson Comorbidity Index classified prognostic comorbidities.[23] Obesity was defined as a body mass index of ≥ 30 kg/m^2. We determined the frequency of potential CC complications based on the occurrence of sleep disturbance, stress incontinence, costochondritis, vomiting, and subconjunctival hemorrhage determined by ICD-9 and ICD-10 codes.[16] Respiratory-specific events as causes of emergency department (ED) visits and hospitalizations have been reported previously.[16] The current Medi-Span Generic Product Identifier at 14 characters level granularity (https://www.wolterskluwercdi.com/clinical-drug-information) identified relevant studied dispensed medications. Persistence of CC was defined for the specialist-diagnosed CC patients if they had a repeated CC-specific encounter code in the follow-up year in 1 of the 4 specialist departments described above. For event-diagnosed CC patients, persistence of CC required at least 3 individual events in the follow-up year that met the event-diagnosed CC definition.

Statistical Analyses

Patient demographic characteristics, comorbidities, HCRU, and dispensed medications were determined in the baseline and follow-up years. Comparisons between specialist-diagnosed and event-diagnosed groups were performed using the γ^2 test or Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables.

The prevalence of CC was calculated by using the formula (N/D) × 100, where D is the number of health plan enrollees between 18 and 85 years of age with at least 1 clinic visit at a KPSC facility without taking ACE-I who were continuously enrolled with pharmacy benefits for at least 120 days in the year of interest, and N is the number of CC patients in D who met the definition of CC. The requirement of 120 days ensures a minimum length of insurance and benefit coverage for chronic cough or its individual events to be recorded. The annual prevalence of CC was estimated using the same definition mentioned

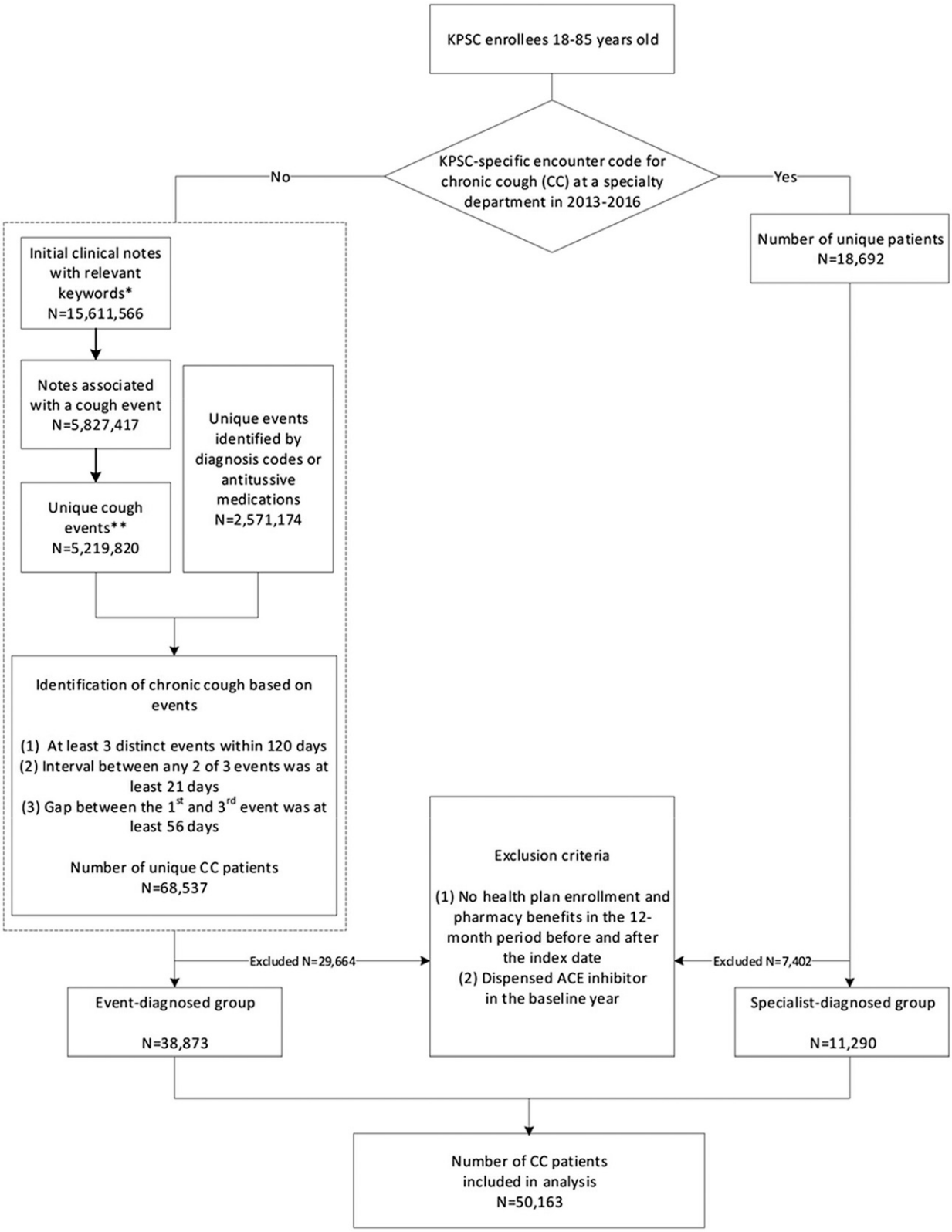

Figure 1. Administrative logistics for patient identification, and number of patients identified with administrative databases. Administrative algorithm for patient identification of adult chronic cough (CC) cohort. *Refer to Table 1 for list of keywords. **No more than one event per patient per day. ACE = angiotensin-converting enzyme; KPSC = Kaiser Permanente Southern California.

Table 1. Cough related keywords, encounter types, department specialties, clinical note types used to identify cough events, and natural language processing

Category	Specifics
Identifying cough events from clinical notes	Notes containing the concept of cough during the study period among patients 18-85 years of age. Notes not used when cough was historical, negated, resolved, nonpatient self, not referred to actual event or without affirmation, and in which angiotensin-converting enzyme inhibitors (ACE-I) were mentioned.
Cough-related keywords	Based on the list in the Merck/Regenstrief Institute collaboration study,[20] ontologies in the Unified Medical Language System,[21] and possible linguistic variations and misspelling or mistyping. The compiled keywords included cough, coughed, coughing, coughs, expectorate, expectorated, expectorates, expectorating, expectoration.
Notes extraction	Specific types of clinical notes with the cough-related keywords for certain medical encounters that occurred at certain departments during the study period were extracted from the Kaiser Permanente Southern California electronic medical record system.
Encounter type	Office visit, urgent care, telephone visit, email, phone, message, video visit, emergency department visit, long term care, home health care, hospice care, skilled nursing facility care
Department type	Allergy, Asthma and Immunology, Continuing Care, Family Practice, Gastroenterology, Geriatric Medicine, Home Health Care, Infectious Diseases, Internal Medicine, Obstetrics, Gynecology, Occupational Medicine, Otolaryngology, Pulmonary Diseases, Respiratory Therapy, Sleep Clinic, Speech Therapy, Urgent Care, Urology, Emergency Medicine, Pediatric Allergy, General Practice, Immunology, Primary Care, Pediatric Ambulatory Care, Medical Ambulatory Care, Pediatric Urgent Care, Continuing Care, Residential Care, Skilled Nursing Facility, Ambulatory Care Unit, Addiction Medicine, Adolescent Medicine, Employee Health, Hospice Care, Occupational Therapy, Preventive Medicine, Urology, Emergency
Type of clinical notes	Progress notes, emergency department provider notes, history and physical notes, consult notes, telephone encounter notes
Pre-processing of notes	Clinical notes were preprocessed through sentence separation and tokenization (ie, segmenting text into linguistic units such as words and punctuations). The sentence boundary detection algorithm in Natural Language Toolkit[3] and an additional customized sentence boundary detection algorithm were used to separate sentences. For example, the special symbol "¶" in the clinical notes indicated the end of sentences. In addition, potential detected misspelled words/terms were corrected, including misspellings such as "cogh worse at night" and "couhg was mild."
NLP algorithm development	A computerized NLP algorithm was developed through an iterative process in which the developed algorithm was refined to match with the results of the reference standards derived through chart review and adjudication of 200 notes at a time. A total of 1,600 clinical notes was randomly selected from the entire set of cleaned notes and split into eight subsets, each containing 200 notes that were sequentially reviewed by trained abstractors and adjudicated by clinical experts.

NLP = natural language processing.

above, and the calculation of D for each calendar year was based on the year of CC index date. The overall and annual prevalence rates were stratified by age, sex, and race/ethnicity using the same definitions described above within each stratum. To estimate 95% confidence intervals for prevalence, the normal approximation method was applied: $\hat{p} \pm z\sqrt{\frac{\hat{p}(1-\hat{p})}{n}}$, where $\hat{p}$ is the estimated prevalence, z is the value from the standard normal distribution for 95% confidence level, and n is the number of people included in the denominator.

All analyses were conducted using SAS (version 9.4 for Unix; SAS Institute, Cary, NC). Statistical significance was set at $p < 0.001$ to account for the large sample size and was 2-sided.

RESULTS

CC Cohort

We identified 50,163 unique patients with CC. A total of 11,290 patients (22.5%) met the definition of specialist-diagnosed CC, and 38,873 (77.5%) were event-diagnosed CC (Figure 1). Roughly half of specialist-diagnosed CC cases also met the definition for event diagnosis, indicating the cohort would be 10.8% smaller without the specialist-diagnosed definition.

Demographics

The CC patients were 57.4±16.5 years of age, with length of enrollment of 18.6±12.5 years and median household income of $75,486±31,811. The majority of the patients were female (67.6%) and from non-White ethnicities (56.7%) (Table 2). Among CC patients, 36.5% had Medicare insurance, and 5.9% were current smokers.

Comorbidities

Respiratory comorbidities reached the following frequencies for more common conditions: asthma (31.2%), chronic sinusitis (28.1%), allergic rhinitis (27.3%), pneumonias (23.1%), chronic rhinitis (18.8%), chronic obstructive pulmonary disease (COPD) (14.1%), and upper airway cough syndrome (postnasal drip) (12.1%). Common non-respiratory comorbidities among the CC patients included hypertension (41.3%), gastroesophageal reflux disease (GERD) (32.5%), obesity (27.4%), depression (22.4%), and

Table 2. Baseline year demographic characteristics and comorbidities of entire chronic cough cohort and subgroups

Characteristic	Entire chronic cough (CC) cohort and subgroups			
	Entire CC cohort (N = 50,163)	Specialist-diagnosed CC (n = 11,290)	Event-diagnosed CC (n = 38,873)	p value[a]
Demographics				
Age, y	57.4 (16.5)[b]	60.9 (14.3)	56.4 (16.9)	<0.001
Female sex	33,919 (67.6)	7535 (67.7)	26,384 (67.9)	0.024
Ethnicity				<0.001
White	21,723 (43.3)	5693 (50.4)	16,030 (41.2)	
Hispanic	15,665 (31.2)	2809 (24.9)	12,856 (33.1)	
Black	5918 (11.8)	1045 (9.3)	4873 (12.5)	
Asian/Pacific Islanders	5595 (11.2)	1482 (13.1)	4113 (10.6)	
Others/multiple/unknown	1262 (2.5)	261 (2.3)	1001 (2.6)	
Median household income ($)[c]	75,486 (31,811)	73,275 (32,597)	76,042 (31,586)	<0.001
Highest education ≤ grade 12 (%)[c]	18.9 (14.4)	20.5 (16.8)	18.5 (13.7)	<0.001
Years of health plan enrollment	18.6 (12.5)	19.1 (13.1)	18.5 (12.4)	0.042
Insurances				
Commercial	28,060 (55.9)	5849 (51.8)	22,211 (57.1)	<0.001
Medicare	18,442 (36.8)	4740 (42.0)	13,702 (35.2)	<0.001
Private pay	12,909 (25.7)	3290 (29.1)	9619 (24.7)	<0.001
Medi-Cal	3674 (7.3)	495 (4.4)	3179 (8.2)	<0.001
Smoking status[d]				<0.001
Never	30,786 (61.4)	7338 (65.0)	23,448 (60.3)	
Quit	15,901 (31.7)	3591 (31.8)	12,310 (31.7)	
Current	2948 (5.9)	261 (2.3)	2687 (6.9)	
Passive	417 (0.8)	92 (0.8)	325 (0.8)	
Unknown	111 (0.2)	8 (0.1)	103 (0.3)	
Comorbidities				
Charlson comorbidity index	1.8 (2.0)	1.7 (1.9)	1.8 (2.1)	0.04
Respiratory disorders				
Asthma	15,635 (31.2)	3525 (31.2)	12,110 (31.2)	0.888
Chronic sinusitis	14,097 (28.1)	2753 (24.4)	11,344 (29.2)	<0.001
Allergic rhinitis	13,675 (27.3)	3689 (32.7)	9986 (25.7)	<0.001
Pneumonias	11,607 (23.1)	2048 (18.1)	9559 (24.6)	<0.001
Chronic rhinitis	9449 (18.8)	3557 (31.5)	5892 (15.2)	<0.001
COPD	7094 (14.1)	1440 (12.8)	5654 (14.5)	<0.001
Upper airway cough syndrome	6057 (12.1)	2306 (20.4)	3751 (9.6)	<0.001
Obstructive sleep apnea	3921 (7.8)	981 (8.7)	2940 (7.6)	<0.001

(continued on following page)

Table 2. Baseline year demographic characteristics and comorbidities of entire chronic cough cohort and subgroups (continued)

Characteristic	Entire chronic cough (CC) cohort and subgroups			
	Entire CC cohort (N = 50,163)	Specialist-diagnosed CC (n = 11,290)	Event-diagnosed CC (n = 38,873)	p value[a]
Bronchiectasis	1802 (3.6)	620 (5.5)	1182 (3.0)	<0.001
Pulmonary fibrosis	1687 (3.4)	540 (4.8)	1147 (3.0)	<0.001
Hemoptysis	1494 (3.0)	370 (3.3)	1124 (2.9)	0.034
Nasal polyp disease	436 (0.9)	92 (0.8)	344 (0.9)	0.48
Nonrespiratory disorders				
Hypertension	20,717 (41.3)	4734 (41.9)	15,983 (41.1)	0.12
Gastroesophageal reflux disease	16,325 (32.5)	4,977 (44.1)	11,348 (29.2)	<0.001
Obesity	13,736 (27.4)	2749 (24.3)	10,987 (28.3)	<0.001
Depression	11,238 (22.4)	2291 (20.3)	8947 (23.0)	<0.001
Anxiety	10,770 (21.5)	2008 (17.8)	8762 (22.5)	<0.001
Atrial fibrillation/flutter	2705 (5.4)	541 (4.8)	2164 (5.6)	0.001
Coronary artery disease	4021 (8.0)	846 (7.5)	3175 (8.2)	0.02
Congestive heart failure	2594 (5.2)	432 (3.8)	2162 (5.6)	<0.001
Potential cough complications				
Any complication (any one below)	10,594 (21.1)	2191 (19.4)	8403 (21.6)	<0.001
Sleep disturbance	5631 (11.2)	1210 (10.7)	4421 (11.4)	0.052
Stress incontinence	3398 (6.8)	687 (6.1)	2711 (7.0)	0.001
Costochondritis	1157 (2.3)	210 (1.9)	947 (2.4)	<0.001
Subconjunctival hemorrhage	631 (1.3)	150 (1.3)	481 (1.2)	0.44
Vomiting	673 (1.3)	104 (0.9)	569 (1.5)	<0.001
Rib fracture	254 (0.5)	55 (0.5)	199 (0.5)	0.74

COPD = chronic obstructive pulmonary disease; pneumonias = pneumonias, influenza, and acute lower respiratory tract infection.

[a] Comparisons were made are between specialist-diagnosed and event-diagnosed subgroups; p values determined by γ^2 test or Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables.

[b] Data presented as n (%) and mean (SD).

[c] Median household income and education by geocoding.

[d] Smoking based on the last measure prior to the index date.

anxiety (21.5%). Any potential cough complication was observed in 21.1% of the CC patients (Table 2).

CC Prevalence

The annual prevalence of CC was generally consistent from 2013 to 2016 (0.92% in 2013, 0.87% in 2014, 0.97% in 2015, and 1.04 in 2016) (Table 3), with event-diagnosed CC annual prevalence being about 4-fold higher than specialist-diagnosed CC. The relative annual prevalence of CC among female patients was about 40% higher than among male patients during the study period. CC annual prevalence increased by age, with those 65 to 85 years of age exhibiting the highest prevalence, reaching 2.2% in 2016. Blacks had the highest prevalence of CC, followed in decreasing order by Whites, Asian/Pacific Islanders, and Hispanics (Table 3).

Characteristics of CC Patients in Baseline Year

Compared with event-diagnosed CC patients, specialist-diagnosed CC patients were older, had lower median household incomes, and were less likely to have commercial health insurance. The CC patient group also exhibited a substantially lower frequency of minority ethnicity, high-school graduates, and current smokers. Additionally, specialist-diagnosed CC patients had a higher frequency of chronic and allergic rhinitis, upper airway cough syndrome, and GERD and a lower frequency of pneumonia, COPD, obesity, depression, anxiety, cardiac conditions, and any potential cough complication compared with event-diagnosed CC patients (Table 2).

Compared with event-diagnosed CC patients, specialist-diagnosed CC patients had significantly 1) a lower frequency of all-cause and respiratory-associated ED visits and hospitalizations; 2) a higher frequency of visits to different relevant specialty departments; 3) more laboratory testing, including chest and sinus imaging, pulmonary function testing, allergy radioallergosorbent tests, laryngoscopy, esophageal endoscopy, and nasal/sinus endoscopy; 4) a higher frequency of dispensed intranasal rhinitis medications, short-acting β_2-agonists (SABA), asthma controller medication (inhaled corticosteroids, inhaled corticosteroids/long-acting β_2-agonist [LABA], and leukotriene modifiers), proton pump inhibitors, and H2-blockers; and 5) a lower frequency of dispensed COPD medications (SABA/short-acting muscarinic antagonist and LABA/long-acting muscarinic antagonist), potential respiratory antibiotics, narcotics, antitussives including codeine, and anti-anxiety medications (anxiolytics) (Table 4).

Characteristics of CC Cohort in Follow-up Year

Persistence of CC

Persistence of CC in the follow-up year was observed in 17.9% of the CC cohort. Compared with event-diagnosed CC patients (11.3%), specialist-diagnosed CC patients (40.6%) exhibited a significantly higher prevalence of persistent CC in the follow-up year (Table 5).

Healthcare Resource Utilization

Patient Visits

The frequency of ED visits and hospitalization from all-cause or respiratory causes appeared similar in the follow-up year compared with the baseline year. Consistent with the baseline year, the event-diagnosed subgroup exhibited a significantly higher frequency of ED visits and hospitalization for all-cause or respiratory causes compared with the specialist-diagnosed subgroup (Table 5). Compared with the event-diagnosed subgroup, the specialist-diagnosed subgroup continued to have significantly higher frequency of visits to multiple specialist departments (Table 5).

Laboratory Tests

Laboratory testing for the entire CC cohort was frequent in the follow-up year but generally less than during the baseline year (Tables 4 and 5). Most tests remained significantly higher in the specialist-diagnosed compared with event-diagnosed cohort including pulmonary function tests, advanced chest and sinus imaging, allergy radioallergosorbent test tests, laryngoscopy, esophageal endoscopy, barium swallow and upper gastrointestinal testing, nasal/sinus endoscopy, and bronchoscopy (Table 5).

Dispensed Medication

Specialist-diagnosed CC patients were dispensed controller asthma medication and intranasal rhinitis medications significantly more frequently than event-diagnosed CC patients (Table 5). COPD medications (SABA/short-acting muscarinic antagonist and LABA/long-acting muscarinic antagonist) and H-1 were dispensed significantly more frequently in event-diagnosed CC patients compared with specialist-diagnosed patients (Table 5).

Gastrointestinal medication was generally dispensed at a similar frequency during the follow-up year (Table 5) compared with the baseline year (Table 5); however, proton pump inhibitors were dispensed significantly more frequently in the specialist-diagnosed CC subgroup (41.3%) compared with the event-diagnosed subgroup (28.9%) (Table 5).

Potential respiratory antibiotics and oral corticosteroids were dispensed less frequently during the follow-up year (Table 5) compared with the baseline year (Table 4) and more frequently in the event-diagnosed compared with specialist-diagnosed CC patients (Table 5).

Antitussives were dispensed less frequently in the follow-up year (Table 5) than during the baseline year (Table 4). Similar to the findings during the baseline year, event-diagnosed CC patients were dispensed antitussives including codeine

Table 3. Annual prevalence of entire chronic cough cohort and by type of CC diagnosis, age, sex, and ethnicity, stratified by diagnosis year

Characteristic	Annual prevalence (% and 95% confidence interval[a])			
	2013	2014	2015	2016
CC cohort				
Entire cohort	0.92 (0.91-0.93)	0.87 (0.86-0.88)	0.97 (0.96-0.98)	1.04 (1.03-1.06)
Event-diagnosed cohort	0.81 (0.80-0.83)	0.76 (0.75-0.77)	0.84 (0.83-0.86)	0.91 (0.89-0.92)
Specialist-diagnosed cohort	0.19 (0.18-0.20)	0.21 (0.20-0.21)	0.23 (0.22-0.24)	0.24 (0.23-0.25)
Sex				
Female	1.07 (1.05-1.09)	1.01 (0.99-1.03)	1.13 (1.11-1.15)	1.21 (1.19-1.23)
Male	0.72 (0.70-0.73)	0.68 (0.66-0.70)	0.75 (0.73-0.77)	0.81 (0.80-0.84)
Age, y				
18-44	0.42 (0.40-0.43)	0.36 (0.35-0.37)	0.41 (0.40-0.42)	0.43 (0.41-0.44)
45-64	1.02 (1.00-1.05)	0.93 (0.91-0.95)	1.00 (0.98-1.03)	1.07 (1.05-1.10)
65-85	2.07 (2.02, 2.11)	1.98 (1.93, 2.02)	2.10 (2.06, 2.15)	2.20 (2.16, 2.25)
Ethnicity				
Black	1.31 (1.25-1.36)	1.24 (1.19-1.30)	1.30 (1.25-1.35)	1.38 (1.32-1.43)
White	1.06 (1.04-1.08)	1.02 (1.00-1.04)	1.13 (1.11-1.16)	1.21 (1.18-1.24)
Asian/Pacific Islanders	0.95 (0.90-0.99)	0.91 (0.87-0.96)	1.00 (0.95-1.04)	1.11 (1.06-1.16)
Hispanics	0.72 (0.71-0.74)	0.67 (0.65-0.68)	0.76 (0.74-0.78)	0.82 (0.80-0.85)
Multiple/others/unknown	0.51 (0.47-0.56)	0.49 (0.44-0.54)	0.64 (0.58-0.70)	0.70 (0.64-0.77)

CC = chronic cough.
[a] The 95% confidence intervals were based on the binomial confidence interval using normal approximation.

at follow-up significantly more frequently (44.6%) compared with specialist-diagnosed CC patients (39.1%). Psychotherapeutic medications (antidepressants, anxiolytics, and the neuromodulators gabapentin, pregabalin, and triptans) were dispensed during the follow-up year (Table 5) at frequencies similar to those in the baseline year (Table 4), and anxiolytics were dispensed significantly more frequently in the event-diagnosed compared with specialist-diagnosed CC subgroups (Table 5).

DISCUSSION

Given the lack of a standard ICD diagnosis code to identify patients with CC, we demonstrated that CC patients could be identified using electronic medical records. During the period 2013 to 2016, the prevalence of CC in the entire CC cohort was approximately 1%. Notably, this prevalence estimate is dependent on participants actively engaging the healthcare system to satisfy CC definitions. This approach may better reflect the perspective of a payer or healthcare system because CC is a chronic condition with a long duration and because CC patients may not be continuously visiting healthcare providers for diagnosis or management of CC. The prevalence of CC as measured with electronic medical records in this study was lower than published CC prevalence estimates, which have ranged from 2.5% to 12%.[1,3,5,6] These estimates vary by study design and on whether determined by survey, patient report, or physician diagnosis, none of which used administrative coding or information extracted from clinical notes through NLP as in the present study. The CC prevalence reported in the present study is lower than the 2.5% CC prevalence reported in a large Korean National Health and Nutrition Examination Survey study of 11,928 adults aged over 40 years.[6] The present CC prevalence estimated by administrative data may underestimate the prevalence of CC for the following reasons: 1) patients with long-standing refractory CC may not seek visits due to failure of prior care and thereby may not be captured; 2) to increase the specificity of CC in the event-diagnosed subgroup, we used a more conservative definition that included 3 cough events to increase specificity of diagnosis; and 3) we excluded patients dispensed ACE-I in the prior year given the high frequency of cough with this class of medication.[24] We may have overestimated CC prevalence by only including patients with at least 1 clinic-based healthcare visit.

CC prevalence was about 30% higher in female patients than in male patients, was 5-fold higher in patients 65 to 85 years of age compared with those 18 to 44 years, and differed by ethnicity. The higher prevalence of CC in female patients and in elderly patients is consistent with findings of other studies with different designs.[14,25,26] A lower tolerance to cough triggers such as capsaicin has been demonstrated in female patients; this may, in part, explain their higher prevalence of CC.[25] The increase in comorbidities such as

Table 4. Baseline year health resource utilization and dispensed medications of the entire chronic cough cohort and subgroups

Characteristic	Entire chronic cough (CC) cohort and subgroups			
	Entire CC cohort (N = 50,163)	Specialist-diagnosed CC (n = 11,290)	Event-diagnosed CC (n = 38,873)	p value[a]
All-cause patient visits				
Outpatient	50,102 (99.9)[b]	11,290 (100)	38,812 (99.8)	<0.001
≥ 1 emergency department (ED)	18,138 (36.2)	3222 (28.5)	14,916 (38.4)	<0.001
≥ 1 Hospitalization	6990 (13.9)	1103 (9.8)	5887 (15.1)	<0.001
Respiratory cause patient visits[c]				
Outpatient	39,631 (79.0)	9477 (83.9)	30,154 (77.6)	<0.001
≥ 1 ED	8858 (17.7)	1463 (13.0)	7395 (19.0)	<0.001
≥ 1 Hospitalization	4334 (8.6)	630 (5.6)	3704 (9.5)	<0.001
Specialist visits				
Pulmonologist	14,434 (28.8)	7442 (65.9)	6992 (18.0)	<0.001
Otolaryngology	8913 (17.8)	3036 (26.9)	5877 (15.1)	<0.001
Allergist	7800 (15.5)	3707 (32.8)	4093 (10.5)	<0.001
Gastroenterology	7664 (15.3)	2008 (17.8)	5656 (14.5)	<0.001
Urology	3982 (7.9)	933 (8.3)	3049 (7.8)	0.15
Speech therapy	638 (1.3)	127 (1.1)	511 (1.3)	0.11
≥ 1 different specialty department	29,708 (59.2)	11,290 (100)	18,418 (47.4)	<0.001
≥ 2 different specialty departments	10,465 (20.9)	4459 (39.5)	6006 (15.5)	<0.001
≥ 3 different specialty departments	2714 (5.4)	1238 (11.0)	1476 (3.8)	<0.001
≥ 4 different specialty departments	502 (1.0)	246 (2.2)	256 (0.7)	<0.001
Laboratory tests (>1%)				
Complete blood count	38,189 (76.1)	8729 (77.3)	29,460 (75.8)	0.001
Chest x-ray	33,167 (66.1)	9062 (80.3)	24,105 (62.0)	<0.001
Pulmonary function tests	13,225 (26.4)	5428 (48.1)	7797 (20.1)	<0.001
Advanced chest imaging	8434 (16.8)	2399 (21.2)	6035 (15.5)	<0.001
Allergy RAST testing	6433 (12.8)	3154 (27.9)	3279 (8.4)	<0.001
Laryngoscopy	3646 (7.3)	1661 (14.7)	1985 (5.1)	<0.001
Sinus imaging	3418 (6.8)	1191 (10.5)	2227 (5.7)	<0.001
Esophageal endoscopy	3113 (6.2)	835 (7.4)	2278 (5.9)	<0.001
Barium swallow or upper GI	1225 (2.4)	311 (2.8)	914 (2.4)	0.015
Nasal/sinus endoscopy	1097 (2.2)	348 (3.1)	749 (1.9)	<0.001
Bronchoscopy	887 (1.8)	226 (2.0)	661 (1.7)	0.032
Respiratory medication (oral or inhaled)				
SABA singly	24,161 (48.2)	5698 (50.5)	18,463 (47.5)	<0.001
Nasal corticosteroids	23,047 (45.9)	6215 (55.0)	16,832 (43.3)	<0.001
ICS/LABA	10,153 (20.2)	3025 (26.8)	7128 (18.3)	<0.001
ICS monotherapy	9603 (19.1)	2687 (23.8)	6916 (17.8)	<0.001
Leukotriene modifiers	6204 (12.4)	2106 (18.7)	4098 (10.5)	<0.001
SABA and SAMA combination	3654 (7.3)	741 (6.6)	2913 (7.5)	0.001
Nasal antihistamines	2812 (5.6)	1136 (10.1)	1676 (4.3)	<0.001
H1 antihistamines	2524 (5.0)	457 (4.0)	2067 (5.3)	<0.001
LABA/LAMA	2298 (4.6)	444 (3.9)	1854 (4.8)	<0.001
Nasal SAMA	2,18 (4.2)	898 (8.0)	1220 (3.1)	<0.001
LAMA monotherapy	548 (1.1)	151 (1.3)	397 (1.0)	0.004
Gastrointestinal (oral)				
Proton pump inhibitors	16,654 (33.2)	5084 (45.0)	11,570 (29.8)	<0.001
H2 blockers	6881 (13.7)	1793 (15.9)	5088 (13.1)	<0.001

(continued on following page)

Table 4. Baseline year health resource utilization and dispensed medications of the entire chronic cough cohort and subgroups (continued)

Characteristic	Entire chronic cough (CC) cohort and subgroups			
	Entire CC cohort (N = 50,163)	Specialist-diagnosed CC (n = 11,290)	Event-diagnosed CC (n = 38,873)	p value[a]
Miscellaneous (oral)				
Potential respiratory antibiotics	39,624 (79.0)	8171 (72.4)	31,453 (80.9)	<0.001
Corticosteroid	22,814 (45.5)	5287 (46.8)	17,527 (45.1)	0.001
Narcotics, antitussive, psychotherapeutics (oral)				
Narcotics, including codeine	35,271 (70.3)	6875 (60.9)	28,396 (73.0)	<0.001
Antitussives, including codeine	34,038 (67.9)	6652 (58.9)	27,386 (70.4)	<0.001
Codeine	27,684 (55.2)	5143 (45.6)	22,541 (58.0)	<0.001
Narcotics, no codeine	18,952 (37.8)	3783 (33.5)	15,169 (39.0)	<0.001
Antitussives, no codeine	16,915 (33.7)	3823 (33.9)	13,092 (33.7)	0.72
Antidepressants	13,482 (26.9)	29,34 (26.0)	10,548 (27.1)	0.016
Anxiolytics	8884 (17.7)	1749 (15.5)	7135 (18.4)	<0.001
Neuromodulators	7253 (14.5)	1566 (13.9)	5687 (14.6)	0.60

CC = chronic cough; GI = gastrointestinal; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; RAST = radioallergosorbent test; SABA = short-acting β_2-agonist; SAMA = short-acting muscarinic antagonist.

[a] Comparisons were made between specialist-diagnosed and event-diagnosed subgroups; p values determined by γ^2 test or Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables.

[b] Data presented as n (%).

[c] Asthma, chronic obstructive pulmonary disease, vocal cord dysfunction, hyperventilation, allergic rhinitis. chronic rhinitis, nasal polyp disease, post-nasal drip (upper airway cough syndrome), chronic sinusitis, bronchiectasis, bronchiolitis obliterans, laryngomalacia, tracheomalacia, bronchomalacia, granulomatosis, cystic fibrosis, allergic bronchopulmonary aspergillosis, eosinophilic bronchitis/pneumonia, sarcoidosis, pulmonary fibrosis, hemoptysis, respiratory foreign body, obstructive sleep apnea, tonsillar enlargement, chronic tonsillitis, pertussis, pneumonia, influenza, and other acute lower respiratory infections.

COPD and more frequent use of healthcare resources in elderly patients may be responsible in part for their higher prevalence of CC compared with younger patients.[27] The prevalence of CC by ethnicity was explored in a meta-analysis, which reported higher prevalences in the US and Europe than in Asia or Africa, yet no ethnic difference in the cough reflex was noted between White, Indian, and Chinese subjects.[28] Differences in environmental exposures, comorbidities such as obesity and asthma (which are higher in Blacks), and of HCRU may be factors associated with ethnic differences in CC.[29]

Most prior studies relied on patient reporting of CC events and use based on local or national surveys or questionnaires, with the limitation of accurate recall.[5,6,13,15,26,30,31] In the present study, comorbidity and HCRU were captured based on recorded patient encounters and dispensed medications. Several comorbidities in the present study were similar in frequency to the chronic rhinosinusitis (40%), asthma (36%), and GERD (24%) reported in a cross-sectional study among all public service employees of two middle-sized towns in central Finland (n = 13,980) diagnosed with daily CC.[31] In comparison, lower prevalences for GERD (16%), asthma (14%), and Upper airway cough syndrome (7%) were reported in the Copenhagen General Population CC epidemiology study[26] and for asthma (24%) in a cross-sectional postal UK survey of CC patients with a mean age of 65 years.[32] Results are not directly comparable due to different study populations, designs, and methods.

In the present CC cohort, ED visits and hospitalizations for all causes and respiratory causes were frequent, appeared consistent during the baseline and follow-up years, and were significantly less in specialist-diagnosed CC patients than in event-diagnosed CC patients. The lower frequency of acute care in specialist-diagnosed CC patients may in part be due to a higher frequency of the following occurrences noted among specialist-diagnosed patients during both the baseline and follow-up years: 1) visits to specialists, including asthma specialists, whose care has been shown to reduce acute care visits,[33-35] 2) dispensing of relevant medications for the treatment of respiratory conditions (asthma and rhinitis controllers) and GERD (proton pump inhibitors) by these specialists, and 3) laboratory investigations (chest imaging, pulmonary function testing, laryngoscopy, and allergy testing) for the cause of CC. Another possible reason for differences in HCRU between event-diagnosed and specialist-diagnosed CC patients in the baseline year but not in the outcome year was that patients presenting to acute care settings were included in the criteria to identify the event-diagnosed group during the baseline year.

The burden of CC is also evident in its persistence in the follow-up year. CC persisted in 17.9% of the CC cohort,

Table 5. Follow-up year healthcare resource utilization and dispensed medications of the entire chronic cough cohort and subgroups

	Entire chronic cough (CC) cohort and subgroups			
Characteristic	**Entire CC cohort (N = 50,163)**	**Specialist-diagnosed CC (n = 11,290)**	**Event-diagnosed CC (n = 38,873)**	**p value[a]**
Persistence of CC[b]	8970 (17.9)	4586 (40.6)	4384 (11.3)	<0.001
All-cause patient visits				
Outpatient visits	49,453 (98.6)	11,159 (98.8)	38,294 (98.5)	0.009
≥ 1 emergency department (ED)	16,933 (33.8)	3183 (28.2)	13,750 (35.4)	<0.001
≥ 1 Hospitalization	7261 (14.5)	1344 (11.9)	5917 (15.2)	<0.001
Respiratory cause patient visits†				
Outpatient visits	32,602 (65)	8014 (71.0)	24,588 (63.3)	<0.001
≥ 1 ED	8629 (17.2)	1583 (14.0)	7046 (18.1)	<0.001
≥ 1 Hospitalization	4575 (9.1)	862 (7.6)	3713 (9.6)	<0.001
Specialist visits				
Pulmonologist	12,477 (24.9)	5558 (49.2)	6919 (17.8)	<0.001
Otolaryngology	8540 (17.0)	2728 (24.2)	5812 (15.0)	<0.001
Gastroenterology	7899 (15.7)	2303 (20.4)	5596 (14.4)	<0.001
Allergist	6106 (12.2)	2368 (21.0)	3738 (9.6)	<0.001
Urology	4070 (8.1)	976 (8.6)	3094 (8.0)	0.019
Speech Therapy	685 (1.4)	209 (1.9)	476 (1.2)	<0.001
≥1 specialty department	26,769 (53.4)	8580 (76.0)	18,189 (46.8)	<0.001
≥2 different specialty departments	9745 (19.4)	3932 (34.8)	5813 (15.0)	<0.001
≥3 different specialty departments	2665 (5.3)	1315 (11.6)	1350 (3.5)	<0.001
≥ 4 different specialty departments	523 (1.0)	282 (2.5)	241 (0.6)	<0.001
Laboratory tests (> 1%)				
Complete blood count	35,277 (70.3)	7822 (69.3)	27,455 (70.6)	0.006
Chest x-ray	21,018 (41.9)	4553 (40.3)	16,465 (42.4)	<0.001
Pulmonary function tests	10,795 (21.5)	4796 (42.5)	5999 (15.4)	<0.001
Advanced chest imaging	7816 (15.6)	2693 (23.9)	5123 (13.2)	<0.001
Allergy RAST testing	3902 (7.8)	1601 (14.2)	2301 (5.9)	<0.001
Laryngoscopy	3113 (6.2)	1272 (11.3)	1841 (4.7)	<0.001
Sinus imaging	3162 (6.3)	1293 (11.5)	1869 (4.8)	<0.001
Esophageal endoscopy	3339 (6.7)	1013 (9.0)	2326 (6.0)	<0.001
Barium swallow or upper GI	1350 (2.7)	499 (4.4)	851 (2.2)	<0.001
Nasal/sinus endoscopy	1186 (2.4)	381 (3.4)	805 (2.1)	<0.001
Bronchoscopy	990 (2.0)	465 (4.1)	525 (1.4)	<0.001
Respiratory medication (oral or inhaled)				
SABA singly	16,507 (32.9)	3605 (31.9)	12,902 (33.2)	0.012
Nasal corticosteroids	16,202 (32.3)	4327 (38.3)	11,875 (30.5)	<0.001
ICS/LABA	10,058 (20.1)	2802 (24.8)	7256 (18.7)	<0.001
ICS monotherapy	6494 (12.9)	1719 (15.2)	4775 (12.3)	<0.001
Leukotriene modifiers	6430 (12.8)	2046 (18.1)	4384 (11.3)	<0.001
Nasal antihistamines	3104 (6.2)	1277 (11.3)	1827 (4.7)	<0.001
SABA and SAMA combination	3081 (6.1)	535 (4.7)	2546 (6.5)	<0.001
LABA/LAMA	2609 (5.2)	487 (4.3)	2122 (5.5)	<0.001
H1 antihistamines	2352 (4.7)	388 (3.4)	1964 (5.1)	<0.001
Nasal SAMA	1937 (3.9)	888 (7.9)	1049 (2.7)	<0.001
LAMA monotherapy	587 (1.2)	157 (1.4)	430 (1.1)	0.013

(continued on following page)

Table 5. Follow-up year healthcare resource utilization and dispensed medications of the entire chronic cough cohort and subgroups (continued)

Characteristic	Entire chronic cough (CC) cohort and subgroups			
	Entire CC cohort (N = 50,163)	Specialist-diagnosed CC (n = 11,290)	Event-diagnosed CC (n = 38,873)	p value[a]
Gastrointestinal (oral)				
Proton pump inhibitors	15,907 (31.7)	4658 (41.3)	11,249 (28.9)	<0.001
H2 blockers	6266 (12.5)	1531 (13.6)	4735 (12.2)	<0.001
Miscellaneous (oral)				
Potential respiratory antibiotics	31,489 (62.8)	6446 (57.1)	25,043 (64.4)	<0.001
Corticosteroids	17,903 (35.7)	3872 (34.3)	14,031 (36.1)	<0.001
Narcotics, antitussive, psychotherapeutics (oral)				
Narcotics, including codeine	28,199 (56.2)	5726 (50.7)	22,473 (57.8)	<0.001
Antitussives, including codeine	21,762 (43.4)	4420 (39.1)	17,342 (44.6)	<0.001
Narcotics, no codeine	18,764 (37.4)	3818 (33.8)	14,946 (38.4)	<0.001
Codeine	17,145 (34.2)	3309 (29.3)	13,836 (35.6)	<0.001
Antidepressants	13,786 (27.5)	3015 (26.7)	10,771 (27.7)	0.036
Antitussives, no codeine	9464 (18.9)	2206 (19.5)	7258 (18.7)	0.038
Anxiolytics	8846 (17.6)	1715 (15.2)	7131 (18.3)	<0.001
Neuromodulators	7665 (15.3)	1660 (14.7)	6005 (15.4)	0.053

Abbreviations: SABA = short-acting β2-agonist, SAMA = short-acting muscarinic antagonist, LABA = long-acting β_2-agonist, LAMA = long-acting muscarinic antagonist, ICS = inhaled corticosteroid, GI = gastrointestinal.

