OFP

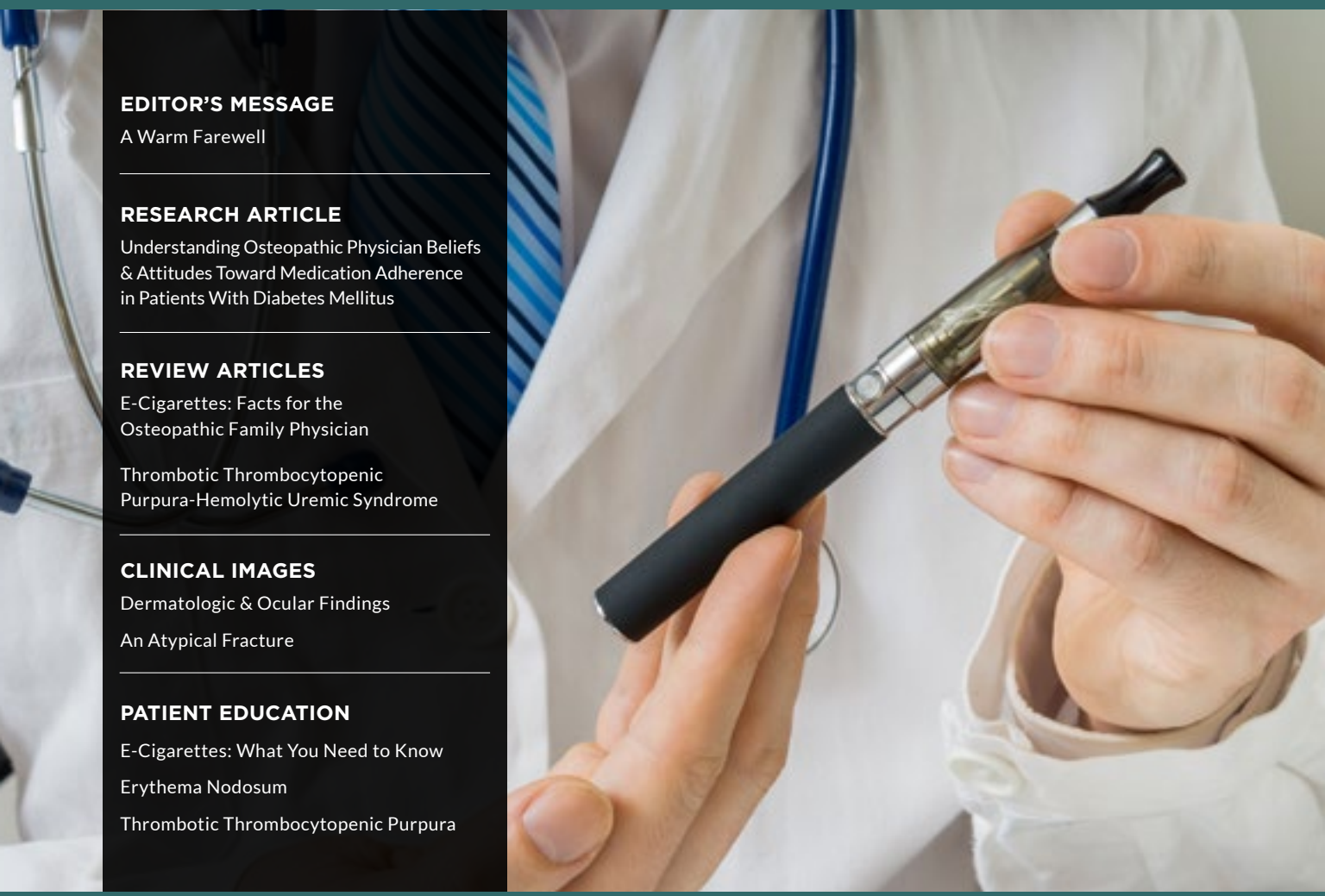
Osteopathic Family Physician

THE OFFICIAL PEER-REVIEWED PUBLICATION OF THE AMERICAN COLLEGE OF OSTEOPATHIC FAMILY PHYSICIANS

March/April, 2018

Volume 10 | Number 2

ofpjournal.com



acofp American College of Osteopathic Family Physicians

Advocacy • Education • Leadership

www.acofp.org

Guide for...

READERS

Osteopathic Family Physician (ISSN 1877-573X) is published bimonthly by the American College of Osteopathic Family Physicians. Periodicals postage paid at Arlington Heights, IL and additional mailing offices.

USA POSTMASTER

Send address changes to:

American College of Osteopathic Family Physicians
Membership Department:

330 East Algonquin Rd, Suite 1
Arlington Heights, IL, 60005
membership@acofpca.org

CUSTOMER SERVICE

(orders, claims, online, change of address)

American College of Osteopathic Family Physicians

330 East Algonquin Rd, Suite 1
Arlington Heights, IL 60005

800-323-0794 | membership@acofp.org

YEARLY SUBSCRIPTION RATES

United States & Possessions:

Individual $116 | Institution $208 | Student $57

All other countries: *(prices include airspeed delivery)*

Individual $146 | Institution $26 | Student $74
Single issues $42

To receive student/resident rate, orders must be accompanied by name of affiliated institution, date of orders must be accompanied by name of affiliated institution, date of term and the signature of program/residency coordinator on institution letterhead. Orders will be billed at the individual rate until proof of status is received.

Current prices are in effect for back volumes and back issues.

ADVERTISING INFORMATION:

Advertising orders and inquiries can be sent to:

Matt Van Wie
804-550-2312 | matt@esvw.com

AUTHOR INQUIRIES

For inquiries relating to the submission of articles (including electronic submission) please visit www.ofpjournal.com.

Content details for questions arising after acceptance of an article, especially those relating to proofs will be provided by the publisher.

You can track accepted articles and view Author Guidelines through Scholar One at mc04.manuscriptcentral.com/ofp.

The paper used in this publication meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).

AUTHORS

For a full and complete Guide for Authors, please go to:
mc04.manuscriptcentral.com/ofp.

REPRINTS:

For queries about author reprints, or to order 100 or more reprints for education, commercial or promotional use, contact ACOFP at 800.323.0794 or email ashleyd@acofp.org.

EXAM SCHEDULE
CERTIFICATION & OCC (RECERTIFICATION)

AOBFP EST. 1972

EXAMS	LOCATIONS	POSTMARK DATE
Family Medicine / OMT Certification / OCC Cognitive Exam	**Electronic Testing** Regional Sites September 22, 2018	**May 1, 2018** *Late fee through June 1*
Family Medicine / OMT Certification / OCC Performance Evaluation Only	**AOA OMED Conference** **San Diego, CA** October 6 - 10, 2018 October 5 - 7, 2018	**May 1, 2018** *Late fee through June 1*
Family Medicine / OMT Certification / OCC Performance Evaluation Only	**ACOFP Annual Convention** **Las Vegas, NV** March 21 - 24, 2019 exam dates TBD	**October 1, 2018** *Late fee through December 1*
Family Medicine / OMT Certification / OCC Cognitive Exam	**Electronic Testing** Regional Sites May 4, 2019	**October 1, 2018** *Late fee through December 1*
Family Medicine / OMT Certification / OCC Cognitive Exam	**Electronic Testing** Regional Sites September 28, 2019	**April 1, 2019** *Late fee through June 1, 2019*
Family Medicine / OMT Certification / OCC Performance Evaluation Only	**AOA OMED Conference** Fall, 2019 exam dates TBD	**April 1, 2019** *Late fee through June 1, 2019*

AMERICAN OSTEOPATHIC BOARD OF FAMILY PHYSICIANS
If you have questions, please call 847.640.8477 or email aobfp@aobfp.org.

OFP
Osteopathic Family Physician
The Official Peer-Reviewed Publication of the
American College of Osteopathic Family Physicians

MAR/APR, 2018
VOLUME 10 | NUMBER 2

CONTENTS

OSTEOPATHIC FAMILY PHYSICIAN SPECIALTY PEER REVIEWERS

Nazem Abdelfatta, MD
Family Medicine, Obstetrics, Women's Health

Richard L. Averitte, Jr, MD
Dermatology

Dana Baigrie, DO
Clinical Images

Jeffrey Benseler, DO
Radiology

Shagun Bindlish, MD
Diabetes and Endocrinology

John Bissett, DO
Clinical Images

Warren Bodine, DO
Sports Medicine & Family Medicine

Grace Brannan, PhD
Statistics/Design

Natasha Bray, DO
Ethics

Omar Bukhari, MD
Research

Janis Coffin, DO
Practice Management

Philip Collins, DO
Patient Education

Danielle Cooley, DO
OMM

Rob Danoff, DO
Emergency Medicine, Preventive

Robin Devine, DO
Statistics/Design

Brian Downs, DO
HIV, Wound Care

Dennis Eckles, DO
Diabetes, Rural Medicine

Gail Feinberg, DO, FACOFP
Academic

Matthew Goldfinger
Neurology, OMM

Patricia Happel, DO
Nutrition and Obesity

Nadia Hasan, DO
Clinical Images

Robert Hunter, DO
Health Policy, Hospice/Palliative Care, ER, Diabetes, Wound Care

Ronald P. Januchowski, DO
Military & Rural/Underserved

Holly Kanavy, DO
Dermatology

Amy Keenum, DO, PharmD
Healthy Literacy, International & Patient Education

Uzma Khan, DO
Family Medicine

Frank Komara, DO
Geriatrics

Paul Lazar, DO
Adult Family Medicine, Geriatrics, Academic

Mana Lazzaroto, DO
Clinical Images

Mohammad Mansour, MD
Inpatient Medicine, Cardiology, Pulmonary, Geriatrics, Obstetrics

Sarah Mitchell, DO
Family Medicine

Merideth Norris, DO, FACOFP
Addiction

Michael O'Connell, DO
Pain, Rehabilitation, Musculoskeletal, Neurology, & Sports Medicine

Jon Parham, DO
Preventive Medicine, Pulmonary, Public Health, Geriatrics, Medical Errors

Raena Pettitt, DO
Disease Prevention & Wellness

Kim Pfotenhauer, DO
Diabetes

Prabhat Pokhrel, MD, MS, PhD, FAAFP
Pharmacology, Cardiology, Nephrology, Pulmonology

M. Jay Porcelli, DO, FACOFP *dist.*
Pain Management

Joseph Reyes, DO
Pain Management

Bernadette Riley, DO
Medical Education, Academic, Simulation Medicine, Physician Leadership, Health Policy

Mark Rogers, DO, MA, CAQSM, FAAFP
Family Medicine, Sports Medicine, OMM, Medical Ethics

Lawrence Sawicki, DO
Clinical Images

Kary Schroyer, DO
Direct Primary Care

Christopher Scuderi, DO
Family Practice, Practice Management

Jay Shubrook, Jr., DO, FACOFP
Endocrinology

Leslie Sleuwen, MD
Community Medicine

Frederick Stine, DO
Pediatrics, Nephrology, Emergency & Critical Care

Lindsay Tjiattas-Saleski, DO
Clincial Images, Emergency Medicine

Johnathon Torres, DO
OMM

Michael Watkins, DO
OB/GYN & Women's Health

Stuart Williams, DO
OMM

Barbara Wolf, DO
Psychology

William Woolery, DO, PhD, FACOFP
Geriatrics

Julian Vega, DO
Clinical Images

Sheldon Yao, DO
Cardiology

Peter Zajac, DO, FACOFP
Patient Education

OFP
Osteopathic Family Physician
JOURNAL

2018 CALL FOR PAPERS

Osteopathic Family Physician is the ACOFP's official peer-reviewed journal
The bi-monthly publication features original research, clinical images and articles about preventive medicine, managed care, osteopathic principles and practices, pain management, public health, medical education and practice management.

RESERVE A TOPIC

Reserve a review article topic today by emailing ACOFP Managing Editor, Belinda Bombei at belindab@acofp.org. Please provide your name and the review title you would like to reserve. Once you reserve a review article topic, you will receive an email confirmation from ACOFP. This will initiate a three-month deadline for submission. If the paper is not received within three months, the system will release the review article topic for other authors to reserve. Articles submitted for publication must be original in nature and may not be published in any other periodical. Materials for publication should be of clinical or didactic interest to osteopathic family physicians. Any reference to statistics and/or studies must be footnoted. Material by another author must be in quotations and receive appropriate attribution. ACOFP reserves the right to edit all submissions. Visit ofpjournal.com to view author guidelines, policies, and manuscript checklist.

CLINICAL IMAGES

We are seeking clinical images from the wards that covers essential concepts or subject matter to the primary care physician.
Please provide a brief synopsis of how the case presented along with 1-4 questions and approximately 1 page of education with reference to the image and questions.

REVIEW ARTICLE TOPICS

- Acute & Chronic Urticaria: Evaluation & Treatment
- ADHD Management in Primary Care: with osteopathic component
- Aseptic & Bacterial Meningitis: Evaluation, Treatment, & Prevention
- Disorders of Puberty: An Approach to Diagnosis & Management
- Epilepsy: Treatment Options
- Lupus: Review article with osteopathic component
- OMT Treatments for Pediatric Conditions: Systematic Review
- Probiotics for Gastrointestinal Conditions: A Summary of the Evidence
- Treating Psychosis, Delirium & Dementia in the Elderly

RESEARCH TOPICS

We are seeking original clinical or applied research papers. Original contributions include controlled trials, observational studies, diagnostic test studies, cost-effectiveness studies, and survey-based studies. The OFP will accept basic scientific research only if the work has clear clinical applications. For randomized controlled trials, study flow diagrams must be submitted. For all other types of original contributions, flow diagrams are encouraged. Original contributions should be 3000 words with no more than 50 references and 5 tables or figures. OFP requires you to submit a 250-word abstract, along with four to six keywords.

The content should include the following:

Abstract
Introduction
Methods
Results
Discussion
Conclusions
Acknowledgments

EDITOR'S MESSAGE

A Warm Farewell

Amy J. Keenum, DO, PharmD, Editor, *Osteopathic Family Physician*

Winter is always the best time for reading. A fire, a cup of cocoa, and the *Osteopathic Family Physician*.

In this edition we have a review article on electronic cigarettes. When asking about smoking, is the question phrased in a way that the patient might be talking about electronic cigarettes? After reading the article this month, we knew that propylene glycol is commonly vaporized. The "vapes" also contain nicotine and various flavors and chemicals. Smoking cannabis and cannabis oils can be part of the use of these devices. The article reviews the various devices and the fact that they can be purchased in many places, including on-line.

Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome-An Evidence Based Clinical Review presents a case embedded in a review article on the topic. Patients may have renal impairment, thrombocytopenia, microangiopathic hemolytic anemia, fever and or neurologic deficits. Depending on when in the course of the disease the patient presents, all the elements may not be present when first seen. Plasma exchange is the mainstay of treatment, so nephrology consultation is in order. The authors have done a nice review which is included in this volume.

