VOLUME 91 • NUMBER 8 • AUGUST 2024 • www.ccjm.org

CME MOC

Cleveland Clinic Journal of Medicine

Foxglove, not quite gone or forgotten

Persistent erosions of the glans penis and foreskin

What fluids should I order for my patient with acute pancreatitis?

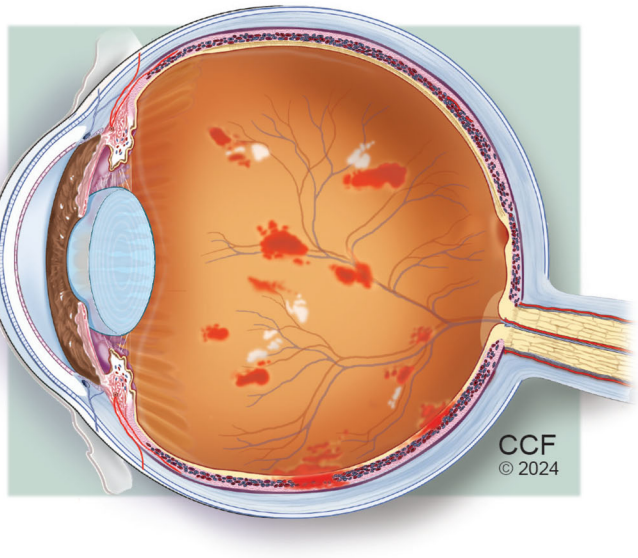
Recurrent syncope in a 62-year-old man

Helicobacter pylori: A concise review of the latest treatments against an old foe

Digoxin is still useful, but is still causing toxicity

Diabetic retinopathy: Screening, prevention, and treatment

COMPLETE TABLE OF CONTENTS ON PAGE 454



CLEVELAND CLINIC JOURNAL OF MEDICINE

EDITORIAL STAFF
Brian F. Mandell, MD, PhD, Editor in Chief
Craig Nielsen, MD, Deputy Editor
James C. Pile, MD, Deputy Editor
George Thomas, MD, MPH, Deputy Editor
Mary T. Cusick, MS, Executive Editor
Robert Litchkofski, MA, Managing Editor
Allison Siegel, MSSA, Senior Editor
Concetta M. Caporuscio, Senior Editor
Ross Papalardo, CMI, Medical Art Director
Martin Porter, Program Manager

PUBLISHING OPERATIONS
Peter G. Studer, Executive Publisher
Bruce M. Marich, Production Manager
Iris Trivilino, Production Manager, Special Projects
John Thorn, Assistant Finance Director (Billing)

ASSOCIATE EDITORS
Mohammad Alamer, MD
Alejandro C. Arroliga, MD
Moises Auron, MD
Daniel J. Brotman, MD
Adam J. Brown, MD
Abhijit Duggal, MD
Ruth M. Farrell, MD, MA
Brandon Francis, MD
Kathleen Franco, MD
Steven M. Gordon, MD
Brian Griffin, MD
Kristin Highland, MD
David L. Keller, MD
Mandy C. Leonard, PharmD
Angelo A. Licata, MD, PhD
Atul C. Mehta, MD
Christian Nasr, MD
Mariah Ondeck, MD
Robert M. Palmer, MD
Ian P. Persits, DO, MS
David D.K. Rolston, MD
Gregory Rutecki, MD
Bernard J. Silver, MD
Joseph Sipko, MD
Tyler Stevens, MD
Theodore Suh, MD, PhD, MHSc
Vikas Sunder, MD
Tom Kai Ming Wang, MBChB, MD
Marc Williams, MD
Michael Yim, MD

CCJM-UK EDITION
Narbeh Melikian, BSc, MD, Chief Editor
Heather Muirhead, MHA, Clinical Institute Education and Training Manager

EDITORS EMERITI
John D. Clough, MD
Herbert P. Wiedemann, MD
James S. Taylor, MD

CLEVELAND CLINIC
Tom Mihaljevic, MD
President and Chief Executive Officer

CLEVELAND CLINIC EDUCATION INSTITUTE
James K. Stoller, MD, MS, Chairman
Steven Kawczak, PhD, Senior Director, Professional Development and Knowledge Resources

ADVERTISING
Sima Sherman, Director of Sales and Marketing
SHERMAN MEDICAL MARKETING GROUP
1628 John F. Kennedy Blvd., #2200, Philadelphia, PA 19103
(610) 529-0322 • sima@shermanmmg.com

SUBSCRIPTIONS
U.S. and possessions: Personal $160; institutional $188; single copy/back issue $20

Foreign: $205; single copy/back issue $20

Institutional (multiple-reader rate) applies to libraries, schools, hospitals, and federal, commercial, and private institutions and organizations. Individual subscriptions must be in the names of, billed to, and paid by individuals.