[a] Comparisons were made between specialist-diagnosed and event-diagnosed subgroups; p values determined by γ^2 test or Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables.

[b] Data presented as n (%).

[c] Respiratory conditions: asthma, chronic obstructive pulmonary disease, vocal cord dysfunction, hyperventilation, allergic rhinitis. chronic rhinitis, nasal polyp disease, post-nasal drip (upper airway cough syndrome), chronic sinusitis, bronchiectasis, bronchiolitis obliterans, laryngomalacia, tracheomalacia, bronchomalacia, granulomatosis, cystic fibrosis, allergic bronchopulmonary aspergillosis, eosinophilic bronchitis/pneumonia, sarcoidosis, pulmonary fibrosis, hemoptysis, respiratory foreign body, obstructive sleep apnea, tonsillar enlargement, chronic tonsillitis, pertussis, pneumonia, influenza, and other acute lower respiratory infections.

which was higher in the specialist-diagnosed CC patients (40.6%) compared with the event-diagnosed CC subgroup (11.3%). The frequency of CC cough persistence in the specialist-diagnosed CC cohort is similar to what is seen in specialist cough clinics.[36] A small, prospective, observational study noted that CC persisted in 46% of 68 CC patients at a 5-year follow-up.[37] More long-term follow-up studies of CC patients are needed to better understand its natural history, particularly studying its clinical burden and economic cost. Cross-sectional surveys of CC patients documented a decrease in quality of life experienced by these patients.[13,14] Specifically, CC worsens the quality life of patients with asthma[38] or COPD[39] compared with those without CC.

There is an absence of approved FDA or European Medicines Agency treatments specific for refractory or idiopathic CC.[3,40] Presently treatments for CC rely on nonspecific cough suppressants, including narcotic and nonnarcotic antitussives,[41] and neuromodulators such as the anticonvulsant gabapentin[12] and amitriptyline[42], owing to some efficacy in reducing neuronal hypersensitivity.[43,44] The present study documented the frequent use of antitussives, including codeine in the CC cohort during the baseline and follow-up years. Neuromodulators were used in about 15% of the CC patients during the baseline and outcome years, which was a higher prevalence than seen in a non-cough Southern California Permanente Medical Group cohort (9%).[16] Although codeine and codeine containing antitussives are commonly used in CC, they remain largely ineffective to treat and manage CC.[45]

The cough hypersensitivity syndrome was proposed by The European Respiratory Society Task Force as a major trigger for CC, which was characterized by "troublesome coughing often triggered by low levels of thermal, mechanical, or chemical exposure."[46] Coughing is manifested by the cough hypersensitivity syndrome by typically innocuous factors such as laughing, talking, deep breathing, exercise, temperature changes, and aerosol exposure. Chronic activation of sensory nerves in the upper and lower airways act to initiate the cough process, which, being hypersensitized, leads to the symptoms of the pathologic cough.[40,47] Medications that target the specific upper and lower respiratory tract sensory nerve receptors to suppress the hypersensitivity in CC are being studied, one of which, an antagonist to the P2X purinoceptor 3 receptor, is in Phase III trials.[48]

This study has some limitations. The absence of patient-reported outcomes and the study's retrospective design are limiting factors that do not allow capturing of patient-reported outcomes. The consequences of varying coding expertise of physicians are not known. The present characteristics of the CC patients identified by administrative data in the large Southern California Permanente Medical Group managed care system may not be generalizable to populations identified by other methods and different medical care organizations. The full medication burden of the CC patients could not be determined because several upper respiratory, GERD, and antitussive medications are nonprescription and cannot be captured administratively. Moreover, patient use of and adherence to CC medications was not determined.

The study has several strengths, including the use of the comprehensive electronic KPSC research database, which permitted accurate capture of complete patient encounters, laboratory testing, and dispensed medications. In addition, the process of information extraction from clinical notes through NLP helped identify patients with CC, demonstrating the usefulness of the technique in a large managed care organization with comprehensive electronic medical records. The present study is one of few studies that have used clinical notes extracted by NLP to identify and characterize CC patients.

In summary, the present study demonstrates that CC patients can be identified with administrative data techniques including clinical notes, diagnosis codes, and antitussives medications. The study documented an overall 1% prevalence of CC, which was considerably higher in female patients and in elderly patients and varied by ethnicity. Comorbidities such as asthma, chronic sinusitis, allergic and chronic rhinitis, COPD, and GERD were frequently associated with CC. The burden of CC was supported by frequent laboratory testing, HCRU, dispensed medications including narcotic antitussives, and a 17.9% persistence into the follow-up year.

The present administrative data study accurately identified a CC cohort, overcoming the challenges posed by the absence of specific ICD9/10 codes for CC. The CC cohort had considerable laboratory testing, HCRU, and medications documenting the substantial burden of the condition. The methods used to identify CC patients in the present study should help foster more intensive study of CC to better understand its clinical and economic burden. This is particularly important given the promising new treatments for CC in Phase III study.[49] ❖

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Authors' Contributions

Robert S Zeiger made major contributions to the conception, design, statistical analysis, execution of the study, and interpretation of the findings; drafted the manuscript and revised it critically for important intellectual content; gave final approval of the version to be published; Fagen Xie, Benjamin D Hong , Wansu Chen made substantial contributions to the design of the study as well as interpretation of the findings; data capture and analysis; revised the manuscript critically for important intellectual content; and gave final approval of the version to be published. Michael Schatz, Jessica P Weaver, Vishal Bali, Jonathan Schelfhout made substantial contributions to the design of the study as well as interpretation of the findings; revised the manuscript critically for important intellectual content; and gave final approval of the version to be published.

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ORIGINAL RESEARCH ARTICLE

Validation Study of Kaiser Permanente Bedside Dysphagia Screening Tool in Acute Stroke Patients

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ABSTRACT

Introduction: Dysphagia occurs in up to 50% of patients with acute stroke symptoms, resulting in increased aspiration pneumonia rates and mortality. The purpose of this study was to validate a health system's dysphagia (swallow) screening tool used since 2007 on all patients with suspected stroke symptoms. Annual rates of aspiration pneumonia for ischemic stroke patients have ranged from 2% to 3% since 2007.

Methods: From August 17, 2015 through September 30, 2015, a bedside dysphagia screening was prospectively performed by 2 nurses who were blinded to all patients age 18 years or older admitted through the emergency department with suspected stroke symptoms at 21 Joint Commission accredited primary stroke centers in an integrated health system. The tool consists of 3 parts: pertinent history, focused physical examination, and progressive testing from ice chips to 90 mL of water. A speech language pathologist blinded to the nurse's screening results performed a formal swallow evaluation on the same patient.

Results: The end study population was 379 patients. Interrater reliability between 2 nurses of the dysphagia screening was excellent at 93.7% agreement (K = 0.83). When the dysphagia screenings were compared with the gold standard speech language pathologist professional swallow evaluation, the tool demonstrated both high sensitivity (86.4%; 95% confidence interval = 73.3-93.6) and high negative predictive value (93.8%; 95% confidence interval = 87.2-97.1).

Conclusion: : This tool is highly reliable and valid. The dysphagia screening tool requires minimal training and is easily administered in a timely manner.

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INTRODUCTION

This study was performed to test the validity, sensitivity, and positive predictive value of a bedside screening tool to detect risk of aspiration pneumonia due to dysphagia. Difficulty swallowing or dysphagia is common among acute stroke patients, occurring in approximately 30% to 78% of the population.[1-3] About 50% of patients aspirate, and one-third of those who aspirate develop pneumonia.[3-5] Dysphagia is associated with a 3-fold increase in mortality risk, mainly attributable to pneumonia.[3,4] Other adverse consequences of dysphagia may include dehydration, malnutrition, weight loss, increased morbidity, increased length of stay, reduced rehabilitation capabilities, and psychological illness.[2,6] Rapid screening for dysphagia by a bedside nurse was developed to optimize resource utilization and to improve patient satisfaction. Speech language pathology services are limited. Waiting for these services may unnecessarily lengthen the time the patient is without oral intake.[7]

Dysphagia screening tools have been developed, such as the Barnes Jewish Hospital Stroke Dysphagia Screen, the Modified Mann Assessment of Swallowing Ability, the Emergency Physician Swallowing Screening, the Toronto Bedside Swallowing Screening Test,[8] and Gugging Swallow Screen.[9] Agreed-upon criteria for a dysphagia screening tool include adequate sensitivity and specificity to identify dysphagia and aspiration risk, a scoring system of "pass/fail," ease of use for health care providers other than a speech language pathologist (SLP), and the ability to rescreen with a change in clinical condition.[10,11] The use of dysphagia protocols to reduce the risk of pneumonia, death, or dependency has not been proven; however, the American Heart Association 2018 Guidelines for Early Management of Acute Stroke Guidelines state that it is reasonable to screen patients before oral intake.[12,13]

The bedside dysphagia screening tool used at the large integrated health system was developed in 2007. The annual aspiration rates for ischemic stroke patients have averaged 2% to 3% over a period of 12 years. The tool incorporates components of the Massey Bedside Swallowing Screen and the Burke dysphagia screening tool.[14,15] The dysphagia screening tool is divided into 3 parts. Part I includes selected history with a failed test for a tracheostomy, history of aspiration pneumonia, or currently nothing by mouth (NPO) with tube feeding. Part II includes a cognitive and motor skills

assessment by the registered nurse (RN). Patients must effectively swallow their own secretions, move the tongue, smile and pucker the lips, and cough on command. In Part III, the patient must swallow without coughing or throat clearing during and 1 minute after taking ice chips. Then the patient may progress to drinking 90 mL of water continuously (Figure 1). The patient may fail the screening at any point or may pass and be allowed oral intake.

Inclusion/Exclusion Criteria

Study inclusion criteria were all patients 18 years or older exhibiting suspected stroke symptoms who were admitted to the emergency department (ED) at 1 of the 21 participant hospitals and had a diagnosis of stroke or transient ischemic attack (TIA) upon discharge. Exclusion criteria were a history of dysphagia, pre-existing gastrostomy tubes, being currently intubated, having had received alteplase upon admission, and not having a diagnosis other than stroke or TIA upon discharge. Patients who received alteplase were excluded because they may change rapidly between the RN screening and evaluation by speech therapy.

METHODS

This study received approval from the governing Institutional Review Board. Informed consent was waived because both the dysphagia screening tool and speech language therapy evaluation were considered standard of care. The study was conducted from August 17, 2015 through September 30, 2015. The dysphagia screening tool was prospectively performed by 2 ED nurses who were blinded. The first nurse recorded the results of the dysphagia screening on a paper form. A second nurse completed a second dysphagia screening within 1 hour and recorded the results in the electronic medical record. The goal was to conduct both screens within a short period of time. An SLP consult was requested for all patients screened. The SLPs were asked to complete their dysphagia evaluation within 12 hours. Per usual practice, the patient was allowed oral intake before the SLP evaluation if both screenings were passed. If either dysphagia screening was failed, the patient was kept NPO until the SLP evaluation was completed. The SLP was blinded to the results of the screening and did not review the electronic medical record. In usual practice, they do not use the presence of food or drink at the bedside as an indication of NPO status because family members may unknowingly bring in food or give their loved ones water.

Results of the first and second dysphagia screenings were entered into a database. The portion of the screening prompting a fail result was recorded. The results of the SLP formal swallow evaluation, including the type of liquids tolerated by the patient (eg, honey thick, nectar thick, or nectar thin), were entered. For purposes of this study, only tolerance of thin liquids was considered a passing score; tolerance of all other modified liquids was considered to be a fail. Validity was determined by a comparison of the second RN dysphagia screening to the results of the SLP dysphagia evaluation.

Statistics were calculated using a SAS computer program. Reproducibility of the dysphagia screening was quantified by the percent agreement and the interrater reliability. To assess the performance of the dysphagia screening in comparison to the formal assessment by an SLP, both the sensitivity and negative predictive value were quantified. The specificity and positive predictive value (PPV) were analyzed. The point estimate and 95% confidence interval (CI) were determined.

RESULTS

There were 726 patients screened using the Dysphagia Screening Tool. After applying the exclusion criteria, 392 stroke patients were enrolled. The average age was 70 ± 14 years, and 48% were female (n = 188). The group was composed of 52% (n = 203) white non-Hispanic, 12% (n = 45) Black, 11% (n = 44) Asian/Pacific Islander, 20% (n = 78) Hispanic, and 6% (n = 22) Other/Unknown (Table 1). Members of the health system constituted 86% (n = 338) of the population. Seventy-one percent (n = 278) of subjects had experienced an ischemic stroke, 25% had experienced a TIA (n = 96), and 5% had experienced a hemorrhagic stroke (n = 18). The screening was done on all patients presenting with suspected stroke symptoms. The median National Institutes of Health Stroke Scale score was 1, with a range of 0 to 23. Sixty-nine percent (n = 272) of patients were discharged home, and 9% (n = 34) had home health assistance. Four percent (n = 15) were discharged to a rehabilitation facility and 7% (n = 28) to a skilled nursing home. Less than 1% (n = 3) of patients died (Table 1).

Seventy-seven percent (n = 297) of patients passed the dysphagia screening. In Part I, 4 patients failed the medical history section, and an additional 4 failed by not being able to sit properly for the examination. In Part II, which assessed cognitive and motor skills, 79 patients failed: 16 failed due to altered level of consciousness or inability to attend to cues; 24 failed to control saliva, lacked tongue control, or were unable to smile and/or pucker; and 39 failed voice quality. In Part III, which included water tests, 2 patients failed because they did not respond to ice chips in the mouth, 4 did not tolerate ice chips, and 2 did not tolerate water without clearing the throat during and 1 minute afterward (Table 2).

A total of 379 subjects received 2 dysphagia screenings for comparison; 13 patients had only one dysphagia screening. Seventy-two percent (n = 272) of patients passed both dysphagia screenings; 22% (n = 83) failed both screens. The reliability of the dysphagia screening across nurses was high, with 93.7% agreement and interrater reliability of $\kappa = 0.83$ (Table 3).

A total of 169 subjects had both a screening and an evaluation completed to determine the validity of the dysphagia

	Admission (Discharged) 03/21/12 Discharge Unit: TCE						
	3/21/12						
	1600	1622	1635	1650	1700	1715	1730
Tracheostomy	No			No			
Aspiration Pneumonia	No			No			
Currently NPO with Tube Feeding	No			No			
	PART I - PREPARE PATIENT						
Is patient seated appropriately for eating	Yes			Yes			
Oral Cavity and back of throat clear	Yes			Yes			
	PART II - LEVEL OF CONSCIOUSNESS - If NO, refer immediately to ST/OT for dysphagia evaluation. Keep patient NPO including meds. Initiate Aspirations Precautions - Place aspiration precautions sign, elevate head of bed at least 30 degrees, place suction at bedside, no water or straws at bedside. Notify MD to consider need for alternative nutrition, hydration, and route to administer medications.						
Is patient awake/alert for 20 min continuously	Yes			Yes			
Does the patient attend with cues	Yes			Yes			
	PART II - SECRETIONS TONGUE CONTROL - If NO, refer immediately to ST/OT for dysphagia evaluation. Keep patient NPO including meds. Initiate Aspirations Precautions - Place aspiration precautions sign, elevate head of bed at least 30 degrees, place suction at bedside, no water or straws at bedside. Notify MD to consider need for alternative nutrition, hydration, and route to administer medications.						
Able to swallow own secretions	Yes			Yes			
Handles secretions without drooling	Yes			Yes			
Able to manage saliva without coughing	Yes			Yes			
Able to move tongue side to side up and down	Yes			Yes			
Able to smile and pucker	Yes			Yes			
	PART II - SOUNDS AND COUGH - If NO, refer immediately to ST/OT for dysphagia evaluation. Keep patient NPO including meds. Initiate Aspirations Precautions - Place aspiration precautions sign, elevate head of bed at least 30 degrees, place suction at bedside, no water or straws at bedside. Notify MD to consider need for alternative nutrition, hydration, and route to administer medications.						
Able to make sounds (e.g. grunting OR Speech)	No			Yes			
Able to cough on command	No			Yes			
	PART II - LARYNGEAL MOVEMENT - If NO, refer immediately to ST/OT for dysphagia evaluation. Keep patient NPO including meds. Initiate Aspirations Precautions - Place aspiration precautions sign, elevate head of bed at least 30 degrees, place suction at bedside, no water or straws at bedside. Notify MD to consider need for alternative nutrition, hydration, and route to administer medications.						
A rise in the larynx is felt when patient swallows							
	PART III - LARYNGEAL MOVEMENT WITH 1/2 TSP ICE CHIPS - If NO, refer immediately to ST/OT for dysphagia evaluation. Keep patient NPO including meds. Initiate Aspirations Precautions - Place aspiration precautions sign, elevate head of bed at least 30 degrees, place suction at bedside, no water or straws at bedside. Notify MD to consider need for alternative nutrition, hydration, and route to administer medications.						
Patient responds to ice (1/2 tsp) in mouth							
Rise in the larynx is felt when patient swallows ice							
Tolerates w/o coughing during AND 1 minute after							
Tolerates w/o throat clearing during AND 1 minute							
Voice clear when saying and extended "ahh"							
	PART III - IF PT PASSES ICE CHIP TEST: REPEAT WITH WATER progressing from sip , from cup and then 90ml (3oz) drinking CONTINUOUSLY without interruption (may use straw) - If NO, refer immediately to ST/OT for dysphagia evaluation. Keep patient NPO including meds. Notify MD to consider need for alternative nutrition, hydration, and route to administer medications; *initiate Aspiration Precautions						
Patient responds to water (90 ml) in mouth							
Rise in the larynx is felt when patient swallows water							
Tolerates w/o coughing during AND 1 minute after							
Tolerates w/o throat clearing during AND 1 minute							
Voice clear when saying and extended "ahh"							
Patient passed swallow screen							

Figure 1. Dysphagia screening tool.

Table 1. Demographic information

Characteristics	Received swallow screening and evaluation (n = 169) Total (%)	Received swallow screenings (n = 223) Total (%)	p value	Overall (n = 392) Total (%)
Patient characteristics				
Female, %	74 (43.8)	114 (51.1)	0.15	188 (48.0)
Age (mean ± SD)	72 ± 13	68 ± 14	0.01	70 ± 14
Race, %			0.41	
White, non-Hispanic	85 (50.3)	118 (52.9)		203 (51.8)
Black	18 (10.6)	27 (12.1)		45 (11.5)
Asian/Pacific Islander	16 (9.5)	28 (12.6)		44 (11.2)
Hispanic	41 (24.3)	37 (16.6)		78 (19.9)
Other/unknown	9 (5.3)	13 (5.8)		22 (5.6)
NIHSS			<0.001	
Mean ± SD	4 ± 5	2 ± 3		3 ± 4
Median	3	1		1
Range	0-23	0-23		0-23
Case characteristics				
Discharge status			<0.001	
Home	83 (49.1)	155 (69.5)		238 (60.7)
Home health	22 (13.0)	12 (5.4)		34 (8.7)
Rehab facility	11 (6.5)	4 (1.8)		15 (3.8)
Skilled nursing facility	20 (11.8)	8 (3.6)		28 (7.1)
Expired	2 (1.2)	1 (0.4)		3 (0.8)
Other	31 (18.3)	43 (19.3)		74 (18.9)
Type of stroke			0.07	
Ischemic	130 (76.9)	148 (66.4)		278 (70.9)
Hemorrhagic	6 (3.6)	12 (5.4)		18 (4.6)
TIA	33 (19.5)	63 (28.2)		96 (24.5)
Time between screenings, minutes (median)	22	19.5		20
Time from screening to SLP evaluation, h	13	NA		13

NIHSS = National Institutes of Health Stroke Scale; SLP = speech language pathologist; TIA = transient ischemic attack.

screening tool. Among the 97 patients who passed the RN dysphagia screening, 91 also passed the SLP swallow evaluation. Of the 72 patients who failed the RN dysphagia screening, 38 also failed the SLP swallow evaluation (Table 4). The dysphagia screening performed well when compared with the formal SLP swallow evaluation, demonstrating both high sensitivity (86.4%; 95% CI = 73.3-93.6) and high negative predictive value (93.8%; 95% CI = 87.2-97.1). It also demonstrated moderately high specificity (72.8%; 95% CI = 64.4-79.8), with a PPV of 52.8% (95% CI = 45.3-60.2) (Table 4).

DISCUSSION

The tool demonstrated high sensitivity (86.4%) to accurately detect dysphagia. The dysphagia screening tool had high specificity (72.8%) to identify patients who do not have dysphasia, which minimizes the time spent without oral intake. The low PPV (52.8%) indicates an increased failure rate by the nurse vs the SLP evaluation, providing increased safety for the patient. Patients without dysphagia may be mistakenly identified as positive; however, the patients can then be cleared by the SLP evaluation. Thus, the risk of those with dysphagia receiving fluids or medications is reduced.[8,16] This dysphagia screening tool compares favorably with other screening tools for reliability and validity.[8] The tool also includes necessary components: identification of possible dysphagia, a simple scoring system, ease of completion for health care workers outside of an SLP, and the ability to rescreen when clinical changes indicate.[17,19,20] The screening is a reliable preliminary assessment of a patient's ability to swallow. The protocol's validity was measured against the gold

Table 2. Results of dysphagia screening

	Passed	Failed	Passed	Failed	Passed	Failed
Screen section	Region 1		Region 2		Combined	
Part I History	284	3	104	1	388	4
Part I Patient able to sit properly	281	3	103	1	384	4
Part I Patient level of consciousness: Patient awake for 20 min	269	12	99	4	368	16
Part II Patient level of consciousness: Able to attend to cues	260	9	96	3	356	12
Part II Secretions tongue control: Able to swallow secretions/handle secretions without drooling	258	2	95	1	353	3
Part II Secretions tongue control: Able to manage saliva without drooling	256	2	94	1	350	3
Part II Secretions tongue control: Able to move tongue side to side	254	2	94	0	348	2
Part II Secretions tongue control: Able to smile and pucker	251	3	93	1	344	4
Part II Sounds and cough: Able to make sounds	249	2	93	0	342	2
Part II Vocal quality and speech: Speech is clear, not slurred/dysarthric	224	25	90	3	314	28
Part II Vocal quality and speech: Voice sounds strong and clear	221	3	88	2	309	5
Part II Vocal quality and speech: Voice does not sound wet/weak/hoarse	221	0	87	1	308	1
Part II Vocal quality and speech: Able to say extended "ahh"	221	0	86	1	307	1
Part II Laryngeal movement: A rise in larynx is felt with swallow	219	2	86	0	305	2
Part III Ice chip test: Patient responds to ice in mouth	217	2	86	0	303	2
Part III Ice chip test: Rise is felt in larynx when patient swallows	217	0	86	0	303	0
Part III Ice chip test: Tolerates w/o coughing during AND 1 min after	213	4	86	0	299	4
Part III Ice chip test: Tolerates w/o throat clearing during AND 1 min after	213	0	86	0	299	0
Part III Ice chip test: Voice is clear when saying an extended	213	0	86	0	299	0
Part III Water test: Patient responds to water in mouth	213	0	86	0	299	0
Part III Water test: Rise is felt in larynx when patient swallows	213	0	86	0	299	0
Part III Water test: Tolerates without coughing during AND 1 min after	211	2	86	0	297	2
Part III Water test: Tolerates without throat clearing during AND 1 min after	211	0	86	0	297	0
Part III Water test: Voice is clear when saying an extended "ahh"	211	0	86	0	297	0

standard of an SLP evaluation.[20] The tool is easy to learn and quick to perform, taking an average of 10 minutes to complete.

Limitations

There was variation in the elapsed time between the 2 RN dysphagia screenings and between the RN screenings and the SLP evaluation. The demands on the RN's time due to unit acuity affected the time between RN screenings. The time between RN screenings and SLP evaluation was affected by the SLP's availability. However, the impact was minimal because the median time between the 2 dysphagia screenings was 20 minutes, and there were 13 hours between the dysphagia screening and the SLP evaluation (Table 1). Blinding between the 2 RNs was done on the honor system because the subinvestigators were not present for all dysphagia screenings. Hospitalists were informed of the study. However, there were subjects who had passed the screening but did not receive a physician order for an SLP evaluation. These subjects were eliminated. Individual outcome data for the occurrence of aspiration pneumonia in

Table 3. Interreliability of 2 registered nurse-blinded dysphagia screenings

Swallow evaluation agreement	n	%
Both pass	272	71.8
Both fail	83	21.9
No agreement	24	6.3
Total	379	
Measure of reliability	Reliability estimate	
Percent agreement	93.7%	
Probability of passing	74.9%	
Expected Agreement	62.4%	
Interrater reliability (kappa)	83.1%	

Table 4. Validation of registered nurse swallow screening against the speech language pathologist swallow evaluation

	Combined Region 1 and Region 2		
	Speech evaluation result		
Swallow screening result	Pass*	Fail*	Total
Pass	91	6	97
Fail	34	38	72
Total	125	44	169
	Validation estimate		
Measure of validation	Estimate	95% CI lower	95% CI upper
Sensitivity	86.4%	73.3	93.6
Specificity	72.8%	64.4	79.8
PPV	52.8%	45.3	60.2
NPV	93.8%	87.2	97.1

* "Pass" (low dysphagia risk) = thin liquids; "Fail" (high dysphagia risk) = nothing by mouth or modified liquids. For predictive value: "positive" = dysphagia (fail screen); "negative" = no dysphagia (pass screen).

CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.

patients who passed the screening were not available. Only the aggregate rate of aspiration pneumonia is known.

CONCLUSION

The Dysphagia Screening Tool is reliable and valid and has minimal training requirements. Thousands of patients in both large and smaller acute care settings have been screened in a timely manner by nurses. Although this study was not able to correlate use of the tool with outcomes, the healthcare system overall has low aspiration rates (2%-3%) for patients with acute ischemic strokes. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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ORIGINAL RESEARCH ARTICLE

Presentation of Rash in a Community-Based Health System

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ABSTRACT

Introduction: Coordination of care between primary care providers and dermatologists is important to ensure high quality and cost efficiency. In our integrated care setting, we used a retrospective cohort study to assess which patients self-refer to dermatology and which returned for a follow-up visit in dermatology.

Methods: We identified 107,832 patients with a new rash diagnosis who presented to primary care or dermatology between January and March 2017. We compared patients who self-referred to dermatology with those who used primary care, using multi-level generalized estimating equations with adjustment for patient-level covariables and medical center. We also characterized patients who returned for a follow-up visit in dermatology.

Results: Among patients with a new rash diagnosis, 99% were originally seen in primary care. Patients with a history of a dermatological condition were more likely to present to dermatology. Patients with a history of a dermatological condition or with psoriasis, pigment, hair, bullous, or multiple conditions were more likely to have a follow-up visit with a dermatologist. For each outcome, initial location of care and return for a follow-up visit, we found minimal clustering by medical center or provider.

Conclusion: One percent of patients with a new rash diagnosis self-refer to dermatology in this setting. Patients with a history of a dermatological condition were more likely to self-refer to dermatology and to have a follow-up visit with a dermatologist. Individual dermatologists and primary care providers had little impact on a patient's odds of returning for a follow-up visit.

Introduction

Dermatologists should be used for their highest scope of practice because their workforce is limited and specialty care is costly.[1] With respect to rash, access to dermatologists may be important for making difficult diagnoses, selecting treatments, and educating the patient. However, many rashes are self-limiting, and it is important to improve management and coordination of care between primary care providers (PCPs) and dermatologists.

Kaiser Permanente Northern California, a community-based health system, provides integrated, capitated care. For rash, patients are strongly encouraged to start their care in the primary care department. However, patients are permitted to self-refer to dermatology. We sought to understand which patients with rash self-refer to dermatology and which have a follow-up visit to dermatology. This information is important for understanding how best to manage dermatology utilization to achieve high-quality, affordable care.

Methods

Data for this study were collected from the Kaiser Permanente Northern California electronic medical record system. We identified patients presenting to primary care or dermatology with a rash between January 1 and March 31, 2017. Rash diagnoses included ICD-10 codes for acne and other follicular disorders, bullous and other systemic disorders, alopecia and other disorders of hair, viral infections of the skin, inflammatory dermatoses, disorders of pigmentation, psoriasis, pruritis, radiation-related conditions, and sweat disorders (ICD-10 diagnostic codes: B00-B06, B08-B09, B35-B36, L00-L56, L58-L59, L63-L75, L77-L81, L83, L85-L95, and R21). Patients with complicating skin conditions (B07, C4A, C43-C44, D03-D04, D17-D18, D22-D23, D48-D49, D69, L57, L60-L62, L76, L82, L84, L96-L99, and R21) diagnosed on the same day or in the year prior to their initial rash diagnosis, or with a rash diagnosis or dermatology encounter in the preceding year were excluded from the study.

We fit 3 models to understand the use of dermatology visits in the care of rash initially and within 90 days of the first encounter, 90 days allowing for a range of follow-up practices, including time for patients whose rash did not resolve with initial management to schedule a follow-up visit. First, we modeled the outcome of location of initial rash encounter (dermatology vs primary care). Then, for the outcome of whether a patient had a follow-up visit in dermatology within 90 days of the first encounter (yes, no), we fit separate models for patients whose initial rash encounter was in dermatology and for patients whose initial rash encounter was in primary care. All models were fit using generalized linear mixed models adjusted for patient age, sex, race/ethnicity, history of dermatologist-diagnosed skin conditions, and initial diagnosis, with random effects to account for clustering by provider and/or medical center. We also computed the intra-class correlations (ICC) for the random effects using the latent-variable method, assuming a standard logistic distribution with a mean of 0 and variance $\frac{\pi^2}{3}$.[2] The model for location of the initial encounter included a random

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intercept for medical center. The ICC for medical center can be interpreted as the correlation of patients at the same medical center. The model for follow-up visit in dermatology among patients who received initial care in dermatology included a random intercept for dermatologist. The dermatologist ICC represents the correlation between 2 patients with the same dermatologist. The model for follow-up visit in dermatology among patients who received initial care in primary care included random intercepts for both PCP and medical center. Because PCPs are nested within medical centers, the medical center ICC is the correlation between 2 patients at the same medical center with different PCPs, and the PCP ICC is the correlation between 2 patients with the same PCP at the same medical center.

Results

We identified 247,546 patients presenting in-office or via telephone to primary care or dermatology with a rash diagnosis between January 1 and March 31, 2017. Patients with a concurrent lesion or other non-rash dermatological condition, or with a dermatological diagnosis or dermatology encounter in the preceding year, were excluded from the study leaving 107,832 eligible patients (Table 1). Of these, 106,489 (99%) new rash patients initially presented to 3830 primary care providers, and 1373 (1%) initially presented to 166 dermatologists. The patients who had their first visit in the dermatology department were more likely to be 30-69 years of age and female, with half having been diagnosed with a skin condition in the past 10 years (although those with a condition in the past year were excluded from the study) (Table 1).

Having a first visit in dermatology was directly associated with having a history of a dermatological condition and inversely associated with diagnoses of inflammatory and infectious disorders, young and old age, and Hispanic ethnicity. For those with a history of a dermatological condition, 70% of the diagnoses recorded for the present episode were the same as recorded for the history. After accounting for patient-level covariates, patients who self-referred to dermatology were somewhat clustered within medical centers, although the effect was small (medical center ICC: 0.10).

In the subgroup whose first visit was in dermatology, 213 (16%) returned for a follow-up visit in dermatology in the 90 days following the original encounter, and this was directly associated with past acute skin conditions and with present hair and multiple conditions, as well as Hispanic ethnicity. Return for a follow-up visit in dermatology barely clustered by initial dermatologist (ICC: 0.02).

In the subgroup whose first visit was in primary care, 5755 (5%) returned for a follow-up visit in dermatology. This visit was directly associated with past chronic and acute dermatologic conditions and with present hair, psoriasis, pigment, bullous, and multiple conditions. It was inversely associated with young age and Asian-American and Hispanic race/ethnicity. Return for a follow-up visit in dermatology clustered minimally by medical center (ICC: 0.04) and PCP (ICC: 0.09).

Discussion

In our integrated system, we found 99% of patients with a new rash diagnosis were initially managed in primary care, of whom 5% required a dermatology office visit. The 1% of patients who started in dermatology had more complex histories of dermatologic diseases and were more likely to have a return dermatology office visit. We speculate that this stemmed from the patient having a prior relationship with the dermatologist. Current diagnosis was an important predictor of initially presenting to dermatology and of having a return dermatology office visit. Patients presenting with bullous disorders or disorders of pigmentation were especially likely to initially present to dermatology, most likely because these conditions require more extensive specialist knowledge and expertise, and consideration should be given to more rapidly escalating these patients to the care of a dermatologist. The minimal clustering in care patterns by medical center suggests relatively standardized care from one medical center to the next. Similarly, the minimal clustering by provider suggests that dermatologists and PCPs schedule follow-up visits in response to the patient needs and not because they have propensities to routinely schedule follow-up visits. Standardized care often reflects high-quality care.[3]

Our finding that PCPs manage most rash cases is consistent with a study of National Health Service Walk-in Centres that noted 21% of patients had a skin-related problem, of which 89% were rash.[4] To our knowledge, few papers have been published that separate rash from lesion. In a study of 208 primary care patients with rashes and lesions, nearly 40% were referred for a dermatology office visit, which is higher than our proportion of 5%.[1] However, the primary reason for referral was for biopsy or excision of a skin lesion, which would occur with few rash patients. The same study reported that after lesions, inflammatory diseases and infections were the most common diagnoses in primary care, similar to our study.

For 2 additional reports, to be published separately, we are examining the effectiveness of teledermatology modalities for managing rash and the use of e-consult and roving dermatologists (ie, specialist dermatology providers in the primary care department) for improving the coordination of care for rash. The present report identifies

Table 1. Characteristics of 107,832 Kaiser Permanente Northern California members presenting with rash, aged 0-89 years, January through March 2017, %

	Department of first visit		Outcome = first visit in dermatology (N = 107,832)		Outcome = follow-up visit in dermatology			
	Primary care (N = 106,489)	Dermatology (N = 1,343)			First visit in primary care (N = 106,489)		First visit in dermatology (N = 1373)	
Characteristic	%	%	OR	95% CI	OR	95% CI	OR	95% CI
Initial diagnosis								
Acne	16	25	2.8	2.4-3.2	0.9	0.8-1.0	0.9	0.5-1.4
Bullous	<1	2	8.3	5.2-13.2	1.9	1.3-2.7	1.8	0.6-5.4
Hair	3	5	3.4	2.6-4.4	3.0	2.6-3.3	2.2	1.2-4.2
Infection	24	3	0.3	0.2-0.3	0.4	0.3-0.4	0.6	0.2-1.7
Inflammatory	40	22	1.0	[Reference]	1.0	[Reference]	1.0	[Reference]
Pigment	1	7	10.3	8.1-13.1	2.1	1.8-2.6	1.2	0.7-2.3
Psoriasis	2	4	2.0	1.4-2.7	2.2	1.9-2.4	0.6	0.2-1.7
Other	7	15	4.8	4.0-5.7	1.0	0.9-1.1	0.8	0.5-1.4
Multiple	6	17	3.2	2.7-3.9	1.5	1.4-1.7	1.6	1.0-2.6
Age (y)								
0-17	27	14	0.7	0.6-0.9	0.6	0.6-0.7	1.3	0.8-2.2
18-29	17	17	1.0	[Reference]	1.0	[Reference]	1.0	[Reference]
30-49	28	33	1.2	1.0-1.4	1.0	1.0-1.1	0.9	0.5-1.3
50-69	22	29	1.1	0.9-1.3	1.1	1.0-1.2	0.8	0.5-1.3
70-89	6	8	0.8	0.6-1.0	1.0	0.9-1.1	0.3	0.1-0.8
Sex/gender								
Female	56	63	1.0	[Reference]	1.0	[Reference]	1.0	[Reference]
Male	44	37	0.9	0.8-1.0	1.0	1.0-1.1	0.8	0.6-1.1
Race/ethnicity								
Asian-American	21	20	0.9	0.8-1.1	0.8	0.7-0.9	1.2	0.8-1.8
African-American	7	7	1.0	0.8-1.3	1.0	0.9-1.1	0.8	0.4-1.6
Hispanic	24	20	0.7	0.6-0.9	0.8	0.7-0.9	1.4	1.0-2.1
White	40	44	1.0	[Reference]	1.0	[Reference]	1.0	[Reference]
Other/missing	9	8	1.0	0.8-1.2	0.9	0.8-1.0	0.8	0.4-1.5
History of dermatological diagnosis[a]								
Any chronic	11	42	6.2	5.5-7.0	1.5	1.4-1.6	1.1	0.8-1.5
Acute, not chronic	3	9	3.8	3.1-4.6	1.2	1.1-1.4	1.7	1.1-2.8
None	86	50	1.0	[Reference]	1.0	[Reference]	1.0	[Reference]

[a] History of dermatological diagnosis was categorized as chronic (acne, inflammatory, psoriasis, skin cancer, actinic keratosis); acute, not chronic (bullous, hair, infectious, pigmentation, other conditions, or seborrheic keratosis); or none, in that order, based on 10-year history of primary care and dermatology diagnoses available in the electronic medical record.

patients with more complex needs and with greater access to dermatology because of existing relationships. Further characterization of these patients could lead to interventions to further improve care quality and cost efficiency. We also noted that Hispanic patients were less likely to have a first visit or follow-up visit with a dermatologist. To our knowledge, this has not been reported in the past, and additional research is merited.