The clinical image articles continue in this edition and are always a quick learning item. One is an elder with a fracture and the other a young adult with a rash and ocular findings.

The research article this month studies us, osteopathic family physicians and what we believe about our patient's adherence to diabetes medicine. We apparently think they do what we suggest. The response rate was low, but it is an interesting read.

It has been my honor to edit this journal for the past three years after serving as associate editor for the prior three years. Dr. Januchowski will take over as editor after this edition. Please consider writing or reviewing for the Journal.

 Print ISSN: 1877-573X

FROM THE PRESIDENT'S DESK

Advocating for the Future We Desire

Rodney M. Wiseman, DO, FACOFP *dist*.
2017 - 2018 ACOFP President

I cannot believe that it has been a year since I joined with you at the 2017 ACOFP Annual Convention to start my term as ACOFP President. It has been a most meaningful year for me due to the people I met and the conversations we had.

Many talked about what a quandary medicine is in today, followed quickly by the question, "what can ACOFP do to affect change?" I have been asked by many, what is coming over the horizon and my answer is, that while I cannot see, we need to advocate for the future we desire.

A year ago, I focused my speech on characteristics that I believed represented ACOFP and members of the osteopathic profession – Integrity, Competency, Engagement, Vision, Diversity, Leadership, and Advocacy. I have seen many examples of each as I have made my way across the U.S. this past year.

What I am most proud about during my tenure is the progress that ACOFP has made in finding its legislative voice. It is in 2017-2018 that the ACOFP began taking assertive steps towards building *our* future of medicine. As oppressive as they seem, we can't allow forces to dominate our profession, and not take action.

ACOFP engaged with CMS, the FDA, and organizations to express our concerns and ideas about the increasing complexity of medicine in a meaningful way - not clouded with emotion, not angry and demanding, but with *integrity*.

Through comment letters requested by the government, ACOFP shared opinions on pressing issues, backed by examples of what Family Physicians face every day. We tackled the opioid crisis, the Quality Payment Program (QPP), the burden of increasing paperwork and EMR entry, the Teaching Health Center program, Graduate Medical Education, the increasing shortage of Primary Care Physicians, disparity in pay vs specialists, and funding for Rural Health programs and Disproportionate Share Hospitals (DSH), and the Children's Health Insurance Program (CHIP).

Out of these six areas, there were some big wins. Disproportionate Share Hospital funding, which was scheduled to be cut, was extended for two more years. CHIP, which was also to be severely reduced, was extended for 10 years.

After several months of work by the ACOFP Board, the Federal Legislation Committee, the Alternative Payment Model Committee, our lobbying firm Alston & Bird, and ACOFP Staff, a guiding legislative instrument was completed - The ACOFP 2018 Principles of Health Care Reform. This definitively states what ACOFP's priorities are in making the practice of medicine better through the power of lobbying for policy change.

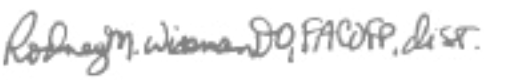
Ask yourself "why does this work matter to you?" As osteopathic family physicians we all need to come together as a united health care force that will act positively to improve health care with positive patient outcomes, improve quality at a lower cost, and improve physician payment. Maybe it is just a matter of joining with all of us - your membership, and asking what you can do to help. You may want to write to your Representative in Washington, volunteer to serve on a committee, share your expertise by recording a webinar or podcast that members can learn from, write articles for the OFP Journal, or be a moderator at an ACOFP state or annual meeting.

It has been my pleasure to serve you as your President and I encourage you to continue your support for my successor, Dr. Duane Koehler. As I continue on the Board as Past President, I will continue to keep my heart, mind, and ears open to your comments and suggestions.

As you know, I like to add quotations to my communication, so will close with this:

> *"The ultimate measure of a man/woman is not where s/he stands in moments of comfort and convenience, but where s/he stands at times of challenge and controversy."*
>
> *- MLK from Strength to Love, 1963*

Osteopathically yours,



Rodney M. Wiseman, DO, FACOFP *dist*.
2017-2018 ACOFP President

OFP
Osteopathic Family Physician

www.ofpjournal.com

CONGRATULATIONS

The journal of *Osteopathic Family Physician* applauds the following 2017 award recipients!

Attending Paper of the Year:

Osteopathic Considerations in the Infections of the Respiratory Tract

Sheldon Yao, DO, Allison Coombs, OMS III, Nardine Mikhail, OMS III, George Koutsouras, OMS III, & Michael J. Terzella, DO

Resident Paper of the Year:

The Use of Occipital Nerve Blocks & Trigger Point Injections in Headaches with Occipital Tenderness

Samuel D. Madore, DO

Student Authors of the Year:

Abnormal Weight Loss

Matthew Hadfield, OMS IV & Sriharsha V. Kota, OMS III

RESEARCH ARTICLE

Understanding Osteopathic Physician Beliefs & Attitudes Toward Medication Adherence in Patients with Diabetes Mellitus

Kevin Junus BS, OMS IV, Clipper Young PharmD, MPH, CDE & Jay H. Shubrook DO, FACOFP

College of Osteopathic Medicine, Touro University California, Vallejo CA

KEYWORDS:

Diabetes

Adherence

Medications

Aim: Develop a greater understanding of healthcare providers' beliefs on patients' medication adherence with an emphasis on the factors clinicians perceive being the most contributory toward non-adherence in type 1 (T1DM) and type 2 diabetes patients (T2DM).

Methods: A 40-item survey was sent to osteopathic family physicians exploring beliefs pertaining to medication adherence, including most important factors that felt to be the most influential to non-adherence. Each of these factors was classified into different categories as proposed by the World Health Organization (WHO) to determine the level of attribution and significance.

Results: A total of 183 osteopathic family physicians completed the survey. The physicians perceived that the mean patient adherences were 81.7% for oral anti-diabetic medications (e.g. metformin) and 72.4% for insulin. The physicians rated social and economic factors as the most impactful factors (e.g. high cost of healthcare and medication as well as poor socioeconomic status) contributing to non-adherence and condition-related factors as the least influential. Overall, physicians also rated patient-related factors as more significant than physician or healthcare team-related factors.

Conclusions: Physicians generally believe medication adherence is high in their patients. Interventions to improve medication adherence and overall glycemic control may be effective at the provider level by educating them of their impact, which may include conversations of hypoglycemia, depression, and overall importance of the provider-patient relationship that may play a more significant role than previously believed.

INTRODUCTION

The burden of diabetes mellitus (DM) in our country is increasing and will continue to rise for the foreseeable future. Approximately 9% of the population in the United States has diabetes, with 1 - 2 million more diagnosed each year.[1] It is estimated that 1 in 3 people will have diabetes by 2050.[2] Diabetes is largely self-managed, and keeping diabetes in control is a complex balance involving significant lifestyle changes, adherence to complex medication regimens, and unique requirements in health care providers with providing intentional encouragement and guidance for chronic disease management.[3]

Despite an array of effective treatments, including an abundance of new advances that can help promote optimal glycemic targets, it has been shown that only about 50% of patients achieve a target HbA1c of less than 7.0%.[1,4] Non-adherence of prescribed therapies is a significant but underappreciated facet of the management of diabetes.[5] Along with pulmonary disorders, diabetes was found to be a chronic condition among the highest associated with non-adherence.6 Large studies have reported variable findings in medication adherence in both oral medications (36% to 93%) and insulin (38% to 69%).[7,8]

Understanding the lack of adherence to diabetes medications is an ongoing problem, and several studies have tried to elucidate factors that contribute to poor medication adherence. Studies have shown factors, including age, gender, socioeconomic status, are all significantly associated with medication adherence, but meta-analyses thus far have not been able to show consistent results in definite factors that can be specifically implemented and improved upon to increase adherence, implying the complexity of factors that lead to adherence.[9,10]

Research suggests that a physician's role may have a larger influence on patient adherence than originally believed, with positive correlations between clear physician-patient communication and

CORRESPONDENCE:
Jay H. Shubrook DO, FACOFP | jay.shubrook@tu.edu

 Print ISSN: 1877-573X

adherence.[11] The World Health Organization (WHO) released a report, Adherence to Long-Term Therapies: Evidence for action in 2003[12] that acknowledges management strategies in combating non-adherence in chronic diseases, including diabetes, suggesting that optimal management requires a multidisciplinary strategy initiated by physicians that also promotes shifting away from patient-blaming with regards to non-adherence.

Hence, the goal of this study is to determine what healthcare providers believe is the level of adherence in their patients with diabetes and what specific factors lead to low-adherence to treatment recommendations. Low adherence to American Diabetes Association (ADA) treatment guidelines is not uncommon,[13] and it has been found that physicians often do not follow recommended guidelines in their management of diabetes due to their own beliefs and attitudes,[14] thus physicians' beliefs are essential to understanding. It is worthwhile to also investigate the extent to which providers believe their role is in improving adherence in their patients.

METHODS

The present study is a cross-sectional, descriptive study that seeks to elucidate the beliefs of practicing physicians through a survey distributed by email. A 40-item survey was utilized to explore attitudes of osteopathic family physicians who regularly manage patients with diabetes. The initial nine survey questions were related to demographics and also requested quantitative inputs on perceived levels of adherence to oral anti-diabetic medications and insulin nationwide. The next set of questions looked at 21 items designated as factors that might affect medication adherence and asked the physicians to rate the influence of these items on patient adherence. These items were based on the World Health Organization recommendations: social and economic factors; condition-related factors; therapy-related factors; healthcare team and system-related factors; and patient-related factors.[12] Survey participants were asked to rank from 1 to 5 for each proposed factor with five being most relevant in affecting medication adherence and one being the least.

The remaining ten items consisted of ordinal five-point Likert-scale items designed to measure beliefs regarding different aspects of diabetes management and medication adherence, wherein participants designated that they either "strongly disagree," "disagree," are "neutral," "agree," or "strongly agree" with the particular statement in question.

The survey questions were developed and designed by the first author and pretested for validity and clarity by a primary-care physician with specialization in diabetology and a faculty member the College of Pharmacy at the institution, both independently, and listed as authors in the present study. Further revisions were additionally made in discussions in a diabetes-focused research group at the institution. This study and the survey in its final form was reviewed and determined to be exempt by the University Institutional Review Board.

The survey was distributed via email to the American College of Osteopathic Family Physicians (ACOFP) mailing list of 8368 physicians. The survey was sent via an electronic link to the email database of the ACOFP in January and May of 2016, asking healthcare providers to contribute their time and thoughts if they regularly managed patients with diabetes. Inclusion criteria consisted of providers (DOs) in the US and are directly responsible for diabetes management in their patients.

Completion of the survey qualified them to enter in a gift card lottery that was drawn at random and delivered via email at the conclusion of the survey. Survey distribution and generated reports for analysis were completed in Qualtrics and SPSS. Ranked factors relevant to adherence underwent Mann-Whitney U analysis to explore differences in ranked factors between two groups of providers that were divided at the median by years of experience in practice post-residency (less than 15 years versus greater than or equal 15 years) and also divided by age of provider, also split at the median (less than 46-years-old versus 46-years-old and older)

RESULTS

There were in total 227 survey responses (a response rate of 2.7%), of which 183 of the responses were complete, detailed in Table 1 *(page 12)*. Surveys that were not complete were excluded from the present analysis. All responses were from physicians, among which 97.8% (n = 179) designated themselves as generalists, and 2.2% (n = 4) as specialists in diabetes (diabetologists). The mean year at which physicians have been in practice post-residency was 17 years; each physician saw a mean estimated 86 patients a month whom they directly managed their diabetes. Osteopathic physicians from all but 14 states were represented in the responses.

In general, physicians believed that the level of adherence in their patients was high, with a reported perceived adherence mean of 81.7% of prescribed doses of oral anti-diabetic medications and 72.4% of prescribed doses of insulin. Additionally, the participating physicians believed the nationwide level of adherence was 65.5% for oral anti-diabetic medications and 57.0% for insulin. Furthermore, 77.6% of participating physicians inquired about their patients' adherence to their anti-diabetic medications at every appointment, 17.5% inquired at most appointments, and less than 5% inquired at half or fewer of their appointments.

With regards to patients on insulin therapy, just under half (44.3%) of survey participants believed that the risk of drug-induced hypoglycemia is adequately regarded among healthcare providers in the context of diabetes care, while 30.6% believed that the risk of hypoglycemia is not adequately addressed among healthcare providers (25.1% responded neutrally). When asked about the care of their patients, 70.5% of participating physicians inquired about hypoglycemic events at every appointment, 22.5% asked more than half of the time, and 7.1% asked half of the time or fewer. The physicians reported that 79.3% of their patients were aware of signs and symptoms of hypoglycemic events.

Factors that the physicians rated as the most influentially toward medication non-adherence in diabetes are shown in Table 2 *(pages 14 and 15)*. Physicians rated social and economic factors as the highest in contributing toward non-adherence (mean = 4.83), followed by therapy-related factors (mean = 3.15), patient-related factors (mean = 3.11), healthcare team and system-related factors (mean = 2.95), and lastly, condition-related factors (mean = 2.76). The high cost of healthcare and medication was the highest rated factor, and lack of knowledge or training of health care providers in managing chronic diseases was rated as the least contributory to non-adherence.

TABLE 1:

Survey participant demographics of completed surveys.

CHARACTERISTIC		#	%
Age		Mean: 48 SD: 13.0	
Number of Years In Practice Post-Residency		Mean: 16 SD: 12.1	
Number of Patients with Diabetes Seen Per Month		Mean: 64 SD: 48.5	
Type of Provider	Generalist (Family Medicine, Internal Medicine, Pediatrics)	177	96.7%
	Specialist (Diabelologist, Endocrinologist)	3	1.6%
	Other Specialist*	3	1.6%
Practice Type	Single-Specialty Group	43	23.5%
	Hospital Employment	35	19.1%
	Multi-Specialty Group	37	20.22%
	University or Academic	14	7.7%
	Solo Practice	34	18.6%
	Military or Government	7	3.8%
	None of Above	13	7.1%
Practice Setting	Rural	60	32.8%
	Suburban	91	49.7%
	Urban	32	17.5%
Which guidelines do you follow to treat patients with diabetes?	AACE/ACE**	51	27.9%
	ADA/EASD***	84	45.9%
	Hospital or Office algorithm	23	12.6%
	No guidelines	19	10.4%
	Other (combination of guidelines, c-peptide level, guideline not listed)	6	3.3%

**Sports Medicine, Osteopathic Manipulative Treatment, Emergency Medicine*

***American Association of Clinical Endocrinologists/American College of Endocrinology*

****American Diabetes Association/European Association for the Study of Diabetes*

When providers were divided into two equal groups based on age by the median (providers younger than 46-years-old versus providers 46-years-old and older), there were significant differences in factor ratings for the following factors: fear of injections for insulin (p=0.009), increasing age in their patients (p=0.02), patient forgetfulness (p=0.015), and a long duration of diabetes (p=0.038) *(Table 2, pages 14 and 15)*. With the same respondents divided into two groups equally according to length of practice split at the median, only one factor was significant: there was a significant difference in rating increasing age in their patients between physicians who were practicing at least 15 years after their residency versus practicing physicians with less than 15 years of experience (p=0.005).