A limitation of this study was our inability to assess rash severity. A premise of the design was that rash severity was distributed similarly across centers and providers. If so, then the minimal correlations observed across centers and providers indicate that the patients with the most severe disease were the ones who needed a dermatology follow-up visit. Because many rashes are self-limiting, patients may be scheduled for a follow-up visit that is cancelled if the rash resolves with or without treatment.

It should also be kept in mind that results from our integrated care setting may not generalize to fee-for-service settings, where referral rates to dermatology are higher.[5] Primary care providers at Kaiser Permanente have access to teledermatology, e-consult, and roving dermatologists, system-level factors that

undoubtedly drive patient choice, although these care pathways could be implemented in fee-for-service settings if payment rules allowed. Notwithstanding these limitations, the study improves understanding of care patterns for rash, which is important for realizing health care value. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Authors' Contributions

Jennifer Dusendang, MPH, contributed to data collection, data analysis, and manuscript preparation. Sangeeta Marwaha, MD, contributed to study design, data collection, data analysis, and manuscript preparation. Stacey Alexeeff contributed to study design, data analysis and manuscript preparation. Lisa Herrinton, PhD, contributed to study design, data collection, data analysis, and manuscript preparation.

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REVIEW ARTICLE

A Clinical Approach to Catamenial Epilepsy: A Review

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ABSTRACT

Importance: Catamenial epilepsy (CE) is exacerbated by hormonal fluctuations during the menstrual cycle. Approximately 1.7 million women have epilepsy in the United States. CE affects more than 40% of women with epilepsy. There is a paucity of literature addressing this condition from a clinical standpoint, and the literature that does exist is limited to the neurological community. This article reviews the diagnosis and management of CE for the non-neurologist. Women with CE have early touch points in their care with numerous health care providers before ever consulting with a specialist, including OB/GYNs, pediatricians, emergency department physicians, and family medicine providers. In addition, women affected by CE have seizures that are more recalcitrant to traditional epilepsy treatment regimens. To optimize management in patients affected by CE, menstrual physiology must be understood, individualized hormonal contraception treatment considered, and adjustments and interactions with antiepileptic drugs addressed.

Observations: CE is a unique subset of seizure disorders affected by menstrual fluctuations of progesterone and estrogen. The diagnosis of CE has been refined and clarified. There is an ever-increasing understanding of the importance and variety of options of hormonal contraception available to help manage CE. Furthermore, antiepileptic drugs and contraception can interact, so attention must be directed to optimizing both regimens to prevent uncontrolled seizures and pregnancy.

Conclusion and Relevance: CE can be diagnosed with charting of menstrual cycles and seizure activity. Hormonal treatments that induce amenorrhea have been shown to reduce CE. Optimizing antiepileptic drug dosing and contraceptive methods also can minimize unplanned pregnancies in women affected by CE.

INTRODUCTION

Catamenial epilepsy (CE) is a prevalent and serious seizure pattern characterized by periodic fluctuations in seizure frequency corresponding to the menstrual cycle.[1] Studies estimate that the prevalence of CE ranges from 10% to 70% in women with epilepsy (WWE).[1-7] The wide range in prevalence depicts the early ambiguity in its classification. Herzog defined CE as the point of inflection on a graph of multiples of greater seizure frequency versus percentage of women with this increase in seizure frequency.[1] This was used to define the 3 distinct subtypes of CE: perimenstrual (C1), periovulatory (C2), and inadequate luteal phase (C3). Today, a ≥twofold increase in seizure frequency during a specific period in the menstrual cycle is used as the clinical diagnosis.[1] A large-scale National Institutes of Health (NIH) trial found 44.2% (130/294) of their randomized female patients with seizure have CE.[8]

The purpose of this review was to provide a comprehensive clinical understanding of CE and to outline treatment options for all clinicians who care for women affected by this disorder. We first give a brief description of the pathophysiology of this disorder, which is commonly associated with fluctuations in serum estrogen and progesterone levels. Second, we discuss common presentations and best practices for evaluation and diagnosis. Third, we summarize the most effective modern-day treatments for CE. We review the evidence supporting the role of hormonal management in CE. Last, contraception management in patients with CE is reviewed.

DISCUSSION

Pathophysiology

CE is strongly associated with the neuroendocrine system. These seizure fluctuations are modulated by the predominately proconvulsant properties of estrogen and anticonvulsant properties of progesterone and its metabolites.

Estrogen

Estrogens, specifically estradiol (E2), have been shown to have excitatory proconvulsant effects on the brain. In neurons, specifically excitatory CA1 pyramidal neurons in the hippocampus, E2 acts as a posttranscriptional modulator to positively regulate the density of spines and of excitatory N-methyl-D-aspartate receptors, leading to increased excitability.[9-13] Other proposed actions of E2 are the genetic repression of inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA),[14] and short-acting membrane-mediated current induction.[15,16] Multiple female rat studies have found activation of spike discharges and a decrease in the seizure threshold when rats are administered E2.[10,13,17-21] In female subjects with epilepsy, intravenously

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administered conjugated estrogen (a mixture including estrone sulfate, equilin sulfate, delta 8,9-dehydroestrone sulfate, 17-alpha estradiol sulfate, and 17-alpha dihydroequilin sulfate) produced seizures in 11 of 16 subjects and clinical seizures in 4 subjects.[22] The role of estrogen in seizure activity is complex, and studies have suggested that the effects are "dependent on dose, route of administration, acute versus chronic administration, natural hormonal environment, and estrogenic species."[16]

Progesterone

Conversely, progesterone has been found to have anticonvulsant effects. Most of the anticonvulsant actions occur via the reduced metabolites of progesterone, most notably allopregnanolone (AP). Studies have found that AP has sedative-hypnotic and anticonvulsant properties.[13,23,24] AP may exert these inhibitory effects by aiding the potentiation GABAergic neurons.[13,23-26] AP levels rise and fall based on a woman's serum progesterone levels.[13,23] Several studies have demonstrated that progesterone acts via a genetic pathway in which it controls the synthesis of various neurotransmitters. In multiple mouse studies, increased progesterone levels had an overall inhibitory effect on the brain, leading to decreases in seizure occurrence.[13,21,27-29] In human models, progesterone injections that produce luteal-phase levels of progesterone led to significant reduction in the frequency of characteristic seizure brain wave spikes in 4 of 7 women with partial epilepsy.[30]

Diagnosis

CE is the occurrence or worsening of seizure activity related in timing to a woman's menstrual cycle. CE is commonly diagnosed in women after no other explanation of seizure patterns can be made. Awareness of the menstrual hormonal fluctuations and their impact on seizure activity can help clinicians provide an earlier and more precise diagnosis. Important questions to ask include the following: Are seizures continuing despite traditional antiepileptic drugs (AEDs)? Are the seizures occurring in a cyclic fashion? Has the patient charted her menstrual cycle and noted increase in seizure activity during particular times?

For clinicians, the first step in diagnosis of CE is to advise the patient to track menstrual cycles and seizures. This is commonly done by having the patient keep a seizure and menstrual diary (see Figure 1).[31] In addition to tracking bleeding, physicians also may consider tracking basal body temperature. Temperatures should be taken orally each morning. A ≥0.7 °F change signifies the beginning of the postovulatory phase.[31] Serum progesterone measurements also can be made, with >3 ng/mL marking the ovulatory phase.[31] Physicians also can track serum progesterone levels. For patients with irregular or anovulatory cycles, hormone levels and the use of ovulation kits can better elucidate cyclic relationship of seizures to the menstrual cycle. The specific increase in seizure frequency to make a diagnosis of CE is specific to the subtype (C1: 1.69-fold; C2: 1.83-fold; C3: 1.62-fold). In practice, a diagnosis of CE can be made if the patient presents

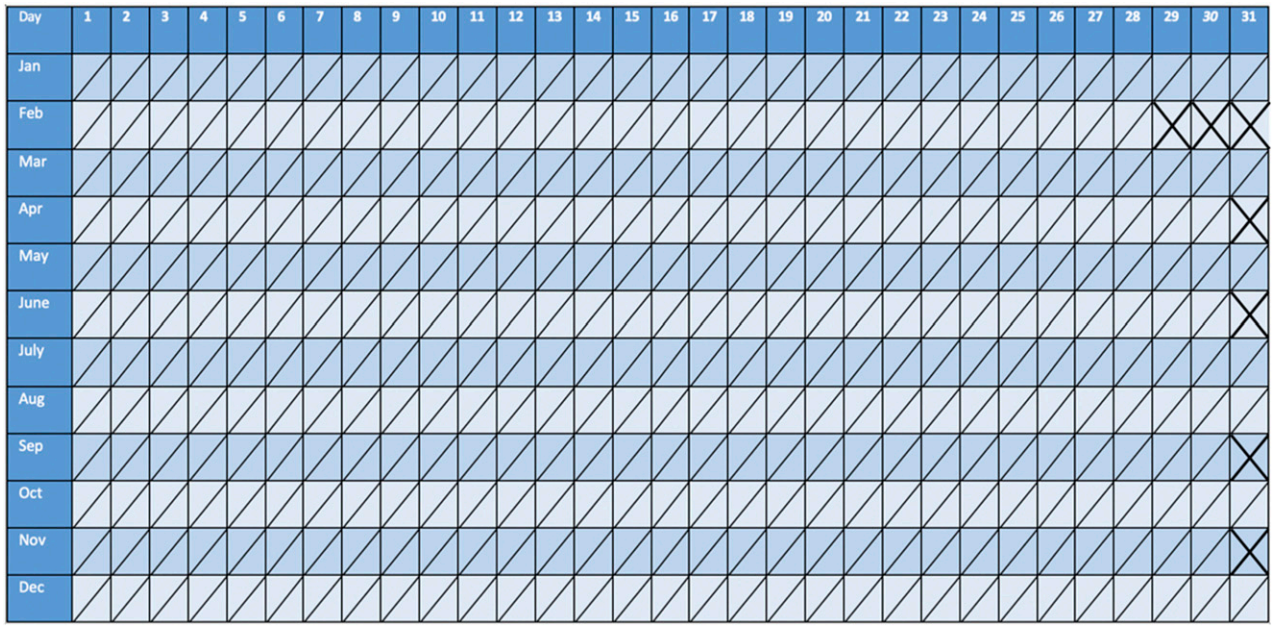

Figure 1. Diagnosis calendar. This calendar tracks the menstrual cycle and seizure cycle to help with diagnosis.

with ≥twofold increase in seizure frequency during one of the menstrual times noted as follows, or if the increase is simply repeated at similar times in the patient's menstrual cycle. The 3 subtypes, in which the seizure frequency typically increases ≥twofold, are perimenstrual (C1), periovulatory (C2), or inadequate luteal phase (C3) (see Figure 2).[1]

Classification is based on a 28-day cycle, with day 1 being the onset of menstrual flow. The follicular phase is during days 1 to 14, and the luteal phase is during days 15 to 28. The perimenstrual subtype (C1) is characterized by the rapid drop in progesterone during menstruation (days 25 to 3 of the following cycle). Although the proconvulsant estrogen does drop as well in this period, the progesterone experiences a more rapid decrease. This pattern has been the most responsive to treatment. The periovulatory subtype (C2) is characterized by the rapid surge of estrogen at day 10 to 15. The inadequate luteal phase subtype (C3) is characterized by an inadequate rise of progesterone during the luteal phase (days 10 to 3 of the following cycle).

This classification is applicable only to patients with anovulatory cycles. This is because of an inadequate development of the corpus luteum, which causes reduced levels of progesterone, but normal levels of estrogen (see Figure 3).[1,16] A 1997 study found that 42.3% of WWE presented with at least one of these classifications (C1: 35.7%, C2: 28.5%, C3: 41.4%).[1] Similarly, a 2015 NIH study found that of the 47.1% of WWE who presented with at least one of these classifications, 39.8% are C1, 33.9% are C2, and 47.1% are C3.[32]

Treatment

The role of the hormonal milieu in women with CE and the impact of hormones via contraceptives is extremely complex.

Figure 2. Diagnosis for catamenial epilepsy. This 4-step diagnosis process begins with signs and symptoms of cyclic seizure patterns that should raise suspicions. When clinicians become aware of these, they should attain more information with the Diagnosis Methods. With this information, they can make a diagnosis and subtype diagnosis. AED = antiepileptic drug.

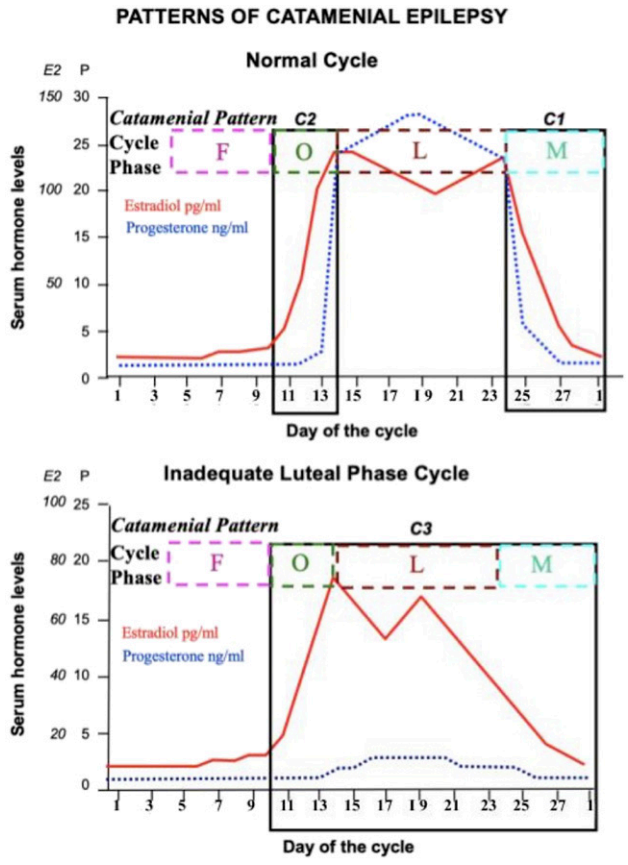

Figure 3. Hormone cycle and catamenial epilepsy (CE) classification. Estradiol and progesterone follow a consistent cyclical pattern during the menstrual cycle. Hormone levels and CE subtypes are shown for normal cycles and inadequate luteal-phase cycles. Because menstrual cycle intervals vary but, in the general population, most women ovulate 14 days before menstrual onset, this image transcribes the patient calendars to ones that designate the last 14 days as −14, −13, −12, and so on. The following stages are shown in this figure: follicular (F), ovulatory (O), luteal (L), and menstrual (M).[62]

Hormone treatment for CE should be considered after traditional methods have been tried. The most promising hormonal treatments for CE in studies are not hormonal contraception, but are actually natural progesterones (for example, a well-known hormone used in hormone replacement therapy: Prometrium) and amenorrhea-inducing drugs, such as gonadotropin-releasing hormone (GnRH) analogues and medroxyprogesterone acetate (MPA). However, studies are limited, as neither GnRH analogues nor MPA have undergone large-scale clinical trials for use in patients with CE.

Natural Progesterone

Natural progesterone can reduce the frequency of seizures. To date, there have been 5 important studies using natural progesterone as a treatment. Natural progesterone is sold in compound pharmacies in lozenge, suppository, lotion, and pill form (Prometrium). A large-scale, randomized, double-blind NIH study in 2015 concluded that natural progesterone in lozenge form given 3 times a day in 200-mg doses during day 14 through day 25 can decrease seizure frequency in C1-type CE. For a the subset of those with C1 type who normally had a ≥threefold increase in seizures during the perimenstrual period, the percentage of patients with a greater than 50% decrease in seizure rates increased from 21.3% to 57.1% when given natural progesterone lozenges versus 19.6% to 20.0% for those administered placebo.[32,33] In a second study of 8 women with C3 class CE, 6 of 8 women receiving 50 to 400 mg of natural progesterone suppositories twice a day had an average 68% decreased seizure activity.[34] A small earlier study on 25 patients with C1 and C3 pattern using cyclic natural progesterone treatment resulted in 72% of the subjects having reduced seizure activity, which persisted at a 3-year follow-up study.[35,36]

In addition, a randomized study of 38 women with C1 or C3 seizures found that the number of seizures after treatment was significantly decreased compared with placebo state ($p = 0.024$) when treated with 200-mg lozenges 3 times per day.[37] Based on these findings, natural progesterone has been shown to be an effective treatment for those with CE with a subset of C1 patterns, and possibly for C3. The advisable treatment based on these studies is 50 to 200 mg natural progesterone in lozenge for suppository form 3 times per day. It is recommended that this treatment is tapered during the final 3 days of the cycle to prevent withdrawal seizures. For example, Herzog[13,32,33,34,35,36] recommends one-half to 1 dose 3 times a day for days 14 to 25; then one-half dose 3 times a day on days 26 to 27, and one-quarter dose on day 28 before stopping. The limitation to these studies is the small number of patients and the equal efficacy of the easy-to-obtain Prometrium (natural progesterone in pill form vs. lozenge).

GnRH Analogues

GnRH analogues may be an effective treatment because they reduce hormone variations in patients with CE. These GnRH agonists work by blocking pituitary gonadotropin secretions such as follicle-stimulating hormone and luteinizing hormone by desensitizing the pituitary through constant stimulus.[38] In 1 study of 10 patients with CE, patients were given 3.75 mg of intramuscular triptorelin (a synthetic GnRH analogue) every 4 weeks for an average of 11.8 months. Once all were amenorrhoeic, 3 were seizure free, 4 had nearly a 50% reduction in seizure frequency, 2 experienced no benefit, and none had an increase in seizure activity ($p < 0.02$).[39] In 1 case study, a woman with frequent catamenial status epilepticus, who was unresponsive to combined oral contraceptive pills (COCs), received 3.6 mg of goserelin (a synthetic GnRH analogue) every 4 weeks. Her inpatient hospital admissions, due to status epilepticus, decreased from 10 admissions in a 4-week

period to only 3 admissions in a 4-week period.[40] One study found that during the first 3 weeks of GnRH analogue treatment, there can be an increase in seizure activity, as there is an initial stimulation of estrogen production before its production is inhibited. Experts recommend daily progesterone use for 2 to 3 weeks following the first injection to minimize this risk of transient flare of seizures that are mitigated by the progesterone.[41] Side effects of GnRH analogues include hot flashes and vaginal dryness. Serious potential long-term use can increase risks of osteoporosis and cardiovascular disease.[13] Common measures to prevent bone loss in patients using GnRH analogues include the addition of MPA.[42] Regular exercise and calcium with vitamin D supplementation are also recommended in women using GnRH agonists. GnRH analogues are effective and important treatment considerations in these patients, as they suppress menses, diminish hormone fluctuations, and reduce seizure activity in women with CE.

MPA Pills and Injections

MPA, in doses to produce amenorrhea, has been another successful hormonal treatment for CE, to date. In 1 study, 11 patients were administered 10-mg MPA pills 2 to 4 times per day. Of these 11, 7 became amenorrheic. The 4 who continued to have menses, received an additional 120 to 150 mg of intramuscular Depo Medroxyprogesterone acetate (DMPA) every 6 to 12 weeks to induce amenorrhea. Once amenorrheic, a total of 7 of 11 patients experienced a clear improvement in seizure activity, with an average seizure activity reduction of 30% ($p = 0.02$).[43] The Birth Control Registry study of Herzog and colleagues[44,45] found that DMPA had the highest rate of decreased seizure frequencies compared with any other hormonal contraception (COC, vaginal ring, hormonal patch, progestin-only pill [POP], and progestin implant) ($p = 0.0008$). Of the 200 patients taking DMPA, 19% had increased seizure frequency, 17.5% had decreased seizure frequency, and 63.5% saw no change.[44,45] Those surveyed in this study were not diagnosed with CE or a CE subtype specifically, only with epilepsy. This could suggest that those unaffected by treatment were unaffected because they are WWE, but not specifically women with cyclic exacerbations of seizures, or in other words, diagnosed with CE. Studies have demonstrated that inducing amenorrhea with MPA or DMPA may lead to reductions in seizures in WWE. It is possible that the women who benefit most from the reduction in hormone variations that comes with amenorrhea are those affected by CE, thus their seizures are most responsive to suppression of hormonal fluctuations. This is an area in which further research is needed to better optimize treatment for patients with CE.

Other Treatment Options for CE

Last, acetazolamide (also known as Diamox), commonly used to treat glaucoma, epilepsy, and edema, has long been used as a nonhormonal treatment for women with CE. A retrospective study of women admitted to the Cleveland Clinic Emergency Department who presented with seizures and were given acetazolamide found that 40% of the women reported decreased seizure frequency.[46] Large-scale studies still are needed.

Hormonal Contraception Considerations

Oral Contraceptive Pills

COCs are birth control pills containing both progestin and ethinyl estradiol. Several studies of WWE using COCs have shown that seizure frequency is unaffected. The Birth Control Registry study, by Herzog and colleagues[44,45] in 2016, surveyed 1144 WWE who were not specifically diagnosed with CE.

Of those surveyed, 635 were taking COCs. The survey did not separate cyclical and continuous COC use. Eighteen percent had increased seizure frequency when taking COCs, whereas 9% had decreased frequency. However, COC use was associated with the lowest overall increase of seizure frequency compared with all other hormonal contraceptive methods (COC, vaginal ring, hormonal patch, POP, and progestin implant).[44,45] It is important to note that nearly 75% of all COC users had no change in seizure frequency. These studies show that COC use in patients with CE does not significantly increase risk of seizures and can possibly reduce such seizures; however, more research is needed to address COC patterns of use (specifically menstrual suppression) in women with CE.

Progestin-only Pills

Little research has been done on POPs in WWE and CE. Herzog and colleagues[44,45] found patients taking POPs had a higher incidence of seizures. For those using POPs, the percentage of those with increased and decreased seizure frequencies were 29.3% and 8.6%, respectively. This result suggests a clear difference in the effect of natural progesterone and synthetic progestin taken orally. Natural progesterone increases AP levels in the brain (GABA agonist), but synthetic progestins lower AP levels. Synthetic progestins do not seem to suppress seizures unless administered in doses to suppress menses.[44,45] Clearly, not all progesterones have similar effects.

Progesterone Intrauterine Device

Some studies found no change and others found a slight decrease in seizures for patients with a progesterone (levonorgestrel or LNG) intrauterine device (IUD). In

addition to being one of the most effective contraceptive modalities available, the IUD is a top-tier choice for women with complex medical conditions, as it has no known AED interactions.[47,48] The LNG IUD is an effective modality to suppress menses. Thirty percent to 40% and in some studies up to 70% of patients experience amenorrhea after 1 year of use.[49] Of the 228 patients in the Birth Control Registry using an IUD, 6.1% reported an increase in seizure frequency, 13.2% reported a decrease, and 80.7% reported no change. Interestingly, there were no significant differences between the effect of LNG IUDs and the copper IUDs on seizure activity. The percentage of patients who saw increases and decreases in seizure frequency was 6.7%/14.7% for the LNG IUD and 5.1%/10.3% for copper T-IUD, respectively.[44,45]

Other Hormonal Contraception Options

More research is needed regarding other contraceptive options. Women who used the (etonogestrel) implant (Nexplanon) saw increased and decreased seizure frequencies of 24.3% and 5.4%, respectively.[44,45] The contraceptive patch and ring have had few studies evaluating their impact on WWE and CE. Although the implant has fewer patients with amenorrhea over time (20%), the ring and patch can effectively suppress menses when used continuously. All 3 options warrant further investigation to determine if they, too, reduce seizure frequency in women with CE.

AED Considerations and Contraceptive Efficacy

It is important for clinicians to consider how AEDs and contraceptives will interact for 2 significant reasons. First, contraceptive interactions with AEDs can reduce the effectiveness of hormonal contraceptives (HCs), and lead to unplanned pregnancy. Second, interactions between HCs and AEDs can reduce the levels of the AED itself, thus potentially inadequately treating WWE and leading to more seizure activity. Studies have found that a proper balance of hormone levels (birth control) and AED levels is paramount in controlling CE and optimizing the effectiveness of birth control.

Enzyme-Inducing and Non–Enzyme-Inducing AEDs

For patients taking both AEDs and HCs, the levels of serum progesterone and estrogen can be reduced if hepatic enzyme-inducing AEDs (EIAED) are used. Non-EIAEDs do not cause a reduction in hormone levels of the HC and therefore do not pose a risk in decreased HC efficacy (see Table 1). EIAEDs increase the levels of P450 3A4 enzymes in the liver, which also metabolize estradiol and progestin. This metabolism has been shown to reduce serum estradiol and progestin

Table 1. Antiepileptic drug and hormonal contraception interactions

When AED is taken with hormonal contraception		
Effect	**Type**	**Name**
No change in contraceptive efficacy	NEIAED	Gabapentin
		Levetiracetam
		Tiagabine
		Vigabatrin
		Zonisamide
		Pregabalin
		Lacosamide
		Ethosuximide
Possible decreased contraceptive efficacy	EIAED	Carbamazepine
		Felbamate
		Oxcarbazepine
		Phenobarbital
		Phenytoin
		Primidone
	Weak EIAED	Topiramate
		Clobazam
Decreased AED levels, no change in contraceptive efficacy	Glucuronidated AED	Lamotrigine
Decreased AED levels and contraceptive efficacy	Enzyme-inhibiting AED	Valproate

Non–enzyme-inducing AEDs (NEIAEDs) do not interact with hormonal contraceptives. Enzyme-inducing AEDs (EIAEDs) have been found to reduce levels of systemic hormonal contraception, leading to potentially reduced contraceptive efficacy. Lamotrigine and valproate levels also can be reduced in patients taking hormonal contraceptives.
AED = antiepileptic drug.

levels by 50%.[50-52] This significant drop in hormone levels in HCs can lead to birth control failures and probably unwanted side effects (unscheduled bleeding and spotting) for women taking EIAEDs.[50] One double-blind study found a 42% decrease in serum progestin levels, and no decrease in estradiol in patients given felbamate and a COC with 30 μg ethinyl estradiol.[50,53] Similarly, topiramate use was associated with a reduced concentration of estradiol in 2 studies of women taking COCs with 35 μg of ethinyl estradiol. Both found no effect on estradiol below 200 mg of topiramate use daily, and no decrease in progestin levels.[50,54,55] Both felbamate and topiramate are considered moderately enzymatic inducing, whereas others reduce levels more drastically. Clobazam has been found to be an effective treatment for CE. It, however, has enzyme-inducing activity much like an EIAED. One study found that of the 18 patients given 20 to 30 mg of clobazam, none had increased seizure frequency and 50% reported a reduction.[56] Clobazam has gained a growing acceptance as an intermittent treatment for CE, but given its enzyme-inducing activity, caution is indicated for patients using COCs, as it may decrease contraceptive efficacy. EIAEDs can also reduce levels of folic acid. Health care providers recommend that all women considering having children take folic acid supplements to reduce the incidence of birth defects. This is particularly important in WWE who may have particularly lower folic acid levels because of their medication use. Folic acid is often recommended to be taken at prescription dosage (0.8 mg or 1 mg).[57]

WWE, Contraception, and Pregnancy Planning

As shown previously, WWE can have their seizures exacerbated by hormonal variations. It is important to have proper consideration of HCs for all WWE to prevent catamenial exacerbation, as well as providing reliable contraception for those patients who do not desire a pregnancy. All birth control options can be considered safe and as options for patients with WWE. It is important for the provider to review their individual risks and benefits of the methods and help in shared decision making. All WWE who are not planning a pregnancy should be offered and counseled about the full range of contraceptive options available. Studies have shown that seizure activity is not increased by the use of hormonal contraception, and depending on the method chosen, HC may benefit CE by reducing seizure activity. At least preliminarily, this seems to be the case particularly in WWE who use DMPA and those with CE who experience amenorrhea on their birth control method. Contraception counseling for reproductive-age WWE should occur at every medical touch point. WWE have particular pregnancy risks: many medications used for epilepsy are teratogenic, extra folic acid supplementation is recommended preconceptually, and optimizing health and medication regimen, before planning a pregnancy, is paramount to a healthy pregnancy and infant. The full range of contraceptive methods for women currently include implantable rods (Nexplanon); IUDs, progesterone containing (all durations and doses) and Copper T; the shot or injection (Depo Provera), the contraceptive patch; vaginal contraceptive ring; combined oral contraceptive pills (extended or continuous use); progestin-only contraceptive pills; female and male sterilization; female and male condoms; diaphragms; sponges; cervical caps; and spermicide. In addition, instruction infertility awareness-based methods, including the lactation amenorrhea method, although less effective, should be provided for women desiring alternative contraceptive methods. WWE who use non-EIAEDs have not been shown to experience an increase in unplanned pregnancy. However, for those WWE who take EIAEDs, special consideration to choosing a birth control method and dose is critical to contraceptive efficacy. WWE who prefer to use a COC as their contraceptive of choice, and have no medical contraindications, should be prescribed a birth control pill that contains at least 50 μg of ethinyl estradiol. That is higher than the low-dose pills (20-35 μg routinely prescribed). If they have contraindications to COCs or experience untoward side effects, they should be counseled about other HC options and collaborate with their provider in shared decision making for another contraceptive option. An underutilized and superb contraceptive method for WWE is the hormonal and nonhormonal IUD. In women with CE, menstrual suppression as a result of their contraceptive method may have dual benefits of preventing an unplanned pregnancy and reducing seizure activity. Consideration to DMPA and nonoral contraceptive methods may minimize disruption of AED dose and optimize contraceptive efficacy. Further resources and patient-friendly graphics can be found in the US Medical for Contraceptive Use of the Centers for Disease Control and Prevention.[58]

HCs and Lamotrigine and Valproic Acid: Special Circumstances

In the presence of HCs, levels of the AED lamotrigine have repeatedly been found to be reduced (see Table 1). This is significant because patients taking both lamotrigine and HCs have increased seizure activity requiring adjustments to dosing. In a study of 22 women taking both lamotrigine and a COC, lamotrigine levels were decreased by 50% compared with those taking lamotrigine only.[59] In the Birth Control Registry study, 18.2% of those taking HCs and glucuronidated AEDs, such as lamotrigine, reported increased seizure frequency as a result of the decreased AED levels compared with those who used AEDs alone. Estradiol, not progestins, reduce lamotrigine levels.[60] Much like lamotrigine,

one study found valproate levels are decreased by 23.4% when used with HCs.[61] Interestingly, lamotrigine is the most commonly used AED among WWE.[44] In the Birth Control Registry study, valproate had the highest increased seizure frequencies in patients taking HCs.[45] Women taking both COCs and lamotrigine or valproate require close AED-level monitoring after starting their COC regimen. Adjustments should be made and monitored periodically to ensure effective levels. In addition, doses should be adjusted during the COC placebo period if continuous use is not prescribed.[50]

CONCLUSIONS

CE is a unique condition that affects a subset of WWE. Clinicians should be aware of this subset of epilepsy and understand the patients' seizure activity in the context of their menstrual cycle. Using menstrual calendars, the clinician can identify patients with CE, and ideally classify the pattern. Once a diagnosis is made, clinicians can optimize treatments for patients with CE. In general, traditional AEDs with fluctuating doses throughout the menstrual cycle are a common antiseizure regimen. Unlike traditional epilepsy, for which AED dosage is steady and consistent, AED dosage for patients with CE are increased and decreased during their menstrual cycle. The classification as C1, C2, or C3 allows the provider to individualize and optimize their medication. Initial trials have shown promise for hormonal treatments for CE. To date, the most consistently effective hormonal treatments are natural progesterone, MPA (pills and injection), and GnRH analogues. The studies do have several limitations. First, use of natural progesterone alone for premenopausal women is less common in practice and is not an option for effective pregnancy prevention. The studies of natural progesterone, to date, were small and did not use common or available-to-prescribe delivery systems (ie, lozenges, not oral or vaginal Prometrium). It is likely that oral and vaginal preparations are analogous to the regimens used in the study protocols, but randomized controlled trials are needed. WWE of reproductive age also should be counseled about contraception at their medical visits. Contraceptive counseling and joint decision making should be made with special consideration to their medications, pregnancy plans, and special consideration to the role of menstrual suppression as a result of their contraceptive method. Their contraceptive method of choice may have additional health benefits of pregnancy prevention and mitigating seizure activity. Further research in this area is needed. The ideal study would mirror the Birth Control Registry by recruiting patients with CE delineating their specific birth control methods and controlling for their AED (drug and dose). In addition, it would be helpful to tier the results based on contraceptive method and regimen, such as cyclic, extended, or continuous use. CE is a fascinating subset of epilepsy, and future research in this arena can offer promising treatments, a better understanding of HC and AED interactions, and further reduce unplanned and often high-risk pregnancies for patients with this complex condition. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Authors' Contributions

Mr. Frank performed a detailed literature review and wrote the manuscript. Dr. Tyson performed a brief initial literature review, provided expert input, and edited the manuscript.

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REVIEW ARTICLE

CRISPR/Cas9 for the Clinician: Current uses of gene editing and applications for new therapeutics in oncology

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ABSTRACT

Precise genomic editing has given rise to treatments in previously untreatable genetic diseases and has led to revolutions in treatment for cancer. In the past decade, the discovery and development of clustered regularly interspaced short palindromic repeats (CRISPR) technologies has led to advances across medicine and biotechnology. Specifically, the CRISPR/Cas9 system has improved translational discovery and therapeutics for oncology across tumor types. In this review, we briefly summarize the history and development of CRISPR, explain CRISPR-Cas systems and CRISPR gene editing tools, highlight the development and application of CRISPR technologies for translational and therapeutic purposes in different oncologic tumors, and review novel treatment paradigms using CRISPR in immuno-oncology, including checkpoint inhibitors and chimeric antigen receptor T cell therapy.

INTRODUCTION

In 2020, the US is expected to have over 600,000 deaths due to cancer.[1] To date, treatment has largely focused on surgery, chemotherapy, and targeted therapies. Genetic mutations are among the most common causes of cancer. Therefore, gene therapy has a potential to guide therapy in oncologic patients in the future. Recently, the gene-editing tool CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) has been used in oncology translational research, and therapeutics. CRISPR is derived from the natural adaptive immune system of bacteria. Current applications of research in CRISPR have been in studying gene knockout in cancers, editing mutated genes, and engineering T cells for chimeric antigen receptor T cell (CAR-T) therapy. This review summarizes CRISPR techniques and highlights the applications of the technology to cancer therapeutics.

Background

The family of repetitive, mobile DNA sequences in prokaryotes was first described in 1987 in *Escherichia coli* and later named CRISPR.[2,3] Some bacteria have CRISPR present, and other species within the same family do not contain CRISPR; additionally, unrelated species have been found to harbor identical CRISPR sequences.[2] CRISPR sequences are a naturally occurring phenomenon and are protective against bacteriophages and conjugative plasmids.[4] In microbiology, CRISPR sequences demonstrate a record of past infections and can be used to fight those pathogens in the future by direct degradation of foreign genome.[4] To date, an array of invertebrates and vertebrates, bacteria, and plants have had their genomes edited by CRISPR.[5]

The *Streptococcus pyogenes* CRISPR system consists of precursor-CRISPR RNA, which is cleaved to form single-guide RNA (sgRNA), which is the mature CRISPR RNA.[6] sgRNA contains complementary DNA to the target site and hybridizes with trans-activating CRISPR RNA, which then forms a complex with CRISPR-associated protein 9 (Cas9).[6] The CRISPR-Cas9-sgRNA complex then edits the genome of interest. There are many Cas proteins; however, Cas9 is the most efficient and widely used.[7] The Cas9 protein acts as scissors to cleave the targeted DNA sequence.[7] Cas9 cuts 3 to 4 nucleotides upstream from the protospacer-adjacent motif.[7]

Genetics, lifestyle, and environmental components contribute to cancer risk through carcinogenesis and chromosomal damage. One manifestation of this is via double-strand DNA breaks (DSBs), which are common occurrences in cells and which play a key role in cancer development. To potentially counter this, repair mechanisms may be used to influence the applicability of CRISPR. Two main methods of repair are seen in eukaryotic cells: nonhomologous end joining (NHEJ) and homology-directed repair (HDR), most commonly as homologous recombination (Figure 1). When cells use each mechanism of repair is still debated; however, if a cell is in S phase, where the sister chromatid is nearby to act as a donor template, HDR is the preferred mechanism of repair.[8] NHEJ is error prone and can lead to insertion-deletion or frameshift mutations; it is therefore the less preferred mechanism for CRISPR gene editing.[5] However, NHEJ is efficiently used with CRISPR for gene knockout studies. When HDR is preferred in CRISPR, such as in gene editing for genetic diseases, it is possible to use an antagonist of an enzyme required for the NHEJ pathway because the two mechanisms naturally compete with each other to repair the DSBs.[9]

There are various methods of delivery and carriers of the CRISPR-Cas9 system. The delivery of sgRNA and Cas9

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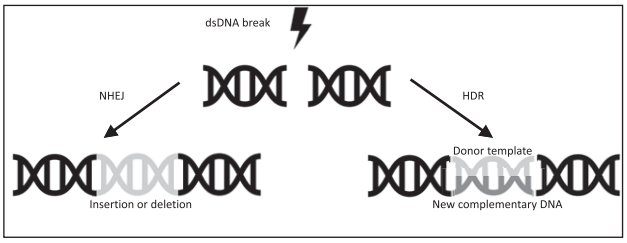

Figure 1. Pathway for dsDNA break in CRISPR. NHEJ = Non-homologous end joining; HDR = Homology-directed repair.

can be achieved via viral vectors, plasmid microinjection or lipofection of the sgRNA-Cas9 complex, and cell-penetrating peptides.[10] Viral vectors, including the adeno-associated virus and lentivirus, allow for introduction of exogenous DNA and incorporation via HDR.[11] The delivery mechanisms vary on efficiency and gene editing errors.

Review

Translational CRISPR Research in Oncology

Lung adenocarcinoma (ADC) is the leading cause of cancer death among men and women in the US.[1] Lung cancer is broadly divided into small cell lung cancer and non-small cell lung cancer. Non-small cell lung cancer compromises the majority (80%) of cases and consists of histological types: large cell carcinoma, squamous cell carcinoma, and adenocarcinoma. Lung adenocarcinoma is the most common type diagnosed in both men and women.[12] KRAS and EGFR are major genetic targets in lung adenocarcinoma. Patients with EGFR mutations can be susceptible to targeted therapy with gefitinib and erlotinib, which are first-generation competitive, reversible inhibitors of the EGFR-tyrosine kinase. These therapies have provided significant improvement in the progression-free survival of EGFR-mutated lung adenocarcinoma; however, these agents have not shown significant benefit to overall survival.[13] Moreover, many of these patients eventually develop resistance to these first-line agents.[13] The most common mechanism of EGFR tyrosine kinase inhibitor (TKI) resistance is via the T790M mutation in exon 20 of the EGFR gene, followed by MET amplification.[14] Approximately 60% of patients develop T790M mutations while on TKI therapy.[15] In a recent study of the third-generation EGFR TKI, osimertinib, CRISPR/Cas9 was used for gene knockout of MEK/ERK signaling in lung adenocarcinoma resistant to osimertinib.[16] Viral production and transduction methods were used for this study.[16]

In KRAS-mutant lung ADC, the overall response rate to treatments remains low despite the introduction of novel agents, including immunotherapies.[17] Enhancing the immune responsiveness to checkpoint inhibitor therapy with epigenetic modification is one method of improving response to therapy. Epigenetic modifications consist of DNA base methylation and histone modification, which affects gene expression.[18] A study of KRAS-mutant lung ADC constructed an in vivo CRISPR screen of epigenetic-focused sgRNAs.[19] This study found that the loss of anti-silencing function 1a histone chaperone in lung ADC tumor cells led to immunogenicity in the tumor microenvironment and increased sensitivity to anti-programmed cell death-1 (PD-1) immunotherapy.[19] Using CRISPR gene knockout for epigenetic modifiers, this study demonstrated a potential therapeutic strategy using gene therapy for KRAS-mutant lung ADC.

The Warburg theory of cancer hypothesizes that cancer cells prefer anaerobic metabolism over aerobic metabolism or oxidative phosphorylation.[20] In a recent study on the oxidative phosphorylation gene, pyruvate dehydrogenase E1 alpha subunit (PDHA1), a precursor to oxidative phosphorylation, CRISPR was used to knockout the PDHA1 gene in esophageal cancer cells.[21] Plasmid-based CRISPR/Cas9 technology applied to human esophageal cancer cells, which consisted of a plasmid encoding the Cas9 protein and sgRNA, edits the genome inside cells. This strategy led to the deletion of 34 bases in exon 1 of the PDHA1 gene, which led to a terminator codon, resulting in PHDA1 knockout.[21] The study of this gene knockout cell line demonstrated the Warburg effect, along with decreased functional tumor suppressor gene p53 and elevated angiogenesis genes.[21]

Immune Checkpoint Inhibition

Another treatment paradigm in oncology in the past decade has been the use of immune checkpoint inhibitors. The PD-1 and programmed cell death receptor 1 ligand (PD-L1) pathway has formed the basis for an array of immune checkpoint inhibitors that have been FDA approved for a variety of tumor types.[22] The expression of PD-L1 on dendritic and tumor cells suppresses antitumor activity and allows cancer to escape the immune system.[23] Optimizing T cell activity and function enhances the immune system attack on cancer cells. A recent study administered Cas9 ribonucleoproteins to human T cells to replace specific sequences of the T cell genome.[24] Scientists were able to insert targeted nucleotide replacements in T cells at C-X-C chemokine receptor type 4 and PD-1, which has broad applications in the treatment of both HIV and cancer.[24]

Current checkpoint inhibitor immunotherapy with monoclonal antibodies targets PD-1 on activated T cells and regulatory T cells or PD-L1 on tumor cells to block the inhibitory signaling of T cell activation.[25] In a recent study using CRISPR/Cas 9, scientists were able to knock out the PD-1 gene without affecting the viability of primary human T cells in vitro.[26] Gene knockout was conducted by electroporation of plasmids encoding the sgRNA-Cas9 DNA.[26] This study followed the principle that using 2

Table 1. Applications of CRISPR in Oncology

Cancer	CRISPR mechanism	NHEJ/HDR	Gene targeted	Reference
Lung adenocarcinoma	Plasmid	NHEJ	EGFR-mutated, MEK/ERK signaling	16
Esophageal squamous carcinoma	Plasmid	NHEJ	PDHA1	21
Hematologic malignancies	Electroporation of Cas9 ribonucleoproteins	NHEJ and HDR	CXCR, PD-1	24
Hematologic malignancies, CAR-T therapy	Electroporation of Cas9 and invitro transcribed sgRNA	NHEJ	TCRα subunit constant	32

CAR-T = chimeric antigen receptor T cell; CRISPR = Clustered Regularly Interspaced Short Palindromic Repeats; HDR = homology-directed repair; NHEJ = nonhomologous end joining; TCR = T cell receptor.

sgRNAs to target a gene improves the targeting efficiency and reduces off-target results.[27] Gene targeting in T cells is likely to produce a more favorable side effect profile than the immune checkpoint inhibitors, which have immune-related adverse events of colitis, pneumonitis, and transaminitis, among other side effects.[28]

CAR-T Cell Therapy

Recent developments in another type of immunotherapy, CAR-T therapy, has been shown to have positive response rates in acute lymphoblastic leukemia, chronic lymphoid leukemia, and B-cell lymphoma.[29-31] Standard CAR-T therapy is derived from the patient's own T cells via adoptive T cell transfer, which consists of the ex vivo expansion of the patient's T cells.[32] With the development of CRISPR technology, it is possible to make CAR-T cells from healthy donors in order to maximize CAR-T therapy for a greater number of patients, some of whom may not have enough of their own T cells to harvest for CAR-T therapy. The limitations of this method include graft-versus-host disease (GVHD) and rejection. The T cell receptor is responsible for GVHD because it recognizes antigens as foreign. Using CRISPR knockout, T cell receptors have been silenced in vivo to prevent GVHD in universal CAR-T therapies.[33,34] sgRNA and Cas9 were mixed and then electroporated into human T cells isolated from umbilical cord blood.[33] The modified CAR-T cells were selected for and expanded and injected back into the patient.[33] Although CRIPSR-Cas9 gene editing technologies have enabled the development of universal CAR-T cells in vivo, future studies are warranted in vitro to assess the side effect profile, propensity for GVHD, and efficiency on a larger scale.

CONCLUSIONS

In the last decade, gene editing has been revolutionized by CRISPR-Cas9 technology. Most of the research in solid tumors has been in translational research, focusing on mouse models of gene knockout and their applications to future therapies. CRISPR-Cas9 gene knockout has been applied in EGFR- and KRAS-mutated lung cancer and esophageal squamous cell cancer, as described. These applications of CRISPR-Cas9 are summarized in Table 1. Applications of CRISPR to clinical medicine have been demonstrated in hematologic malignancies, specifically acute lymphoblastic leukemia, chronic lymphoid leukemia, and lymphoma.[29-31] In current treatment with CAR-T therapy, the patient's own T cells are used to edit the genome of interest, which is transfused back into the patient. However, many patients, especially children and elderly patients, do not have viable cells for editing. The use of CRISPR to establish universal CAR-T therapy from healthy donors would broaden the availability of CAR-T therapy and allow for more efficient and timely treatment in hematologic malignancies. Additionally, CRISPR has been used successfully in vitro studies of T cell editing, such as CXCR and PD-1 knockout for immune checkpoint inhibition. Potential risks of this method of therapy include GVHD, transfusion reactions, and rejection. Research is ongoing to continue to find improvements in the efficiency and precision of CRISPR gene editsing. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Authors' Contributions

Julia Boland MD participated in acquisition and analysis of the literature and drafting and submission of the final manuscript. Elena Nedelcu MD participated in analysis of the literature and drafting the final manuscript. Both authors have given final approval to the manuscript.

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REVIEW ARTICLE

Identifying Risk Factors Associated With Postoperative Infection Following Elective Lower-Extremity Total Joint Arthroplasty

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ABSTRACT

This article addresses the importance of identifying risk factors associated with postoperative infection following elective lower-extremity total joint arthroplasty. Specifically, this review discusses risk factors recognized by the American Academy of Orthopaedic Surgeons that should be carefully considered and assessed by the orthopaedic team in collaboration with the primary care provider before proceeding with surgery.

INTRODUCTION

This review addresses the importance of identifying risk factors associated with postoperative prosthetic joint infection (PJI) following elective lower-extremity total joint arthroplasty (TJA). Addressing associated risk factors before surgery is essential to reducing PJI after surgery. Although the literature differentiates risk factors as modifiable or nonmodifiable, we take the position that all risk factors (to some extent) are modifiable prior to elective TJA surgery. Therefore, this review discusses risk factors recognized by the American Academy of Orthopaedic Surgeons (AAOS)[1] that should be carefully considered and assessed by the orthopaedic team in collaboration with the primary care provider (PCP) before proceeding with surgery (see Tables 1, 2, and 3 and Sidebar: Advance Organizer Quiz to Organize the Materials Presented). These associated risk factors include the following: substance abuse, diabetes mellitus (DM), anemia, mental health disorders and neurological disorders, obesity/increased body mass index (BMI), low BMI, malnutrition/hypoalbuminemia, vitamin D deficiency/insufficiency, HIV/AIDS, hepatitis C virus (HCV), liver disease, obstructive sleep apnea (OSA), rheumatoid arthritis, immunocompromised status, cardiovascular disease (eg, congestive heart failure, arrhythmia, atrial fibrillation, postoperative myocardial infarction), hypothyroidism, chronic renal failure/kidney disease, blood clotting disorders, peripheral vascular disease (PVD), homelessness/low socioeconomic status, and special surgical considerations.

What Is a TJA?

TJA is a surgical operation performed to provide the most effective relief of pain and is appropriate for patients with advanced, end-stage arthritic disease or inflammatory arthritis of a large joint who nonsurgical treatment modalities have failed.[2] For the purposes of this review, TJA includes both total knee arthroplasty (TKA) and total hip arthroplasty (THA).

Prevalence of TJA

The prevalence of TJA procedures is more than 1 million THA and TKA operations performed each year in the United States[3,4] and that number is expected to rise steadily over the next 10 years.[5] According to the Agency for Healthcare Research and Quality,[6] more than 400,000 total hip replacements and more than 600,000 knee replacements are performed each year in the United States.

Possible Complications with TJA

Risks associated with TJA comprise systemic complications, such as those related to anesthesia, including deep vein thrombosis, pulmonary embolism, stroke, heart attack, and pneumonia. In addition, risks associated with TJA include surgical complications such as infection (at the site of incision and in deeper tissues near the affected joint), fracture, dislocation, nerve injury, leg length discrepancy, implant loosening, inflammation and swelling, increased pain, stiffness in the affected joint, allergic reaction to the bone cement, and damage to structures around the joint.

Possible Complications of PJI in TJA

Possible complications related to infection associated with TJA may involve a range from self-limited problems such as superficial skin infections (SSIs) to more detrimental problems seen with deep PJIs, which can lead to loss of limb or amputation. Infections that enter the bloodstream (eg, septicemia) can be fatal and lead to death. These infecting microorganisms may be introduced at the time of surgical intervention, through the bloodstream (hematogenously), by contiguous spread from another site, or from recurrence of a previously infected joint.[7]

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Table 1. Careful consideration of risk
1. Active infection of joint, bloodstream, or local tissue
2. Anticoagulation status, active thromboprophylaxis
3. Autoimmune disease
4. HIV status
5. Institutionalized patients
6. Prior bariatric surgery

Adopted by the American Academy of Orthopaedic Surgeons[1] on March 11, 2019.

Table 2. Unclear effect on risk of prosthetic joint infection
1. Age (conflicting evidence)
2. Dementia (insufficient evidence)
3. Poor dental status (insufficient evidence)
4. Asymptomatic bacteriuria (conflicting evidence)

Adopted by the American Academy of Orthopaedic Surgeons[1] on March 11, 2019.

Prevalence of PJI in TJA

The rate of PJI is highest during the first 2 years following surgery,[8] with the risk of PJI greater for knee arthroplasty than hip arthroplasty.[8,9] The rate of PJI in most medical centers ranges between 0.5% and 2% for knee replacements and 0.5% and 1.0% for hip replacements.[5,10,11] The higher rate of PJI in TKAs may be attributed to greater mobility in the joint and soft tissue and less protective soft tissue coverage.[5]

Diagnosis of PJI in TJA

PJI is among the most serious complications of prosthetic joint implantation. After completing a comprehensive medical history that includes a review of associated TJA risk factors, the clinician should perform a focused clinical examination of the affected hip or knee and compare it to the contralateral side. The examination should include an assessment of the identified signs and symptoms noted above and inspection of the affected joint. Presence of fever (lasting more than 48 hours in the first month after primary surgery) and persistent wound drainage are 2 of the most important aspects of the examination. In addition, it is important to note both the presence or history of chronic pain at the site of the joint prosthesis and a history of superficial or deep infection or prior wound healing problems.

Plain radiographs, laboratory testing for inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), evaluation of synovial fluid, and tissue biopsy are important to establish a diagnosis of PJI. Other scans and imaging studies (eg, leukocyte count, positron emission tomography, computed tomography, bone scan, and magnetic resonance imaging) usually do not provide a definitive diagnosis in PJI and are generally not useful for routine diagnosis of suspected PJI.[12]

Management of PJI

Once a PJI is clinically established (see Table 4), the goals for management include eradication of the infection, alleviation of symptoms, restoration of function, and minimization of PJI-related morbidity and mortality.[13] Management of PJI almost always requires surgical intervention and prolonged courses of intravenous or oral antimicrobial therapy.[13] The approach to management of infection depends on the timing (eg, early, delayed onset, or later) and microbiology (eg, virulence) of infection, condition of the joint and implant, quality of the soft tissue envelope, and individual patient circumstances (see Table 5).[14]

There are 3 categories of onset of PJI infections (see Table 6).[15,16] Early onset occurs within 3 months of implantation. Later infections (ie, occurring more than 24 months following implantation) typically originate in the blood. Antimicrobial therapy should be delayed until culture specimens are obtained (by joint aspiration, debridement, and/or removal of hardware). Clinical approaches for surgical management of PJI include 1) debridement and retention of the prosthesis, 2) resection arthroplasty with reimplantation, 3) permanent resection arthroplasty, or 4) amputation (see Table 7).[17]

Organism Profile Causing SSI/PJI in TJA

The published literature depicts *Staphylococcus aureus* as the leading cause of PJI after TJA,[18-20] and there is limited evidence to support a difference in the organism profile causing SSI/PJI between hip and knee arthroplasty. Isolated studies have reported an increased prevalence of streptococcal and culture-negative PJI around the knee, whereas staphylococcal, enterococcal, and pseudomonal PJI may be more prevalent around the hip.[21] The incidence of PJI affecting TKA versus THA is estimated at 1% to 3% and 0.3% to 2%, respectively.[20] Several studies have examined the organism profile causing PJI after arthroplasty, but few have identified any significant difference in the organism's profile between hip and knee arthroplasty.[21]

PATIENT OPTIMIZATION OF RISK FACTORS

Prior to referring a patient for evaluation of TJA, we recommend that the PCP assess the following risk factors for PJI and treat and/or refer the patient accordingly.

Substance Use

Substance use includes 1) excessive alcohol use, 2) cigarette smoking, and 3) chronic opioid use, illegal drug use, and/or intravenous drug abuse. Substance use can lead to substance use disorders, which may contribute to medical and related physical health problems such as an increased

Table 3. Absolute contraindication to elective TJA
1. Active infection of arthritic joint, presence of septicemia, and/or presence of active local cutaneous, subcutaneous, or deep tissue infection
2. Superobesity, body mass index > 50
3. Active intravenous drug abuse
4. Intra-articular injection within 3 mo of surgery
5. Uncontrolled hyperglycemia with blood glucose > 200 mg/dL
6. Severe malnutrition with serum albumin < 3 g/dL
7. Untreated HIV

Adopted by the American Academy of Orthopaedic Surgeons[1] on March 11, 2019.

Table 4. Clinical practice guidelines and recommendations for suspicion of prosthetic joint infection
a. Presence of fever
b. Persistent wound drainage (which may reflect sinus tract) at the site of a joint prosthesis
c. Acute onset of pain at the site of a joint prosthesis
d. Chronic pain at the site of a joint prosthesis, particularly in the absence of a pain-free interval following implantation
e. History of superficial or deep infection or prior wound healing problems

Adapted from Osmon et al.[12]

risk of liver, lung, or cardiovascular disease, infectious diseases such as hepatitis B or C, and HIV/AIDS.[22] PCP identification of patients with substance use disorders preoperatively can provide an opportunity to refer these individuals for early intervention and subsequently avoid delay in scheduling TJA.[23]

Excessive Alcohol Use

Excessive alcohol use increases the risk of PJI. Alcohol use disorder remains the most common form of substance use disorder in the United States and begins as early as age 12 years.[22,24,25] The US Centers for Disease Control and Prevention[26] defines excessive alcohol consumption as 4 or more drinks on a single occasion or 8 or more drinks per week for women and 5 or more drinks on a single occasion or 15 or more drinks per week for men. Excessive alcohol consumption increases individuals' risk for cardiopulmonary problems, alcohol withdrawal symptoms/delirium, immune system dysfunction, and metabolic stress responses.[27,28]

Although the optimal period of alcohol cessation remains unspecified, a period of at least 4 weeks of abstinence is required to reverse certain physiologic abnormalities.[29] In some cases, orthopaedic surgeons require a medically documented 6-month period of abstinence before they will perform elective TJA (Eric L Smith, MD, personal communication, October 16, 2017).[a]

Cigarette Smoking

Clinical studies demonstrate that smokers undergoing both THA and TKA are 9 times more likely to experience superficial SSIs, smokers undergoing THA are 6.5 times more likely to have deep SSIs, and smokers undergoing TKA are 2.5 times more likely to develop deep SSIs.[30] Bone healing is an essential component of successful TJA, requiring bone to grow into the implant. However, the restricting effect of nicotine on microvascular (small blood vessel) constriction places smokers at an increased risk of TJA infection because there is as much as 25% less blood flow to the wound in smokers compared to nonsmokers with less oxygenation and there are fewer healing nutrients and white blood cells protective to wounds, thereby slowing and potentially interfering with the healing process.[31] Smoking cessation is advised at least 6 weeks prior to surgery to at least 6 weeks postoperatively, although permanent cessation of smoking is preferred.[32,33]

Chronic Opioid Use/Illegal/Intravenous Drug Abuse

Ongoing illegal drug abuse (eg, opioids, barbiturates, or amphetamines) is an absolute contraindication for elective TJA.[34] Patients with a history of intravenous drug use are more likely to develop a deep infection compared with other patients undergoing TJA.[35] Chronic opioid use in patients often leads to tolerance requiring a higher than usual opioid dose in the intraoperative and postoperative period. Identifying individuals with a chronic opioid addiction or illegal/intravenous drug abuse problem and referring them to inpatient or outpatient rehabilitation programs prior to surgical evaluation provides the best solution for optimal care. Twelve-step programs, psychotherapy or cognitive behavioral therapy, and medication are other recommended options.[36-38]

DM Control

Patients with a sole diagnosis of well-controlled DM control do not confer a clinically significant risk for PJI.[37] DM, preoperative hyperglycemia, and elevated hemoglobin

Table 5. Clinical practice guidelines
a. Not intended to be a fixed protocol
b. Not all patients in any given clinical situation are the same
c. Individual patient's specific circumstances must always be considered
d. Clinician's medical judgement always provides basis of patient care and treatment

Adopted by the American Academy of Orthopaedic Surgeons[1] on March 11, 2019.

Table 6. General categorization of prosthetic joint infections
Early onset within 3 mo of implantation
Delayed onset within 3 to 24 mo of implantation
Later onset later than 24 mo following implantation
Considerable overlap between early- and delayed-onset prosthetic joint infections (PJIs), and hip PJIs tend to occur sooner than knee PJIs

Adapted from Brusch et al[15] and Lewis et al.[16]

A_{1C} are generally not independent risk factors for PJI, but they are considered to be indirect markers of and associated with an increased risk of more serious systemic comorbid conditions (eg, chronic kidney disease, stroke, urinary tract infection, ileus, postoperative hemorrhage, transfusion) and surgical complications (eg, wound infection, PJI), higher mortality, and increased length of hospital stay.[37,38] Conversely, others report that without a diagnosis of DM, perioperative hyperglycemia at the time of primary knee or hip arthroplasty has been associated with an increased risk of subsequent PJI.[39] Severely uncontrolled DM (eg, serum glucose of 200 mg/day or higher) is an absolute contraindication for TJA. For those with hemoglobin A_{1C} of 8% to 9% or greater or glucose levels between 180 and 200 mg/dL, optimization of the elevated levels is mandated in the preoperative period.

PCP evaluation and optimization of a patient's DM with an elevated hemoglobin A_{1C} greater than 8 and possible referral for an endocrine consultation is the mainstay of treatment prior to referring the patient for TJA evaluation. Several months or more of ongoing care and management can be expected prior to achieving optimization of DM in TJA.

Anemia

Anemia is common in patients undergoing TJA and is linked to more PJI in patients undergoing TJA than those without anemia, affecting 4.3% and 2% of anemic and nonanemic patients, respectively.[40,41] Preoperative anemia, as defined by a hemoglobin level of less than 13.0 g/dL in men and 12.0 g/dL in women, is an independent risk factor for postoperative SSI/PJI following TJA.[42] Low hemoglobin levels can increase a patient's risk for perioperative allogenic blood transfusions and PJI after surgery.[43]

Mental Health and Neurological Disorders

Patients with mental health disorders and psychiatric diagnoses (eg, depression psychosis, schizophrenia) are demonstrated to have increased complication rates after primary TJA.[44-46] The most common etiologies of mental health disorders and neurological disorders include acute changes due to 1) delirium, stroke, and Alzheimer dementia; 2) movement disorders (eg, Parkinson disease, multiple sclerosis, epilepsy, and tardive dyskinesia); and 3) mood/behavior disorders (eg, major depressive disorder, anxiety, bipolar disorder, schizophrenia).[47] Patients who have a history of delirium, stroke, and Alzheimer disease are shown to be at greater risk of unfavorable outcomes (in particular, higher mortality and longer lengths of hospital stay leading to greater chances of infection) and may acquire greater levels of dependence. Patients undergoing TJA who have movement disorders are known to have longer postoperative hospitalizations and higher rates of perioperative complications.[48] Patients undergoing TJA who have mood/behavior disorders, such as major depressive disorders, may have perceptions of pain and disability that encourage a greater need to consume more opioids during the immediate postoperative period compared to similar patients without major depressive disorders.[49] Patients with moderate anxiety or depression also appear to have an increased risk of wound complications (eg, infection) after THA.[50]

Obesity/Increased BMI

Obesity is associated with a higher risk for PJI following THA among elderly individuals (defined as older than 75 years), but no such association was found for patients undergoing TKA.[51] It is not yet known whether PJI correlates with higher BMI (above 30 kg/m^2) in patients undergoing TKA.

A BMI threshold of 35 kg/m^2 is most commonly used to define obesity, but a BMI of 40 kg/m^2 or greater (severely obese) is the threshold in some medical centers. Under no circumstance should elective surgery be performed on patients diagnosed as superobese (ie, BMI greater than 50). Patients who have an increased BMI are more likely to experience PJI, deep vein thrombosis, and pulmonary embolism. Possible reasons for the increased risk associated with obesity are postulated to be prolonged operative duration, vascular insufficiency leading to decreased capacity to fight infection and decreased ability to support the healing process.[52,53]

Current management guidelines indicate that weight loss is helpful in reducing PJIs in this patient population. Weight loss prior to surgery will help to reduce the risk of PJIs and other perioperative complications, including anesthesia-related complications, and reduce the risk of surgical revision.[54] However, the current approach to weight loss protocols remains controversial, with no absolute guidelines for which methodology (eg, diet/exercise versus medically prescribed very low-calorie diets versus bariatric

Table 7. Clinical approaches for surgical management of prosthetic joint infection

Approach	Description
Debridement, antibiotics, and retention of prosthesis (DAIR) procedure	The DAIR procedure can be a successful treatment option for prosthetic joint infection (PJI) in total joint arthroplasty (TJA). It can effectively eradicate infection, resulting in improved functional outcome and a reduction in the need for more extensive surgery, which may be associated with far greater morbidity.[103] The effectiveness of DAIR is still unclear due to a lack of comparative data among the treatment options and limited evidence to suggest superiority of any one treatment. The treatment decision must be made on a case-by-case basis and account for underlying medical conditions, infection history, organism characteristics, and surgical history. DAIR is most appropriate for acute PJI without complicating factors such as extensive and pervasive infection or organism virulence or resistance.[104]
Resection arthroplasty with reimplantation	Reimplantation of a total hip or knee arthroplasty after a previous resection arthroplasty for infection can be performed with a low risk of reinfection. However, the incidence of infection following arthroplasty revision surgery is higher than that following primary implantation arthroplasty in this setting and is especially challenging because of the potential for significant bone and soft tissue deficits. The incidence of infection following arthroplasty revision surgery is higher than that following primary implantation.[105-109] Postulated reasons for this include prolonged operating time during the revision surgery or unrecognized infection at the time of revision, with subsequent recrudescence. The abnormal soft tissue envelope may also be a contributing factor.[13]
Permanent resection arthroplasty	Resection arthroplasty is a procedure in which the prosthetic components (implants) are removed as a consequence of failed surgery, in the setting of a periprosthetic infection. This is only performed when no other reconstructive options are possible and is typically reserved as a salvage strategy to avoid amputation after prior failed treatment attempts or for patients who are not candidates for DAIR or 1-stage arthroplasty exchange.[5,13]
Arthrodesis of amputation of limb	This approach is reserved for patients for whom all other treatment options for PJI have failed[110] or who have life-threatening infections in which emergent source control is required.[111] Failure of the repeat 2-stage exchange arthroplasty appears to be dependent on the host grade and status of the extremity. Surgeons thus should consider the patient's comorbidities and expectations when deciding whether to undergo repeat 2-stage exchange arthroplasty.[112]

surgery) is best. It is suspected that in patients undergoing bariatric surgery prior to TJA, the risks for PJIs are reduced due to decreasing BMIs but this is offset by the increased risk for malnutrition.[54]

Low BMI

Underweight and low BMI are associated with suppressed immune systems in some patients, possibly reflecting an altered physiological state[55] and higher morbidity and mortality rates.[56] A low BMI is typically defined as less than 18.5 kg/m^2,[57-60] and these patients comprise approximately 2.3% of the US population.[61] A low BMI is hypothesized to be an indirect measure of nutritional status, as patients with a lower BMI are shown to have lower levels of albumin, prealbumin, and/or protein.[62] Patients with a low BMI who have decreased nutritional reserves and reduced ability to accurately react to stress because of a suppressed immune system are at increased risk of PJI and should be referred for a nutritional consultation before undergoing TJA.[56]

Malnutrition/Hypoalbuminemia

Malnutrition and hypoalbuminemia are known to increase the risk of postoperative wound complications, SSIs, and PJIs in patients undergoing TJA.[63-67] Patients diagnosed with malnutrition are 2 times more likely to have postoperative wound complications compared to those with adequate nutritional stores.[68,69] While the mechanism of how malnutrition leads to postoperative wound complications is not entirely clear, malnutrition is believed to impair wound healing, cause persistent wound drainage, and prolong inflammation by reducing collagen synthesis and fibroblast proliferation.[63] In addition, malnutrition may impair the ability of the immune system to fight infection through lymphocytopenia and cause PJI.[63] In the event of an SSI or deeper wound infection, malnourished patients demonstrate low success rates of initial irrigation and debridement procedures.[70,71] Thus, evaluation is essential for patients who have malnutrition to determine whether the cause is due to not eating enough key nutrients or if an underlying medical condition such as liver failure may be causing malabsorption of key nutrients into the body.

Vitamin D Deficiency/Insufficiency

Risk factors associated with vitamin D deficiency (25-hydroxy vitamin D of 20 ng/mL or lower) or insufficiency (25-hydroxy vitamin D less than 30 ng/mL) and PJI remain controversial and undefined.[72] Some research has reported a higher prevalence of vitamin D deficiency in patients with PJI compared to patients without infection, thereby suggesting an association between low vitamin D levels and possible suboptimal postsurgical outcomes.[73] Most research, however, demonstrates little evidence to support hypovitaminosis D as a risk factor linked to reduced postoperative functional recovery or increased risk of PJIs.[74,75] Some orthopedists nevertheless recommend screening and treating hypovitaminosis D prior to undergoing orthopaedic surgery.[74] When recommended, a standard vitamin D regimen consists of 50,000 units of vitamin D^3 weekly for 6 to 8 weeks to increase low levels to an optimal level of 30 to 60 ng/mL. Maintenance doses of 2,000 units of vitamin D^3 daily or 5,000 units 3 times a week are recommended

SIDEBAR. Advance Organizer Quiz to Organize the Materials Presented
Please answer true or false to the following items:
1. True/False. Estimates indicate that by 2030, more than 3 million total joint arthroplasties (TJAs) will be performed each year in the United States.
2. True/False. Prosthetic joint infection (PJI) in TJA is associated with an increase in morbidity, implant failures, and financial and emotional costs.
3. True/False. Associated risk factors for PJI in TJA can be modified to reduce the incidence of systemic comorbid systemic complications and implant failure postoperatively.
4. True/False. For patients with a hemoglobin A_{1C} of 8% to 9% or greater or glucose levels between 180 to 200 mg/dL, optimization of the elevated levels is mandated prior to undergoing TJA.
5. True/False. High hemoglobin levels can increase a patient's risk for perioperative allogenic blood transfusions and PJI after surgery.
6. True/False. Mental health disorders in patients undergoing TJA are relatively easy to detect.
7. True/False. Malnutrition is not a risk factor in patients with an elevated body mass index (greater than 40) undergoing TJA.
8. True/False. Hyperalbuminemia significantly increases the risk of superficial site infections following TJA.
9. True/False. Homelessness is often overlooked as a potential barrier to recovery.
Answers
1. True
2. True
3. True
4. True
5. False
6. False
7. False
8. False
9. True

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thereafter. Fifteen minutes of exposure to sunlight daily if possible is also recommended.[74]

HIV/AIDS

Patients who have HIV with a CD4 level below 200/mm^3 are known to have a 10-fold increase in infection.[76] Research demonstrates that patients with well-controlled HIV who receive highly active antiretroviral therapy with undetectable viral loads and have a CD4 level above 200/mm^3 are at similar risk of PJI as the average population.[77] Thus, for patients with HIV who are medically optimized with highly active antiretroviral therapy, the risk is small and comparable to patients who are HIV negative in conjunction with optimization of underlying associated conditions such as malnutrition, renal disease, and liver disease.[1]

HCV

Research indicates that patients with HCV are at increased risk of both acute and long-term medical and surgical complications.[78] Treatment for HCV prior to THA appears to be associated with fewer postoperative complications, primarily periprosthetic joint infection.[78] For patients with known HCV, many orthopaedic surgeons require that patients complete HCV treatment in entirety prior to elective TJA (Eric L Smith, MD, personal communication, October 16, 2017).[a]

Patients with liver disease (eg, hepatitis and/or cirrhosis) are at increased risk for SSI/PJI and intraoperative and postoperative bleeding.[79] Patients with cirrhosis are found to have longer lengths of hospital stay, increased costs, and higher rates of mortality, readmission, and reoperation.[80] Although currently there are no universal treatment guidelines for managing liver disease prior to elective TJA, referring patients with known liver disease to a liver disease specialist for preoperative optimization of care is recommended.

OSA

The American Society of Anesthesiologists recommends screening patients for OSA before they undergo elective TJA.[81] While there is no apparent association between OSA and PJI reported in the literature, there may be some indirect links. As previously noted, patients with alterations in mental status (eg, delirium) and neurological disorders (eg, stroke) may have prolonged postoperative lengths of hospital stay and higher rates of perioperative complications, which can increase their risk for PJI.

Clinical studies demonstrate that patients undergoing primary TJA who have OSA are at greater risk of postoperative cardiovascular and pulmonary complications, and

death.[82,83] In elderly patients without a history of dementia who elect to undergo elective TJA, there is an association between preexisting OSA and postoperative dementia, which can lead to longer lengths of hospital stay and perioperative complications.[84]

Rheumatoid Arthritis

It is postulated that immunosuppressive therapies collectively contribute to increased PJI susceptibility for patients who have rheumatoid arthritis and associated comorbidities.[13] Immunosuppressive therapies involving corticosteroids (eg, prednisone) and disease-modifying antirheumatic drugs (eg, methotrexate) place patients with rheumatoid arthritis undergoing TJA at greater risk of infection.[85] Some studies report no increase in the incidence of PJI, regardless of whether these treatments are discontinued perioperatively.[86,87] The American College of Rheumatology and the British Society for Rheumatology[88-90] both recommend withholding tumor necrosis factor-α inhibitors perioperatively to TJA. Likewise, the International Consensus Group on Periprosthetic Joint Infection[91] recommends stopping disease-modifying antirheumatic drugs within the clinical judgement of the medical team for at least 14 days prior to elective TJA.

Immunocompromised Status

Patients who are concurrently undergoing immunosuppressive therapies involving corticosteroids and disease-modifying antirheumatic drugs are at greater risk of PJI due to their compromised ability to heal, fight infections, and maintain homeostasis.[1] Therefore, a risk-benefit analysis is recommended for these types of patients.

Cardiovascular Disease

Specific cardiovascular diseases are shown to significantly predispose patients to PJI. Congestive heart failure, PVD, valvular heart disease, atrial fibrillation, and myocardial infarction are independent comorbid factors associated with a higher risk of PJI.[20] It is postulated that the increased risk of infection associated with these conditions could be related to more aggressive treatment with anticoagulation.[20]

Hypothyroidism

There is some evidence of an association between hypothyroidism and PJI.[92] In one clinical study, patients who developed PJI demonstrated a statistically significant, 2.46 times greater thyroid-stimulating hormone than those without PJI.[92] Buller et al[93] reported that hypothyroidism was associated with greater risk of postoperative complications compared to matched controls. Evaluation and proper management of thyroid function in patients with thyroid disease is important prior to elective TJA.

Chronic Renal Failure/Kidney Disease

Reports suggest that patients who have chronic renal failure are at greater risk of developing PJI after TJA. One study demonstrated that hemodialysis patients had approximately twice the rate of infection than patients who had undergone a renal transplant.[94] The reason for this is thought to be multifactorial, including the immunosuppressive nature of therapies associated with chronic kidney disease, which may increase susceptibility to infection.[94,95]

Blood Clotting Disorders

Blood clotting disorders (eg, hemophilia and von Willebrand disease) are associated with significantly higher rates of infection, transfusions of blood products, medical complications, and revision surgery after TKA.[1] Patients with blood clotting disorders require referral to a hematologist or vascular surgeon for risk assessment and perioperative recommendations, followed by close monitoring by the surgical team after TJA. Intraoperative use of tranexamic acid, an antifibrinolytic agent, promotes blood clotting and reduces bleeding in the surgical wound.[96,97] Utilizing tranexamic acid during surgery in patients with hemophilia has demonstrated 1) lower perioperative blood loss, 2) lower hidden blood loss, 3) a lower transfusion rate, 4) lower postoperative joint swelling and pain, and 5) lower levels of inflammatory biomarkers resulting in enhanced overall joint function.[98]

PVD

PVD is an identifiable risk factor for arterial insufficiency that can lead to wound complications and PJI.[99] Defined as decreased arterial perfusion to the lower extremities, PVD can be clinically identified by intermittent claudication or the absence of arterial pulses in the lower extremities.[99] Patients who have known or suspected PVD should be referred to a vascular specialist for evaluation of arterial perfusion and potential for postoperative blood clots.

Homelessness/Low Socioeconomic Status

Patients who are homeless have potential barriers to recovery because of these common health issues. These barriers include the following: 1) mental illness, 2) drug and alcohol dependence, 3) risk of violence, 4) HIV, 5) hepatitis B and C, 6) neurological disorders, 7) anemia, 8) cardiac disease, 9) tuberculosis and other respiratory infections, and 10) increased mortality rates.[100] These potential recovery barriers often lead to longer lengths of hospital stay, reduce the likelihood of attending follow-up clinic appointments, increase the likelihood of returning to the emergency department, and have higher readmission rates for infections. Interventions such as providing stable housing are essential

to improve the health outcomes of people who are homeless and to reduce the associated costs to the health care system.[101]

Special Surgical Considerations

Special surgical considerations to optimize postoperative outcomes include 1) appropriate patient selection, 2) infection control practices, and 3) attentive postoperative management protocols.[102] Additionally, other surgical factors that appear to reduce the rate of PJI include shorter duration of surgery, prophylactic antibiotics given within 60 minutes of the surgical incision, *S. aureus* decolonization with mupirocin ointment, and preoperative chlorhexidine wash.[54]

DISCUSSION

It is apparent that when addressing the challenge of PJI, orthopaedic surgeons play an important role in limiting the impact of associated risk factors in the preoperative, intraoperative, and postoperative phases of TJA. Reducing emotional and economic burdens associated with PJI is a primary objective undertaken by orthopaedic surgeons when considering surgical candidates for elective TJA. Although in most cases, orthopaedic surgeons and their teams perform the essential role of identifying and addressing associated risk factors that affect perioperative morbidity and mortality, the role of identifying and addressing these associated risk factors should start with patients' PCPs. Therefore, it is incumbent on the PCP to ensure patient optimization prior to undergoing TJA and referring patients for surgical evaluation. Through preoperative identification and modification of patient-associated risk factors, along with patient compliance to related medical recommendations, improved overall postoperative clinical outcomes are achievable. ❖

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CASE REPORT

Management of Spontaneous Liver Hematoma in Ehlers-Danlos Syndrome Type IV: A Case Report

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ABSTRACT

Introduction: Liver hematoma is an uncommon feature of Ehlers-Danlos syndrome (EDS) type IV. The limited literature that exists to guide management does not establish a standard of care.

Case Presentation: A 26-year-old man presented with acute abdominal pain caused by a large, spontaneous liver hematoma. Invasive prophylactic arterial embolization was done twice, but surgical evacuation was not offered because of concern for poor healing and brittle vasculature, later diagnosed as symptoms of the patient's EDS type IV. During hospitalization the patient died of spontaneous intracerebral and intra-abdominal hemorrhaging.

Conclusion: This case illustrates a nonsurgical management option for spontaneous liver hematoma in a patient with EDS type IV. An interdisciplinary team should help guide care, including consideration of invasive procedures such as arterial embolization and surgery. Patient and family education, genetic testing, and timely medical record documentation may reduce the morbidity and mortality of patients with this syndrome.