Physicians were split on believing whether patients' locus of control affected adherence to their management of their diabetes; 33.3% of physicians agreed or strongly agreed that patients have a strong internal locus of control (patients believing they have strong sense of control over their diabetes), 36.6% of responders disagreed or strongly disagreed that patients have a strong internal locus of control while 30.1% remained neutral. A majority of physicians (68.3%) also agreed or strongly agreed that patient factors (e.g., their knowledge, attitudes, expectations) play a larger role in contributing to non-adherence than healthcare team-related factors, such as poor education of diabetes by caregivers (16.4% disagree/strongly disagree and 15.3% neutral).

DISCUSSION

In general, physicians believed that the level of adherence in their patients was relatively high (81.7% for oral anti-diabetic medications and 72.4% for insulin) when compared to large systematic reviews that investigated medication adherence (36%-93% for oral medications and 38-69% for insulin).[8,15] These findings are rather surprising given the well-accepted notion that a majority of

adults with diabetes are not achieving adequate glycemic control, with patient nonadherence found to be one of the most influential factors contributing to such poor outcomes.[16] Large survey data that analyzed diabetes care over the past decade show that up to 48.7% of adult patients assessed did not meet adequate glycemic targets.[15] Given our results, medication non-adherence may overall still be an underappreciated aspect of diabetes care among physicians.

The factor that responding physicians rated as the most influential with regards to non-adherence in diabetes management was the cost of care and medications. This is well agreed upon, and consistent with literature.[9] In a separate systematic review, over 85% of the studies examined reveal a correlation between increasing patient share of costs and decreased medication adherence.8 In general, the high cost of care in patients is a well-acknowledged barrier to both adherence to treatment regimens and subsequently achieving HbA1c targets.

The majority of responding physicians (68.3%) believed that patient-related factors (e.g., patient forgetfulness) were more substantial than physician/healthcare team-related factors (e.g., poor physician communication or lack of proper education of diabetes). This was consistent with the higher mean rating as well (healthcare team-related factors ranked second to last). This may suggest that providers might underestimate their role in the management of their patients. Improved communication between providers and patients, especially in providing training to patients that also include sharing risks and benefits of insulin is an area of intervention that is highly associated with medication adherence.[17] It has been recently reported that patient perceptions of the quality of physician-patient interactions--whether they appeared rushed or distracted--are linked with insulin adherence behavior and glycemic control,[18] and it may be valuable for physicians to take this into consideration.

Condition-related factors and more specific factors related to other comorbidities that included depression were ranked the lowest factors in this study, implying a possible area of intervention. Some meta-analyses have shown strong associations between depression and non-adherence to medications. It has been found that patients with depression had a significant association between its severity and impact on medication adherence, and providers may need to recognize even more the impact of depression on adherence when it comes to treating their patients with diabetes.[9,19]

Interestingly, patients' fear of hypoglycemia was rated as the second lowest factor in contributing toward non-adherence by survey participants. A majority of survey participants responded that the risk of drug-induced hypoglycemia among all providers is adequately acknowledged, which may partially explain why the factor is rated so lowly. This is consistent with other reports that investigated barriers to optimal glycemic control, with one showing that only 19% of physicians acknowledged patients' fears of hypoglycemia being a significant contributor toward non-adherence.[20] However, patient-focused studies found that hypoglycemic episodes can lead to immense changes in adherence including self-alteration of their insulin regimen, and more research needs to be done to explore the extent physicians understand this area of diabetes care.[21,22] A recent study also reported a majority of patients (65% of patients with type 1 diabetes and 50 - 59% of patients with type 2 diabetes) rarely or never informed their healthcare provider of hypoglycemic episodes.[23] Low ratings of the fear of hypoglycemia in the present study may signify a prompt for greater need of discussion between physicians and patients on an underestimated burden which opens the discussion for the need of improved communication between them, as studies have shown that there is often a significant difference in between physicians' and patients' beliefs of hypoglycemia, most notably in knowledge of symptoms.[24]

When examining physician's ratings of factors that lead to adherence, there were some significant differences in ratings between younger (<45-years-old) and older (≥46-years-old) physicians, but this does not necessarily correspond to experience in practice. When comparing physicians' ratings in terms of years in practice, physicians with more years of experience (≥15 years out of residency) and physicians with comparatively fewer years of experience (<15 years out of residency) rated factors nearly identically with one exception—there was a significant difference in ratings for increasing patient age as a factor in contributing toward non-adherence. It has been proposed that physicians over time may gain a greater intuition in the context of reading social and behavioral cues with increasing age and years of experience in practice, which can translate substantially in the care of elderly patients with chronic conditions with relative complexity such as diabetes.[25] Whether this difference in factor ratings implies that more experienced physicians understand elderly patients in a different light is yet to be investigated.

Adherence to medication in a chronic disease is complex, and a recent systematic review revealed that no single intervention exists to promote global adherence to anti-diabetic medications in patients with type 2 diabetes.[10] However, to address improving medication adherence, a multifactorial approach will be needed.[4,10] Improved physician-patient communication -- provider-level intervention in particular -- is where published research is sparse but appears to play an important role in medication adherence.[26]

Our current study provides important insight into physician beliefs on barriers to adherence in patients with diabetes, an area of research that is few and far between with regards to the provider level, but certain limitations must be recognized. The number of responses was smaller than expected, which also opens the possibility of selection bias, which the survey may not be representative of all providers who manage diabetes. The authors acknowledge that the small response rate may limit generalizability, and at best, only provides a small representation of osteopathic family physicians. It is unclear if there is a difference that may be attributed to osteopathic philosophy in affecting physician-and-patient-level barriers to medication adherence. A recent study showed that empathy is maintained in graduating osteopathic medical students, but it is yet to be determined if this affects patient adherence.[27] Further study is recommended to assess beliefs that also expands beyond the realm of osteopathic family physicians who treat diabetes, ideally with the inclusion of specialists, the inclusion of allopathic physicians, and also non-physician providers (e.g., physician assistants and nurse practitioners).

All in all, these findings reveal the provider-level factors need further study and emphasis and analysis when assessing patients' medication adherence. It may also be worthwhile to quantitatively assess relationships between patient-provider relationship differences (e.g., length of appointment time) and medication adherence.

TABLE 2:

Factors that contribute to medication non-adherence, rated from most relevant to least according to responses.[1] (least relevant),[5] (most relevant).

FACTORS: Social and economic, condition-related, therapy-related, health care team and system-related, patient-related	Average Value	Median
High cost of healthcare and medication	4.04	4
Fear of injections for insulin	3.72	4
Poor socioeconomic status	3.68	4
Low level of education	3.56	4
Poorly developed health services (e.g. inadequate reimbursement by health insurance plans)	3.55	4
Lack of motivation in patients (lack of perceived importance of adherence)	3.49	4
Complexity of medical regimen (e.g. duration of treatment)	3.46	4
Short provider-patient consultations	3.40	3
Weak capacity of the system to educate patients and provide follow-up	3.32	3
Lack of effective social support networks	3.26	3
Increasing age	3.18	3
Patient forgetfulness	3.08	3
Lack of immediate medical beneficial effects of medicine	3.04	3
Medication side effects	2.95	3
Poor physician communication (e.g. failure to explain benefits and side effects of a medication adequately)	2.92	3
A long duration of diabetes (10 years)	2.77	3
Other co-morbidities such as depression, drug and alcohol abuse	2.75	3
Low self-esteem and self-efficacy in patients	2.70	3
Lack of provider knowledge on adherence and effective interventions for improving adherence	2.62	3
Fear of hypoglycemia	2.54	2
Lack of knowledge or training in health care providers on managing chronic conditions	2.51	2

**SD = standard deviation*

Mode	SD*	Average Value (<15 years post-residency, n=81)	Average Value (≥15 years post-residency, n=81)	2-tailed p-value (Mann-Whitney U)	Average Value (age<46, n=81)	Average value (age≥46, n=81)	2-tailed p-value (Mann-Whitney U)
5	1.09	4.13	3.89	0.113	4.15	3.86	0.054
4	1.12	3.93	3.54	0.083	4.01	3.47	0.009
4	1.09	3.7	3.57	0.606	3.75	3.52	0.252
4	1.10	3.58	3.43	0.433	3.60	3.41	0.317
4	1.17	3.43	3.65	0.378	3.45	3.63	0.467
4	0.99	3.52	3.36	0.259	3.56	3.32	0.107
4	1.10	3.58	3.33	0.188	3.58	3.33	0.148
3,4	1.10	3.40	3.38	0.924	3.42	3.36	0.864
4	1.18	3.28	3.33	0.846	3.36	3.26	0.594
3	1.07	3.24	3.30	0.731	3.35	3.19	0.321
3	1.01	2.91	3.38	0.005	2.96	3.33	0.020
3	0.93	3.20	2.93	0.060	3.23	2.89	0.015
3	1.07	3.10	2.96	0.423	3.11	2.95	0.406
3	1.06	3.08	2.90	0.240	3.08	2.90	0.241
3	1.15	2.79	2.93	0.435	2.83	2.89	0.808
3	1.15	2.83	2.64	0.288	2.90	2.57	0.038
3	1.12	2.89	2.60	0.110	2.85	2.64	0.190
3	1.12	2.77	2.63	0.359	2.81	2.58	0.135
2	1.13	2.53	2.72	0.333	2.65	2.59	0.690
2	1.09	2.46	2.60	0.372	2.51	2.56	0.675
2	1.14	2.38	2.65	0.086	2.46	2.57	0.482

Lastly, as the study asks participants to respond based on their beliefs, there is an element of recall bias to be attributed when comparing this study with others, especially in measuring their perceived adherence. Thus, it would be prudent to view them as approximate estimates, especially when referring to literature.

CONCLUSION

Medication non-adherence is a pervasive and multi-factorial hidden problem that affects the care of our patients and the outcomes we can achieve in diabetes care. This survey reveals that physicians may underestimate medication non-adherence as a whole in diabetes management, including in their potential role as providers and also burdens associated with several factors such as the impact of hypoglycemia. This survey study reveals that social and economic factors play an essential role from the perspective of osteopathic family physicians. The role (positive or negative) of the osteopathic family physician on adherence needs further exploration.

ACKNOWLEDGEMENTS:
We would like to thank the American College of Osteopathic Family Physicians (ACOFP) for providing the means to distribute the survey mentioned in the present study to the physician membership mailing list, which made the completion of this study possible.

DISCLOSURES:
JS serves as a consultant for Lilly Diabetes and Novo Nordisk

CONFLICTS:
None of the authors (KJ, CY, JS) have any conflicts to declare regarding the content of the manuscript.

REFERENCES

1. Centers for Disease Control and Prevention. A1c Distribution Among Adults with Diagnosed Diabetes, United States, 1988–1994 to 1999–2006. 2014; https://www.cdc.gov/diabetes/statistics/a1c/a1c_dist.htm. Accessed May 14, 2017.
2. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr. 2010;8:29.
3. Bailey CJ, Kodack M. Patient adherence to medication requirements for therapy of type 2 diabetes. Int J Clin Pract. 2011;65(3):314-322.
4. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient Prefer Adherence. 2016;10:1299-1307.
5. Currie CJ, Peyrot M, Morgan CL, et al. The impact of treatment noncompliance on mortality in people with type 2 diabetes. Diabetes Care. 2012;35(6):1279-1284.
6. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care. 2004;42(3):200-209.
7. Cramer JA. A systematic review of adherence with medications for diabetes. Diabetes Care. 2004;27(5):1218-1224.
8. Davies MJ, Gagliardino JJ, Gray LJ, Khunti K, Mohan V, Hughes R. Real-world factors affecting adherence to insulin therapy in patients with Type 1 or Type 2 diabetes mellitus: a systematic review. Diabet Med. 2013;30(5):512-524.
9. Krass I, Schieback P, Dhippayom T. Adherence to diabetes medication: a systematic review. Diabet Med. 2015;32(6):725-737.
10. Sapkota S, Brien JA, Greenfield J, Aslani P. A systematic review of interventions addressing adherence to anti-diabetic medications in patients with type 2 diabetes--impact on adherence. PLoS One. 2015;10(2):e0118296.
11. Ratanawongsa N, Karter AJ, Parker MM, et al. Communication and medication refill adherence: the Diabetes Study of Northern California. JAMA Intern Med. 2013;173(3):210-218.
12. World Health Organization. Adherence to Long-Term Therapies: evidence for action. 2003; http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf. Accessed May 14, 2017.
13. Lian J, Liang Y. Diabetes management in the real world and the impact of adherence to guideline recommendations. Curr Med Res Opin. 2014;30(11):2233-2240.
14. Qiu Y, Li Q, Tang J, et al. Why physicians do not initiate dual therapy as recommended by AACE guidelines: A survey of clinicians in the United States. Diabetes Res Clin Pract. 2015;108(3):456-465.
15. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999-2010. N Engl J Med. 2013;368(17):1613-1624.
16. Blackburn DF, Swidrovich J, Lemstra M. Non-adherence in type 2 diabetes: practical considerations for interpreting the literature. Patient Prefer Adherence. 2013;7:183-189.
17. Garcia-Perez LE, Alvarez M, Dilla T, Gil-Guillen V, Orozco-Beltran D. Adherence to therapies in patients with type 2 diabetes. Diabetes Ther. 2013;4(2):175-194.
18. Linetzky B, Jiang D, Funnell MM, Curtis BH, Polonsky WH. Exploring the role of the patient-physician relationship on insulin adherence and clinical outcomes in type 2 diabetes: insights from the MOSAIc study. J Diabetes. 2016.
19. Bauer AM, Parker MM, Moffet HH, et al. Depressive symptoms and adherence to cardiometabolic therapies across phases of treatment among adults with diabetes: the Diabetes Study of Northern California (DISTANCE). Patient Prefer Adherence. 2017;11:643-652.
20. Dalal MR, Grabner M, Bonine N, Stephenson JJ, DiGenio A, Bieszk N. Are patients on basal insulin attaining glycemic targets? Characteristics and goal achievement of patients with type 2 diabetes mellitus treated with basal insulin and physician-perceived barriers to achieving glycemic targets. Diabetes Res Clin Pract. 2016;121:17-26.
21. Lopez JM, Annunziata K, Bailey RA, Rupnow MF, Morisky DE. Impact of hypoglycemia on patients with type 2 diabetes mellitus and their quality of life, work productivity, and medication adherence. Patient Prefer Adherence. 2014;8:683-692.
22. Edridge CL, Dunkley AJ, Bodicoat DH, et al. Prevalence and Incidence of Hypoglycaemia in 532,542 People with Type 2 Diabetes on Oral Therapies and Insulin: A Systematic Review and Meta-Analysis of Population Based Studies. PLoS One. 2015;10(6):e0126427.
23. Ostenson CG, Geelhoed-Duijvestijn P, Lahtela J, Weitgasser R, Markert Jensen M, Pedersen-Bjergaard U. Self-reported non-severe hypoglycaemic events in Europe. Diabet Med. 2014;31(1):92-101.
24. Bohme P, Bertin E, Cosson E, Chevalier N, group G. Fear of hypoglycaemia in patients with type 1 diabetes: do patients and diabetologists feel the same way? Diabetes Metab. 2013;39(1):63-70.
25. Elstad EA, Lutfey KE, Marceau LD, Campbell SM, von dem Knesebeck O, McKinlay JB. What do physicians gain (and lose) with experience? Qualitative results from a cross-national study of diabetes. Soc Sci Med. 2010;70(11):1728-1736.
26. Polonsky WH. Poor medication adherence in diabetes: what's the problem? J Diabetes. 2015.
27. Kimmelman M, Giacobbe J, Faden J, Kumar G, Pinckney CC, Steer R. Empathy in osteopathic medical students: a cross-sectional analysis. J Am Osteopath Assoc. 2012;112(6):347-355.

E-Cigarettes: Facts for the Osteopathic Family Physician

Andrea Perloff, OMS II, Katie Smeltzer, MS, OMS IV, W. Joshua Cox, DO, FACOFP, & Gautam J. Desai, DO, FACOFP

The Kansas City University of Medicine and Biosciences College of Osteopathic Medicine, Kansas City, Missouri

KEYWORDS:

Electronic Cigarettes

E-Cigarettes

Nicotine

Disease Prevention & Wellness

Smoking Cessation

Vaping

Electronic cigarettes are becoming increasingly popular in the United States, but misperceptions among consumers are common. There is a sense that they are safer than traditional cigarettes, however, there is limited research on long-term effects regarding the safety of these devices. They have not been proven to be efficacious for use in smoking cessation. The toxic effects may be increased in those using cartridges with flavoring compounds in the solution. The younger demographic is more likely to utilize e-cigarettes, especially flavored versions, than traditional cigarettes. Manufacturers are aware of this and produce flavoring additives such as bubble gum and cotton candy to sell more of these products. Parents may be unaware that their children use e-cigarettes as a delivery mechanism for cannabis. Osteopathic physicians should be aware of the health risk of e-cigarettes to their patients, and counsel appropriately.

INTRODUCTION

Electronic cigarettes are nicotine-delivering devices that create a vapor from a solution to make an inhalable aerosol. The device consists of an electrical unit which heats (activated by inhalation) a cartridge (which is either inserted or attached to the device) to create the vapor. Some cartridges are removable and contain a variety of chemical solutions. Multiple device designs are available to increase their market appeal. Some larger devices can control the amount of vapor that is produced while some resemble a traditional cigarette or cigar. The consumer may continue to use these devices until either the battery or cartridge has run out, with the added benefit that some are rechargeable or have refillable cartridges. Electronic cigarettes are also known as e-cigarettes, e-cigs, e-cigars, personal inhalers, e-hookahs, vape pens, and vaporizers. Colloquially, the act of inhaling the vapor from the e-cigarette is known as "vaping" and stores selling these products are often referred to as "vape shops." Current loose regulations have permitted manufacturers of these products to target younger patients, as well as individuals trying to discontinue traditional cigarette or cigar use.

FIGURE 1:

From Grana R, Benowitz N, Glantz SA: Background paper on e-cigarettes (electronic nicotine delivery systems): prepared for the 7th meeting of the WHO Study Group on Tobacco Product Regulation. San Francisco, 2013, UCSF.

Product	Description	Some Brands
Disposable e-cigarette 	Cigarette-shaped device consisting of a battery and a cartridge containing an atomizer to heat a solution (with or without nicotine). Not rechargeable or refillable and is intended to be discarded after product stops producing vapor.	NJoy, Blu, Green Smoke
Rechargeable e-cigarette 	Cigarette-shaped device consisting of a battery that connects to an atomizer used to heat a solution typically containing nicotine. Often contains an element that regulates puff duration and/or how many puffs may be taken consecutively.	V2 Cigs, Halo G6, Mark Ten
Pen-style, medium-sized rechargeable e-cigarette 	Larger than a cigarette, often with a higher capacity battery, may contain a prefilled cartridge or a refillable cartridge (often called a clearomizer). These devices often come with a manual switch allowing the smoker to regulate length and frequency of puffs.	eGo, Kanger EVOD, Halo Triton
Tank-style, large-sized rechargeable e-cigarette 	Much larger than a cigarette with a higher-capacity battery and typically contains a large, refillable cartridge. Often contains manual switches and a battery casing for customizing battery capacity. Can be easily modified.	Kanger Aerotank, Innokin iClear, Aspire Nautilus

CORRESPONDENCE:

Gautam J. Desai, DO, FACOFP | gdesai@kcumb.edu

 Print ISSN: 1877-573X

CONTENTS

One component of the e-cigarette is the cartridge (atomizer), which can be prefilled and disposable, or multiple use, and refillable. The contents of the cartridges vary greatly and often contain a chemical solution composed of nicotine, propylene glycol, and other compounds. Cartridge labeling is not currently required, so chemical content may vary from product to product, with the user unable to determine what is being inhaled.

Nicotine is an addictive agent that leads to the pathogenicity of some diseases and is extremely harmful to fetal brain development. During pregnancy, nicotine can cross the placenta and can negatively affect the growing fetus. Nicotine may inhibit brain development, and directly causes problems with learning, attentiveness, and being more prone to addiction. While most adults know that nicotine is present in traditional cigarettes, this may be less apparent to those who use e-cigarettes, especially younger users. The Food and Drug Administration has mandated that beginning in 2018, and e-cigarettes will be required to have a package label stating that they contain nicotine.

Although every company makes a different solution of chemicals for their cartridges, propylene glycol is used in almost all e-cigarette cartridges. This chemical is vaporized by the device and provides the aerosol. Propylene glycol is commonly used in food additives, intravenous diluents, and smoke generators utilized in theaters and nightclubs. Acute exposure to vaporized propylene glycol can cause acute upper airway and eye irritation. This may be problematic in asthmatics or patients with other respiratory issues.[1] There is no research on human subjects regarding the effects of long-term exposure to the propylene glycol alone, or in combination with nicotine and other additives being vaporized and inhaled. However, studies have proven there is oxidative stress and inflammatory effects on lung cell tissue samples of mice.[2]

ADDITIVES

Other common additives utilized as part of the production of e-cigarettes are chemicals that produce different flavors. One study demonstrated that the addition of flavor compounds to e-cigarettes could alter the rate of nicotine absorption, possibly due to the differences in pH between flavored and non-flavored e-liquids. It showed an increased rate of nicotine absorption with the use of strawberry flavored e-liquid when compared to the non-flavored e-liquid. The study also demonstrated that users of the strawberry flavored e-liquid incurred a greater total systemic exposure to nicotine resulting from a combination of the faster nicotine absorption rate and an increased frequency of use by those who found the flavored vapor enjoyable.[3]

In addition to their ability to alter nicotine absorption and intake, the chemicals that make up the flavored compounds in e-cigarettes must also be considered. E-cigarette products often market their flavoring ingredients as safe; however, the safety levels recognized by the Flavor Extracts Manufacturers Association pertain to ingestion of these chemical compounds, and high doses of the same flavoring ingredients may not be safe for inhalation. The types of chemicals and their concentrations vary widely among the different brands and flavors of e-cigarettes, and most e-cigarette products do not list the chemical ingredients of their flavoring compounds. A 2016 study out of Portland, Oregon analyzed the chemical content of 30 different flavored e-cigarette fluids, and found that a significant number of flavor compounds contained aldehydes (i.e. vanillin, benzaldehyde), which are known to cause inflammation of the mucosa of the respiratory tract and can be harmful with prolonged use or to those who have respiratory problems.[4] Some of the chemicals used to produce different flavors were found to be present at concerning levels; the authors reported that e-cigarette users might be exposed to as much as two times the daily-recommended workplace exposure limits by inhalation of chemicals such as vanillin and benzaldehyde.[4]

OTHER USES

There are commercially available cartridges and refills containing cannabis oil for those who use marijuana, both recreationally and medicinally. Alternatively, cannabis may be incorporated into the cartridge by grinding the dried bud/leaf of the plant or utilizing wax infused THC oil. As with other cartridges, the consumer may not be aware of all of the additives and chemicals that are present in combination with the cannabis oil. Any pesticides or herbicides used in the harvest of the marijuana plant generally will be present in the oil and inhaled along with the vaporized oil. Sometimes, parents and others are unaware that people using e-cigarettes are vaporizing cannabis oil, as the odor is far less noticeable than traditionally smoked marijuana cigarettes, and it dissipates quickly. Users may utilize cannabis oil in public venues, such as concerts, with less concern of being caught. Flavored cannabis oil is available, making it more attractive to younger consumers, and also increasing the quantity used. A survey conducted in Connecticut asked 3847 high school students about cannabis use and electronic cigarettes. The results showed that 5.4% of the total sample had used e-cigarettes to vaporize cannabis (compared to 0.2% of adults reported in a previous study), revealing that high school students are 27 times more likely to use electronic devices to vaporize cannabis than adults.[5] Of note, among the 1075 students who reported using e-cigarettes, 18% had tried using them to vaporize cannabis, indicating that high school students who are already using e-cigarettes may be at an increased risk for using electronic devices to vaporize cannabis.[5]

These devices are ubiquitous, are sold online, and in local gas stations, specialty smoking stores, retail stores such as Wal-Mart and other chain drug stores. Current laws state they may only be purchased by consumers 18 years and older. Prices for the devices vary greatly based on the design and range from $10 to $300 for higher-end products.

SMOKING CESSATION

Some people use electronic cigarettes in an attempt to quit smoking traditional cigarettes. One of the selling points that some manufacturers make is that their product can limit the amount of nicotine one receives during inhalation. However, one study measured saliva cotinine (a metabolite of nicotine) levels of electronic cigarette vs. traditional cigarette users. It was found that users of electronic cigarettes had the same amount of cotinine in their saliva as those who smoked regular cigarettes.[6] At the time of writing this article, the FDA has not approved for utilizing electronic cigarettes as smoking cessation aids. There is limited research comparing the efficacy of e-cigarettes for smoking cessation to other means, such as transdermal patches or nicotine gum.[7] As electronic cigarettes are a relatively newer product, research is lacking in many aspects of their safety and use.

YOUTH APPEAL

Electronic cigarettes are now the most popular nicotine product used by children in middle and high school. A report of the US Surgeon general cited the fact that more than 25% of children in middle school and high school had tried e-cigarettes, and that this use is positively correlated with the use of other tobacco products. One study of middle and high school students asked why they first tried electronic cigarettes, and one factor cited was that electronic cigarettes were less expensive than regular cigarettes. Children also liked the fact that they can be used anywhere and some saw them as a tool to quit smoking traditional cigarettes.[8]

A study done in Oregon surveyed students between eighth grade and ninth grade. The results showed almost 30% of these eighth graders had tried electronic cigarettes and 16.8% had used in the past 30 days. This study demonstrates the prevalence of electronic cigarette use, with an additional finding that those who smoked electronic cigarettes were more likely to use other drugs such as marijuana.[9]

NON-PRIMARY CHEMICAL EXPOSURE

Not enough research has been done to define the long-term effects to patients who are around others who use electronic cigarettes. The secondhand aerosol contains nicotine and other toxins known to cause cancer. In 2013 a study found that not only was there nicotine being exhaled, but also volatile organic compounds and ultrafine particles. The levels of these compounds (excluding nicotine) were not concerning in this study. However, the secondhand nicotine exposure is, on average, ten times less than from combustible tobacco products. Although the amount of nicotine emitted is less than from classic cigarettes, non-smokers and vulnerable populations such as children, pregnant women, and those with cardiovascular problems may still be at risk of involuntary exposure to nicotine. This may be directly from the vapor or it can be from exposure to nicotine that has adhered to different indoor surfaces. Nicotine is hard to remove from surfaces and may be transmitted by touching these nicotine coated surfaces. Currently, however, there are no studies on the effects of such exposure among these populations, and further research is needed to determine if exposure to the low levels of nicotine emitted from e-cigarettes can be deemed as harmful to these individuals. [10]

SUMMARY

There is limited research on long-term effects regarding the safety of electronic cigarette use. These products may be perceived as being safer by patients and their families. However, until further research is done, patients should be counseled to avoid using both traditional and electronic cigarettes. (Figure 2) The aerosol that the devices create is not harmless. With the lack of labeling and control of these devices users should be aware that they are inhaling chemicals that can cause adverse effects to their health. The toxic effects are especially prominent for those using cartridges with flavoring compounds in the solution. Parents should be warned that their children may be using these as a delivery mechanism for cannabis. Pregnant women should not use these devices because of the toxic effects on the fetus and postnatal development. These devices put others at risk by the generation of second and third-hand nicotine exposure. Physicians should ask about the use of electronic cigarettes as part of their well patient visits, as many children have tried these products, and may be unaware of the potential health hazards.

FIGURE 2:

Physician counseling patient to avoid using both traditional and electronic cigarettes

AUTHOR DISCLOSURES
No relevant financial affiliations.