INTRODUCTION

Ehlers-Danlos syndrome (EDS) is a heterogeneous and inherited group of connective tissue disorders. Thirteen phenotypically distinct EDS subtypes exist.[1] EDS type IV, or vascular subtype, is autosomal dominant and is associated with spontaneous arterial, uterine, and colonic rupture caused by structurally abnormal type III collagen.[1] Liver hematoma is an uncommon feature of EDS type IV, and the limited literature on its management includes descriptions of intraoperative and postoperative deaths.[2-4] A standard of care is not established. Exhaustive unsuccessful attempts were made to reach the patient's next of kin. An effort has been made to anonymize patient information.

CASE PRESENTATION

The institutional review board determined that this case study did not meet the criteria for human subjects research and therefore did not require board approval.

Presenting Concerns

A 26-year-old man was watching TV in bed when he experienced acute, severe abdominal pain. The pain felt similar to when he sustained a spontaneous liver hematoma 7 years earlier, which necessitated a right hepatic lobectomy; thus, he went to the Emergency Department. An abdominal computed tomography (CT) scan revealed a 14-cm subcapsular liver hematoma, so he was admitted to the intensive care unit for hemorrhage monitoring. Concern was raised for EDS because he also had a spontaneous pneumothorax 2 years earlier and a younger teenaged brother had died of a spontaneous aortic rupture. The hepatobiliary surgical team was consulted for hematoma evacuation; however, surgery was not offered because of concern for a poor surgical outcome subsequent to poor healing and the brittle vasculature believed to be caused by EDS.

Therapeutic Intervention and Treatment

During the following 4 days, 3 episodes of tachycardia, worsening pain, and increased intra-abdominal pressure suggested episodes of recurrent bleeding (Figure 1). Results of a repeated CT scan showed enlargement of the hematoma. Results of an angiogram performed by Interventional Radiology showed no extravasation; therefore, the nonbleeding left hepatic artery was prophylactically embolized (Figure 2A). Later, the right hepatic artery branches reconstituting the left hepatic artery were also prophylactically embolized (Figure 2B). Invasive interventions were stopped thereafter because the bleeding was attributed to capillary leakage from capsule shearing. He received medical management of pain and anemia.

Follow-Up and Outcomes

The patient's bleeding was believed to have stopped once his pain improved. His mentation remained intact, and tachycardia resolved, so he was transferred to a ward. That night, he experienced a hyperacute headache, with systolic blood pressure above 200 mmHg. Evolving neurologic impairment developed during the physical examination. Results of a CT scan revealed a large subarachnoid and intraventricular hemorrhage resulting from a dissecting right posterior inferior cerebellar aneurysm. He was intubated and emergently transferred to the regional neurosurgery center to get an external ventricular drain plus aneurysm clipping.

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Keywords: Ehlers-Danlos syndrome, Ehlers-Danlos syndrome type IV, invasive prophylactic arterial embolization, liver hematoma

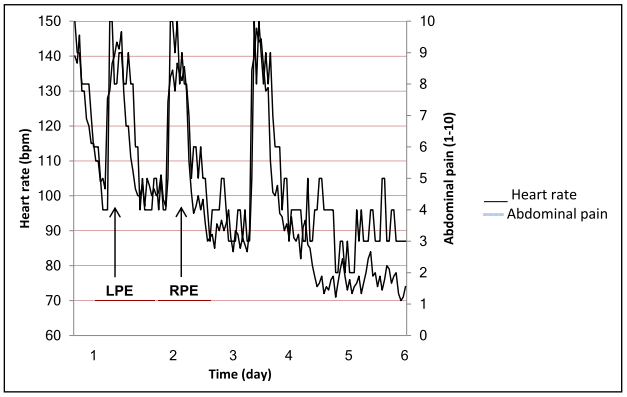

Figure 1. Elevated heart rate and abdominal pain as markers of recurrent bleeding over time. Left axis is heart rate (60-150/min). Right axis is abdominal pain scale (0-10, with 0 indicating no pain and 10 indicating most severe pain possible). LPE = left (hepatic artery) prophylactic embolization; RPE = right (hepatic artery) prophylactic embolization.

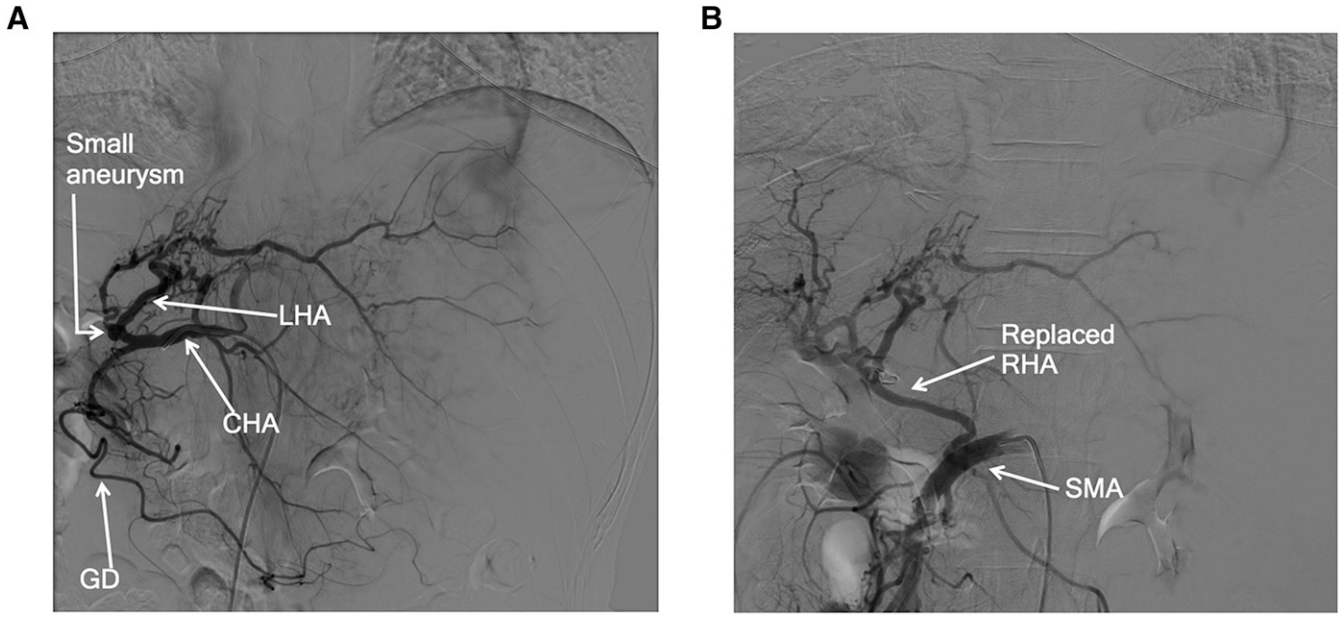

Figure 2. (A) Hepatic angiogram before prophylactic embolization of left hepatic artery (LHA). There is no evident site of extravasation, yet there is a small aneurysm in a tangled hepatic arterial system. CHA = common hepatic artery; GD = gastroduodenal artery. (B) Hepatic angiogram before prophylactic embolization of the right hepatic artery (RHA). RHA branches off superior mesenteric artery (SMA) because of previous right hepatic lobectomy. There is no evident site of extravasation.

He remained intubated and sedated for 3 more days; however, he died on hospital day 14 after an acute intra-abdominal hemorrhage. Genetic test results eventually revealed a *COL3A1* gene variant (c.1610G>T; p.Gly537Val) consistent with EDS type IV. A timeline of the case appears in Figure 3.

DISCUSSION

This case illustrates a management option for spontaneous liver hematoma in a patient with EDS type IV, an uncommon complication of a rare disease. Interdisciplinary management by intensivists, hepatobiliary surgery, interventional radiology, neurosurgery, genetic testing, and social work are challenging but beneficial for these medically fragile patients. Clinicians should use symptoms such as pain, signs such as tachycardia and increased intra-abdominal pressure, and imaging findings to identify recurrent bleeding episodes that compel invasive intervention. Prior case reports on EDS-related subcapsular liver hematomas recommend avoiding surgical intervention, so we attempted embolectomy to achieve source control. However, the patient did recover from a previous liver hematoma evacuation and lobectomy, suggesting he may have tolerated another surgery. In the end, the patient may have benefited

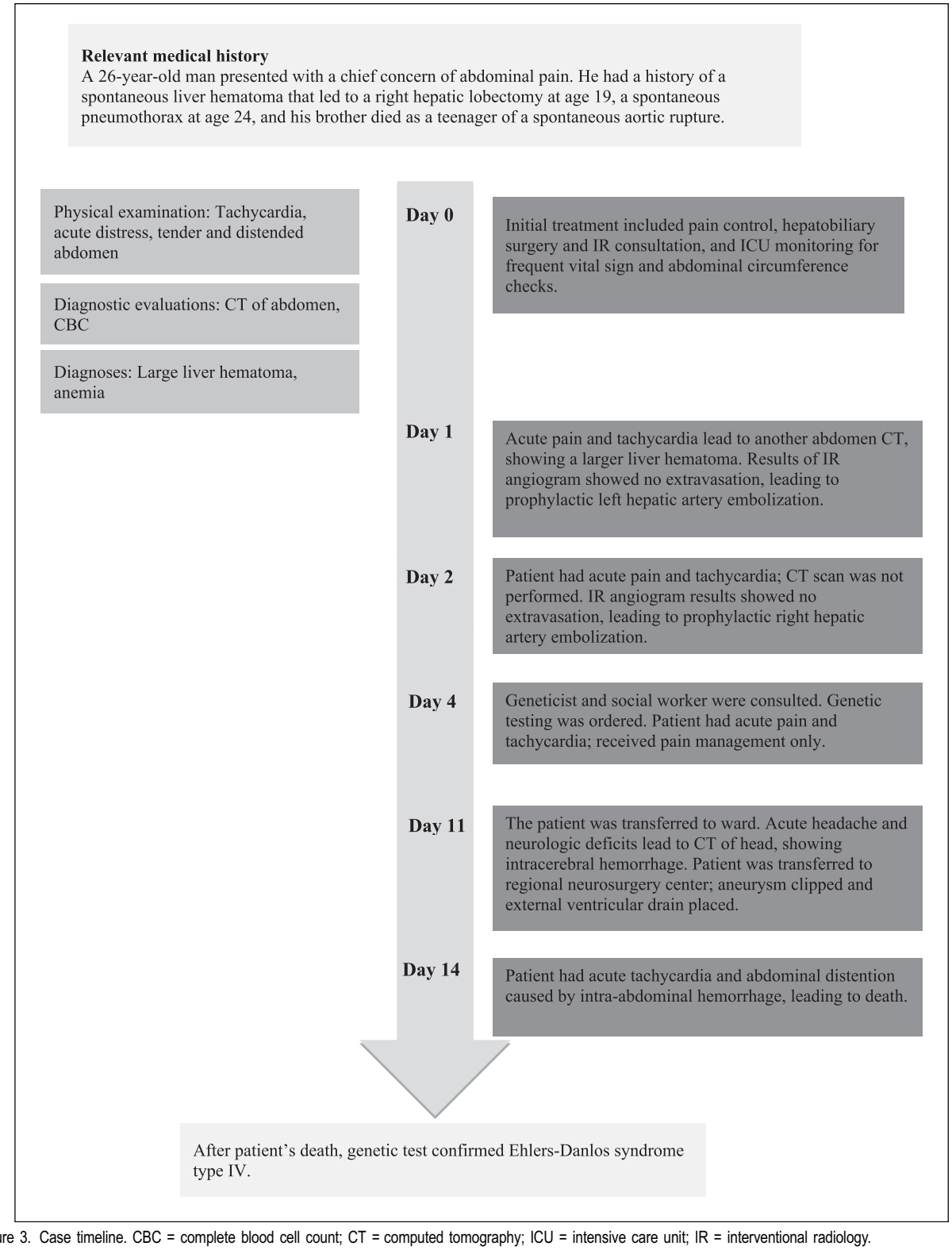

Figure 3. Case timeline. CBC = complete blood cell count; CT = computed tomography; ICU = intensive care unit; IR = interventional radiology.

from hematoma evacuation for pain relief and to avoid the fatal large intra-abdominal hemorrhage.

The patient's family planning may have been affected by an honest discussion with clinicians after his first liver hematoma; at the time of his death, he had a young child, and his wife was pregnant. This time, a genetic consultation was obtained early in the hospitalization. The genetics team oversaw the genetic testing and counseled the patient and family throughout hospitalization. Once the patient's *COL3A1* gene variant was confirmed, outpatient family genetic counseling and testing were done. The patient's child, nephew, and sister had the same variant. They now all carry the Ehlers-Danlos Society Wallet Card containing emergency information[5]; wear medical alert bracelets; have updated medical records including emergency, colonoscopy, and pregnancy recommendations; and have been given handouts of warning signs and symptoms to keep at home. His child now gets regular echocardiograms and cardiology appointments to monitor for aortic aneurysms. His nephew stopped playing contact sports. His sister has since had a carotid cavernous fistula requiring drainage and embolization; her presenting symptoms were headache and diplopia, and her medical record documentation of EDS type IV led to a quick and accurate diagnosis. Imaging also revealed many healed carotid dissections and pseudoaneurysms, so she will receive aspirin therapy indefinitely to prevent embolic strokes. We encourage clinicians to have honest communication with patients and families about genetic inheritance and the high morbidity and mortality of EDS type IV, even in unconfirmed cases.

CONCLUSION

EDS is a very rare connective tissue disorder that impacts many organ systems. Because of the rarity of this disease, even rarer complications and their management have not been well studied. Patient and family education, genetic testing, and timely medical record documentation may reduce the morbidity and mortality of patients with EDS type IV. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Authors' Contributions

All authors assisted in study design, data collection, and manuscript preparation. All authors have given final approval to the manuscript.

Prior Presentation

Dr Imp presented the case at the American College of Physicians Northern California Chapter Meeting in Santa Clara, CA, on November 3, 2018. He was a finalist in the case report poster competition.

How to Cite this Article

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CASE REPORT

Synergistic Effect and Tolerance of Concurrent Radiotherapy and Lenalidomide Use in Relapsing Mantle Cell Lymphoma: A Case Report

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ABSTRACT

Introduction: Mantle cell lymphoma is an aggressive disease. Limited treatment options are available for refractory or relapsing presentation. We report the first case, to the best of our knowledge, of concurrent radiotherapy and lenalidomide use in this setting, focusing on its possible synergy and tolerance.

Case Presentation: A 76-year-old man with a history of mantle cell lymphoma presented with ptosis of the left eyelid, eyelid swelling, and nasal obstruction. Results of positron emission tomography-computed tomography revealed a pathologic fluorodeoxyglucose uptake at the pharynx and left eyelid. He received treatment with ibrutinib, which was stopped 3 months later because of digestive toxic effects. Radiotherapy for the eyelid and pharynx was performed at a dose of 18 Gy, with concurrent lenalidomide administration. Evaluation 3 months later revealed complete disappearance of the 2 relapse sites.

Discussion: This case highlights the role of concomitant lenalidomide treatment and low-dose radiotherapy in patients with relapsing mantle cell lymphoma. Use of this combination treatment has achieved a complete local control with a safe toxicity profile. The case also illustrates the possible lenalidomide-induced radio sensitization.

INTRODUCTION

Mantle cell lymphoma (MCL) is a subtype of B-cell lymphoma that accounts for 3% to 6% of non-Hodgkin lymphoma.[1] It is commonly considered to have aggressive behavior with poor prognosis. Refractory or relapsing presentation that involves the eyelid and pharynx is observed in only 10% of cases.[2] There is no standard therapy for patients with relapsing MCL. We report a case of relapsing MCL of the eyelid and pharynx treated with concurrent low-dose radiotherapy and lenalidomide with complete response and safe toxicity profile.

CASE PRESENTATION

Presenting Concerns

A 76-year-old man with a history of coronary bypass was diagnosed with stage IV MCL disease (bone morrow infiltration) in 2008. He received 8 courses of R-CHOP (rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone). Complete remission was achieved. Maintenance rituximab was administered for 2 years. In 2017, after 7 years of clinical, biological, and radiologic remission, the patient presented with a pathology-proven nasopharyngeal relapse. He underwent chemotherapy with rituximab, dexamethasone, and bortezomib, and his condition improved. One year later, he presented with ptosis of the left eyelid, eyelid swelling, nasal obstruction with dyspnea, and snoring. The patient had systemic B symptoms (fever and night sweats). Results of positron emission tomography-computed tomography revealed pathologic fluorodeoxyglucose uptake at the pharynx (maximum standardized uptake value = 3.8) and the left eyelid (maximum standardized uptake value = 3.4) (Figures 1 and 2). According to the Mantle Cell Lymphoma International Prognostic Index scoring system,[3] the patient was considered high risk. Pharyngeal biopsy confirmed the diagnosis of MCL. Immunohistochemical studies showed overexpression of CD20, CD5, and cyclin D1. His Ki-67 level was 30%.

Therapeutic Intervention and Treatment

The patient started receiving treatment with ibrutinib in September 2018. Treatment was stopped 3 months later because of gastrointestinal intolerance. Subsequently, the patient was treated with 3-dimensional conformal radiotherapy for the eyelid and pharynx at a dose of 18 Gy per 10 fractions with concurrent lenalidomide (25 mg/d for 3 weeks per month). Clinical improvement was observed after 3 fractions (5.4 Gy), with a complete disappearance of swelling and nasal obstruction at the end of treatment. Grade II dysphagia occurred early during treatment but was well manageable and resolved within 2 weeks.

Follow-Up and Outcomes

Three months later (in May 2019), a complete clinical and radiologic response in the 2 relapsing sites was observed with no sequelae (Figures 3 and 4). A timeline of the case appears in Table 1.

DISCUSSION

MCL is a distinct subtype of non-Hodgkin lymphoma with specific clinical, biological, and molecular characteristics.

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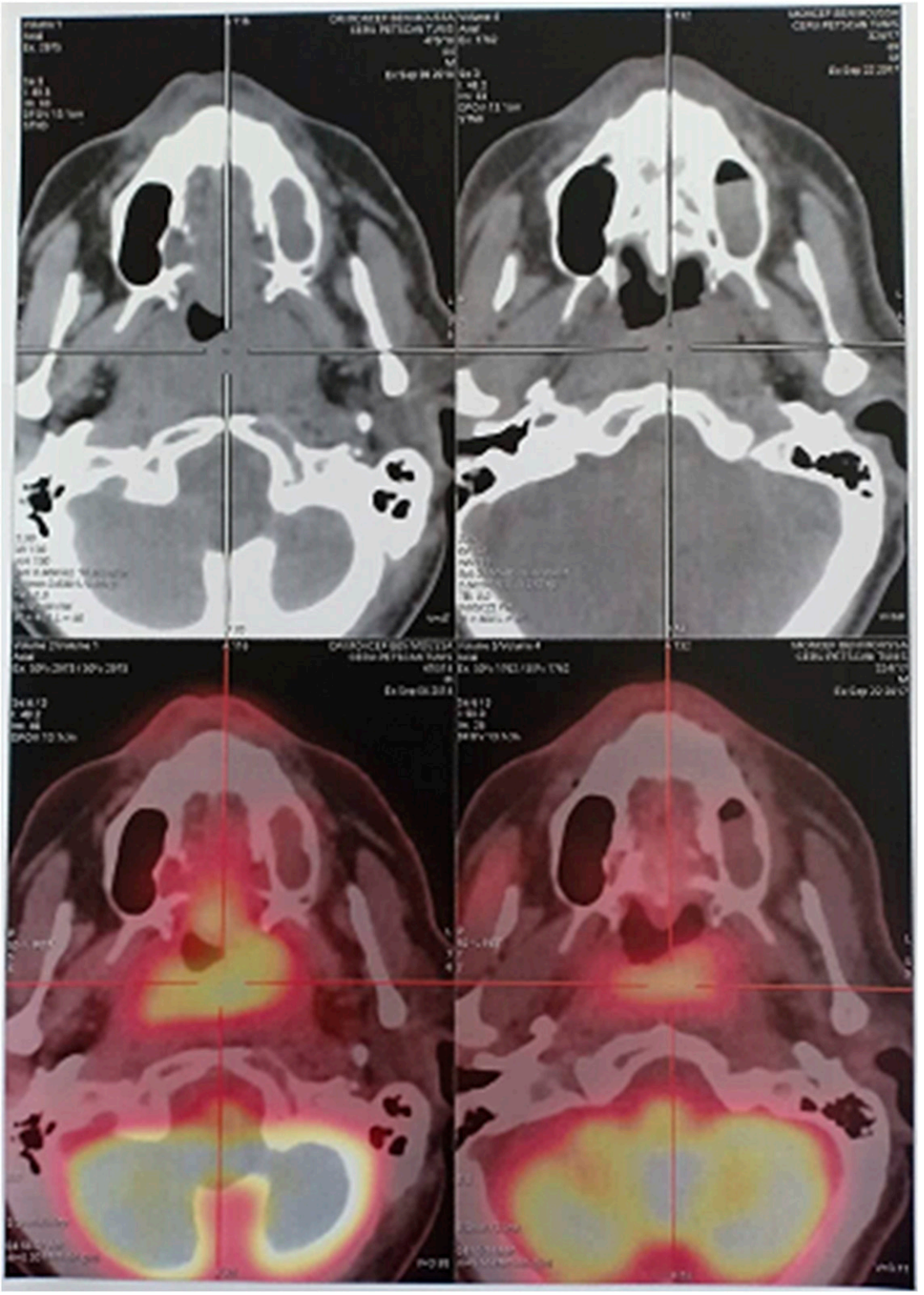

Figure 1. Positron emission tomography-computed tomography with the full-color images showing pathologic fluorodeoxyglucose uptake in the pharynx.

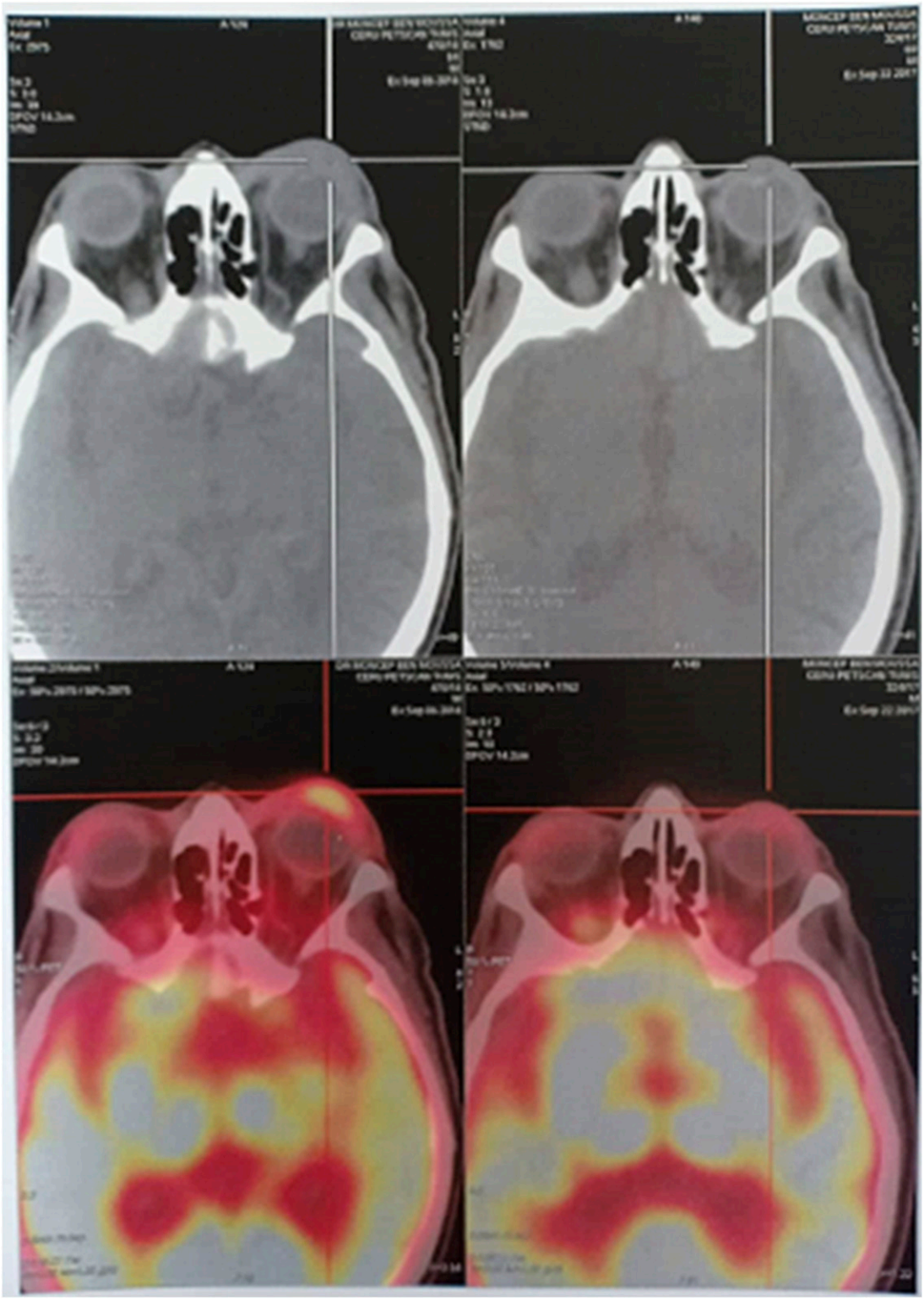

Figure 2. Positron emission tomography-computed tomography with the full-color images showing pathologic fluorodeoxyglucose uptake in the eyelid.

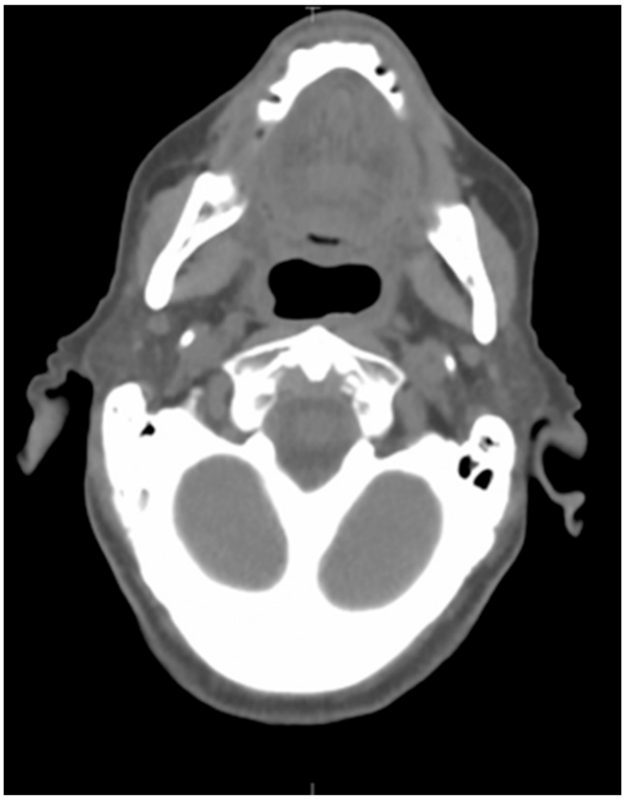

Figure 3. Axial computed tomography showing radiologic remission in the pharynx.

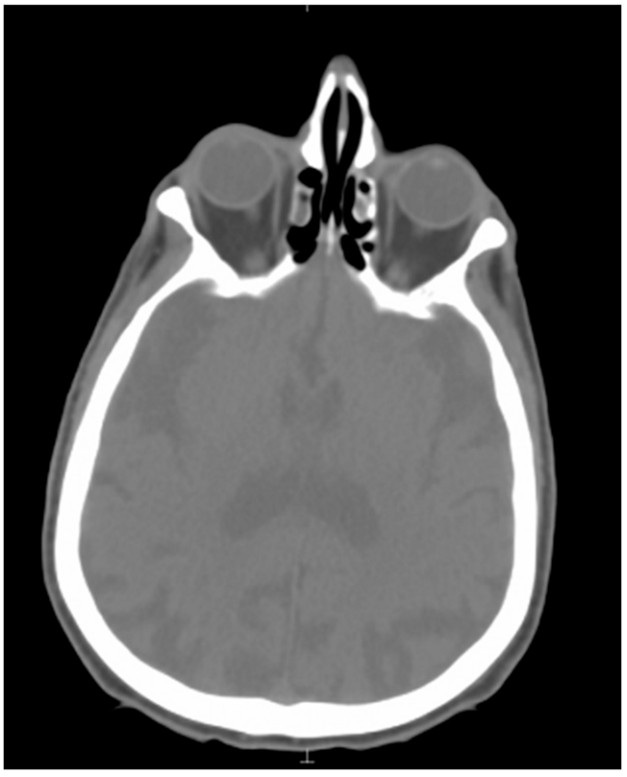

Figure 4. Axial computed tomography showing complete radiologic remission in the eyelid.

MCL demonstrates heterogeneity in its histopathologic and molecular genotypes, which relate to different clinical presentations. Thus, MCL management varies greatly among different subtypes.

Extranodal involvement is common, especially in the bone marrow, peripheral blood, gastrointestinal tract, and Waldeyer ring.[4] Ocular involvement is rare but most commonly occurs in the orbit (90%), lacrimal gland (50%), and eyelids (50%).[2] Our patient had ocular involvement that was detected on positron emission tomography-computed tomography 8 years after a complete response of primary treatment.

Outcome is poor for patients with relapsing or refractory disease, and there is no standard therapy in such cases. The treatment choice should be primarily made on the basis of the patient's previous treatment, the patient's comorbidities and performance status, the regimen's expected toxic effects, and the clinician's experience with regimens. Several chemoimmunotherapy regimens have been explored, including aggressive combination therapy, such as R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) and R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin) for some patients, particularly as a bridge to hematopoietic cell transplantation.

The mainstay of therapy in this setting relies on targeted therapy to disrupt the B-cell receptor signaling pathway with ibrutinib, a Bruton tyrosine kinase inhibitor.[4] In our case, treatment with ibrutinib was associated with severe gastrointestinal toxic effects. Other emerging drugs that have received approval in relapsing and refractory disease are immunomodulators, such as thalidomide and lenalidomide.

To the best of our knowledge, this is the first reported case of relapsing MCL treated with concomitant lenalidomide administration and radiotherapy to a total dose of 18 Gy with complete local control. Use of this combination treatment has achieved an excellent local control in a patient with myeloma.[5] Considering the high efficacy of radiotherapy, this case could point to possible lenalidomide-induced radio sensitization; however, further studies are needed to support this hypothesis.

Several phase 2 studies tested lenalidomide as monotherapy for relapsing MCL and revealed encouraging outcomes and a safe toxicity profile.[6] Overall response ranged from 28% to 53%. Grade 3 to 4 hematologic adverse events occurred in at least 5% of patients, including neutropenia, thrombocytopenia, leukopenia, anemia, and febrile neutropenia.[6] Nonhematologic adverse events,

Table 1. Timeline of the case

Relevant medical history and interventions			
A 76-year-old man with a history of a coronary bypass			
Date	Diagnosis	Treatment	Results
2008	Stage IV mantle cell lymphoma (bone morrow infiltration)	8 courses of R-CHOP plus maintenance rituximab	Complete remission
2017	Nasopharyngeal relapse	Chemotherapy with rituximab, dexamethasone, and bortezomib	Complete remission
2018	Eyelid and pharyngeal recurrence	Ibrutinib (3 mo)	Gastrointestinal intolerance
		Conformal radiotherapy for the eyelid and the pharynx to a dosage of 18 Gy for 10 fractions with concurrent lenalidomide	Complete remission
May 2019	—	—	No tumor recurrence on physical examination or computed tomography

R-CHOP = rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone.

including neuropathy, thrombosis, and teratogenicity, were also reported.[6]

The role of radiotherapy for MCL is still unknown, although radiosensitivity has been demonstrated in vitro.[7] Retrospectives studies have reported favorable outcomes with the use of involved field radiotherapy for advanced or relapsing MCL. Rosenbluth and Yahalom[8] reported results of 21 patients treated with involved field radiotherapy for MCL (mainly stage IV or relapsing disease). The mean radiotherapy dose was 30 Gy (10-45 Gy).[8] Encouraging results were reported (overall response rate of 100%, a complete response in 64%, and a median time to progression of 10 months). The authors suggested that a total dose of 24–30 Gy was reasonably effective for MCL. However, Neville et al.[9] suggested a dose effect on the risk of local failure. Higher doses increased time to local progression.

This case report suggests that low-dose radiotherapy with lenalidomide use is effective. However, caution must be taken with combination therapies because there can be increased toxic effects. The dysphagia seen in our patient at a dose of 18 Gy was unexpected and can be attributed to a synergistic effect on toxicity. Thus, lower-dose radiotherapy in combination with lenalidomide is encouraged for relapsing disease.

CONCLUSION

Low-dose radiation therapy and lenalidomide use may be an effective and safe alternative in the treatment of relapsing or refractory MCL. A possible synergistic effect is suggested, and caution should be applied. This observation should be followed up with further studies to assess efficacy and early and late toxic effects. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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CASE REPORT

Acquired Amegakaryocytic Thrombocytopenia Misdiagnosed as Immune Thrombocytopenia: A Case Report

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ABSTRACT

Introduction: Acquired amegakaryocytic thrombocytopenia (AATP) is a rare bleeding disorder that causes severe thrombocytopenia with preserved hematopoiesis of other cell lineages. Many cases are misdiagnosed and treated as immune thrombocytopenia.

Case Presentation: We report a case of AATP, in a 50-year-old man, that was treated as immune thrombocytopenia for years with no clinical response. The disorder later was diagnosed as AATP after bone marrow biopsy and was successfully treated with cyclosporine.

Discussion: The exact mechanism of AATP remains unclear; it is suspected to be an immune-mediated process. Patients with AATP present with severe bleeding and thrombocytopenia, which is usually unresponsive to high-dose corticosteroids. There are no standard treatment guidelines for AATP. Cyclosporine and antithymocyte globulin are found to be effective in some cases. The prompt diagnosis of AATP is vital because it carries high mortality because of excessive bleeding, and it can progress into aplastic anemia or myelodysplastic syndrome.

INTRODUCTION

Acquired amegakaryocytic thrombocytopenia (AATP) is a rare hematologic disorder characterized by thrombocytopenia resulting from marked reduction or absence of bone marrow megakaryocytes with preserved hematopoiesis of other cell lineages.[1] Although the exact prevalence of AATP is not known,[2] it is very likely that the incidence rates could be higher than reported because many of the cases are either underdiagnosed or misdiagnosed as immune thrombocytopenia (ITP), formerly called idiopathic thrombocytopenic purpura. It is crucial to differentiate AATP from other acquired causes of thrombocytopenia, the most common being ITP, because corticosteroids and intravenous immunoglobulins (IVIG), which are the mainstay for management of ITP, have been found to be mostly ineffective in AATP.[3,4]

Although the exact pathogenesis of AATP has not been fully elucidated, a dysregulated immune system is suspected to be the primary culprit.[2] Standard treatment guidelines for AATP are yet to be established because the available literature contains only case reports and a few small case series. We describe a patient who was treated for ITP for several years but had gradually worsening platelet counts and later received a diagnosis of AATP and was successfully treated with cyclosporine.

CASE PRESENTATION

Presenting Concerns

A 50-year-old man with a previous diagnosis of ITP (chronic idiopathic thrombocytopenic purpura) reestablished care in our clinic because of a recent drop in his platelet count. He reported that ITP was diagnosed 6 years earlier, in 2012, and his platelet count was $50 \times 10^3/\mu L$ at the time of initial diagnosis. He received a 15-day course of prednisone, 1 mg/kg daily, at that time, with some improvement in his platelet count. His platelet count remained stable at around $100 \times 10^3/\mu L$ to $150 \times 10^3/\mu L$ for 5 years after the diagnosis of ITP and then gradually started to trend down. His platelet count on presentation to our clinic in August 2018 was $19 \times 10^3/\mu L$. He denied a history of major bleeding or hematoma but reported having easy bruisability and prolonged bleeding after trivial trauma for years. He had no personal or family history of bleeding disorders, autoimmune disorders such as rheumatoid arthritis or lupus, or malignancy.

Results of his laboratory workup on presentation to our clinic showed anemia with a hemoglobin level of 11.5 g/dL, thrombocytopenia with a platelet count of $19 \times 10^3/\mu L$, and normal white blood cell count. Results of the physical examination were unremarkable. Workup including HIV, hepatitis C virus, *Helicobacter pylori*, and liver function tests as well as a coagulation panel, antinuclear antibody panel, and rheumatoid factor yielded negative or normal results. Vitamin B_{12} and folate levels were normal. A peripheral blood film ("peripheral smear") had unremarkable findings except for a decreased number of platelets. Abdominal images showed no splenomegaly or malignancy.

Therapeutic Intervention and Treatment

The patient received a 4-day course of oral dexamethasone, 40 mg daily, without experiencing any improvement in platelet count. A bone marrow biopsy specimen showed

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Keywords: acquired amegakaryocytic thrombocytopenia (AATP), chronic idiopathic thrombocytopenic, hematologic process, immune thrombocytopenia (ITP), immune-mediated process

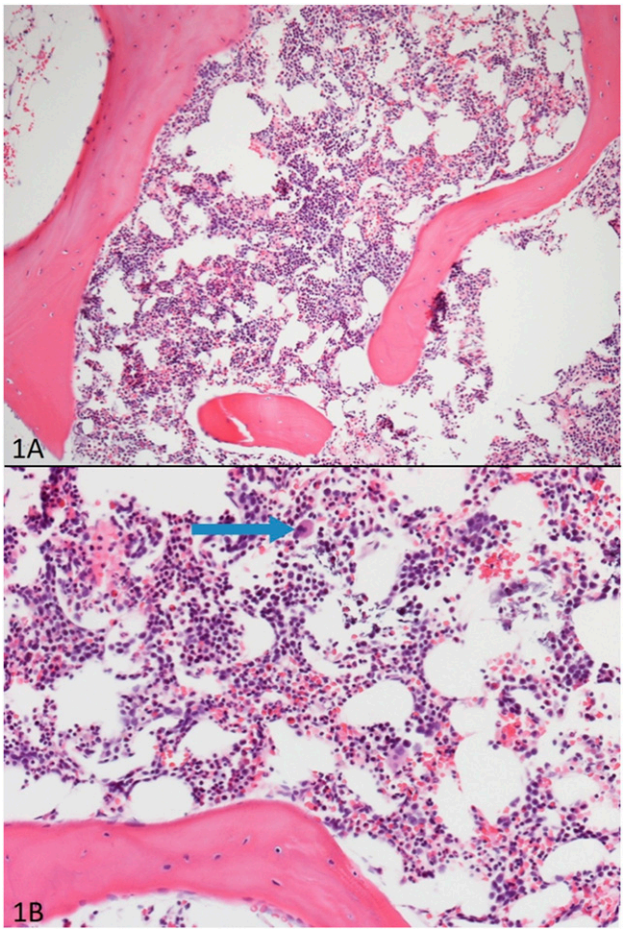

Figure 1. Varying cellularity in the bone marrow of a man with a misdiagnosis of immune thrombocytopenia. (Compare these photomicrographs with Figure 2.) A. Bone marrow shows a region of 40% cellularity (×10). B. Higher magnification view (×20) of the same area showing a rare megakaryocyte in the bone marrow (arrow).

varying cellularity with an average cellularity of approximately 20%. The biopsy specimen also showed normal erythropoiesis and myelopoiesis, but a markedly decreased number of megakaryocytes with no morphologic evidence of myelodysplastic syndrome (MDS). There was less than 1 megakaryocyte per high-power field (Figures 1 and 2). Fluorescence in situ hybridization and cytogenetic test results were negative for MDS. Flow cytometry results of bone marrow demonstrated no monoclonality or malignancy. This picture was consistent with amegakaryocytic thrombocytopenia rather than ITP because there is usually a compensatory increase in megakaryocytes in the bone marrow in ITP. Antibodies against thrombopoietin (TPO) were not detectable. Additionally, an antiplatelet antibody panel was performed by an external laboratory, and results were negative as well. We could not find a cause of the AATP in this case.