REFERENCES:

1. Wieslander G., et al, Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects. Occupational and Environmental Medicine. 2001;58(10):649-655. doi:10.1136/oem.58.10.649.
2. Lerner CA, Sundar IK, Yao H, et al. Vapors Produced by Electronic Cigarettes and E-Juices with Flavorings Induce Toxicity, Oxidative Stress, and Inflammatory Response in Lung Epithelial Cells and in Mouse Lung. Plos One. 2015;10(2). doi:10.1371/journal.pone.0116732.
3. St.Helen G, Dempsey DA, Havel CM, Jacob P, Benowitz NL. Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. Drug and Alcohol Dependence. 2017;178:391-398. doi:10.1016/j.drugalcdep.2017.05.042.
4. Tierney PA, Karpinski CD, Brown JE, Luo W, Pankow JF. Flavour chemicals in electronic cigarette fluids. Tobacco Control. 2016;25(e1):e10-e15. doi:10.1136/tobaccocontrol-2014-052175.
5. Morean ME. High School Students Use of Electronic Cigarettes to Vaporize Cannabis. Pediatrics. 2015;136(4):611-616. doi:10.1542/peds.2015-1727d.
6. Etter J-F, Bullen C. Saliva cotinine levels in users of electronic cigarettes. European Respiratory Journal. 2011;38(5):1219-1220. doi:10.1183/09031936.00066011.
7. U.S. Department of Health and Human Services. E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General—Executive Summary. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2016.
8. Bold KW, Kong G, Cavallo DA, et al, Reasons for Trying E-cigarettes and Risk of Continued Use. Pediatrics. 2016;138(3). doi:10.1542/peds.2016-0895.
9. Westling E, Rusby JC, Crowley R, Light JM. Electronic Cigarette Use by Youth: Prevalence, Correlates, and Use Trajectories From Middle to High School. Journal of Adolescent Health. 2017;60(6):660-666. doi:10.1016/j.jadohealth.2016.12.019.
10. Czogala J, Goniewicz ML, Fidelus B, et al, Secondhand Exposure to Vapors From Electronic Cigarettes. Nicotine & Tobacco Research. 2013;16(6):655-662. doi:10.1093/ntr/ntt203.ticle – you can find the jpg at http://circ.ahajournals.org/content/circulationaha/129/19/1972/F1.large.jpg/

REVIEW ARTICLE

Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome

Jodie Bachman DO, MBS,[1] William Cieplinski MD, PhD,[2]
Aliss Markosian DO, MPH[3] & Jay H. Shubrook, DO, FACOFP[4]

[1] Saint Barnabas Medical Center, Livingston, NJ
[2] Goshen Medical Associates, Goshen, NY
[3] UCLA Health, Los Angeles, CA
[4] Touro University California, Primary Care Department, Vallejo, CA

KEYWORDS:

ADAMTS13

Hematology

Hemolysis

HUS

TTP

Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome is an acute illness with abnormalities in multiple organ systems. Patients typically present with thrombotic microangiopathy, thrombocytopenia, and microangiopathic hemolytic anemia without another apparent cause. Additional features include fever, neurologic, and renal abnormalities depending on the site of microangiopathic damage. Potential causes include congenital deficiencies, Shiga-Toxin producing bacteria, numerous drugs, factors related to malignancy, allogeneic hematopoietic cell transplant, cardiovascular surgery, and pregnancy. A medical emergency, appropriate treatment needs to be initiated promptly or the disease can be fatal. Plasma exchange is the initial treatment of choice, but plasma infusion can be used until plasma exchange is available. Adjunctive treatment with glucocorticoids may be used in certain scenarios. If left untreated, the syndrome typically progressively worsens. Affected individuals experience irreversible renal failure, progressive neurological deterioration, cardiac ischemia, and death. With a prompt recognition of the disease and treatment initiation, patients have a better prognosis and mortality rate.

INTRODUCTION

Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome (TTP-HUS) is an acute illness with abnormalities in multiple organ systems. Patients typically present with thrombotic microangiopathy, thrombocytopenia, and microangiopathic hemolytic anemia without another apparent cause. Additional features include fever, neurologic, and renal abnormalities depending on the site of microangiopathic damage. Potential causes include congenital deficiencies, Shiga-Toxin producing bacteria, numerous drugs, factors related to malignancy, allogenic hematopoietic cell transplant, cardiovascular surgery, and pregnancy. A medical emergency, appropriate treatment needs to be initiated promptly or the disease can be fatal. Plasma exchange is the initial treatment of choice, but plasma infusion can be used until plasma exchange is available. Adjunctive treatment with glucocorticoids may be used in certain scenarios. If left untreated, the syndrome typically progressively worsens. Affected individuals experience irreversible renal failure, progressive neurological deterioration, cardiac ischemia, and death. With the prompt recognition of the disease and treatment initiation, patients have a better prognosis and mortality rate.[1]

CORRESPONDENCE:
Jodie Bachman DO, MBS | Jodie.Bachman@gmail.com

 Print ISSN: 1877-573X

CASE:

In August of 2013, a 62-year-old female presented to the hospital emergency department complaining of abdominal pain, nausea, vomiting, diarrhea, and generalized weakness after returning from a trip to the Dominican Republic. Four days after she returned to the United States, she began having non-bloody diarrhea that lasted for three days. The day after diarrhea stopped, she began vomiting up anything she ate or drank, appeared increasingly weak, and felt lightheaded/dizzy. Her vomiting was associated with subjective chills which resolved with each episode of emesis. She denied using any tap water while there and stated that they only used bottled water for drinking and cooking.

On physical examination in the emergency department, she was awake and alert, but appeared very weak and was non-verbal. Tenderness to palpation was noticed in the left lower quadrant of her abdomen. The remainder of her exam was within normal limits. Her labs were significant for a prothrombin time (PT) of 18.4, international normalized ratio (INR) 1.52, blood urea nitrogen (BUN) 20, Creatinine (CR) 2.0, Albumin 2.2, Calcium 6.2, white blood cell count (WBC) 13.53, Hemoglobin 8.4, Hematocrit 25.3, and a manual platelet count of 104. Cerebrospinal Fluid Cultures (CSF) were performed which showed clear colorless fluid with no growth on the gram stain. The CSF glucose was 107, and the CSF protein was 207.9. A CT of the abdomen and pelvis without contrast was ordered which showed colonic diverticula without definitive diverticulitis.

The patient was admitted to the general medical floor, and placed on Ciprofloxacin and Metronidazole for a diagnosis of Diverticulitis.

The following day, labs revealed an increased BUN at 32 and a Creatinine of 3. That evening she had a seizure and was moved to the ICU. Emergent labs drawn at that time showed a BUN of 41, Cr of 4.7, and lactate of 5.9. The following day she had three witnessed tonic-clinic seizures lasting approximately 2-3 minutes each followed by a post-ictal state. An electroencephalogram (EEG) showed a deep focal structural malfunction. Labs drawn the same day showed her BUN/Cr had increased to 44 and 5.7 respectively, and Hemodialysis treatments were started. A hematology consult was placed on hospital day four. After reviewing the patient's medical record and hospital course up to that point, a workup for TTP-HUS was done.

An ADAMTS-13 level was ordered, and found to be abnormal at 63. A blood smear was done and reviewed showing red cell fragments indicating microangiopathic hemolytic anemia and thrombocytopenia. With all these clinical and laboratory findings the diagnosis of TTP-HUS was made. The patient was emergently transferred to a neighboring institution with the ability to perform plasma exchange. Due to the prompt recognition of this patients symptoms, she was able to receive plasma exchange to treat her illness and save her life. While she was left with residual evidence of chronic renal failure, the remainder of her symptoms completely resolved.

TABLE 1:

Laboratory values seen in our patient versus the standard values

LAB TEST	ILLUSTRATIVE CASE PATIENT	NORMAL VALUE
White Blood Cell Count	13.53	5.2-12.4
Hemoglobin	8.4	12-16
Hematocrit	25.3	F 37-47 M 40-54
Blood Urea Nitrogen	20	10-25 mg/dl
Creatinine	2.0	F 0.5-1.1 mg/dl M 0.7-1.3 mg/dl
Albumin	2.2	3.2-4.8 g/L
Calcium	6.2	8.6-10 mL/dl
Prothrombin Time	18.4	9-11/7 sec
International Normalized Ratio	1.52	0.9-1.2
Manual Platelet Count	104	130-400,000

METHODS:

A Google scholar search was completed with the keywords Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome. A total of 7,230 articles were found. This was reduced by only including those articles published since 2010 that specifically covered the topic of TTP-HUS as a whole and not the individual syndromes. A final list of 13 articles were included.

Thrombotic Thrombocytopenic Purpura (- Hemolytic Uremic Syndrome is a multisystem disease defined by a pentad of thrombocytopenia, microangiopathic hemolytic anemia, neurologic defects, renal disease, and fever. Currently only thrombocytopenia and microangiopathic hemolytic anemia are the diagnostic criteria used to make the diagnosis when no other apparent alternate etiology is found. The majority of patients typically present with no identifiable precipitating factor for this illness. As a result, one should have this diagnosis at the top of their differential in the appropriate clinical context with patients presenting with microangiopathic hemolytic anemia and thrombocytopenia with no obvious explanation. It is best to begin treatment if suspicion is high for the illness to avoid a delay that could potentially be very harmful to the patient.[2]

CLINICAL PRESENTATION:

Thrombotic Thrombocytopenic Purpura is a clinical syndrome that can present to clinicians in a wide variety of settings. The particular case that I referenced presented in a hospital emergency room, but patients with this condition can show up in a primary care office as well if their symptoms are not severe. Thus, if a patient presents with any number of these clinical symptoms one should have this diagnosis in their differential.

TABLE 2:

Etiologies of TTP/HUS

INFECTION	**Hemorrhagic Colitis due to E.Coli O157:H7,O104:H4 Human Immunodeficiency Virus**
Immunosuppressant's	Cyclosporine
Autoimmune Disorders	Systemic Lupus Erythematosus
Chemotherapeutics	Mitomycin, Cisplatin, Gemcitabine
Malignancy	
Drugs	Ticlopidine, Clopidogrel, Gemcitabine 3
Pregnancy	Pregnancy and Postpartum Period
Idiopathic	

The clinical symptoms a patient presents with cover a wide range of body systems. Acute hemolytic anemia can lead to fatigue, dyspnea on exertion, skin pallor, and scleral icterus. Thrombocytopenia can lead to thrombocytopenia purpura, epistaxis, bruising, bleeding in the gastrointestinal tract, hematuria, petechiae, and mucosal bleeding depending on the severity. Microvascular ischemia may appear as neurologic, renal, cardiovascular, and gastrointestinal issues, as well as visual disturbances. These in particular are concerning for widespread platelet microaggregate formation, and thus require urgent evaluation and therapy initiation.[4]

From a laboratory standpoint, severe anemia and thrombocytopenia are characteristic of this illness. An elevated reticulocyte count and elevated indirect bilirubin in the absence of serum haptoglobin indicate ongoing intravascular hemolysis. Serum lactate dehydrogenase is often elevated indicating red blood cell destruction and ongoing tissue ischemia. One may also see fragmented red blood cells on peripheral blood smear. This disorder is however not a result of an issue with coagulation or thrombin activation thus the activated partial thromboplastin time (APTT), the thrombin time (PT), and the fibrinogen concentration will all be normal. [4]

From a laboratory standpoint, severe anemia and thrombocytopenia are characteristic of this illness. An elevated reticulocyte count and elevated indirect bilirubin in the absence of serum haptoglobin indicate ongoing intravascular hemolysis. Serum lactate dehydrogenase is often elevated indicating red blood cell destruction and ongoing tissue ischemia. One may also see fragmented red blood cells on peripheral blood smear. This disorder is however not a result of an issue with coagulation or thrombin activation thus the activated partial thromboplastin time (APTT), the thrombin time (PT), and the fibrinogen concentration will all be normal.[4]

TABLE 4:

Required diagnostic criteria for TTP/HUS[5]

THROMBOCYTOPENIA	PLATELET COUNT OFTEN LOWER THAN 20 X 10^9/L
Microangiopathic Hemolytic Anemia	Fragmented red blood cells on peripheral blood smear, Reticulocytosis, Decreased haptoglobins, Negative direct coombs test, Increased indirect bilirubin level
Fever	>37.5C
Neurologic Abnormalities	Transient Focal Abnormalities, Seizures, Stroke, Coma, Headaches, Mental Status Changes
Kidney Abnormalities	Renal Insufficiency – any serum creatinine value greater than or equal to 1.5 mg/dL Acute Renal Failure – increase in serum creatinine of greater than or equal to 0.5 mg/dL/d for 2 consecutive days or a serum creatinine greater than or equal to 4.0 mg/dL with dialysis

TABLE 3:

Presenting clinical characteristics of TTP/HUS[5]

CHARACTERISTICS	TYPICAL
Age	49 +/- 20
Sex	Female 68%
Ethnicity	African-Americans highest rate
Neurologic Symptoms	>50% - confusion, headache, paresis, aphasia, dysarthria, visual problems, seizure, stroke, coma
Fever	>37.5 Degrees C/99.5 degrees F
Hemoglobin	9.0 +/- 2.1
Platelet Count	Thrombocytopenia - 49,000 +/- 57,000 signs: epistaxis, bruising, petechiae, GI bleeding, hematuria, etc.
Serum Creatinine	Serum creatinine 3.2 +/- 2.6, proteinuria, microhematuria
Comorbid Conditions	Cancer, HIV, Organ Transplant, Sepsis, Hep C, etc.
Gastrointestinal Tract	Abdominal pain, nausea, vomiting, diarrhea
Cardiac	Chest pain, heart failure, hypotension
Jaundice	Typically resulting from microangiopathic hemolytic anemia
Other	Weakness, fever, cough, dyspnea

DIFFERENTIAL DIAGNOSIS:

There are several clinical conditions that can present very similar to TTP-HUS. These include disseminated malignancy, systemic vasculitis, sepsis, and eclampsia/preeclampsia. In acutely ill patients with symptoms of TTP-HUS such as fever, thrombocytopenia, and multiorgan dysfunction, sepsis with disseminated intravascular coagulation (DIC) must be ruled out. Those with preeclampsia or eclampsia along with seizures, thrombocytopenia, and microangiopathic hemolytic anemia typically have milder hematologic manifestations than those with TTP. One can check a plasma antithrombin III level for assistance in these cases as it will be reduced in those with TTP & normal in patients with pure preeclampsia/eclampsia. Autoimmune hemolytic anemia and immune thrombocytopenic purpura, collectively known as Evans Syndrome, can present like TTP-HUS. However, these patients will have a positive direct Coombs test, a lack of red blood cell fragmentation, and absence of other organ involvement.[4]

TREATMENT OPTIONS:

Considered a medical emergency, appropriate treatment needs to be initiated promptly or the disease can be fatal. Plasma exchange is the initial treatment of choice, but plasma infusion can be used temporarily until plasma exchange is available. Adjunctive treatment with glucocorticoids can be instituted in certain clinical scenarios as well.

This syndrome constitutes a medical emergency that can prove fatal if treatment is not initiated promptly Plasma exchange is the treatment of choice, as most patients with this form of the disease have decreased ADAMTS13 activity due to an inhibitory antibody. However, the level of ADAMTS13 activity is not required to make the diagnosis, and treatment should be initiated if the presenting clinical signs and symptoms suggest it.[6] The overall goal of treatment is the complete recovery of body function and return to the pre-illness quality of life. The initial primary goal once treatment has begun is the achievement of a normal platelet count. Plasma exchange removes the inhibitory antibody and supplies replacement ADAMTS13 from the donor plasma. Plasma exchange reverses the microvascular thrombus formation and subsequent symptoms characteristic of TTP-HUS. It should be initiated even if the diagnosis is a possibility but not confirmed. The dangers of rapid deterioration from the illness outweigh the risk of initiating plasma exchange. [7] If the diagnosis is eventually excluded, plasma exchange may be discontinued. There are a few exceptions to using plasma exchange. These include HUS in children, those who have had cancer chemotherapy or hematopoietic cell transplantation, and those with pneumococcal infection. [8]

Large volumes of plasma are needed for exchange treatment. Approximately 115 units per treatment course are required in a 60kg individual. Typical products that are used include Fresh Frozen Plasma, Cryoprecipitate-Poor Plasma, and Virally Inactivated Plasma. This procedure is initially performed daily until the patient's platelet count has normalized and hemolysis largely ceased. This is evident by a return of the serum lactate dehydrogenase concentration returning to normal or near-normal levels. Typically, 7-16 daily exchanges are required to endure remission, but this number has ranged from 3-145 treatments in some patients. Once plasma exchange has been instituted, a clinician must decide whether or not corticosteroids are appropriate for their patient. [9]

Those with a severe ADAMTS13 deficiency are the best candidates for this therapy as corticosteroids suppress the autoantibodies inhibiting ADAMTS13 activity. Individuals, where the cause of TTP-HUS is unclear, should also be treated with steroids. Steroids are contraindicated in those who are unlikely to have a severe ADAMTS13 deficiency (patients with severe renal failure), have a history and clinical features suggesting drug-associated TTP, or an *E. Coli* 0157:H7 infection. Clinical criteria are sufficient to use when deciding whether or not initiating steroids is appropriate for your patient.[10]

Once a normal platelet count has been achieved and maintained for 30 days after stopping plasma exchange therapy, the patient is considered to be in clinical remission.[2] Most often the neurologic symptoms and LDH improve in the first 1-3 days of treatment, followed by the platelet count several treatments later. Improvement in renal function is unpredictable, and many patients have a residual impairment and possibly persistent hypertension. In some cases, twice daily plasma exchange is used for patients with refractory or recurrent illness. After stopping plasma exchange, patients need to have complete blood counts and lactate dehydrogenase (LDH) levels monitored frequently. If levels remain stable, monitoring frequency can be decreased. Exacerbations of a continuing episode of illness occur within thirty days of stopping plasma exchange treatment.

Relapses typically occur within the first year but have been seen as late as ten years following discontinuation of treatment. At a minimum, relapse has been defined as a recurrence of the illness after at least 30 days of no treatment and no evidence of the disease. [11] With severe adamst13 deficiency risk of relapse is approximately

TABLE 5:

Key treatments for TTP/HUS

KEY TREATMENTS	
Plasma Exchange Therapy	Standard first course of treatment for all individuals diagnosed with the illness
Steroids	Indicated for use in those with ADAMTS13 deficiency & in cases of relapse
Rituximab	Indicated for those with an exacerbation (recurrent thrombocytopenia) & in cases of relapse

40%.[2] All patients should have a platelet count checked immediately when any acute symptoms occur as any could indicate recurrent illness. While relapse is the main concern, many patients are left with a significantly abnormal health-related quality of life. They may suffer from fatigue, neurocognitive issues, deficits of attention, decreased processing speed and memory problems. If left untreated, thrombocytopenia purpura-hemolytic uremic syndrome typically progressively worsens. Affected individuals experience irreversible renal failure, progressive neurological deterioration, cardiac ischemia, and death. With the prompt recognition of the disease and treatment initiation, patients have a much better prognosis and mortality rate. [8]

ANALYSIS/DISCUSSION

In reviewing some of the most recent literature on this illness, it appears increasingly rare for a patient to present with all the features of TTP-HUS. Fifty years ago, the majority of patients had the classic pentad (thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, renal abnormalities, and fever). Fast forward to 2009, and a review article published in Kidney International. This article made the following statement, "TTP is the diagnostic term used for adults, with or without neurologic or renal abnormalities...HUS is the term used for children who have renal failure..." [12] In 2012, a publication by the American Society of Hematology stated that, "patients may present with only microangiopathic hemolytic anemia and thrombocytopenia, neurologic and renal abnormalities are often not present, fever rarely occurs; the complete "pentad" of these clinical features almost never occurs in current practice." [4] While it has been noted that the morbidity and mortality rate of this disease has vastly improved since the introduction of plasma exchange therapy, it appears we have changed our perspective on how we name this illness based on the age of presentation. This shows just how rare our case is in medicine today.

Our patient initially presented with signs and symptoms of gastrointestinal illness and was given the presumptive diagnosis of diverticulitis. Over the next twenty-four hours, her renal function dramatically worsened, and she began having seizures. It was not until hematology was brought onto the case that TTP-HUS was considered as a diagnosis. Additional tests including a blood smear and ADAMTS-13 level were ordered and thus lead us to the diagnosis of this patient's ailment. Fifty years ago patients walked in the door like they stepped out of the pages of a hematology textbook with the complete pentad of symptoms making the diagnosis simple. Now in present-day medicine, this is a rare occurrence, and we as clinicians must be diligent to consider this in our differential diagnosis even if a patient only presents with one symptom from the textbook pentad.

SUMMARY/TAKE HOME MESSAGE:

Patients with TTP-HUS benefit from the prompt recognition of their condition, and quick transfer to a facility where plasma exchange can be completed. If left untreated, TTP-HUS typically progressively worsens. Affected individuals experience irreversible renal failure, progressive neurologic deterioration, cardiac ischemia, and death. Due to its rare occurrence, many clinicians do not recognize this syndrome until irreversible damage has been done. A workup for this is warranted in any case that displays these symptoms whether it is just one or all five. The patient's life was saved by the quick recognition of her clinical presentation by an experienced hematologist/oncologist. With the prompt recognition of the disease and treatment initiation, patients have a much better prognosis and mortality rate. This clinical manuscript will ideally help clinicians better recognize this syndrome, and provide patients with the prompt treatment they need. [13]

AUTHOR DISCLOSURES

No relevant financial affiliations.

REFERENCES

1. DeLoughery, Thomas G. "Thrombotic Microangiopathy (TTP/HUS)." Hemostasis and Thrombosis. Springer International Publishing, 2015. 57-62
2. George, James N. "The thrombotic thrombocytopenic purpura and hemolytic uremic syndromes: overview of pathogenesis (Experience of The Oklahoma TTP-HUS Registry, 1989–2007)." Kidney International 75 (2009): S8-S10.
3. George, James N, et al. "Drug-induced thrombotic microangiopathy: a systemic review of published reports." Blood 10.1182 (2015): 616-618
4. Elliott, Michelle A., and William L. Nichols. "Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome." Mayo Clinic Proceedings. Vol. 76. No. 11. Elsevier, 2001.
5. Shenkman, Boris, and Yulia Einav. "Thrombotic thrombocytopenic purpura and other thrombotic microangiopathic hemolytic anemias: Diagnosis and classification." Autoimmunity reviews 13.4 (2014): 584-586.
6. Sadler, J. Evan. "Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura." Blood 112.1 (2008): 11-18.
7. Korkmaz S, et al. Therapeutic plasma exchange in patients with thrombotic thrombocytopenic purpura: a retrospective multicenter study. Transfus Apher Sci. 2013;48(3):353–8.
8. Tsai, Han-Mou. "Advances in the pathogenesis, diagnosis, and treatment of thrombotic thrombocytopenic purpura." Journal of the American Society of Nephrology 14.4 (2003): 1072-1081.
9. Scully, Marie, et al. "Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies."British journal of haematology 158.3 (2012): 323-335.
10. George, James N., and Zayd L. Al-Nouri. "Diagnostic and therapeutic challenges in the thrombotic thrombocytopenic purpura and hemolytic uremic syndromes." ASH education program book 2012.1 (2012): 604-609.
11. Bittencourt, Cassiana E, et al. "Re-Examination of 30-day survival and relapse rates in patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome." PLOS 10.1371 (2015)
12. George, James N. "How I treat patients with thrombotic thrombocytopenic purpura: 2010." Blood 116.20 (2010): 4060-4069.
13. Levandovsky, Mark, et al. "Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS): a 24-year clinical experience with 178 patients." J Hematol Oncol 1.1 (2008): 23.

CLINICAL IMAGES

Dermatologic & Ocular Findings in a 27-Year-Old Male

Michael Moriarty, DO & Craig Bober, DO

Mainline Health - Wynnewood, PA

A 27-year-old African American male presented to the office with a two-month history of intermittent chills without a fever. During this time, he experienced an unintentional weight loss of ten pounds. The symptoms progressed with the development of a painful rash of his bilateral knees. The rash was described as multiple, enlarging, red, painful, warm patches with a dry, flaky, non-pruritic outer edge. Beginning on the dorsum of his right foot, the rash spread to his bilateral shins and knees. After no resolution of the rash within two weeks, the patient sought medical attention.

Recent travel, household pets, sick contacts, sexual activity, occupational exposure, illicit drug use and over the counter or prescription medication usage was denied. He was currently employed as a postal worker. Review of systems was positive for bilateral knee pain, intermittent loose brown stools without diarrhea, fatigue, mild dyspnea on exertion and occasional nausea. One episode of non-bloody, non-bilious vomiting five days before his office visit was noted. Abdominal pain, melena, hematochezia, back pain, fever, cough, wheezing, rhinorrhea, pharyngitis, sinusitis, vision changes, eye pain, photophobia, headache, paresthesias, muscle weakness, oral or genital ulcers, or urethral discharge were all denied.

Physical examination revealed a thin, pale, non-toxic appearing male with normal vital signs. Unbeknownst to the patient, the right eye demonstrated a segmental bright red injection lateral to the cornea. (Figure 1). The conjunctiva was pale bilaterally. Over the patient's bilateral shins and knees were multiple light red, poorly circumscribed annular patches and nodules ranging in size from three to five mm in diameter. (Figure 2, Figure 3). The lesions were non-blanchable, exquisitely tender to palpation, and warm. There was associated +1 pitting edema of the bilateral lower extremities. Residual scaling was noted along the lower aspect of the shins where the initial lesions were resolving.

Initial laboratory study results revealed a significantly elevated C-reactive protein (CRP) of 115.20 mg/L (normal < 7.48mg/L) and erythrocyte sedimentation rate (ESR) of 120 mm/hr (normal 0 -20 mm/hr). Complete blood count results demonstrated a depressed hemoglobin of 7.3 g/dL (normal 13.7 – 17.5 g/dL) and mildly elevated white blood cell count of 13.1 K/uL (normal 3.8 – 10.5 K/uL). Remaining lab tests, including human immunodeficiency virus, antinuclear antibody, rheumatoid factor, rapid plasma regain, herpes simplex virus, and Lyme testing was negative. A chest x-ray was obtained and reported as normal. A digital rectal exam revealed brown stool positive for occult blood on stool guaiac testing.

QUESTIONS

1. What diagnosis are the skin findings most consistent with?

   A) Erythema Induratum

   B) Erythema Multiforme

   C) Erythema Nodosum

   D) Necrobiosis Lipoidica

2. What is the underlying diagnosis?

   A) Coccidiomycosis

   B) Sarcoidosis

   C) Sweet's Syndrome

   D) Ulcerative Colitis

[Answers and discussion can be found on page 28]

CORRESPONDENCE:
Michael Moriarty, DO | moriartym@mlhs.org

FIGURE 1:

Right eye

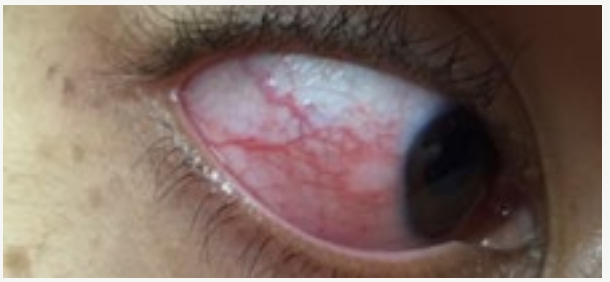


FIGURE 2:

Left leg

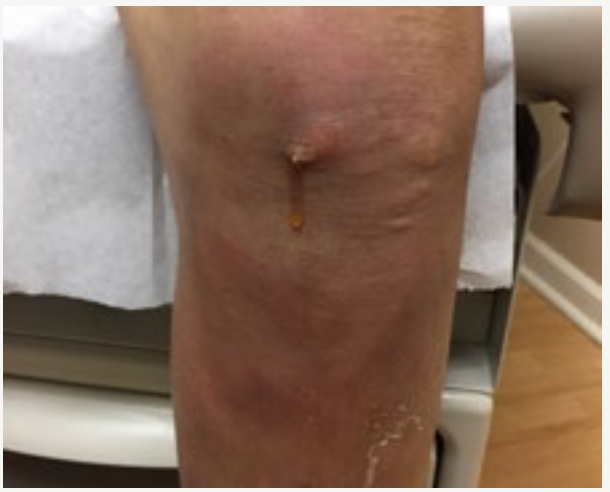
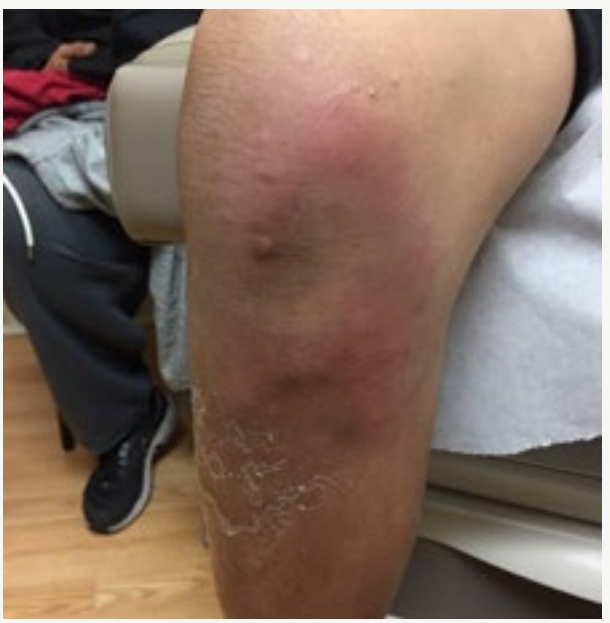


FIGURE 3:

Right leg



ANSWERS

1. What diagnosis are the skin findings most consistent with?

Correct answer: C) Erythema Nodosum

The skin findings discussed in the case study are consistent with Erythema nodosum. Erythema nodosum (EN) is a nodular erythematous eruption typically found on the extensor surfaces of the extremities. Erythema nodosum is associated with several diseases including autoimmune, infection and malignancy. Additionally, EN may develop from medications, particularly with sulfonamides and oral contraceptives.[1,2] Approximately 55 percent of cases of EN are idiopathic.[1,3]

Erythema induratum (EI) is characterized by tender, erythematous nodules of the posterior lower legs. Lesions are typically less than two cm in diameter and can present both unilaterally or bilaterally.[1] Erythema induratum more commonly affects women than men. Tuberculosis is the most common identifiable cause of EI.[1,4]

Erythema multiforme (EM) typically presents as round, erythematous papules that progress to classic target lesions characterized by an erythematous halo on the periphery and a dark red inflammatory zone and dusky central area. Lesions are typically symmetric on the extensor surfaces of the extremities and on the palms and soles. Erythema multiforme is commonly associated with a preceding acute respiratory infection, herpes simplex virus infection, or Mycoplasma pneumoniae infection.[1]

Necrobiosis lipoidica (NL) begins as oval, violaceous or red-brown nodules or plaques typically on the pretibial skin that expands slowly. The advancing border is red and the central area turns a characteristic waxy yellow-brown, often with ulceration and telangectasias.[1] Necrobiosis lipoidica is associated with diabetes mellitus. Studies have produced variable results to this linkage and anywhere from 11 to 75 percent of patients with NL either have or will develop diabetes mellitus.[1,5] Females are more commonly affected than males, and the most common presentations are in the third and forth decades of life.[1]