Follow-up and Outcomes

The patient was started on a regimen of cyclosporine with a goal serum level between 150 ng/mL and 400 ng/mL. He experienced improvement in platelet counts to greater than 50 × 10^3/μL over 8 weeks (Figure 3). He has continued treatment with cyclosporine, 200 mg twice daily, for more than a year, and platelet counts continue to stay above 50 × 10^3/μL. A detailed timeline of the case appears in Table 1.

DISCUSSION

The causes of acquired thrombocytopenia are quite extensive and include acquired marrow hypocellularity, qualitative defect in platelet production with adequate marrow cellularity, defective thrombopoietic control with normal marrow, and peripheral destruction of the platelets.[2]

Our patient was previously given a diagnosis of ITP and received systemic corticosteroids with some initial improvement in his platelet counts. However, the gradual worsening of his platelet counts over the years and a poor response to high-dose corticosteroids the second time raised the possibility of other causes of his thrombocytopenia. Furthermore, the absence of megakaryocytes on bone marrow biopsy in our patient is inconsistent with ITP and more consistent with AATP because there is usually a compensatory increase in megakaryocytes in the bone marrow in ITP. This emphasizes the importance of performing a bone marrow biopsy in patients with unexplained, isolated thrombocytopenia or in patients with an ITP diagnosis if they are not adequately responding to corticosteroids or IVIG.

AATP can be idiopathic and occur as a primary disorder or be seen in association with lymphoproliferative disorders[1];

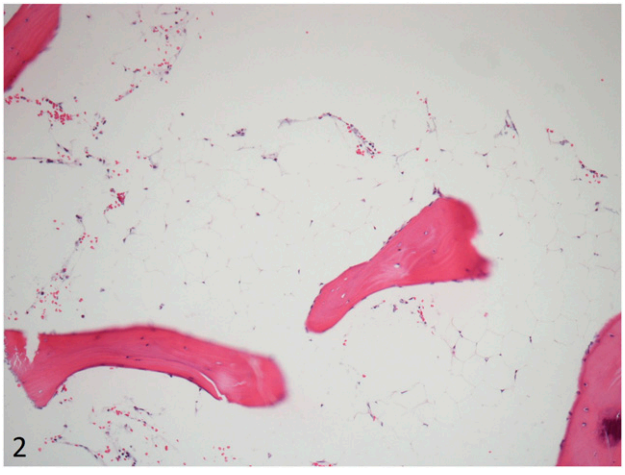

Figure 2. Photomicrograph of a different part of the same patient's bone marrow showing 0% cellularity (with no hematopoietic cells) but intact adipocyte framework (×10).

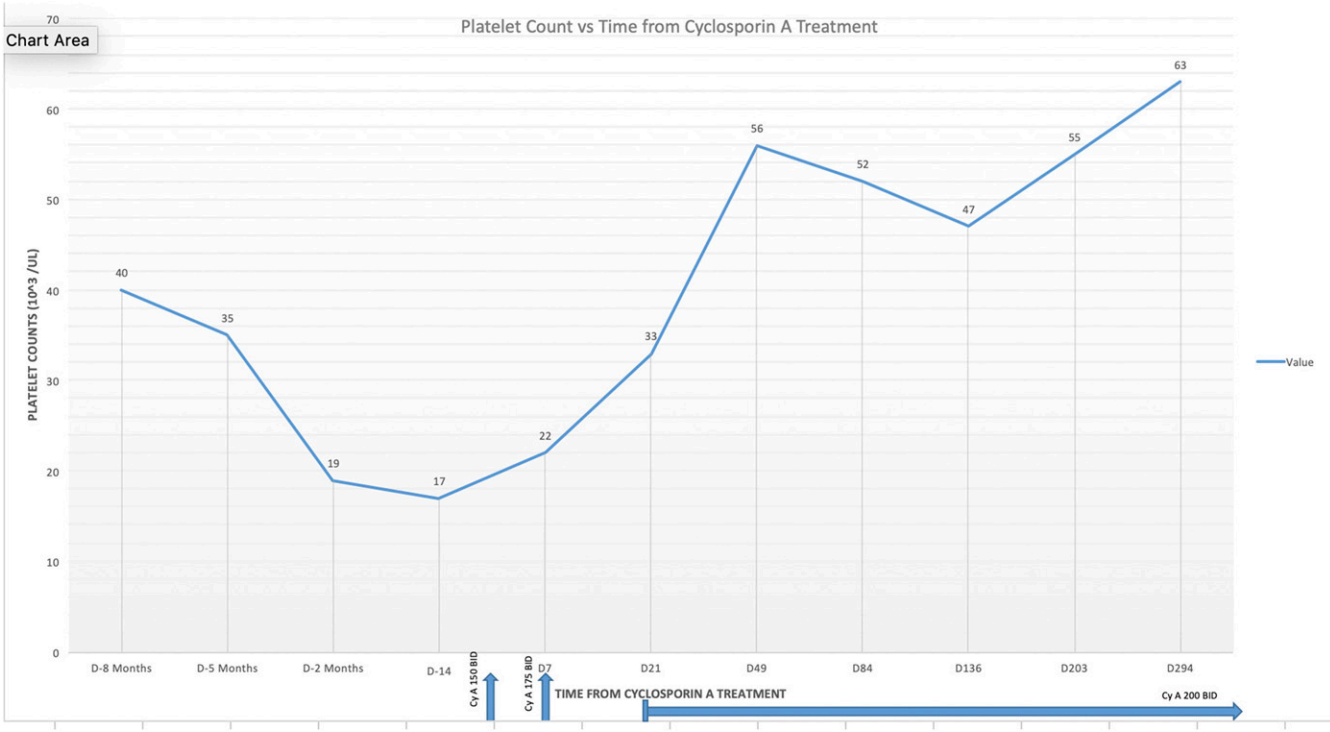

Figure 3. Graph of timeline of platelet count (×10^3/μL) response to cyclosporine therapy. BID = twice daily; CyA = cyclosporine; D = day.

autoimmune disorders such as systemic lupus erythematosus,[5] rheumatoid arthritis,[1] or Still disease[6]; viral infections such as cytomegalovirus,[2] Epstein-Barr virus,[7] parvovirus B19,[8] or hepatitis C[9]; exposure to environmental toxins such as benzene[1]; and vitamin B_{12} deficiency.[10] It could also be a precursor for aplastic anemia,[11] MDS,[12] or acute leukemia.[4] In our patient, we could not find any cause for AATP, and hence it is likely idiopathic.

Although the exact mechanism of AATP remains unclear, it is strongly suspected to be an immune-mediated process. The primary regulator of platelet production is TPO, which is mainly produced by the hepatocytes.[7] It binds to the TPO cellular-myeloproliferative leukemia receptor on megakaryocytes and hematopoietic stem cells, affecting nearly all stages of platelet production including proliferation, differentiation, and maturation of megakaryocyte into platelets. Dysregulated humoral immunity as one of the mechanisms for AATP has been proposed because of the presence of anti-TPO immunoglobulin G antibodies[13] and autoantibodies against the cellular-myeloproliferative leukemia receptor,[5,8] blocking the function of TPO. Cell-mediated immunity appears to play a more important role because T lymphocytes obtained from a patient with AATP were found to selectively inhibit megakaryocyte lineage in vitro.[14] The response of AATP to immunosuppressants further supports the immune-mediated pathogenesis of AATP.

There are no standard treatment guidelines for AATP. Unlike in ITP, prednisone and IVIG have been found to be largely inefficacious or transiently effective in patients with AATP.[2-4] Although there is no expert consensus, cyclosporine monotherapy has been found to be quite effective in several reported cases,[4,6-9] including our patient. Cyclosporine with a target serum level between 150 and 350 ng/mL has been found to be most effective.[2] Cyclosporine needs to be continued for several weeks to months for complete remission. The dose can be tapered after the normalization of platelet counts.[2] In patients with severe bleeding from thrombocytopenia or who are refractory to treatment with cyclosporine alone, administration of antithymocyte globulin along with cyclosporine has been found to be effective.[4]

Other therapies such as rituximab,[3] mycophenolate mofetil,[15] danazol,[16] and azathioprine[17] have also been used to treat AATP with varying success. In patients refractory to cyclosporine or antithymocyte globulin and in patients with relapsed disease or disease progression into aplastic anemia or MDS, allogeneic bone marrow transplant should be strongly considered, especially in relatively young patients with matched siblings.[18] Some case reports showed that alemtuzumab, a T cell-depleting agent[19], and TPO receptor agonists such as eltrombopag and romiplostim have also been found to evoke a satisfactory response in patients with refractory AATP.[20]

Table 1. Timeline of the case

Relevant medical history and interventions:
A 50-year-old man with a diagnosis of chronic idiopathic thrombocytopenic purpura since 2012 presented with no family history of bleeding disorders.

Date	Summaries from initial and follow-up visits	Diagnostic testing	Interventions
8/7/2018	On initial presentation to our clinic, patient reported easy bruising and prolonged bleeding on trivial trauma	Laboratory tests on presentation included: Hemoglobin: 11.5 g/dL WBC: 3.8 × $10^3/\mu L$ Platelet count: 19 × $10^3/\mu L$ HIV, HCV, *Helicobacter pylori,* liver function test, coagulation panel, antinuclear antibody, rheumatoid factor, vitamin B_{12}, folate: Normal results CT scan of abdomen and pelvis: Normal results Peripheral smear: Decreased number of platelets	Dexamethasone, 40 mg daily, for 4 d without improvement in platelet count
9/4/2018	On follow-up visit, no new symptoms	Platelet count: 17 × $10^3/\mu L$	Bone marrow biopsy: Varying cellularity from 40% to 0% with normal erythropoiesis and myelopoiesis but absent megakaryocytes; no morphologic evidence of MDS. Fluorescence in situ hybridization and cytogenetics were negative for MDS. Flow cytometry of bone marrow was negative for monoclonality or malignancy.
9/18/2018	Diagnosis of AATP made from bone marrow biopsy. Reported new spontaneous bruises on inner left thigh	Platelet count: 18 × $10^3/\mu L$ Antibodies against thrombopoietin: Negative Antiplatelet antibody panel: Negative	Started on regimen of cyclosporine, 2.5 mg/kg/d (150 mg twice daily)
9/25/2018	Patient tolerated cyclosporine, denied adverse effects	Platelet count: 22 × $10^3/\mu L$ Cyclosporine level: 116.1 ng/mL	Cyclosporine dose increased to 175 mg twice daily
10/9/2018	Patient tolerated cyclosporine, denied adverse effects	Platelet count: 33 × $10^3/\mu L$ Cyclosporine level: 142.3 ng/mL	Cyclosporine dose increased to 200 mg twice daily
12/11/2018	Patient tolerated cyclosporine	Platelet count: 56 × $10^3/\mu L$ Cyclosporine level: 213.9 ng/mL	Continued cyclosporine, 200 mg twice daily
4/16/2019	No new bleeding; patient tolerated cyclosporine	Platelet count: 62 × $10^3/\mu L$ Cyclosporine level: 202.4 ng/mL	Cyclosporine dose reduced to 175 mg twice daily
11/12/2019	No new symptoms; patient denied bleeding	Platelet count: 67 × $10^3/\mu L$ Cyclosporine level: 183.0 ng/mL	Received cyclosporine, 175 mg twice daily
02/04/2020	On most recent clinic visit, no rash or bleeding	Platelet count: 68 × $10^3/\mu L$ Cyclosporine level: 146.8 ng/mL	Continued Cyclosporine 175 mg twice daily

AATP = acquired amegakaryocytic thrombocytopenia; CT = computed tomography; HCV = hepatitis C virus; MDS = myelodysplastic syndrome; WBC = white blood cells.

The prognosis and clinical course of AATP is variable, with some patients achieving remission and having a durable response, whereas others have a long relapsing-remitting disease course. Furthermore, there are a few patients who progress rapidly to aplastic anemia,[11] MDS,[12] or even leukemia[4] despite aggressive immunosuppressive treatment, which makes regular long-term follow-up necessary.

CONCLUSION

AATP is a rare disease that can easily be confused with other causes of thrombocytopenia, especially ITP. This case report highlights the importance of performing a bone marrow biopsy in cases of unexplained thrombocytopenia and in patients who have a diagnosis of ITP but do not adequately respond to corticosteroids or IVIG, to rule out amegakaryocytic thrombocytopenia. This form of thrombocytopenia requires prompt treatment and close follow-up. Additionally, our observations also confirm successful treatment of this rare entity with cyclosporine. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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CASE REPORT

Concurrent Birt-Hogg-Dubé Syndrome and Hereditary Paraganglioma-Pheochromocytoma Syndrome Presenting as Metastatic Renal Cell Carcinoma in a 25-Year-Old Man: A Case Report

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ABSTRACT

Introduction: Birt-Hogg-Dubé syndrome and hereditary paraganglioma-pheochromocytoma syndrome are rare genetic cancer syndromes that predispose patients to renal neoplasia. We report a case of a 25-year-old man with both Birt-Hogg-Dubé syndrome and hereditary paraganglioma-pheochromocytoma syndrome who presented with painless gross hematuria and was found to have metastatic clear cell renal carcinoma.

Case Presentation: A previously healthy, 25-year-old man presented to his outpatient primary care physician with painless gross hematuria. Urinalysis results demonstrated hemoglobinuria, and serum chemistry results demonstrated a creatinine level of 1.61 mg/dL (baseline of 0.96 mg/dL). A computed tomography scan showed that the patient had a left renal mass, renal vein thrombosis with inferior vena cava extension, and nodal and hepatic metastasis. Biopsy specimens of the left renal mass and liver demonstrated clear cell carcinoma. The patient underwent cytoreductive nephrectomy, caval thrombectomy, and partial colectomy with reanastomosis. He received palliative therapy with 1 mg/kg of ipilimumab and 3 mg/kg of nivolumab for 4 cycles.

Conclusion: To our knowledge, this is the first known case report to date documenting a patient with concurrent Birt-Hogg-Dubé syndrome and hereditary paraganglioma-pheochromocytoma syndrome. This case demonstrates the exceptionally young presentation of metastatic renal cell carcinoma with this genotype.

INTRODUCTION

Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant genetic disease caused by mutations in the folliculin (*FLCN*) gene located at 17p11.2, which is characterized by benign skin lesions of fibrofolliculomas, trichodiscomas, and acrochordons presenting in the third decade of life.[1,2] The most common manifestation of the disease is lung cysts, followed by spontaneous pneumothorax and renal cell carcinoma (RCC).[3]

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Keywords: Birt-Hogg-Dubé syndrome, clear cell renal carcinoma, *FLCN* gene, paraganglioma-pheochromocytoma syndrome, renal cell carcinoma, *SDHB* gene

The most serious complication of BHD syndrome is the increased risk of RCC. One study found that patients with BHD syndrome have a 7-fold increased risk of developing RCC.[4] Renal carcinomas in patients with this syndrome have a variety of different histologic findings, but the most commonly seen renal carcinomas are chromophobe and oncocytic tumors.[5] In a study of histologic findings for 33 patients with RCC and BHD syndrome, 70% had oncocytoma or chromophobe-oncocytoma; 3 patients (9%) had clear cell carcinoma.[6]

Hereditary paraganglioma-pheochromocytoma syndrome (HPPS) is a genetic disease caused by a mutation in the succinate dehydrogenase gene and characterized by an increased risk of paragangliomas, pheochromocytomas, and clear cell renal carcinoma.[7] The diagnosis of HPPS is established by a germline pathologic variant in succinate dehydrogenase gene *SDHB*, *SDHA*, *SDHAF2*, *SDHC*, or *SDHD* or in MYC-associated factor *MAX* or transmembrane protein *TMEM127*.[7] Mutations in the succinate dehydrogenase gene halt the citric acid cycle, which triggers hypoxia pathways in cells leading to tumorigenesis.[8] This is the reasoning behind the observation that HPPS genetic mutations show greater phenotypic expression and decreased mutation frequency in the population at higher altitudes.[8] Another genetic feature of HPPS is that the mutation is inherited in an autosomal dominant fashion that demonstrates parent-of-origin effects, whereby inheriting the pathologic gene mutation from the father leads to a greater risk of manifesting the syndrome.[9] Manifestations include pheochromocytomas, which present with symptoms of excess catecholamines (e.g., high blood pressure, diaphoresis, and headache) or with mass effects.[7] Another presentation of HPPS is symptoms of paragangliomas, which arise from neuroendocrine tissues, commonly the adrenal medulla.[7] Symptomatic paragangliomas also present with symptoms of excess catecholamines, although most paragangliomas are nonsecretory.[7] Paragangliomas can also manifest as mass effects, which can present in patients with symptoms of nerve compression or with an enlarging mass.[7]

A subset of patients with HPPS, specifically those with *SDHB* and *SDHD* mutations, are at increased risk of RCC.[9] Patients with pathologic mutations in *SDHB* have a lifetime risk of RCC of 4.7% compared with 1.7% in the general population.[10]

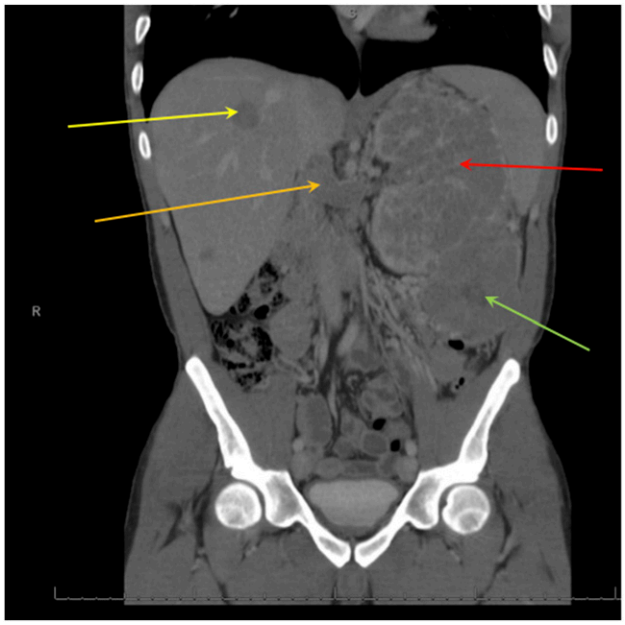

Figure 1. Computed tomography findings for a 25-year-old man. The red arrow indicates a large heterogeneous mass arising from the left kidney replacing the left renal parenchyma. The green arrow indicates an exophytic lesion arising from the lower pole of the left kidney, which measures 8 cm. The gold arrow indicates extensive thrombus within the left renal vein, which extends up to the intrahepatic inferior vena cava. The yellow arrow indicates a rounded hepatic mass compatible with metastasis measuring up to 3 cm.

CASE PRESENTATION

Presenting Concerns

A 25-year-old man with a history of asthma presented to his primary care physician with painless gross hematuria. He denied having flank pain, fever, chills, or weight loss. He did not use anticoagulant medications or supplements and reported no history of kidney disease. Urinalysis results showed hemoglobinuria. His serum creatinine level was 1.61 mg/dL, with a baseline creatinine level of 0.96 mg/dL 6 months earlier. A computed tomography (CT) scan showed that the patient had a left renal mass, renal vein thrombosis with inferior vena cava extension, and nodal and hepatic metastasis, as shown in Figure 1. Interestingly, this patient did not have lung cysts, which are seen in approximately 85% of patients with BHD syndrome.[11]

The patient was admitted to the hospital for further workup and placement of an inferior vena cava filter. Biopsy specimens of the left renal mass and liver demonstrated clear cell carcinoma, as shown in Figure 2. Transcription factor *TFE3* translocation testing yielded normal results. Pathology staining of the renal biopsy specimen was positive for carbonic anhydrase 9 (CAIX), paired box gene 8 (PAX8), and cytokine. Pathology staining of the liver biopsy specimen was positive for PAX8. Further imaging consisted of CT scans of the chest, a bone scan, and brain magnetic resonance imaging (MRI), all of which showed no evidence of further metastatic disease.

Therapeutic Intervention and Treatment

The patient underwent cytoreductive nephrectomy, caval thrombectomy, and partial colectomy with reanastomosis, and he tolerated surgery without complications. He received 4 units of packed red blood cells intraoperatively. His hemoglobin level remained stable throughout his hospital course. He had episodes of hypotension in the first 2 days postoperatively, thought to be related to the epidural anesthesia.

Two days after discharge from the hospital, the patient presented to the emergency department because of nightly fevers to 40.0°C (104°F at home), a 7 of 10 rating of abdominal pain, and ongoing watery diarrhea since the surgery. A chest radiograph showed free air under the diaphragm. A CT scan of the abdomen and pelvis demonstrated free fluid with flecks of gas and linear peritoneal enhancement, which was concerning for an infected abscess. A percutaneous Jackson-Pratt drain was placed by an interventional radiologist, and culture-driven intravenous antibiotics were administered. Cultures yielded heavy growth of *Escherichia coli* and moderate growth of *Enterococcus faecalis*. Gram staining demonstrated many gram-negative rods and gram-positive cocci. A blood culture was positive for *Bacteroides fragilis* with gram-negative rods.

Follow-Up and Outcomes

The patient's postsurgical course was complicated by multiple emergency department visits because of fever, abdominal pain, and left flank pain, which were caused by recurrence of his intraabdominal abscess. He had intermittent clogging of the Jackson-Pratt drain. On imaging, the retroperitoneal abscess demonstrated fistulous connection to the large bowel. Pain management was also an issue with his postoperative course.

After the biopsy proved metastatic renal carcinoma, the patient met with a genetic counselor and underwent genetic testing for cancer syndromes. Testing was conducted with a next-generation sequencing panel that simultaneously analyzed 19 genes associated with increased risk of renal cancer (Ambry Renal-Next; Ambry Genetics, Aliso Viejo, CA). Pathogenic mutations were found in *FLCN* and *SDHB*, specifically at c.1252delC and p.L87S, respectively. No other known pathogenic mutations or variants of uncertain significance were identified in any of the other genes analyzed. This patient did not have other phenotypic characteristics of BHD syndrome (skin lesions, pneumothorax) or HPPS (paragangliomas or pheochromocytomas). His family history was notable for a maternal uncle and maternal grandmother with colon cancer at age 48 and 47 years, respectively, and for a maternal cousin with a history

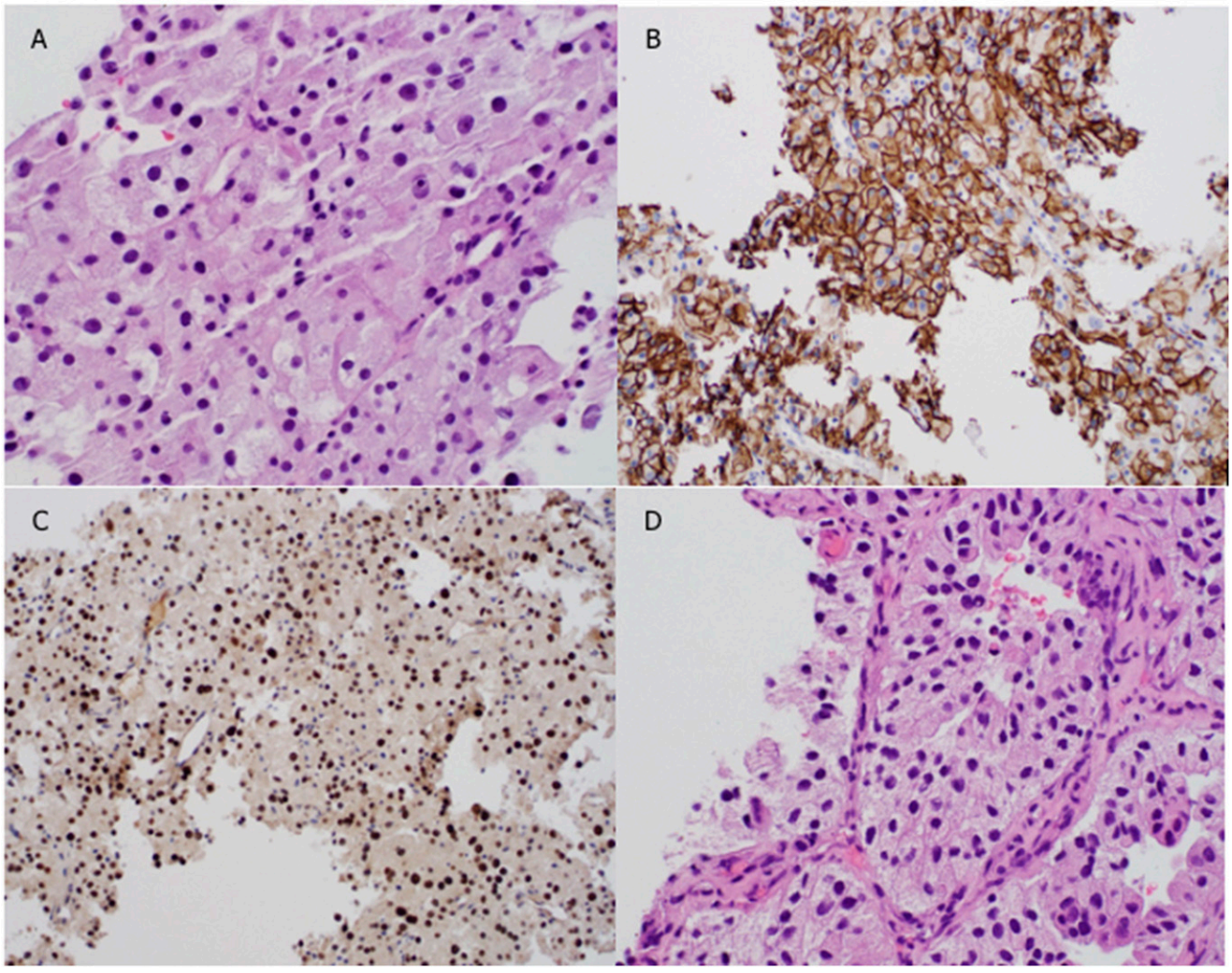

Figure 2. Pathology staining of biopsy specimens. (A) Hematoxylin and eosin stain, renal biopsy. (B) CAIX stain, renal biopsy. (C) KPAX8 stain, renal biopsy. (D) Hematoxylin and eosin stain, liver biopsy. Magnification = ×10 in A and D; ×4 in B and C.

of recurrent pneumothorax. It is possible that the *SDHB* mutation is de novo or paternal in origin, because the father has a granddaughter with congenital ganglioneuroblastoma.

The patient received palliative therapy with 1 mg/kg of ipilimumab and 3 mg/kg of nivolumab for 4 cycles. This patient reported mild gastrointestinal upset after ipilimumab and nivolumab; however, he experienced no serious adverse effects from this treatment. At the end of 4 cycles, imaging showed progressive disease, so treatment was discontinued. The patient then received everolimus for 3 weeks, but everolimus treatment was held when he was admitted to the hospital for fever and ascites. He then developed multiorgan failure requiring a ventilator and blood pressure support. The patient later developed septic shock caused by ventilator-associated pneumonia. He became encephalopathic and had progressive multiorgan failure. His code status was then changed to do not resuscitate, and he was transitioned to comfort care, during which time the patient passed away with his family at the bedside. A summary of this case is shown in Table 1. The patient gave written informed consent for this case report.

DISCUSSION

This is the first case report, to our knowledge, documenting a patient presenting with concurrent BHD syndrome and HPPS. The youngest reported symptomatic presentation with renal cancer in BHD syndrome is in a 14-year-old girl who presented with a bulky abdominal mass.[12] One other patient previously was documented to present with RCC at age 20 years.[13] The average age at presentation of BHD syndrome with RCC is 50.4 years.[14] Of note, the patient described in the current case presented

Table 1. Case timeline

Relevant Medical History and Interventions

A 25-year-old man presented with a history of asthma. He had a family history of a maternal uncle and maternal grandmother with colon cancer at age 48 and 47 years, respectively, as well as a maternal cousin with a history of recurrent pneumothorax and a cousin with congenital ganglioneuroblastoma.

Date	Summaries from initial and follow-up visits	Diagnostic testing	Interventions
March 2019	The patient had painless gross hematuria. Biopsy demonstrated renal clear cell carcinoma	Urinalysis; CT scan showing left renal mass, renal vein thrombosis with IVC extension, and nodal and hepatic metastases. Results of CT scans of the chest, a bone scan, and brain MRI showed no further metastatic disease	Admitted to the hospital for placement of an IVC filter and for renal biopsy; surgery consisted of cytoreductive nephrectomy, caval thrombectomy, and partial colectomy with reanastomosis
April 2019	After discharge, the patient presented to the ED with nightly fevers, abdominal pain, and watery diarrhea	Chest radiograph showed free air under the diaphragm. CT scan of the abdomen and pelvis demonstrated free fluid with flecks of gas and linear peritoneal enhancement, which was concerning for an infected abscess	Drain placement; administration of IV antibiotics
July 2019	The patient presented to the ED for fever, abdominal pain, and left flank pain	Sinogram with fistula; germline pathogenic mutations found in *FLCN* and *SDHB*, specifically at c.1252delC and p.L87S	Drain exchange; administration of antibiotics
March to August 2019	Ongoing metastatic disease		Palliative therapy with 1 mg/kg of ipilimumab and 3 mg/kg of nivolumab for 4 cycles
September to October 2019	Progressive disease on imaging	CT scan of the abdomen and pelvis showed decreasing size of left upper quadrant abscess, increasing ascites, and advanced metastatic disease to the liver	5 mg/d of everolimus
October to December 2019	The patient was admitted to the hospital for fever and ascites. He developed multiorgan failure, and then septic shock because of ventilator-acquired pneumonia	CT scan of the abdomen and pelvis showed persistent left upper quadrant abscess, advanced metastatic disease, and ascites	Antibiotic therapy with cefepime, levofloxacin, and daptomycin
January 2020	The patient's code status was changed to DNR, and he was then transitioned to comfort care, during which time the patient passed away with his family at the bedside		Fentanyl patches and morphine for pain

CT = computed tomography; DNR = do not resuscitate; ED = emergency department; *FLCN* = folliculin; IV = intravenous; IVC = inferior vena cava; MRI = magnetic resonance imaging; *SDHB* = succinate dehydrogenase B.

with metastatic RCC at age 25 years, markedly younger than average for BHD syndrome. This case is unusual because he is the youngest patient reported with BHD syndrome presenting with metastatic RCC. Both young patients documented in the literature had no evidence of local invasion or metastases.[12,13] Previous literature has shown that patients with a mutation in exon 11 in the form of a C-deletion had fewer renal tumors than those who had a C-insertion mutation.[11] Interestingly, this patient had a C-deletion mutation in exon 11, specifically c.1252delC. A prior report from researchers at the National Institutes of Health stated that they had few cases that progressed to metastatic disease, and 2 of those patients had clear cell carcinoma histology, which has notoriously behaved more aggressively than other histologies in BHD syndrome such as chromophobe and oncocytic tumors.[15]

The differential diagnosis of this patient's tumor histology was papillary RCC with cytoplasmic clearing, chromophobe RCC, oncocytoma, epithelioid angiomyolipoma, or clear cell carcinoma. A microphthalmia-associated transcription factor translocation RCC was also considered, because this type commonly presents in young persons.[16] A microphthalmia-associated transcription factor translocation was ruled out by negative staining for transcription factor TFE16. This tumor's positive staining for CAIX suggested that it was less likely to be chromophobe RCC, epithelioid angiomyolipoma, or papillary RCC, all of which stain negative for CAIX.[16,17] This patient's histologic diagnosis of clear cell carcinoma was evident on hematoxylin and eosin staining, as shown in Figure 2. Also, this patient's metastatic tumors were PAX8 and CAIX positive, suggesting metastatic clear cell carcinoma. This patient's pathologic diagnosis was confirmed by a genitourinary pathologist.

Given that this patient's mutation traditionally is less likely to present with renal tumors, another process could have contributed to this patient's young presentation of aggressive metastatic clear cell renal carcinoma. One possible reason for the patient's young presentation of metastatic disease is the concurrent pathologic mutations in both *FLCN* and *SDHB*, both of which predispose to clear cell renal carcinoma. The gene responsible for BHD syndrome may be related to oncogenesis of clear cell carcinoma via loss of heterozygosity at chromosome 3p.[5] Another possible mechanism is via the von Hippel-Lindau disease gene, which was found to be mutated in 33% to 57% of patients with BHD syndrome, consistent with the rate found in sporadic clear cell carcinoma.[5] However, clear cell carcinoma is a rare histology in BHD syndrome, only accounting for 9% of RCCs in a prior study.[6] Because of this, it is likely that this patient's RCC is primarily caused by HPPS, with a possible contribution by the *FLCN* gene of BHD syndrome. Notably, RCC in a patient with BHD syndrome at this young age should prompt practitioners to consider genetic screening for other cancer syndromes.

Although there are no strict guidelines, patients with BHD syndrome are suggested to undergo renal ultrasonography and abdominal MRI at the time of diagnosis, with yearly follow-up screening with renal ultrasonography.[18] A more sensitive option is a yearly MRI scan.[19] Additionally, patients with HPPS should have biennial body MRI scans starting at age 6 to 8 years.[7] This patient's family members were advised to undergo genetic testing to determine whether they should be followed up with screening imaging.

CONCLUSION

This case demonstrates a rare presentation of concurrent BHD syndrome and HPPS presenting as metastatic RCC. This case report is intended to provide education to practitioners about 2 rare genetic cancer syndromes and the indications for genetic screening and imaging for these patients and their family members. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Authors' Contributions

Julia Boland participated in acquisition and analysis of the data and drafting and submission of the final manuscript. Darius Shahbazi, Ryan Stevenson, MD, and Shahin Shahbazi, MD, participated in analysis of the data and drafting of the final manuscript. All authors have given final approval to the manuscript.

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CASE REPORT

Budd Chiari Syndrome and Intrahepatic Cholangiocarcinoma, An Unusual Combination: Case Report and Review of the Literature

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ABSTRACT

Introduction: Intrahepatic cholangiocarcinoma arising in the setting of Budd Chiari syndrome is uncommon and its prognostic and management implications differ from hepatocellular carcinoma.

Case Presentation: We report a case of intrahepatic cholangiocarcinoma in a patient with primary Budd Chiari syndrome. Hepatocellular carcinoma is known to occur with Budd Chiari syndrome. It was difficult to differentiate from hepatocellular carcinoma in the presence of increased alfa-fetoprotein levels. The contrast imaging showed features of progressive enhancement in the arterial, portal, and venous phases. A targeted liver biopsy showed histological features typical for cholangiocarcinoma. Immunostaining for cytokeratin 7 and cytokeratin 20 were positive, whereas that for arginase was negative, suggesting an intrahepatic cholangiocarcinoma. The patient was planned for inferior vena cava angioplasty followed by resection for intrahepatic cholangiocarcinoma.

Conclusion: Previously, only secondary Budd Chiari syndrome developing in the background of primary liver tumor has been described; no report exists of intrahepatic cholangiocarcinoma arising in background of primary Budd Chiari syndrome.

INTRODUCTION

Budd Chiari syndrome (BCS), or hepatic vein outflow tract obstruction, is characterized by obstruction anywhere from the hepatic veins (HV) to the inferior vena cava (IVC) outflow.[1] BCS can be subdivided into primary, characterized by HV stenosis secondary to thrombotic obstruction or phlebitis, or secondary, due to compression of the HV by tumors, cysts, or abscesses.[2] BCS is a risk factor for the development of hepatocellular carcinoma (HCC), with a reported prevalence of 1.9% and cumulative 10-year incidence of 3.5%[3]; however, cholangiocarcinoma has rarely been reported in patients with BCS, and only a few case reports exist. To the best of our knowledge, of the existing case reports, most (5) of them reported the development of secondary BCS with cholangiocarcinoma,[4–7] and there is only a single case report of cholangiocarcinoma developing on a background of primary BCS.[8] Hereby, we report a case of primary BCS presenting as intrahepatic cholangiocarcinoma (ICC), probably only the second case in the English literature and the first from the East.

CASE REPORT

A 42-year-old gentleman presented to the outpatient department with a recent onset of pain in the epigastric region over the past 3 months and noncholestatic jaundice for 15 days (Table 1: Timeline). There was an associated loss of appetite and a weight loss of 3 kg since the onset of symptoms. There was no history of prodromal symptoms, history of jaundice in the past, hematemesis, melena, or altered sensorium. There was a history of tobacco chewing for the past 10 years. He denied a history of chest pain, palpitations, focal neurological deficit, limb pain and swelling, and vision loss in the past. He denied prior blood transfusion, surgery, tattooing, high-risk behavior, family history of liver disease, and injecting drug or alcohol use. The examination was positive for icterus and a palpable firm mass in the epigastric region that was nontender to touch. There were no prominent abdominal veins.

His liver function tests revealed bilirubin of 5.6 mg/dL (normal <1 mg/dL) with a direct fraction of 4.1 mg/dL. Aspartate aminotransferase level was 75 IU/L (normal <40 IU/L), alanine aminotransferase levels 53 IU/L (normal <40 IU/L), and alkaline phosphatase level 595 IU/L (normal <240 IU/L), with a normal total protein and albumin level of 7.3 g/dL and 4.0 g/dL, respectively. Serological tests hepatitis B surface antigen and anti–hepatitis C virus were negative. His alfa-fetoprotein (AFP) was significantly raised, 2500 ng/mL (normal <4 ng/mL), and cancer antigen (CA)-19.9 was 12.9 U/mL (normal <37 U/mL).