2. What is the underlying diagnosis?

Correct answer: D) Ulcerative Colitis

The underlying diagnosis is Ulcerative Colitis. Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) characterized by inflammation limited to the mucosal layer of the colon. Major symptoms of UC include diarrhea, rectal bleeding, tenesmus, the passage of mucous, and abdominal pain.[2,6] Approximately one-third of IBD patients have at least one extraintestinal manifestation.[2]

Coccidiomycosis (San Joaquin Valley fever) is caused by direct exposure to soil containing the dimorphic soil-dwelling fungi Coccidiodes. It is seen in the southwestern United States. Sixty percent of infected individuals can present as asymptomatic, and 40 percent may have a primary focal pneumonia with symptoms of fever, cough, pleuritic chest pain, night sweats or profound fatigue.[2] The infection is followed by the development of EN in ten percent of females and four percent of males.[1] Mediastinal or hilar lymphadenopathy and unilateral infiltrate are commonly seen on chest x-ray. Serology and sputum cultures can help confirm the diagnosis.[1,2]

Sarcoidosis is an inflammatory disease characterized by the presence of noncaseating granulomas that can affect many organs and present with a wide range of symptoms. The lung is involved in greater than 90 percent of sarcoidosis patients with respiratory symptoms such as a cough and dyspnea being the most common. Chest x-ray findings include hilar adenopathy, infiltrate or fibrosis. Ocular, cutaneous, and constitutional symptoms are also common.[2] Erythema nodosum has been observed in up to 39 percent of sarcoidosis cases.[1]

Sweet's syndrome is a neutrophilic dermatosis characterized by abrupt onset of tender, erythematous red to red-brown plaques or nodules. The plaques and nodules have an annular or arciform pattern and primarily present on the head, neck and upper extremities (particularly the back of the hands and fingers).[1] Patients may also have fever, neutrophilia and a predominantly neutrophilic infiltration in the dermis of lesions.[2] As many as 86 percent of cases are idiopathic, occurring in women with a preceding respiratory tract infection.[1] Ten to twenty percent of cases are associated with a malignancy, predominately hematologic, especially acute myelogenous leukemia. Sweet's syndrome has also been found in systemic lupus, IBD, as a medication side effect (all-trans-retinoic acid, granulocyte colony stimulating factor) and solid tumors (especially the genitourinary tract).[1,2]

DISCUSSION

Erythema nodosum is a panniculitis that affects the subcutaneous fat in the skin.[1] The peak incidence is between the ages of 18 to 34 years with a female to male ratio of five to one.[1,7] It presents as painful, bilateral, subcutaneous nodules about two to six cm in size with poorly defined borders most commonly on the anterior lower extremities.[1] The extensor surfaces of the forearm, trunk, and thighs may be involved. Individual lesions typically last for two weeks, do not ulcerate and may be associated with swollen ankles. Prodromal symptoms of malaise, fatigue or symptoms of an upper respiratory infection may precede the skin eruption by one to three weeks.[1,7] Arthralgias occur in approximately 50 percent of patients and consist of erythema, swelling, tenderness over the joints and occasionally effusions.[1] Erythema nodosum commonly involves the knee, but any joint can be affected.[1,7] Rheumatoid factor typically tests negative with this disease process.[1]

Erythema nodosum represents a hypersensitivity reaction to a variety of antigenic stimuli.[1] It is idiopathic in up to 55 percent of cases. However, there are many possible causes. Erythema nodosum can be caused by infections by Streptococci, tuberculosis, Yersinia, and Coccidiomycosis, drugs such as sulfonamides, bromides, and oral contraceptives, systemic illnesses including sarcoidosis, IBD, and Hodgkin's disease and pregnancy.[1,2,7] The most common identifiable cause is streptococcal pharyngitis, responsible for approximately 28 to 48 percent of cases, followed by sarcoidosis, which causes 11 to 25 percent of cases.[3,7] The initial evaluation should include a throat culture, antistreptolysin titer, chest x-ray, purified protein derivative skin test, and erythrocyte sedimentation rate. Skin biopsy is not required in patients with typical presentations and the diagnosis can be made on clinical grounds alone. Patients with gastrointestinal symptoms should have a stool culture for Yersinia, Salmonella, and Campylobacter and stool guaiac test.[1,7]

Erythema nodosum is self-limited, typically resolving within a few weeks without intervention. Quality evidence for treatment is lacking and most cases require only symptomatic relief with NSAIDs.[1,7] A typical regimen is 250 to 500 mg of naproxen twice per day as needed for pain.[7] Supportive measures include leg elevation, rest, and compression stockings or bandages help reduce edema and pain.[1,7] Any associated causes or underlying conditions should be treated if found.[1,7] Potassium iodide has been found to be an effective therapy in small, uncontrolled studies.[1,7] A supersaturated solution of potassium iodide drops (SSKI) at a dose of 300 to 900 mg per day orally for one month has been found to be effective.[1,7] A typical dose for adults with EN is 300 mg (six drops of SSKI 47 mg/drop) three times daily.[1,7] Iodine drops can be mixed in juice or water to dilute the bitter taste. Oral corticosteroids are effective but seldom necessary and underlying infection or malignancy should be excluded before their use.[1,7]

DIAGNOSIS

Ulcerative colitis is a type of IBD characterized by inflammation limited to the mucosal layer of the colon. Its incidence in North America is 2.2 to 19.2:100,000 and affects males and females equally. Age of onset is bimodal at 15 to 30 and 60 to 80.2 Patients can present with diarrhea, abdominal pain, hematochezia, tenesmus, fever, fatigue and weight loss. Extraintestinal manifestations include dermatologic (EN, pyoderma gangrenosum, psoriasis), rheumatologic (arthritis, ankylosing spondylitis), ocular (uveitis, episcleritis), hepatobiliary (hepatitic steatosis, primary sclerosing cholangitis), bone (osteoporosis) and thromboembolic disorders.[2,8]

Active disease is associated with elevated CRP, ESR, and platelet levels and a decreased hemoglobin. Fecal lactoferrin is a highly sensitive and specific marker for intestinal inflammation. Single contrast barium enema may show ulceration of mucosa and loss of haustration. CT scanning is not as helpful as endoscopy or barium enema. Diagnosis is confirmed by endoscopic biopsy. Findings range from erythematous mucosa with a granular surface in mild disease to edematous and ulcerated mucosa with pseudopolyps in severe or long-standing disease. Ulcerative colitis almost always involves the rectum and extends proximally to involve all or part of the colon. Forty to fifty percent of patients have disease limited to the rectum and rectosigmoid, 30 to 40 percent have disease extending beyond the sigmoid but excluding the whole colon and 20 percent have total colitis.[2]

First line treatment is with sulfasalazine or other 5-amino salicylic acids.[2,6] Oral corticosteroids and infliximab may be added to help achieve remission.[2,6] For patients needing hospitalization, intravenous corticosteroids, cyclosporine, or infliximab can be tried.[2,6] Once remission is achieved, the same agent is usually used as maintenance.[2,6] Azathioprine is an additional maintenance medication for those who required corticosteroids or cyclosporine for remission.[2,6] Complications of UC include hemorrhage, toxic megacolon, perforation, strictures, and colon cancer.[2] Patients with UC should have a screening colonoscopy eight to ten years after initial diagnosis.[6]

CASE CONCLUSION

Despite his limited abdominal complaints, this patient had multiple findings on presentation that were consistent with UC including weight loss, arthralgias, elevated inflammatory markers, anemia, blood in his stool and extraintestinal manifestations of EN and episcleritis. Erythema nodosum occurs in ten percent of UC patients.[2,8] Episcleritis occurs in three to four percent of IBD patients and is more commonly seen in Crohn's disease.[2,8] The patient was admitted to the hospital for treatment of his anemia and further evaluation. After receiving appropriate blood products, the patient underwent colonoscopy revealing inflammation of the mucosa from the rectum to the distal transverse colon characterized by edema, erythema, friability, granularity, pseudopolyps and ulcerations in a continuous and circumferential pattern consistent with UC. Biopsies confirmed active colitis.

After the diagnosis of UC was established, the patient was started on intravenous steroids and discharged on a biologic agent for long-term suppression. His skin lesions became less tender and resolved over the next week. His episcleritis also resolved over the course of the next few weeks.

AUTHOR DISCLOSURES:
No relevant financial affiliations.

REFERENCES:

1. Habif, Thomas P. Clinical Dermatology: a Color Guide to Diagnosis and Therapy. St Louis, MO: Elsevier, 2016.
2. Mert A, Ozaras R, Tabak F, Pekmezci S, Demirkesen C, Ozturk R. Erythema nodosum: an experience of 10 years. Scand J Infect Dis. 2004;36:424-7.
3. Mascaro JM Jr, Baselga E. Erythema induratum of bazin. Dermatol Clin 2008; 26:439
4. Kasper, Dennis L., Anthony S. Fauci, Stephen L. Hauser, Dan L. Longo, J. Larry Jameson, Joseph Loscalzo, and Tinsley Randolph Harrison. Harrison's principles of internal medicine. New York: McGraw Hill Education, 2015.
5. O'Toole EA, Kennedy U, Nolan JJ, et al. Necrobiosis lipoidica: only a minority of patients have diabetes mellitus. Br J Dermatol. 1999; 140:283
6. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults. Am J Gastroenterol. 2010;105(3):501-523
7. Blake T, Manahan M, Rodins K. Erythema nodosum-a review of an uncommon paniculitis. Dermatol Online J. 2014; 20:22376
8. Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal disease in inflammatory bowel disease: a population-based study. AM J Gastroenterol. 2001;96:1116-22


acofpca
ACOFPCA
42Nd ANNUAL CONVENTION
& Medical SeMINAr AUGUST 2-5-2018
AT THE
DISNEYLAND HOTEL
BE A PART OF THE CME AND FUN
ACOFPCA
THE BEST CME IN THE WEST
Register Early by 7/20/18 and save! Online Registration at
www.acofpca.org
This program anticipates being approved for 32 hours of AOA Category 1-A CME credits. Application for
32 CME credits has been filed with the American Academy of Family Physicians. Determination of credit is pending.

An Atypical Fracture

Maricel Dela Cruz, DO, MPH, FAWM & Robert Danoff, DO, MS, FACOFP, FAAFP

Aria Jefferson Health, Department of Family Medicine, Langhorne, PA

An 81-year-old female with a past medical history of osteoporosis, hypertension, hypercholesterolemia, and gastroesophageal reflux disease presented to her family practice office in hospital follow-up of a right leg injury she sustained six weeks prior. She had a mechanical fall at home and was taken to the emergency department by ambulance, and underwent x-ray imaging (See Figure 1, 2). Her medications included daily carvedilol, lisinopril, ranitidine, and simvastatin, as well as an eight-year use of weekly oral alendronate. The patient suffered a right diaphyseal (mid-shaft) fracture of the femur and subsequently underwent orthopedic repair with open reduction and internal fixation. The patient was diagnosed with fragility fracture secondary to a history of osteoporosis and fall from standing. Upon discharge, she was kept on alendronate. The patient completed inpatient rehabilitation and later brought the following images to her primary care physician.

QUESTIONS

1. What is the mechanism of action of the medication that may have contributed to the patient's injury?

   A) Non-selective beta-adrenergic receptor blocker (B1, B2) and an alpha adrenergic receptor blocker (alpha-1)

   B) Inhibition of angiotensin-converting enzyme (ACT)

   C) Blocks the production of acid by acid-producing cells in the stomach.

   D) Competitive inhibition of HMG-CoA reductase, the first and key rate-limiting enzyme of the cholesterol biosyn thetic pathway.

   E) An intermediate in the mevalonate pathway prevents inhibition of osteoclast formation, bone resorption, and kinase activation in vitro.

2. What is NOT a common site for fragility fractures?

   A) Lumbar vertebral compression fracture

   B) Fracture of the neck of the femur

   C) Diaphyseal fracture of the femur

   D) Colles fracture of the wrist

   E) Thoracic vertebral compression fracture

FIGURE 1:

X-Ray image of pathologic fracture

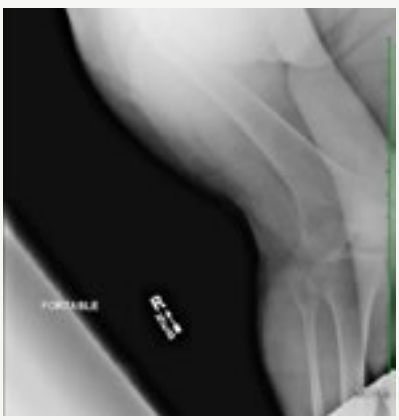
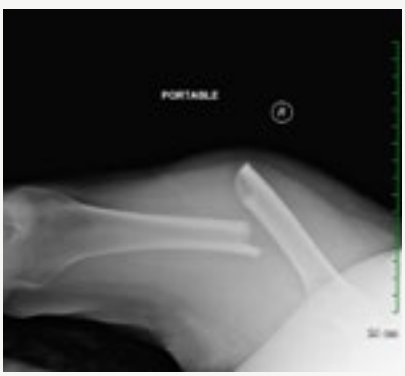


FIGURE 2:

X-Ray image of pathologic fracture



CORRESPONDENCE:
Maricel Dela Cruz, DO, MPH, FAWM | mdelacruz78@gmail.com

ANSWERS

1. What is the mechanism of action of the medication that may have contributed to the patient's injury?

   Correct answer: E) An intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation in vitro

   Oral bisphosphonates are a mainstay pharmacologic treatment for osteoporosis.[1,2] Bisphosphonates work by inhibiting osteoclast activity and reducing bone resorption and turnover.[3] These medications are primarily used for treating osteoporosis in post-menopausal women, and to help prevent hip and vertebral bone fractures.[4,5] Due to unwanted side effects of decreased bone resorption and unsatisfactory repair of the bony matrix, including osteonecrosis of the jaw and atypical fractures, recommendations have been made to limit oral bisphosphonate use to five or less years.[1]

2. What is NOT a common site for fragility fractures?

   Correct answer: C) Diaphyseal fracture of the femur

   Fragility fractures are a subtype of pathologic fractures that occur as a result of normal activity or falls from standing height or less.[6,7] The most common fracture sites of fragility fractures include vertebral compression fractures, fractures of the neck of the femur and Colles fractures of the wrist.[6,7] Pathologic fractures are typically caused by secondary etiologies that lead to weakness in bone structure, including osteoporosis, cancer, infection or bone cysts.[6,7] The remainder of femur fractures are pathologic and atypical, including subtrochanteric and diaphyseal.[8-11]

DISCUSSION

This case exhibits the paradoxical adverse effect of atypical femur fracture with long-term use of the bisphosphonate alendronate. Though rare, several cases have been documented in the literature displaying subtrochanteric and diaphyseal femur fractures with prolonged alendronate use.[12-15] This patient continued alendronate upon discharge from the hospital even after sustaining a fragility fracture. A diaphyseal (mid-shaft) fracture of the femur was documented and it was not until her primary care outpatient follow-up that the patient discontinued the bisphosphonate. Because of these concerns, it is important for family physicians to instruct patients taking oral bisphosphonates to discontinue use within five years as per the recommended guidelines in preventing associated atypical fractures.[1] Family physicians should also be cognizant of the difference between simple fragility fractures versus the wider spectrum of pathologic fractures. Family physicians should also stay up to date on the current United States Preventive Service Task Force screening recommendations regarding DEXA scans and dietary recommendations.[16]

AUTHOR DISCLOSURES:
No relevant financial affiliations.