Multiphasic magnetic resonance imaging (MRI) (Figure 1) revealed a large multilobulated mass of approximate size 10 cm × 8 cm × 10 cm involving segments III and IV, on the background of a cirrhotic liver. The mass was T1 hypointense, T2 hyperintense, showing patchy heterogeneous arterial enhancement that showed progressive enhancement on portal, hepatic venous, and subsequent 3-minute delayed phase. The areas showing enhancement also showed restriction on diffusion-weighted imaging. In addition, there was splenomegaly (spleen size 15 cm), and the main portal vein diameter was 12 mm. The left portal vein and left hepatic artery were involved by the tumor, and there was left-sided intrahepatic biliary radical dilatation. The MRI also showed nonvisualization of right and middle HVs

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Table 1. Timeline

Date	Clinical Details	Investigations	Interventions/advise
October 2018	Presented with right upper quadrant pain for 3 months and jaundice since 15 days.	Liver function tests: bilirubin (total/direct) 5.6/4.1 mg/dL, SGOT/SGPT 75/53 IU/L, ALP 595 IU/L	Multiphase MRI to characterize liver lesion
	No previous decompensation	HBsAg and anti-HCV Ab: negative	
	Examination revealed icterus and epigastric mass arising from liver	AFP: 2500 ng/mL	
		CA 19.9: 12.9 U/mL	
November 2018	Progressive jaundice	Multiphase MRI: a large mass in the background of a cirrhotic liver with feature of hepatic venous outflow obstruction	Biopsy from mass
December 2018		Biopsy from mass: tumor with cholangiolar differentiation Doppler: Inferior vena cava and hepatic venous obstruction	Offered IVC angioplasty followed by tumor resection
			Patient declined therapy

48-year-old gentleman, chronic tobacco chewer, Non-smoker, non-alcoholic, no previous comorbidities.

and distal most intrahepatic and suprahepatic. The hemiazygous vein appeared enlarged. A subsequent Doppler showed evidence of IVC occlusion and nonvisualization of all the HVs with no ascites and a mass lesion in left lobe, as demonstrated on MRI. The patient underwent a targeted biopsy from the mass lesion, which showed cholangiolar differentiation (Figure 2a) with positivity for cytokeratin (CK) 7 (Figure 2b) and CK 20 (Figure 2c) and no evidence of hepatocyte differentiation with negative arginase (Figure 2d), overall consistent with an ICC. Upper gastrointestinal tract endoscopy showed evidence of portal hypertension in the form of severe portal hypertensive gastropathy with no esophageal varices. The patient was planned for IVC angioplasty followed by resection of the left lobe mass lesion. The patient was offered IVC angioplasty for management of BCS followed by curative resection for ICC, which he declined and was lost to follow-up.

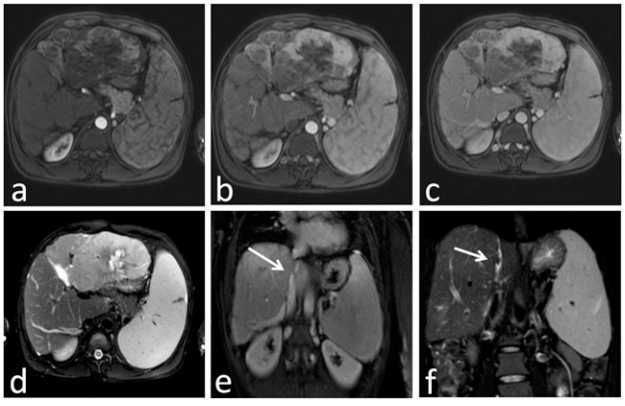

Figure 1. Multiphasic magnetic resonance imaging of the abdomen shows a large mass lesion in segments III and IV, on the background of a cirrhotic liver. The mass shows progressive enhancement on (a) arterial, (b) portal, and (c) venous phases on contrast imaging. The stenotic intrahepatic and suprahepatic part of the inferior vena cava also can be visualized: arrows in (e) and (f).

CONCLUSION

We hereby describe a case of mass-forming ICC in a patient with primary BCS. BCS is a risk factor for HCC; cholangiocarcinoma has been rarely described in patients with BCS. Our patient presented with a mass lesion in a cirrhotic liver background with high levels of AFP, raising the possibility of HCC, which has an association with BCS. However, the findings on multiphasic contrast MRI showed progressive enhancement with no washout and left-sided intrahepatic biliary radical dilatation suggestive of ICC. These findings led us to do a liver biopsy that showed features of cholangiolar differentiation and no hepatocellular differentiation.

Our case had primary BCS with the involvement of both HVs and IVC, which is a common site of block in patients with BCS.[9]

Only 10% of cholangiocarcinomas have an established risk factor.[10] On evaluation for these factors, our patient

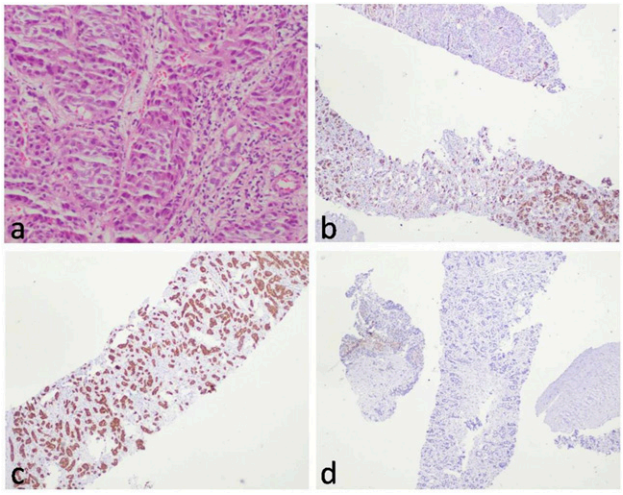

Figure 2. Cholangiocarcinoma. (a) Section stained with hematoxylin and eosin shows clusters of cells with large nuclei showing occasional gland formation on a background of fibrous stroma. (b) CK 7 positivity, (c) CK 20 positivity, (d) arginase is negative. CK = cytokeratin.

had only cirrhosis and tobacco use as evident risk factors. Cirrhosis has been shown to be associated with the development of cholangiocarcinoma, whereas the strength of association with tobacco use is questionable.[11] The possibility of a combined hepatocellular-cholangiocarcinoma (combined HCC-CC) was also contested. Per Park and colleagues,[12] "The World Health Organization (WHO) classification defines combined HCC-CC, classical type as a tumor containing unequivocal elements of both HCC and cholangiocarcinoma (CC), which are intimately admixed, this tumor should be distinguished from separate HCC and CC arising in the same liver."Our patient's biopsy sample did not show any evidence of hepatocyte differentiation, thus questioning the preceding possibility of combined HCC-CC. Combined HCC-CCs are difficult to diagnose preoperatively because of a risk of sampling error (sampling only the area of a single phenotype). Thus, most of the literature reports on combined HCC-CC are based on resected surgical specimens.

Our patient also had a significantly raised AFP level of 2500 ng/mL, which is atypical for cholangiocarcinoma. A study of primary liver cancers in Japan,[13] had shown that 19.2% of cholangiocarcinomas had elevated AFP levels (>200 ng/mL). An exceptionally elevated level of AFP of 12,310.7 ng/mL has been reported as a case report in a histologically proven cholangiocarcinoma.[14] In our case, the exceptionally elevated AFP levels can be explained by the common stem cell origin of both HCC and cholangiocarcinoma.

Our case is also unique in that the patient had a normal CA-19.9 level of 12.9 IU/mL, which can be explained by the fact that the sensitivity of CA-19.9 >37 IU/mL for diagnosing cholangiocarcinoma is only 77.1%.[15]

A diagnosis of ICC, instead of HCC, has prognostic and management implications because of poor median survival of 3 years only with ICC, and also because only a minority (15%) present with resectable disease at the time of presentation.[16] Surgical resection with curative intent is probably the only potentially curative treatment in ICC. Even after a curative intent resection, the probability of cure is only 10%.[17]

The development of secondary BCS due to a primary liver cancer containing a cholangiocarcinoma component has been described previously. Of the 5 case reports in the literature, 4 have reported the primary liver tumor as cholangiocarcinoma,[5-7] and the fifth has reported the tumor to be a combined HCC-CC.[4] All of these reports have shown tumor extension through the HVs leading to tumor thrombus in the IVC and secondary BCS. A single case report previously has described the development of a combined HCC-CC on the background of primary BCS.[8]

Our case was unique in that this is probably the second case in the international literature that describes development of ICC on a background of BCS-related cirrhosis. ❖

Disclosure Statement
None for all authors.

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CASE REPORT

Immunoglobulin A Nephropathy, Celiac Disease, and Immune Complex Pneumonitis: A Rare Case Report of an Immunoglobulin A-Associated Pathologic Trifecta

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ABSTRACT

Introduction: The systemic manifestations of immunoglobulin A (IgA) nephropathy with lung involvement include diffuse alveolar hemorrhage due to monoclonal IgA disorders, IgA-variant Good pasture's syndrome, and Henoch-Schoenlein purpura. However, pneumonitis due to IgA immune complex has rarely been reported as the pulmonary manifestations of IgA nephropathy.

Case Presentation: A 35-year-old woman presented with 2 years of progressive shortness of breath, dry cough, low-grade fever along with progressive loss of appetite, and loss of weight. She underwent renal, duodenal, and lung biopsies. She was diagnosed with a rare combination of IgA-mediated nephropathy, IgA-associated celiac disease, and IgA-mediated immune complex cavitary lung disease.

Discussion: Secretory IgA may be acting as an immune complex or proinflammatory agent to provoke the signs and symptoms in this case. Thus, the respiratory process may incite renal disease or vice-versa. Further research is needed to analyze the possibility of such associations.

INTRODUCTION

Immunoglobulin A (IgA) nephropathy may be a primary disease process or secondary to other disease processes. It may also be the only manifestation of systemic diseases. There is a strong association of IgA nephropathy with liver disease, particularly alcoholic cirrhosis. There is also an association found with hepatitis B- and C-associated liver disease. It is also found that diseases with an impaired gut mucosal barrier are associated with IgA nephropathy. Wide association is found with celiac disease, though inflammatory bowel disease, egg protein allergy, and lactose intolerance are also studied. Systemic diseases like HIV, monoclonal gammopathy, and malignancy are also considered to have associations with IgA nephropathy.[1]

Association of IgA nephropathy with celiac disease can rarely have pulmonary manifestations including obstructive airway disease, interstitial lung disease, or pulmonary hemosiderosis (Lane-Hamilton syndrome).[2]

CASE PRESENTATION

A 35-year-old female patient presented with a history of progressive shortness of breath and dry cough for 2 years. There was no history suggestive of underlying autoimmune disease, clinically significant environmental allergies, serious systemic recurrent bacterial infections, illicit drug exposure, or recent tuberculosis exposure. Treatment of her coughing with bronchodilators over the past 2 years had been ineffective. She presented to us with an increase in symptoms over the previous 4 months including low-grade fever, progressive loss of appetite, and loss of weight. The patient was referred to our hospital with the initial computed tomography showing nodular changes in parenchyma and repeat computed tomography showed cavitation (Figure 1A and 1B). No prior radiographs were available. The pre-admission hemogram reported leucocytosis with neutrophilic predominance, which later changed to lymphocytic predominance. Urine examination was not done prior to admission. Sputum analysis done before admission showed negative results for Acid fast bacilli smear, cartridge based nucleic acid amplification test, and Mycobacteria Growth Indicator Tube culture for mycobacterium. The patient was given repeated doses of antibiotics and nebulization, but steroids were not prescribed.

On admission, the patient was afebrile, with tachycardia (116 beats per minute), tachypnea (36 beats per minute), and pulse oxygen saturation of 82% on ambient air. Respiratory system examination demonstrated bilateral rales. The arterial blood gas analysis documented hypoxemic respiratory failure (pH 7.45, pCo2 35 mmHg, pO2 43 mmHg, HCo3 22.1 mmol/L). There was neutrophilic leucocytosis, with high levels of acute-phase reactants (C-reactive protein = 5 mg/L; erythrocyte sedimentation rate = 80 mm/h). Initial contrast-enhanced computed tomography of the chest demonstrated nodules which progressed to cavitation over 6 weeks (Figure 1A and 1B). Bronchoalveolar lavage revealed neutrophilic predominance with negative pyogenic, fungal, and tubercular cultures. The urine examination showed microscopic hematuria and proteinuria of 1.6 g/d. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, and anti- glomerular basement

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Keywords: cavitary lung disease, celiac disease, IgA nephropathy, immune complex pneumonitis

membrane antibodies were all negative. The complement factor levels were normal.

After informed consent was obtained, the patient underwent renal biopsy; revealing mesangial proliferation with coarse granular deposition of IgA in immunofluorescence (Figure 2A and 2B). The diagnosis of celiac disease was confirmed by a positive serum IgA-tissue transglutaminase and a duodenal biopsy that showed villous atrophy with lymphocytic infiltration into the submucosa. Among immunoglobulin classes, elevated circulating IgA subclass levels were observed (894 mg/dL). She also underwent transbronchial lung biopsy demonstrating proliferation of type 2 pneumocytes and a large area of hemorrhage. Immunofluorescence showed coarse granular deposits of IgA in fibrinogen in alveoli and blood vessel (Figure 3A and 3B).

The unique cooccurrence of IgA nephropathy, celiac disease, and IgA-mediated immune complex pneumonitis with cavitation was established. A gluten-free diet was initiated; however, no response was observed at end of 6 weeks, and, hence, systemic oral corticosteroids (1 mg/kg) were added. The patient showed marked improvement in symptoms and resolution of proteinuria and hypoxemic respiratory failure over a period of 1 month. Table 1 provides a timeline of the case.

DISCUSSION

The association of IgA nephropathy with celiac disease is hypothesized to be secondary to dysfunctional IgA in circulation produced due to abnormal gut response to gluten antigen.[3] The abnormal circulating immunoglobulin triggers kidney dysfunction due to immune complex deposition. Correspondingly, a similar trigger dysfunction in the lungs manifests as diffuse alveolar hemorrhage and bronchiolitis. In this case, the patient did not have evidence of progressive renal failure or diffuse alveolar hemorrhage.

It is considered that the disease is predisposed by mucosal barrier disruption, causing B lymphocytes to be triggered to produce peculiar IgA. This IgA forms an immune complex that gets deposited in the kidneys to cause the disease. Genetic and familial predispositions are being speculated. It is considered that the increase in the circulation of the galactose-deficient form of IgA1 triggers the disease. The degree of circulation of the galactose-deficient form is directly proportional to the probability of disease occurrence. The exposed hinge region in such IgA triggers the antibodies to form complexes that get deposited with complement activation, leading to renal disease. In the current case, there are also high levels of circulating IgA levels. Though the subtyping is not done, it may be hypothesized that deposition of such complexes might have triggered lung injury apart from IgA nephropathy.[4]

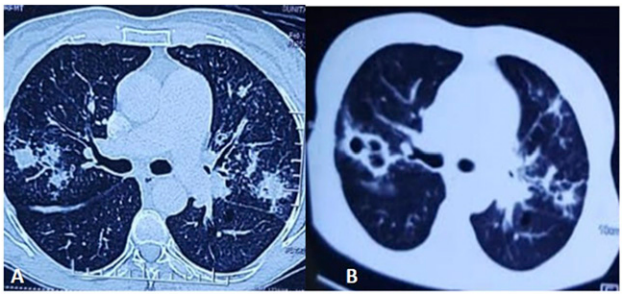

Figure 1. **(A)** Computed tomography thorax shows bilateral nodular opacities in upper lobe. **(B)** The bilateral opacities progressed to cavitation in 6 weeks.

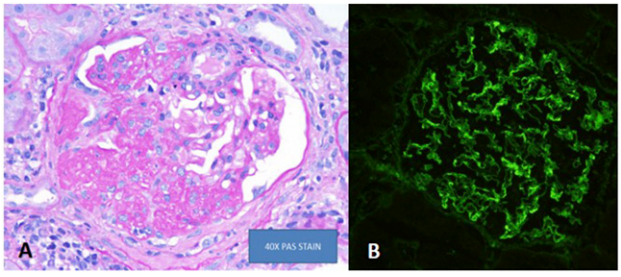

Figure 2. **(A)** Light microscopy: PAS-stained kidney biopsy demonstrated mesangial proliferation. **(B)** Immunoflorescence: IgA granular deposition.

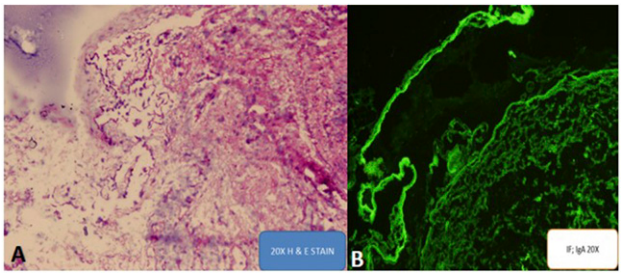

Figure 3. **(A)** Light microscopy: Hematoxylin and eosin-stained lung biopsy demonstrated inflammatory infiltrate. **(B)** Immunoflorescence: IgA granular deposition (2+) in alveolar basement membrane.

The pathologic evaluation now adds crucial prognostic information exceeding the clinical variables alone. MEST or Oxford scores include pathologic features consistently and independently associated with the renal outcome. The score incorporates mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and tubular atrophy and interstitial fibrosis (T). An essential goal of deriving a histologic scoring system is shortening the time frame of observation required to accurately predict which patients are at risk of adverse outcomes.[3]

In the literature, pneumonitis due to IgA immune complex, as the pulmonary manifestation of IgA nephropathy, has only been previously reported once.[5] Cavitary lung disease has not been documented previously.[6] The plausible

Table 1. Timeline table

Date	Visit information	Diagnostic testing	Interventions
February 10, 2019	A 35-year-old female patient presented with progressive dyspnea over the past 4 months, low-grade fever, progressive loss of appetite, and loss of weight. She had received antibiotics but there was no relief.	Initial contrast-enhanced computed tomography of her chest demonstrated nodules, which progressed to cavitation over 6 weeks. Bronchoalveolar lavage revealed neutrophilic predominance with negative pyogenic, fungal, and tubercular cultures. The urine examination showed microscopic hematuria and proteinuria of 1.6 g/d.	Workup for cause of proteinuria initiated.
March 1, 2019	Patient underwent serological investigations. Contraindication for renal biopsy ruled out.	In the workup for proteinuria, antinuclear antibodies, antineutrophil cytoplasmic antibodies, and anti-glomerular basement membrane, antibodies were all negative. The complement factor levels were normal. Renal biopsy revealing mesangial proliferation with coarse granular deposition of IgA in immunofluorescence.	Workup for cause of IgA nephropathy.
March 10, 2019	After receiving the renal biopsy report, the patient underwent serological investigations and duodenal biopsy for evaluation of IgA nephropathy.	In workup for evaluating the cause of IgA nephropathy, her IgA-TTG was positive, and subsequent duodenal biopsy showed villous atrophy with lymphocytic infiltrate in the submucosa. Among immunoglobulin classes, elevated circulating IgA subclass levels were observed. She underwent transbronchial lung biopsy, demonstrating IgA deposition in the alveolar basement membrane and sub-endothelium of bronchioles.	With the possibility of celiac-associated lung disease, she was started on a gluten-free diet with no response and required domiciliary oxygen support.
May 1, 2019	After 6 weeks of gluten-free diet, there was no improvement in symptoms. Hence, systemic oral corticosteroids (1 mg/kg) were added.	Patient's respiratory failure improved. Also, proteinuria resolved completely after 1 month of therapy.	Singular diagnosis of IgA nephropathy, celiac disease, and IgA-mediated immune complex pneumonitis established.

explanation may be due, in part, to the lack of lung biopsy performed in patients with IgA nephropathy.

Secretory IgA is known to exist on the mucosal surfaces of the respiratory and gastrointestinal tracts, providing a primary defense against local infections. Secretory IgA remains the most probable source of IgA nephropathy. It is frequently associated with illness in an IgA-secreting organ, such as those of the respiratory or gastrointestinal tracts.[5] Thus, a respiratory process may incite renal disease or vice-versa. Hence, both processes are end-organ consequences of a single systemic disease mediated by IgA. Further research is needed to analyze the possibility of such associations. ❖

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

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CASE REPORT

Concomitant Large Loculated Pleural and Pericardial Effusions in a Patient with Rheumatoid Arthritis on Methotrexate

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ABSTRACT

Rheumatoid arthritis (RA) is the most common multisystemic autoimmune inflammatory joint disorder, affecting nearly 1.3 million adults in the US. RA has high economic and social burdens. Functional disability may arise in RA from the characteristic chronic progressive inflammation and the erosion of multiple joints and cartilage damage. Systemic manifestations of RA include rheumatoid nodules, pleuropulmonary complications, pericarditis, rheumatoid vasculitis, Felty's syndrome (the rare triad of rheumatoid arthritis, splenomegaly, and neutropenia), amyloidosis, and neurological complications. We present the diagnostic challenges of differentiating pleuropulmonary and pericardial complications of rheumatoid arthritis from side effects of therapy (rheumatoid pleural and pericardial effusions vs immune suppression associated side effects and infections). We use the Naranjo score to facilitate this decision-making process. A 52-year-old man with a history of RA, chronic small right pleural effusion, and hypertension on long-term oral methotrexate and corticosteroid therapy presented to the emergency room after 1 week of worsening respiratory symptoms. A chest radiograph demonstrated a large pleural effusion and pneumonia. Intravenous methylprednisolone and antibiotics were administered. A video-assisted thoracoscopic procedure was performed, chest tubes were inserted, and abatacept was eventually initiated as adjunctive therapy to methotrexate and corticosteroid therapy for the rheumatoid arthritis and lung condition. Abatacept is an immunosuppressive fusion protein composed of the Fc region of immunoglobulin G1 fused to the extracellular domain of cytotoxic T-lymphocyte-associated protein 4, which interferes with the immune activity of T cells.

INTRODUCTION

Pleural disease and pericardial effusion are established systemic manifestations of rheumatoid arthritis (RA) that can further complicate the disease.[1] Pleural disease in RA is typically subclinical and can be primary or secondary to antirheumatic drugs or infections. Methotrexate (MTX) is an immunosuppressive folate antagonist that is used to treat malignancies and autoimmune diseases. High-dose MTX is used in cancer patients, and low-dose MTX is used in RA. Pleuropulmonary disease occurs in 3 to 4% of patients who receive high-dose MTX but may also occur with low-dose MTX.[2] We present a case of suspected MTX-induced pleural and pericardial effusions in a patient with RA.

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CASE PRESENTATION

Presenting Concerns

A 52-year-old, nonsmoking man with a several-year history of RA on long-term MTX (20 mg orally weekly) and prednisone (20 mg orally daily) and hypertension was followed in the pulmonary clinic for chronic right pleural effusion. He had been diagnosed with rheumatoid arthritis 3 years prior after complaining of symmetric swelling and stiffness in his hand, elbow, and knee joints. At this initial presentation for RA, antinuclear antibody was present and homogenous 1:320, SSA/SSB was negative, rheumatoid factor was 34, and anti-CCP was 468. On this admission, he presented to the emergency room with a 1-week history of increased cough, shortness of breath, fever, and an acute flare of symmetric swelling in his hands and feet.

Therapeutic Intervention and Treatment

A chest radiograph demonstrated a large right pleural effusion and pneumonia. The differential diagnosis of his respiratory distress and pleural effusion included pulmonary embolism, pneumoniae, congestive heart failure, autoimmune connective tissue disease, drug reaction, and cyclothorax. A differential diagnosis of his pericardial effusion included acute pericarditis, cardiac tamponade, cardiogenic pulmonary edema, dilated cardiomyopathy, and pulmonary embolism. He was started on methylprednisolone therapy (125 mg intravenous daily for 5 days), antimicrobial therapy with ceftriaxone (2 g intravenous for 10 days), and azithromycin (500 mg intravenous for 7 days). Computed tomography scan of the chest excluded pulmonary embolism and demonstrated a small pericardial effusion and a large right pleural effusion (Figure 1). An echocardiogram revealed a left ventricular ejection fraction of 50%, mild left ventricular hypertrophy, and a small circumferential pericardial effusion without tamponade. A thoracentesis was attempted but was not successful due to the presence of a loculated effusion. The patient was taken to the operating room, where a video-assisted thoracoscopic decortication procedure and pericardial window and pericardiocentesis were performed. A volume of 500 mL of pericardial fluid was drained, and 2,000 mL of pleural fluid was removed from the right pleural cavity.

Pleural fluid studies revealed clear yellow pleural exudate, with 1% red blood cells, 2% eosinophils, 8% lymphocytes,

6% monocytes, 84% neutrophils, 540 nucleated cells, specific gravity 1.031, protein 5.2 gm/dL, lactate dehydrogenase (LDH) 736 U/L, glucose 81 mg/dL, and amylase 36 U/L. The differential diagnosis of this patient's exudative pleural and pericardial effusions was narrowed to malignancy, connective tissue disease, infections (pneumoniae, tuberculosis, fungal disease, viral), and drug reaction. The noneosinophilic result of his effusion argued against a medication side effect. Hence, glucarpidase, an antidote for MTX toxicity, was not considered due to the patient's presentation and the low likelihood of drug-induced pulmonary disease. The pericardial and pleural samples did not demonstrate malignant cells, tuberculosis, or bacterial growth, and pathology on the pleural and pericardial sacs showed acute and chronic inflammation. Subsequently, 2 chest tubes were placed to water seal without air leak and were removed 8 days later following radiographic resolution of the pleural effusions.

Follow-up and Outcomes

A repeat chest radiograph at the patient's pulmonary clinic 10 days after hospital discharge revealed a small right pleural effusion and post-surgical changes. MTX was continued at a dosage of 10 mg orally weekly because the patient's presentation was more consistent with a systemic complication of his RA rather than a medication side effect. This is supported by the onset of an acute rheumatoid joint flare with his effusions and the noneosinophilic nature of his effusions. A course of prednisone was tapered over 3 weeks to his regular 20 mg daily dosage, and a weekly abatacept (125 mg intravenous infusion) was initiated for further immunosuppressive therapy for his rheumatoid arthritis and autoimmune pleural and pericardial disease.

DISCUSSION

Rheumatoid Pleural Effusions and Diagnostic Approach

Rheumatoid pleural effusion (RPE) is the most common pleuropulmonary manifestation.[1-3] Characteristic symptoms of RPE are fever, pleuritic chest pain, and dyspnea; cough is generally absent unless there is a concomitant parenchymal lung disease. Clinical symptoms of RPE arise from irritation and inflammation of the pleura, from underlying coexisting pulmonary pathology, or from compromised respiratory function.[4-6] Physical examination findings include change in tactile fremitus, dullness of chest percussion, and decreased breath sounds. The formation of RPE is postulated to occur from impaired fluid resorption in inflamed pleura, necrosis of subpleural rheumatoid nodules, and endothelial injury and capillary permeability from cytokines and immune complexes.[7-10].

Small pleural effusions are noted in up to 70% of patients with RA on autopsy studies, although only 3 to 5% of RA patients in their lifetime are symptomatic with pleurisy.[1-3, 11] Risk factors for RPE include age over 35 years, male sex, and those with rheumatoid nodules. Seventy percent of rheumatoid pleural effusions are unilateral; the other 30% are bilateral.[2,3,7] In about one-quarter of RA patients, the onset of RPE preceded or occurred at the same time as the onset of joint disease.[8,9] In the majority of other cases, RPE occurs several years after established RA diagnosis, such as in our patient. However, case reports have described RPE occurring 3 decades after RA diagnosis.[8] The duration of RPE is also variable, and in various case series RPE has been described as lasting from several months to years.[3,9,10]

Other pulmonary involvements by RA include pulmonary parenchymal disease (interstitial lung disease) and disease of the airways and pulmonary vasculature (pulmonary hypertension and vasculitis). Smoking may adversely affect the course of RA-related lung diseases.[1-3] There are proposed mechanisms for pulmonary pathogenesis, including chronic immune activation, increased susceptibility to infection due to direct toxicity, or immunomodulation from disease modifying drugs or biologic therapy.[1-3] In some patients with RA, respiratory symptoms from these pulmonary involvements may precede articular symptoms. This is supported by studies of a subgroup of patients who are anti-CCP with lung disease who later developed articular symptoms of rheumatoid disease.[2,4,5]

Chest radiograph is the initial diagnostic test of choice for evaluation of pleural disease. Other imaging modalities may include ultrasound, computerized tomography, and magnetic resonance imaging. Thoracentesis should be performed for any effusion with 1 cm of layering on decubitus films. The typical RPE is sterile, exudative, and yellow-green straw colored. Other characteristics include low pH <7.2, glucose <40, elevated LDH >700, and cholesterol >65.[2,3,12] Low pleural fluid pH occurs because of lactate and carbon dioxide production from enhanced glucose metabolism in the inflamed pleural space.[2,3,7,13] High levels of pleural fluid lactate may suggest an alternate diagnosis, such as tuberculosis or malignancy. High pleural fluid LDH levels in RPE reliably correlate with the degree of pleural inflammation from activated white cells in the pleural fluid.[2,13] Pleural fluid glucose may be similar to serum glucose at the onset of RPE but typically falls to very low levels (10-30 g/dL) in chronic RPE.[3,13] Pleural fluid glucose in RPE lowers as a result of pleural thickening, which prevents the entry of glucose into the pleural space or alternatively from consumption of glucose in the inflamed pleura.[5,10,14] Infection or empyema should always be excluded in the diagnostic workup of RPE due to the similar low pleural fluid pH, low glucose, and high LDH.[3, 15-17]

The approach to the differential diagnosis of pleural or pericardial effusion starts out with confirmation of these

effusions as exudative. The broad categories of exudative pleural and pericardial effusions overlap: malignancy, inflammation, infection, autoimmune disorders, and medication effects. Recently, cocaine-induced pleural and pericardial effusions syndrome has been reported and should be added to this differential diagnosis.[18]

Pericardial Effusion in Rheumatoid Arthritis and Diagnostic Approach Pericarditis is the most common cardiac complication of rheumatoid arthritis. Echocardiogram and autopsy series show up to 50% of RA patients have pericardial effusions, and pericardial disease is more common during RA flares.[16] Pericardial effusions in rheumatoid arthritis are found predominantly in men and may coexist with pleural effusions.[16] Biochemical analysis of pericardial fluid of the exudative fluid typically reveals low glucose, positive latex fixation, and RA cells, which resemble the findings in pleural fluid. Symptomatic pericarditis may rarely lead to constrictive pericarditis or cardiac tamponade, which requires surgical intervention.[16]

The spectrum of heart involvement in patients with RA may include myocardial disease, coronary vasculitis, diastolic dysfunction, accelerated atherosclerosis, and valvular heart disease.[17] Premature mortality among RA patients is frequently from cardiovascular disease (ie, primarily ischemic heart disease and congestive heart failure).[17] Various significant alterations have been detected by echocardiography in asymptomatic RA patients: 1) pericardial effusion, 2) valvular thickening and nodules, 3) isolated valvular insufficiency, 4) aortic root alteration, and 5) increased left ventricular mass and functional diastolic dysfunction (left ventricular changes).[17] These changes may represent possible "silent rheumatoid heart disease," and echocardiographic assessment can be a cornerstone for future research in the field of RA.[17]

Methotrexate and Pleuropulmonary Toxicities

In general, MTX is used in the therapy of various malignancies, psoriasis, and autoimmune diseases. MTX is first-line therapy for initial treatment of active RA and typically serves as an anchor for the most commonly used disease-modifying antirheumatic drug combinations.[20] MTX is an antimetabolite and folate antagonist that inhibits DNA synthesis. Both the absorption and bioavailability of MTX are highly variable, are dose dependent, and decrease at higher doses. At higher oral doses of MTX, there is decreased bioavailability. In a study comparing the 7.5-mg weekly dose and the 15- to 20-mg weekly dose, there was better absorption with the smaller dose. Subsequently, as the dose of MTX was increased from the starting dose of 7.5 mg to typical maintenance doses, the bioavailability was shown to drop off by a mean of 13.5%.[21,22] The variable absorption and bioavailability of MTX can lead to unpredictable serum levels. Adverse effects to MTX can be dose dependent or idiosyncratic in nature.[23]

Drug-induced pleural disease occurs rarely, and manifestations include asymptomatic pleural effusion, acute pleuritis, or symptomatic pleural thickening. Although the precise mechanisms of most drug-induced pleural diseases are largely unknown, potential pathogenic processes are speculated, such as 1) hypersensitivity or allergic reaction, 2) a direct toxic effect, 3) increased oxygen free radical production, 4) suppression of antioxidant defenses, and 5) chemical induced inflammation.[22] Pleural fluid eosinophilia is described by more than 10% of nucleated cells and is a nonspecific finding that is supportive for drug-induced pleural disease. Drugs proven to cause pleural disease include MTX, valproic acid, propylthiouracil, isotretinoin, nitrofurantoin, dantrolene, and gliclazide.[23] Pleuropulmonary toxicity occurs in 3% to 4% of patients who receive high-dose MTX, but these medication effects may also occur with low-dose MTX treatment.[23] These medication effects are fever, cough, and dyspnea, which are identical symptoms found in pleuropulmonary complications of RA. Risk factors for the development of lung injury from MTX include age greater than 60 years, rheumatoid pleuropulmonary involvement, previous use of disease-modifying antirheumatic drugs, higher-dose MTX therapy, and diabetes.[23-25]

Concurrent Pericardial and Pleural Effusions Attributed Directly to MTX Reported in only Two Prior Case Reports and Naranjo Score

To the best of our knowledge, there are only 2 prior cases in the medical literature that attribute the concurrent development of pericardial and pleural disease directly to MTX use.[18,24] Cudzilo et al[18] described eosinophilic effusions in the setting of MTX therapy for psoriatic arthritis, but Savoia et al[26] described noneosinophilic effusions in the setting of MTX for plaque psoriasis. In contrast, Judge et al[27] presented a 54-year-old woman whose initial presentation for rheumatoid arthritis was fever, pleural effusion, pericardial effusion, and ascites. Collectively, these cases illustrate how pleural and pericardial effusions may arise directly from medication effects or conversely signify the onset of RA.

The Naranjo score is an algorithm that is used to validate the probabilities for adverse drug reactions (ie, the existence of prior conclusive reports, temporal occurrence of an adverse drug event relative to time of drug administration, improvement of drug reaction after cessation of the drug, alternative causes of reaction, existence of toxic concentrations of the drug, similar reaction to same or similar drugs with prior exposure, and objective evidence that confirmed adverse drug event).[27] We arrived at a Naranjo score of 3 (possible side effect) (Table 1). Our patient's pleural fluid

Table 1. Naranjo Score 29

Question	Yes	No	Don't know	Score
1.Are there previous conclusive reports on this reaction?	+1	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	2
3. Did the adverse event improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0	0 (Don't know)
4. Did the adverse event reappear when the drug was re-administered?	+2	−1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	−1	+2	0	−1
6. Did the reaction reappear when a placebo was given?	1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0 (Don't know)
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0 (Don't know)
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0 (No)
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
	Total Score: 3			
Total Score 1-4				
Possible. The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.				

glucose was normal (not characteristic of the low pleural fluid glucose in RPE) but was noneosinophilic (ie, not supportive of a medication effect). Therefore, considering the overall Naranjo score, the clinical presentation, the poor bioavailability of oral methotrexate, the paucity of eosinophils in the effusion, and the lack of confirmed recurrence with reexposure, we believe that it is more likely that our patient's pleural and pericardial effusions are secondary to his underlying autoimmune disease.

CONCLUSION

Medication-induced effects should always be considered in the setting of therapy for autoimmune conditions to avoid potentially unnecessary medical and surgical interventions and patient discomfort. Our patient presented with acute rheumatoid joint symptoms at the time of presentation for the pericardial and pleural effusions, and he had noneosinophilic exudative effusions, which both support RPE. On the other hand, elevated levels of eosinophils in the effusion and recurrence with reexposure to MTX are much more suggestive of a drug-induced effusion. Interestingly, our patient's pleural fluid glucose was normal, which is unlike the characteristic low pleural fluid glucose levels in RPE. Thus, sometimes not all possibilities can be resolved, especially when a therapy side effect can mimic the manifestations of the condition. Further, rheumatoid arthritis or other connective tissue diseases should be considered in any patient presenting with pericardial or pleural effusion at any point because extraarticular manifestations of an autoimmune disease may precede or occur concurrently with articular manifestations. In refractory cases of chronic RPE, such as occurred in our patient after repeated thoracentesis and corticosteroid therapy, second-line immunosuppressive therapy such as abatacept may be considered.[20] ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Authors' Contributions

All authors conceptualized this paper, drafted the initial manuscript, and revised the final submission. All authors have given final approval to the manuscript.

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CASE REPORT

From Dyspepsia to Diagnosis: A Rare Gastric Subepithelial Lesion Definitively Diagnosed via Endoscopic Submucosal Dissection and Immunohistochemistry

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ABSTRACT

Introduction: Peripheral nerve sheath tumors, known as perineuriomas, are typically found on the trunk and extremities. They are less commonly described in the gastrointestinal tract (GI), and extremely rarely are described in the stomach.

Case Presentation: We present a case of a 2-cm gastric perineurioma in a 42-year-old patient with nonspecific GI complaints of chronic dyspepsia and epigastric discomfort. Esophagogastroduodenoscopy, followed by endoscopic ultrasound, revealed a 2-cm umbilicated lesion in the stomach, which was subsequently removed with endoscopic submucosal dissection and sent for pathology. Immunohistochemical staining revealed a rare entity known as a gastric perineurioma.

Conclusion: Since the first case of gastric perineurioma was first described in 2004, there have only been 4 reported cases in the English literature. This case highlights the crucial interdisciplinary multidisciplinary effort between pathologists and GI specialists required to reach this diagnosis and showcases endoscopic diagnosis using endoscopic dissection, which allows for complete lesion resection and complete resolution of the patient's symptoms.

INTRODUCTION

Perineuriomas are peripheral nerve sheath proliferation tumors of mesenchymal and spindle cells. These are typically found in the trunk and extremities, and classified into intraneural and extraneural variants. The intraneural variant often involves the sciatic nerve or branches.[1] Although most perineuriomas follow a benign course, because of their rare malignant potential, these tumors are usually resected for cure.[1] They are less commonly seen in the gastrointestinal (GI) tract, with a predilection for the rectosigmoid colon (75%) in 1 small study of 8 intestinal perineuriomas.[2] For unclear reasons, gastric perineuriomas are very rare, with only 4 reported cases since the first description in 2004.[3] Here, we present a 2-cm gastric perineurioma in a 42-year-old female with chronic dyspepsia and epigastric discomfort.

Case Report

A 42-year-old female was referred to the gastroenterology department with chronic dyspepsia and epigastric discomfort for 4 years that persisted despite daily omeprazole and sucralfate. Because of the duration of symptoms, an esophagogastroduodenoscopy was performed, which revealed a 2-cm umbilicated mass in the gastric body. Endoscopic biopsies were nondiagnostic; thus, the patient was referred for an endoscopic ultrasound for further characterization. The lesion was hypoechoic and contiguous with the second echolayer (muscularis mucosa) (Figure 1). To confirm the clinical suspicion for gastrointestinal stromal tumor (GIST), a fine needle aspiration was performed, during which "gelatinous" material was aspirated. However, immunohistochemical (IHC) stains of the sample showed no definitive pattern of staining. Given the patient's favorable health status and her desire for definitive diagnosis, the patient was referred to our center for a repeat endoscopic ultrasound and consideration of en bloc removal via endoscopic submucosal dissection (ESD). The lesion was again confirmed to involve the second and third echolayers (muscularis mucosa/submucosa). The fourth echolayer (muscularis propria) was intact. Despite the central ulceration and intense submucosal fibrosis, the lesion was successfully removed en bloc via hybrid ESD.

The microscopic examination showed a polypoid spindle cell lesion with prominent mucosal and submucosal involvement as well as ulceration of the overlying gastric mucosa. Histologic sections demonstrated a cellular proliferation of elongated spindle cells arranged in short interlacing fascicles within loose collagenous and myxoid stroma (Figure 2). IHC stains for CD117, DOG1, and CD34 were negative, thus arguing against a GIST. Additional stains for smooth muscle antigen, desmin, and pancytokeratin were negative, excluding a smooth muscle tumor and carcinoma. Last, S100 was negative, helping to exclude a neural tumor such as gastric schwannoma.

Because of the initial difficulty in rendering a pathologic diagnosis, this was sent to our regional bone and soft tissue pathology expert for consultation and additional IHC stains. Positive stains included NKIC3, CD56, epithelial

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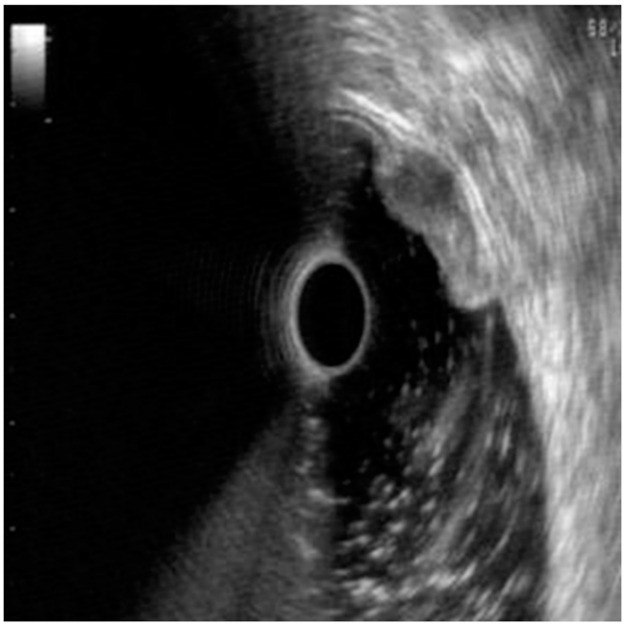

Figure 1. EUS image of lesion in the gastric body involving the mucosa and submucosa. 101x101mm (72 x 72 DPI).

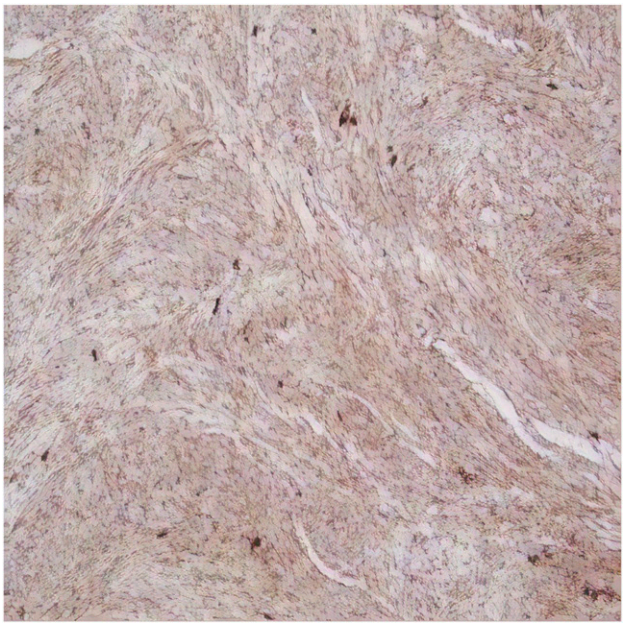

Figure 3. The lesional cells showed expression for NKIC3. 97x97mm (300 x 300 DPI).

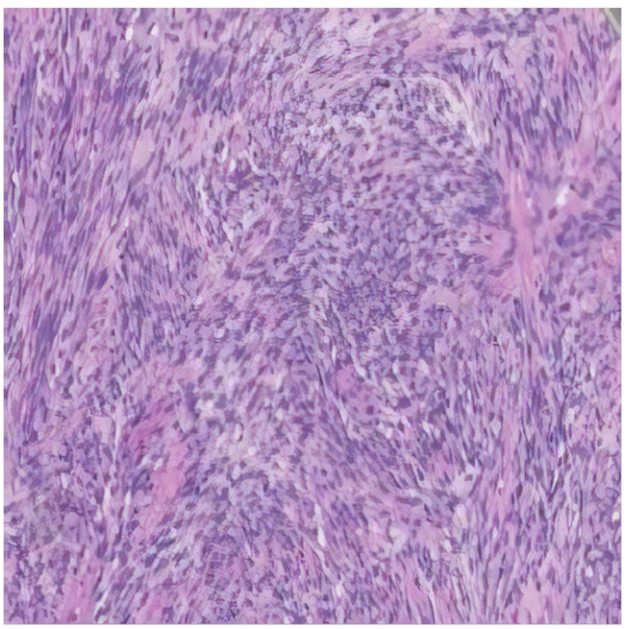

Figure 2. High magnification image showing a cellular proliferation of spindle cells arranged in short interlacing fascicles with collagenous and loosley myxoid stroma. 97x97mm (300 x 300 DPI).

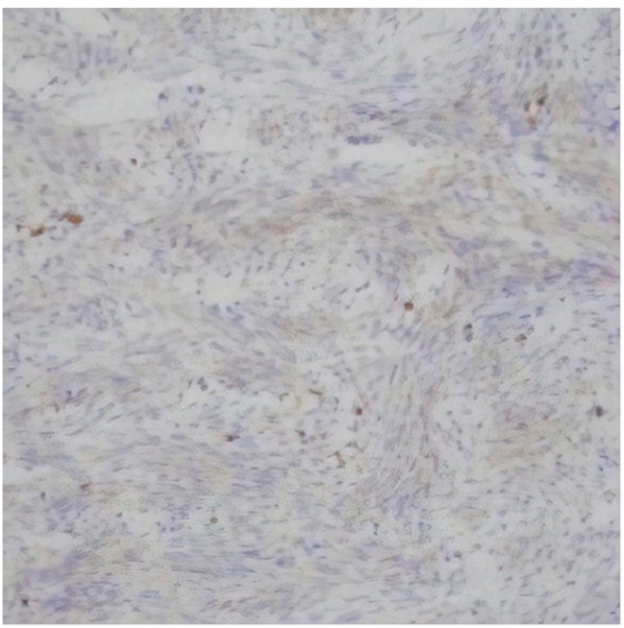

Figure 4. The lesional cells were positive for GLUT-1. 97x97mm (300 x 300 DPI).

membrane antigen (EMA), and glucose transporter protein (GLUT-1) (Figures 3, 4). This pattern of IHC staining most definitively classifies the lesion as gastric perineurioma.

Three months after removal of the perineurioma, the patient reported complete resolution of her dyspepsia and epigastric discomfort.

CONCLUSION

Mesenchymal/spindle cell proliferations comprise a class of gastrointestinal tumors, including GIST, neural tumors, and schwannomas.[3]

Because of the variety of clinical presentations associated with these tumors, diagnosis is challenging. Perineuriomas,

Table 1. From dyspepsia to diagnosis: a rare gastric subepithelial lesion definitively diagnosed via endoscopic submucosal dissection and immunohistochemistry

Relevant medical history and interventions (migraines, obesity, acne, gastroesophageal reflux disease)			
Date	**Summaries from initial and follow-up visits**	**Diagnostic testing (including dates)**	**Interventions**
1/15/2015	Patient complained of epigastric pain, waxing and waning, worse after eating at times. Sometimes worse at night. Took Tums and Prilosec with minimal relief.	CBC, electrolytes, BUN, creatinine, UA, UCx, pregnancy test, liver function panel, lipase, *Helicobacter pylori* (1/15/2015): No significant findings.	Patient told to increased omeprazole to twice daily; added Carafate daily; ciprofloxacin prescribed.
2/6/2019	Patient reported stomach pain with severe flare up despite Carafate and Prilosec.	None	Referral to gastroenterology for EGD.
2/13/2019	Patient presented for EGD.	EGD findings: 8-mm nodule in antrum; 2-cm gastric body mass Pathology: negative. (2/13/2019)	Patient instructed to hold NSAIDs, aspirin. Continue Carafate and omeprazole twice daily. Referred for EUS of subepithelial gastric lesion.
2/19/2019	Patient presented for EUS.	EUS findings: Subepithelial distal gastric lesion measuring 12 × 15 mm arising from the muscularis mucosa going into the submucosa. Fine needle aspiration of lesion performed and sent for cytology. Fine needle aspiration cytology: spindle and epithelioid cell lesion (2/19/2019)	Referred for endoscopic resection via endoscopic mucosal resection or ESD.
3/9/2019	Patient presented with flare up of abdominal pain at night. Had been off Prilosec for 8-9 days because it was not helping.	None	Continue Prilosec and Carafate.
3/18/2019	Patient presented for official gastrointestinal consultation. Describes reflux sensation with partial relief with omeprazole twice daily and Carafate. Symptoms both during the day and night.		Patient told pathology came back inconclusive. Patient already referred for EUS with ESD. Patient instructed to continue Prilosec, Carafate. Avoid late night eating.
5/6/2019	Patient presented for EUS with ESD.	EUS findings: gastric body subepithelial lesion of 2 × 0.7 cm in 1 echoplane, contiguous with second echolayer. Antral subepithelial lesion of 0.7 × 0.5 cm in 1 echoplane, contiguous with second layer. ESD: 2 cm gastric body lesion resected via challenging ESD due to intense submucosal fibrosis	Patient admitted for overnight observation. Start clear liquid diet. Intravenous proton pump inhibitor prescribed for 14 days. Pathology sent immediately.
5/22/2019	Patient with telephone appointment for pathology report.	Pathology: gastric perineurioma (5/21/2019)	Patient instructed to decrease omeprazole to 20 mg daily.
8/12/2019	Patient reports resolution of symptoms via telephone appointment.	None	Patient instructed to wean off omeprazole completely.

a rare subset of mesenchymal cell proliferations, can be found both intra- and extraneurally. When found extraneurally, they are more often painless, soft-tissue lesions found the in the trunk and extremities, though some cases have been noted in the head and neck area, retroperitoneum, brain, kidney, and intestines.[1]

In the English literature, a total of 4 patients with gastric perineuriomas have been described. Because of the paucity of reported cases, gastric perineuriomas are underrecognized culprits for nonspecific gastrointestinal symptoms, and have occasionally even been misdiagnosed as a GIST.[4] In the 4 previously reported cases, patients experienced protean complaints either singly or in combination, including epigastric pain, nausea, gastroesophageal reflux, or upper gastrointestinal bleeding. For unclear reasons, gastric perineuriomas have been described more often in women (4/5 cases including present case), with a wide range in size (0.5-1.5 cm) and age of diagnosis (25-58 years).[2]

IHC stains are critical to the proper diagnosis of perineuriomas. Typically, at least 1 perineural marker will stain positive, such as EMA, GLUT-1, and claudin-1.[1,3,5] Expression of these markers ranged from variable and weak, to strong and diffuse. EMA was positive in 50% of gastric perineuriomas. More prominent expression was noted in those specimens stained for GLUT-1 (n = 2). Claudin-1 was positive in 15/17 intestinal perineuriomas and 1 gastric perineurioma stained for this marker. CD34 expressivity was widely variable.[2]

Adequate tissue sampling is often mandatory for proper pathologic and IHC diagnosis. In this case, an en bloc ESD removal not only secured a diagnosis (where fine needle aspiration could not), but also it allowed for confirmation of complete removal (negative lateral and deep margins) and

offered the patient a definitive cure (complete resolution of symptoms after removal).

As with previously reported cases, our female patient also experienced protean GI complaints including epigastric pain and gastroesophageal reflux disease. Our present case appears to describe the largest described gastric perineurioma (2 cm).

This case highlights the value of an esophagogastroduodenoscopy to evaluate patients with persistent upper GI symptoms. We not only highlight the crucial multidisciplinary effort between pathologists and GI specialists required to reach this diagnosis, but also showcase endoscopic diagnosis using ESD, which allows for complete lesion resection and, in this case, complete resolution of symptoms.

BUN = blood urea nitrogen; CBC = complete blood count; EGD = esophagogastroduodenoscopy; ESD = endoscopic submucosal dissection; EUS = endoscopic ultrasound; NSAID = nonsteroidal anti-inflammatory drug; UA = urinalysis; UCx = urine culture. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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CASE REPORT

Possible Precipitation of Acute Coronary Syndrome with Immune Checkpoint Blockade: A Case Report

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ABSTRACT

Introduction: Immune checkpoint inhibitors (ICI) have led to improved survival in patients with a number of different tumor types. The ICI agent nivolumab induces anti-tumor immune responses by inhibiting the programmed cell death 1 protein, but side effects include cardiac immune-related adverse events (irAE) such as myocarditis.[1] The association of nivolumab with atherosclerotic disease has been rarely reported.

Case Presentation: A 62-year-old man with metastatic melanoma and recent myocardial infarction (MI) presented with recurrent MI after having undergone several cycles of nivolumab therapy. Repeat cardiac catheterization revealed rapidly progressive in-stent restenosis and diffuse coronary artery disease (CAD) requiring bypass surgery and warranting cessation of nivolumab therapy.

Conclusion: Nivolumab has been linked with dysregulation of immune responses including enhanced T cell activity, which is implicated in CAD. The timing of nivolumab therapy and presentation with non ST elevation myocardial infarction in this patient suggests a serious T cell-driven medication adverse effect. Therefore, close monitoring for atherosclerotic disease progression is warranted in patients on immunotherapy.

INTRODUCTION

The recent use of immunotherapy agents such as immune checkpoint inhibitors (ICIs) in patients with advanced cancers has improved outcomes associated with several tumor types.[1] These agents suppress tumor growth by inducing dis-inhibition of tumor specific immune responses. The anti-programmed death 1 (PD-1) antibody nivolumab has shown a significant survival benefit in comparison to standard therapy in patients with untreated metastatic melanoma.[1] However, there have been accounts in the literature of several ICI-associated immune-related adverse events (IrAE) including hepatitis, colitis, dermatitis, pneumonitis, and endocrinopathy.[2] Records of ICI therapy-related adverse cardiovascular events in the literature primarily comprise cases of autoimmune myocarditis, pericarditis, and conduction disease.[3,4] Here, we report a case of rapidly progressive in-stent restenosis (ISR) and severe worsening of coronary artery disease (CAD) in a patient with metastatic melanoma started on nivolumab (Table 1).

Case Presentation

A 62-year-old man with a history of metastatic melanoma and ST elevation myocardial infarction (STEMI) 4 months earlier treated with stenting (Figure 1) presented to the emergency department with substernal chest pain. Approximately 1 week prior to the current presentation, he had completed cycle 4 of ICI therapy with nivolumab for metastatic melanoma. The patient had been diagnosed with stage IIIC melanoma of the scalp 3 months ago. At the time of diagnosis, PET scan demonstrated right level V metastatic adenopathy, and brain MRI revealed a 3 mm enhancing focus in the right parietal lobe suggestive of metastases. Promptly after diagnosis, the patient underwent a right posterior scalp wide excision of the melanoma (Breslow thickness 16 mm, pathologic stage pT4b N3b Mx). Sentinel lymph node dissection at right neck level 5 identified melanoma in 4 out of 11 lymph nodes examined. The biopsied tissue was negative for mutations in codon 600 of the BRAF gene using PCR analysis. The patient was initiated on nivolumab therapy at 3 mg/kg every 2 weeks for 1 year. Approximately 1 month prior to the cancer diagnosis, the patient had experienced the first MI, which was treated with percutaneous coronary intervention (PCI) with two non-bifurcation drug eluting stents delivered to the middle left anterior descending coronary artery (LAD) (2.5 mm × 16 mm) and first diagonal coronary artery (D1) (2.6 mm × 16 mm). Interval echocardiography showed an improvement of ejection fraction from 45% to 55% while on aspirin, clopidogrel, metoprolol, atorvastatin, and lisinopril. The patient's cardiac risk factors included a history of diabetes mellitus type 2 with a recent glycated hemoglobin percentage of 7.9%.

On admission, the patient was afebrile, normotensive, and without signs of dyspnea, lower extremity edema, or elevated jugular venous pulsation. Initial electrocardiogram demonstrated sinus tachycardia and new ST depressions in the anterior and anterolateral leads. Initial troponin was 4.04 ng/mL, and serum BNP was 229 pg/mL (normal reference <300 pg/mL). A diagnosis of non ST elevation

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Table 1. Timeline of events leading to rapidly progressive coronary artery disease and recurrent myocardial infarction

Date	Event	Diagnostic testing	Interventions
2/1/2018	Diagnosed with melanoma	Occipital scalp biopsy revealed ulcerated malignant melanoma	Appointment made for excisional biopsy
2/4/3018	First myocardial infarction	ECG denoted ST elevations in the anterior leads	Received PCI with drug eluting stents delivered to the LAD and D1
3/9/2018	Wide local excisional biopsy of scalp lesion	Biopsy showed stage pT4b N3b Mx melanoma	Decision made to begin adjuvant immunotherapy
4/18/2018–5/30/2018	Received 4 cycles of nivolumab every 2 weeks	Pre-therapy laboratory testing was normal	Nivolumab 3 mg/kg was administrated at each visit
6/9/2018	Second myocardial infarction	Cardiac catherization showed in-stent restenosis of LAD and DI, de novo occlusion of RCA, and marked worsening of MVCAD	Underwent CABG, and decision was made to stop nivolumab indefinitely

ECG = electrocardiogram; PCI = percutaneous coronary intervention; LAD = left anterior descending coronary artery; D1 = first diagonal coronary artery; GDMT = guideline directed medical therapy; LDL = low density lipoprotein; RCA = right coronary artery; MVCAD = multi-vessel coronary artery disease; CABG = coronary artery bypass grafting.

myocardial infarction (NSTEMI) was made for which the patient was heparinized and taken to cardiac catheterization, which showed significant changes in the degree of coronary stenosis from prior (Table 2). The findings were remarkable for ISR of the previously revascularized mid LAD and D1 (Figure 2), de novo significant occlusion of the ramus intermedius coronary artery, and interval worsening of stenosis of the left main coronary artery (LM), proximal LAD, and right coronary artery (RCA). Echocardiography demonstrated a depressed ejection fraction to 49% and extensive wall motion abnormalities diffusely throughout the myocardium. Given the recent use of nivolumab and cardiac catheterization findings, the diagnosis of immunotherapy-related atherosclerotic cardiovascular disease was strongly considered, and nivolumab was stopped indefinitely. Due to ISR and advanced multi-vessel CAD, the patient underwent coronary artery bypass grafting (CABG) with revascularization of the LAD, D1, RI, and RCA involving internal mammary artery to distal LAD and saphenous vein grafts to D1, RI. No other cancer-specific therapy was initiated at the time of discharge.

DISCUSSION

Cardiac adverse events associated with cancer treatment have become an increasingly salient issue given the advent of novel therapeutic agents with unique mechanisms of action. In the case above, we described an instance of rapidly progressive atherosclerotic disease, conceivably potentiated by ICI therapy with nivolumab. This agent has been reported to cause toxicities in 7% to 12% of patients receiving single agent therapy.[1] Although there have been previously reported cases of myocarditis, pericarditis, and heart block associated with ICIs, cases of atherosclerotic disease and acute coronary syndromes (ACS) have been less frequently documented.[5-7] While cancer patients have increased incidences of CAD and ISR[8,9], and traditional risk factors such as diabetes, bifurcation disease, and stent characteristics may have contributed to the restenotic process, the rapidity of progression here is remarkable. Currently, the 1-year restenosis rates with contemporary stents in a real world setting are in the range of 1%.[10] Even accounting for the patient's risk factors, a progression from LAD intervention to multivessel disease requiring CABG in 4 months suggests the possibility of ICI induced cardiotoxicity as a mechanism of disease.

When bound to its ligands programmed cell death ligand 1 and 2 (PD-L1/2), PD-1 is responsible for abrogating T cell proliferation and cytokine production, thereby preventing destructive immune activation. This receptor is expressed on tumor-infiltrating lymphocytes in several types of cancers and its chronic activation by tumor antigens leads to anergy. Therefore, blockade of PD-1 is postulated to reverse this anergy and increase anti-tumor immune responses.[5,6]

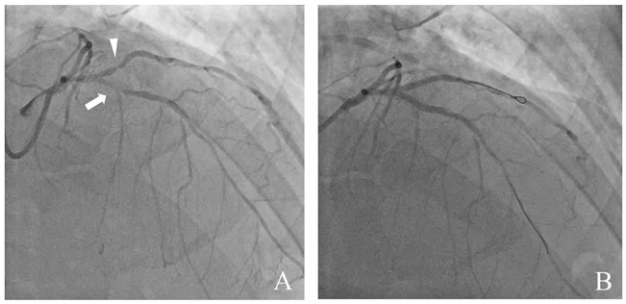

Figure 1. Coronary angiogram demonstrating stenosis of the middle proximal left anterior descending artery (A, arrow) and first diagonal artery (A, arrowhead). The stenotic lesions were successfully treated with drug eluting stents (B).

Generally, toxicity from PD-1 inhibitors is precipitated by the dysregulation of immune responses that provokes pro-inflammatory and autoimmune-like syndromes. These syndromes are typically T cell-mediated, which is corroborated by histopathological examination of myocardium from patients with ICI-related myocarditis showing substantial T cell and macrophage infiltration.[2] Recent literature suggests infiltrating T lymphocytes express T cell receptors against shared common antigens across tumor cells and myocardial cells, which likely contributes to myocardial injury.[11] Additionally, PD-L1 is highly expressed on injured cardiomyocytes, positing a role for defective PD-1/PD-L1 signaling within myocardial tissue in this process.[12]

It is well recognized that CAD is an inflammatory disease mediated by many of the same immune mechanisms implicated in T cell-mediated myocarditis. Atheromata on arterial intima are comprised of lipid-laden cells such as macrophages in conjunction with $CD4^+$, $CD8^+$, and natural killer T cells.[13] These lesions are prone to rupture due to weakening from inflammatory cytokines and proteolytic enzymes secreted from the activated T cells, which may lead to ACS.[13,14] Previous studies using murine models demonstrated a potential association of deficient or blocked PD-1 signaling with pro-atherogenic T cell responses.[15] Bu et al.[15] showed that mice deficient in PD-1 that were fed a cholesterol diet developed larger atherosclerotic lesions that contained more activated $CD4^+$ and $CD8^+$ T cells and macrophages compared to control mice. The $CD4^+$ and $CD8^+$ T cells in these mice were found to have increased expression of pro-inflammatory cytokine and chemokine receptor genes suggesting that these cells may be more competent at migrating to inflammatory sites such as atheromata and producing pro-atherogenic cytokines (ie., *Ifng* and *Tnf*) compared to wild-type T cells. Furthermore, mice with PD-L1-deficient bone marrow had increased lesional inflammation compared to controls.[15] Because PD-L1 is expressed in both hematopoietic and endothelial cells, deficient PD-1/PD-L1 signaling on T lymphocytes as well as within coronary vascular endothelium may contribute to CAD progression.[16] Despite these findings, there have also been reports in the literature of nivolumab therapy associated with shrinkage of atheromatous plaques.[17] This controversy emphasizes the point that causality cannot be determined from a limited number of cases and that further investigation is required to explore the role of PD-1/PD-L1/2 interactions in CAD.

It is also important to note that ISR is classified as a separate phenomenon to atherosclerosis. ISR is largely a result of neointima formation, which is characterized by smooth muscle cell (SMC) proliferation and migration and excessive extracellular matrix production.[18] The patient in this case displayed several risk factors for ISR, including diabetes, large stent diameters, and ostial stenosis. However, systemic inflammation and immune dysregulation from ICI therapy may be possible contributors. Prior literature suggests that intimal inflammation and lymphocytic infiltration are determinants of in-stent neointimal growth.[19] Additionally, studies have demonstrated that inflammatory cytokines stimulate the proliferation of vascular SMC, thereby leading to intimal thickening.[20] Further research is warranted to study the direct effects of immune checkpoint inhibition on the restenosis process.

CONCLUSION

Reported here is the rapid progression of CAD and ISR as potential adverse effects of anti-PD-1 therapy. Despite its efficacy in cancer patients, ICI therapy is associated with various irAEs, a number of which are cardiovascular with high risk for mortality. For patients with established

Table 2. Interval changes in degree of coronary vessel stenosis between cardiac catheterizations

Coronary vessel	Percent stenosis on initial catheterization after PCI	Percent stenosis on repeat catheterization 4 months later
Left main	20	60
Ostial/proximal left anterior descending	30	80
Mid-distal left anterior descending	0 (stented)	60
First diagonal	0 (stented)	99
Ramus intermedius	0	100 (de novo)
Right coronary	60	70

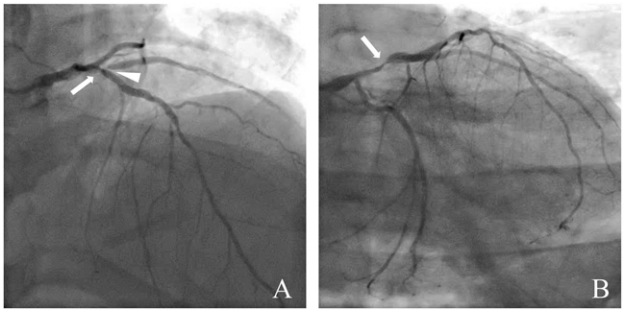

Figure 2. Coronary angiograms showing in-stent restenosis of the middle proximal left anterior descending artery (A and B, arrows) and first diagonal artery (A, arrowhead).

atherosclerotic disease initiated on immunotherapy, active surveillance for disease progression may be warranted. Measurement of serial troponins has been proposed as surveillance for myocarditis and may have utility for CAD as well.[5] Additionally, multi-disciplinary discussion with patient participation should take place when confronting competing risks of metastatic cancer and ACS. Although the decision was made to cease ICI therapy in this case, the approach should be individualized for each patient. Lastly, further research is required to evaluate the role for early cardiac risk stratification, aggressive lifestyle modification, and optimization of cardioprotective therapies for at-risk patients on ICIs. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Authors' Contributions

RM conducted the literature review and wrote the manuscript with support from GM, RL and KM. JT helped supervise the project.

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LETTER TO THE EDITOR

Can Burnout Among Child Abuse Clinicians be Caused by Doubt that They are Doing the Right Thing?

Niels Lynøe, MD, PhD[1]; Anders Eriksson, MD, PhD[2]

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In their interesting paper about the strong association between burnout among child abuse clinicians,[1] the authors discuss whether burnout might have similarities with staff working within emergency departments and pediatric palliative care. This can be a relevant comparison regarding job demands and burnout and it seems also reasonable that increased risk of secondary stress and burnout can be mitigated by hope and meaning in work. Moreover, we also agree with the authors' conclusion that the concerned child abuse clinicians should be offered education in coping strategies in order to minimize burnout.[1]

But perhaps the child abuse clinicians have additional problems when compared to other medical specialties and situations. More specifically, do child abuse clinicians sometimes ask themselves if they are always doing the right thing? This question applies above all to a certain kind of presumed child abuse, namely the very young infants (peak age 2 months) where abusive head trauma is suspected but where no external signs of trauma are present.[2] A systematic literature review disclosed that there is very low evidence of the diagnostic accuracy of the three findings, encephalopathy, subdural hemorrhage, and retinal hemorrhages ("the triad"), without external signs of trauma for predicting violent shaking.[3] Nevertheless, in practice, child abuse clinicians in many countries continue using the triad, without external signs of trauma, to claim with a high degree of certainty that such an infant must have been shaken violently.[4] Hence, we believe that a child abuse clinician might have a difficult time if he/she has given evidence as an expert indirectly or directly in a court of law and contributed to the conviction of a potentially innocent caregiver, to the removal of an infant from a caring family, and to the splitting of this family. Are such expert statements always in the infants' best interest?

If in doubt, we believe that child abuse clinicians sooner or later will suffer from a responsibility crisis. For example, in triad cases without external signs of trauma, child abuse clinicians might begin to doubt that all medical conditions have been ruled out when concluding that the infant must have been shaken. Are there medical conditions that are not yet accepted that can bring about the isolated triad spontaneously? Is the evidence behind the abusive head trauma theories as robust as assumed? Are retinal hemorrhages really pathognomonic for traumatic shaking or are they nonspecific and secondary to an increased intracranial pressure? Are caregivers really always lying when they tell that nothing happened ahead of the infant's symptoms of encephalopathy?

Child abuse clinicians might think that what they are doing is making a difference, but they might also begin to doubt that it always results in a good difference, perhaps even bad consequences, and hence a responsibility crisis, which in turn can bring about "emotional exhaustion, depersonalization, and reduced personal accomplishment". In other words, can such doubt also result in moral distress and burnout? ❖

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In Response

On behalf of our co-authors we appreciate the thoughtful comments and remarks by Dr. Niels Lynoe and Dr. Anders Eriksson[1] to our article[2] on hope, secondary traumatic stress and burnout among child abuse clinicians. We agree that stress associated with potential uncertainty in testifying in a court of law would be a job demand that in the absence of adequate resources, that over time, would be a contributor to burnout. That being said, the robust empirical literature on hope as a psychological protective factor would suggest the hopeful child abuse clinician would develop pathways to compensate and overcome the barrier of uncertainty. For example, accessing additional resources and evidence in making the determination that would be shared during the court hearing. This empirical literature also demonstrates the hopeful individual is better able to manage distress and daily stress.[3,4]

Lynoe and Anders[1] offer meaningful concerns for child abuse pediatrics that will likely influence their well-being, burnout, and ultimately quality of care. Nevertheless, these concerns are better served as empirical questions in future research. First, what is the prevalence of uncertainty experienced by child abuse clinicians in making a clinical diagnosis? Second, what is the association of this uncertainty to stress and burnout? Finally, does hope as a coping resource mitigate this potential job demand and burnout? ❖

Chan M Hellman, PhD
Sarah J. Passmore, DO

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LETTER TO THE EDITOR

ECG Changes in Capecitabine-Induced Takotsubo Cardiomyopathy

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Bhardwaj and colleagues described an interesting case study of Takotsubo cardiomyopathy (TC) in a patient with anal cancer who received chemotherapy with capecitabine, an oral prodrug of 5-fluorouracil (5-FU).[1] Cardiac toxicity is a well reported side effect of fluoropyrimidine chemotherapies (5-FU and capecitabine); however, TC is a rare and less commonly known side effect. TC has been previously reported with the use of 5-FU in some case studies, although other cardiotoxic and systemic side effects of fluoropyrimidine therapies have been well described in large studies.

TC is indeed a rare adverse event associated with use of 5-FU, whereas one of the most common forms of cardiotoxicity associated with 5-FU is ischemia, mediated by coronary artery vasospasm (widely reported). Other less common forms of adverse cardiac effects are vascular endothelial damage related to thrombogenicity and direct myocardial toxicity.[2,3] In the presented case by Bhardwaj et al., the first electrocardiogram (ECG) on presentation interestingly shows peaked and symmetrical large amplitude T-waves in the setting of chest pain. Although TC may be considered a plausible differential diagnosis in the presented case given the apical wall motion abnormality, the possibility of coronary vasospasm associated with transient myocardial stunning should also be strongly entertained as a primary or co-existing differential diagnosis.[3-5] Our reasoning for this is that large amplitude symmetrical T-waves are usually not the typical ECG changes encountered in TC. Typical ECG changes of TC evolve in 3 to 4 different stages that include: ST-elevations in stage 1, followed by ST-normalization often associated or succeeded by deep precordial T-wave inversions in stages 2 and 3, and finally, resolution of repolarization abnormalities in stage 4 (Figure 1).[6-9] These changes have been previously well described in prior reports including the data from large studies comprising TC patients.[6,8] On the contrary, peaked and symmetrical large amplitude T-waves are most commonly observed in coronary vasospasm (>50% patients) and are usually the first finding in vasospasm before the ST elevations that might develop if vasospasm remains persistent.[10]

The two ECGs presented in the case by the authors demonstrated large amplitude symmetric T-waves in the first ECG followed by complete normalization of these changes on the second ECG, which may support primary (or co-existing) coronary vasospasm, whereas the apical motion abnormality may be attributed to transient myocardial stunning associated with the coronary vasospasm.[10] The patient reportedly had negative cardiac biomarkers that are somewhat uncommon for patients of TC. Most often, patients with TC usually have a mild elevation of cardiac troponin levels with the incidence of negative cardiac biomarkers being a rarity (usually <2% to 5%).[5]

A few other important clinical considerations would be useful for clinicians treating patients with 5-FU use. An assessment to clinical response of patient's symptoms with use of nitroglycerine may also sometimes help tease out underlying vasospasm.[2,3] Although it may not be relevant to the presented case, patients receiving 5-FU may also experience tumor lysis effects that may be associated with electrolyte derangements, such as hyperkalemia, that can thus result in large amplitude T-wave amplitude. Thus, these additional clinical markers may serve as a valuable tool for clinicians in teasing out a clinical diagnosis.

In summary, we want to congratulate the authors for presenting such an interesting case that highlights important cardiotoxic effects of chemotherapeutic agent, 5-FU. Clinicians should remain vigilant about the potential cardiotoxic effects of chemotherapeutic agents such as 5-FU and should entertain all the important differential diagnosis as noted above to deliver the best guideline-directed therapy for the patients. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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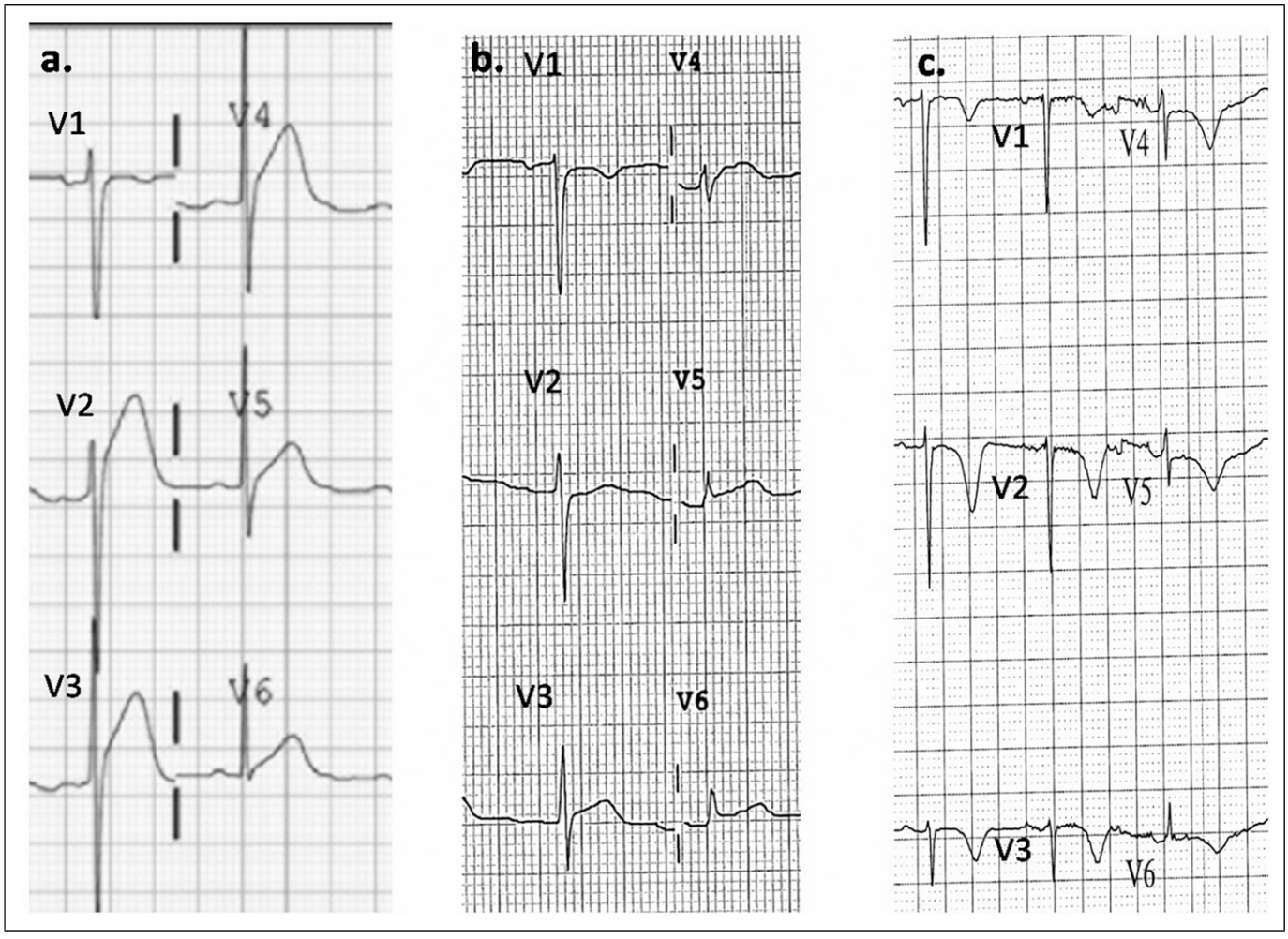

Figure 1. Demonstrates ECG changes in evolution in a patient with Takotsubo cardiomyopathy. (A) Demonstrates precordial ST elevations on initial presentation. (B) Demonstrates ST normalization with early appearance of biphasic T waves in V3 and V4. (C) Demonstrates stage 3 changes demonstrating diffuse T-wave inversions. Eventually in stage 4, these ST-changes demonstrate normalization or somewhat delayed persistence of these repolarization abnormalities. Less commonly, transient Q-waves may also be seen (not seen in this patient).

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In Response

The authors of the originating article were contacted but did not wish to respond. ❖