REFERENCES

1. Jeremiah MP, Unwin BK, Greenwald MH. Diagnosis and management of osteoporosis. American Family Physician. August 2015. 92(4):261-8.
2. Pietri M, Lucarini S. The orthopaedic treatment of fragility fractures. Clinical Cases in Mineral and Bone Metabolism. August 2007. 4(2):108-16.
3. Vasikaran SD. Bisphosphonates: an overview with special reference to alendronate. Annals of Clinical Biochemistry. May 2001. 36:608-23. DOI: acb.sagepub.com/content/38/6/608.full.pdf.
4. Hochberg MC, Thompson DE, Black DM, et al. Effect of alendronate on the age-specific incidence of symptomatic osteoporotic fractures. Journal of Bone and Mineral Research. June 2005. 20(6):971-6. DOI: 10.1359/JBMR.050104.
5. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The New England Journal of Medicine. November 1995. 333:1437-44. DOI: 10.1056/NEJM19951103332201.
6. Shin AY, Gillingham BL. Fatigue fractures of the femoral neck in athletes. Journal of the American Academy of Orthopaedic Surgeons. November 1997. 5(6):293-302.
7. Whyte, MP. Atypical femur fractures, bisphosphonates, and adult hypophosphatemia. Journal of Bone and Mineral Research. June 2009. 24(6):1132-4. DOI: 10.1359/jbmr.081253.
8. Capeci CM, Tejwani NC. Bilateral low-energy simultaneous or sequential femoral fractures on long-term alendronate therapy. The Journal of Bone and Joint Surgery. November 2009. 91(11):2556-61. DOI: http://dx.doi.org/10.2106/JBJS.H.01774.
9. Chan SS, Rosenberg ZS, Chan K, et al. Subtrochanteric femoral fractures in patients receiving long-term alendronate therapy: imaging features. American Journal of Roentgenology. June 2010. 194(6):1581-6. DOI: 10.2214/AJR.09.3588.
10. Chapurlat RD, Palermo L, Ramsay P, et al. Risk of fracture among women who lose bone density during treatment with alendronate. The Fracture Intervention Trial. Osteoporosis International. July 2005. 16(7):842-8.
11. Kwek EB, Goh SK, Koh JS, et al. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? International Journal of the Care of the Injured. February 2008. 39(2):224-31. DOI: http://dx.doi.org/10/1016/j.injury.2007.08.036.
12. Cermak K, Shumelinsky F, Alexiou, J, et al. Case reports: subtrochanteric femoral stress fractures after prolonged alendronate therapy. Clinical Orthopaedics and Related Research. July 2010. 468(7):1991-6.
13. Jayaraman M, Harikumar KV, Verma A, et al. Alendronate therapy in polycystic fibrous dysplasia presenting with pathologic fracture. American Journal of Orthopedics. March 2011. 40(3):48-50.
14. Sayed-Noor AS, Sjoden GO. Case reports: two femoral insufficiency fractures after long-term alendronate therapy. Clinical Orthopaedics and Related Research. July 2009. 467(7):1921-6.
15. Schneider JP. Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. Geriatrics. 2006. 61(1):31-33.
16. Osteoporosis Screening. United States Preventive Services Task Force. January 2011. Accessed on December 17, 2017. https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/osteoporosis-screening.

2018 CALENDAR OF EVENTS

MARCH 7, 2018

DO Day on Capitol Hill
Washington, DC
www.osteopathic.org

MARCH 22 - 25, 2018

ACOFP Annual Convention & Scientific Seminars
Austin, Texas
www.acofp.org

APRIL 13, 2018

Texas ACOFP BLS/ACLS Renewal Course
Rockwall, Texas
www.txacofp.org

APRIL 26 - 28, 2018

Oklahoma Osteopathic Association Annual Convention
Tulsa, Oklahoma
www.okosteo.org

JUNE 8 - 10, 2018

Maine Osteopathic Association Annual Convention
Rockport, Maine
www.mainedo.org

JUNE 13 - 17, 2018

TOMA - Texas ACOFP Joint Annual Convention
San Antonio, Texas
www.txosteo.org

JULY 13 - 15, 2018

Direct Primary Care Summit
Indianapolis, Indiana
www.dpcsummit.org

JULY 16 - 22, 2018

AOA House of Delegates
Chicago, Illinois
www.osteopathic.org

JULY 25 - 29, 2018

Florida ACOFP Annual Convention
Orlando, Florida
www.fsacofp.org

AUGUST 2 - 5, 2018

acofpCA'42
California ACOFP Annual Scientific Medical Seminar
Anaheim, California
www.acofpca.org

AUGUST 2 - 5, 2018

Michigan ACOFP Summer Family Medicine Update
Mackinac Island, Michigan
www.maofpevents.org

AUGUST 3 - 5, 2018

POFPS Annual CME Symposium
Hershey, Pennsylvania
www.poma.org

AUGUST 10 - 12, 2018

North Carolina Society ACOFP Annual Meeting
Pinehurst, North Carolina
www.nc-acofp.org

AUGUST 24 - 26, 2018

ACOFP's Intensive Update & Board Review
Rosemont, Illinois
www.acofp.org

OCTOBER 5 - 9, 2018

OMED®17
AOA/ACOFP Osteopathic Medical Conference & Exposition
San Diego, California
www.acofp.org

CME Resource: Osteopathic Family Physician Offers 2 Hours of 1-B CME

ACOFP members who read Osteopathic Family Physician can receive two hours of Category 1-B continuing medical education credit for completing quizzes in the journal. Visit the eLearning Center at www.acofp.org to access the quizzes.

AN OUNCE OF PREVENTION

WHERE HEALTH IS PRIMARY.

Health is Primary

Patients with access to primary care are more likely to receive preventive services and timely care before their medical conditions become serious – and more costly to treat.

Family doctors work with their patients to keep them healthy. We want to ensure that all patients access regular preventive care.

Let's make health primary in America.
Learn more at **healthisprimary.org**.

Brought to you by
America's Family Physicians

#MakeHealthPrimary

TABLE OF CONTENTS >>

OFP PATIENT EDUCATION HANDOUT

acofp American College of Osteopathic Family Physicians

E-CIGARETTES: WHAT YOU NEED TO KNOW

Stephen K Stacey, DO

Amy J. Keenum, DO, PharmD, Editor • Ronald Januchowski, DO, FACOFP, Health Literacy Editor

E-cigarettes are devices that produce a nicotine-containing vapor that is inhaled. The vapor is designed to look like regular cigarette smoke, but does not produce an odor. For this reason it is sometimes called vaping. Many devices resemble cigarettes, pipes and cigars. They have been legal in the United States since 2006.

WHAT'S INSIDE AN E-CIGARETTE?

- E-cigarettes contain a tank filled with a nicotine-containing fluid.
- A heating element heats the fluid and turns it into a vapor.
- The user activates the device with a button that causes the device to make the aerosol.
- They contain a battery that is either disposable or rechargeable.

BENEFITS:

- E-cigarettes may help people who already smoke quit or cut down on the number of tobacco cigarettes they use.
- The safety of e-cigarettes has not been proven as e-cigarettes haven't existed long enough to study the long-term harms and benefits.

HARMS:

- E-cigarettes contain nicotine, which is a very addictive chemical. It is especially addictive in adolescents.
- Nicotine harms normal brain development from birth through the mid-twenties. Nicotine use during this period can cause permanent problems with attention, mood, learning and addiction.
- Even though nicotine may feel relaxing while it is smoked, it contributes to the body's overall stress level.
- E-cigarettes contain many other chemicals that are known to cause cancer and other permanent lung damage. Some of these chemicals include flavorings such as diacetyl, a chemical linked to bronchiolitis obliterans (also called "popcorn lung").
- The aerosol from e-cigarettes can also harm people who are around users.
- The liquid used for e-cigarettes can cause acute poisoning when it is swallowed or spilled on the skin. It has caused severe illness and even death in children who got into it by accident.
- E-cigarettes are not safe for pregnant women.

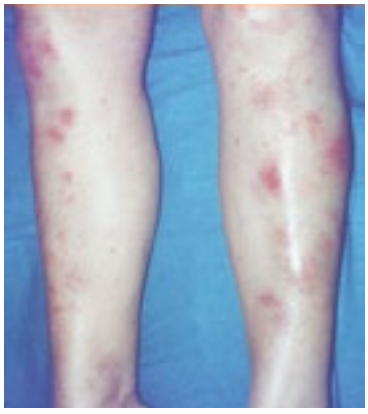
BOTTOM LINE:

- E-cigarettes are not safe for youth, young adults or pregnant women.
- They may help adult smokers quit using regular cigarettes, which are probably more harmful than e-cigarettes.
- You should speak with your physician if you have questions about the medical benefits or harms of e-cigarettes.

SOURCE(S):
The American Academy of Pediatrics,
Centers for Disease Control and Prevention
e-cigarettes.surgeongeneral.gov

ERYTHEMA NODOSUM

Kevin Panasiewicz, DO & Monica Gobrial, DO
Amy J. Keenum, DO, PharmD, Editor • Ronald Januchowski, DO, FACOFP, Health Literacy Editor



Erythema nodosum is a type of inflammation of the fat tissue beneath the skin. It is a skin reaction that can be present from many different causes, as noted below. Your physician can diagnose this condition with a complete history and physical examination, although a skin biopsy may be needed in cases that do not present normally. Erythema nodosum occurs more often in women than men.

SYMPTOMS

Erythema nodosum usually presents as red, warm, tender and immovable bumps that arise on the shins. There is no break in the skin present. They are normally on both sides of the body. They can also appear in other areas such as the arms, elbows, knees, thighs, calves and buttocks. The bumps can range from a half-inch to several inches in diameter. Sometimes, fevers, joint pain, fatigue, or upper respiratory/flu-like symptoms will happen before the bumps occur. The bumps can develop over several days and may be seen with redness or swelling at the involved sites. The redness often changes to a more bruise-like color such as purple, brown, or yellow as the bumps age.

CAUSES:

- Infections, such as *Strep* (most common) or tuberculosis
- Certain medications, such as birth control pills and sulfa drugs
- Inflammatory conditions, such as inflammatory bowel disease or sarcoidosis
- Blood cancers, such as lymphoma or leukemia
- It is possible for no cause to be found during or after a case of erythema nodosum
- Pregnancy

MEDICAL CARE & TREATMENT:

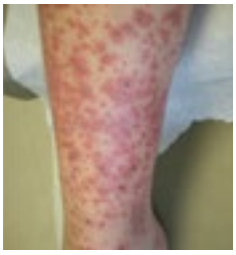
If you are concerned that you may have erythema nodosum, please call your osteopathic family physician. Given that erythema nodosum is often the present from an underlying cause, it is important for that cause to be identified and evaluated. Treatments will vary depending on the underlying cause. The bumps usually will go away over the course of several weeks without any treatment. Medicines like ibuprofen along with bed rest and leg elevation may be helpful for symptoms. Your skin may stay bruised or discolored for weeks to months, but there is usually no scarring.

SOURCE(S): ***Up to Date – Erythema Nodosum, American Osteopathic College of Dermatology – Erythema Nodosum, Medscape- Erythema Nodosum***

TABLE OF CONTENTS >>

THROMBOTIC THROMBOCYTOPENIC PURPURA: TREATMENT OPTIONS

Kathleen Naylor, DO, Tejumade Williams, DO & Larry Witmer, DO
Amy J. Keenum, DO, PharmD, Editor • Ronald Januchowski, DO, FACOFP, Health Literacy Editor



Thrombotic Thrombocytopenic Purpura (TTP) is a rare blood disorder that results in tiny blood clots affecting small blood vessels. This leads to low levels of platelets (blood clotting cells) in the blood and numerous small red-purple skin discolorations. TTP can affect any organ system but typically affects the brain and the kidneys. While the cause of this condition is unclear, we do know that patients with this condition have low levels of certain chemicals in the blood that slow or stop clots from forming. When these low levels are present, multiple clots can form in the body. Patients with TTP may complain of fatigue, seizures, strokes, confusion, decreased urine output, and may have an enlarged spleen. After taking a history and doing a physical, your physician would confirm the diagnosis of TTP with blood work.

STANDARD TREATMENTS:

- Plasma exchange, also known as plasmapheresis, is the treatment of choice. This involves separating the liquid part of blood and exchanging it with donor plasma. Your physician will know this treatment is working by watching for a decrease or reversal of symptoms, normal blood work, and normal kidney function. The most common side effect is a drop in your blood pressure. If you have very low calcium levels, you may not be able to get this treatment.
- Your physician may use steroids (like cortisone) in addition to plasma exchange. These medicines may be given either by mouth or through an IV depending on how severe symptoms are. Treatment is typically continued for 5-7 days after plasma exchange is stopped. The dose is then tapered and discontinued over a few weeks. Steroids have also been used in difficult cases.
- Rituximab is a special medication given through an IV once per week after plasma exchange to help speed up your body's response to therapy. It can reduce the risk of relapses by changing your immune system.
- Rarely, patients may require a platelet transfusion if they experience significant blood loss or undergo an invasive procedure or surgery.
- Your physician will continuously monitor and assess you for worsening or new symptoms, complications from treatment, or lack of response to treatment.

PREVENTIVE MEASURES:

There are no preventive measures that can be taken to prevent TTP; however, there are steps you can take before and during treatment. This includes staying well hydrated and drinking plenty of water, adequate sleep, healthy diet high in protein and low in sodium and potassium, avoid cigarette smoking, and make sure you are up to date with recommended vaccinations. It is also important that you keep all of your appointments and take all of your medications as prescribed.

SOURCE(S): ***Medscape and UpToDate.com***

American College of Osteopathic Family Physicians
330 East Algonquin Road, Suite 1
Arlington Heights, IL 60005

AUGUST 24 - 26, 2018

Loews Chicago O' Hare Hotel
Rosemont, Illinois

acofp
INTENSIVE UPDATE & BOARD REVIEW

INNOVATIVE • COMPREHENSIVE • HANDS-ON

The ACOFP Intensive Update & Board Review in Osteopathic Family Medicine is a 3-day intensive workshop for family physicians and residents who want to update their knowledge, as well as for those preparing for their board exams.

Learn more and register this spring at acofp.org