Please make check payable to *Cleveland Clinic Journal of Medicine* and mail to: Cleveland Clinic Education Foundation, P.O. Box 373291, Cleveland, OH 44193-3291. To purchase a subscription with a credit card, please visit www.ccjm.org.

REPRINTS
(610) 529-0322 • sima@shermanmmg.com

PHOTOCOPYING
Authorization to photocopy items for internal or personal use is granted by *Cleveland Clinic Journal of Medicine* (ISSN 0891-1150 [print], ISSN 1939-2869 [online]), published by Cleveland Clinic, provided that the appropriate fee is paid directly to Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923 USA (978) 750-8400. Prior to photocopying items for educational classroom use, please contact Copyright Clearance Center, Inc., at the address above. For permission to reprint material, please fax your request with complete information to the Republication department at CCC, fax (978) 750-4470. For further information visit CCC online at www.copyright.com. To order bulk reprints, see above.

CHANGE OF ADDRESS
To report a change of address, send a recent mailing label along with new information to:

AMA, Data Verification Unit, 330 N. Wabash Ave., Suite 39300, Chicago, IL 60611-5885 • Phone (800) 621-8335 • Fax (312) 464-4880 • dpprodjira@ama-assn.org

Cleveland Clinic Journal of Medicine uses the AMA database of physician names and addresses. The database includes all US physicians and not just AMA members. Only the AMA can update changes of address and other data.

SUBSCRIPTIONS, EDITORIAL, BILLING, AND PRODUCTION
9500 Euclid Avenue, JJ44, Cleveland, OH 44195
• Phone (216) 444-2661 • ccjm@ccf.org • www.ccjm.org

DISCLAIMER
Statements and opinions expressed in the *Cleveland Clinic Journal of Medicine* are those of the authors and not necessarily of Cleveland Clinic or its Board of Trustees.

Cleveland Clinic Journal of Medicine [ISSN 0891-1150 (print), ISSN 1939-2869 (online)] is published monthly by Cleveland Clinic at 9500 Euclid Avenue, JJ44, Cleveland, OH 44195.

COPYRIGHT© 2024 THE CLEVELAND CLINIC FOUNDATION.
ALL RIGHTS RESERVED. PRINTED IN U.S.A.

PRINTED WITH SOY INK AMM Association of Medical Media Alliance for Audited Media

Table of Contents

CONTINUED ON PAGE 457

Upcoming Features

- Primary adrenal insufficiency in adults: When to suspect, how to diagnose and manage
- Should I refer my patients for renal denervation?

7th Annual

Advanced Management Issues in HIV Care

September 26-27, 2024

A focus on medical care for people living with Human Immunodeficiency Virus (HIV)

Who should attend: Infectious disease and internal medicine physicians, nurse practitioners, physician assistants, pharmacists, nurses, social workers, and other health care professionals who manage the care of people living with HIV.

Presented by:

CASE WESTERN RESERVE UNIVERSITY
Frances Payne Bolton School of Nursing

Cleveland Clinic

In collaboration with:

Case Western Reserve University School of Medicine
The Centers
VA Northeast Ohio Healthcare System
The MetroHealth System
The Midwest AIDS Training + Education Center
University Hospitals Cleveland Medical Center
Cleveland Clinic

This activity has been approved for *AMA PRA Category 1 Credit™.*

September 26, 2024▪ 5:30 p.m.-8:00 p.m.
Keynote Address Dinner

September 27, 2024▪ 7:30 a.m.-5:15p.m.
Full Day Educational Conference

Dinner & Conference Location:
Corporate College East
4400 Richmond Rd
Warrensville Hts, Ohio

Registration & More Information: 2024 HIV Conference

Questions? medcme@case.edu

Sponsored by:

CASE WESTERN RESERVE UNIVERSITY School of Medicine
MetroHealth
ANAC Association of Nurses in AIDS Care
mahec MIDWEST AIDS TRAINING + EDUCATION CENTER
AETC AIDS Education & Training Center Program Midwest

Cleveland Clinic

ABC
Association of Black Cardiologists, Inc.
Saving the Hearts and Minds of a Diverse America

Cardiovascular Update 2024 for Primary Care and General Cardiology

October 31-November 1, 2024

Hilton Cleveland Downtown | Cleveland, OH

Join us at Cardiovascular Update for Primary Care and General Cardiology

Cardiovascular disease (CVD) is the world's leading cause of death, underscoring the priority to develop and deliver education to improve care and outcome for individuals with CVD. Cardiovascular Update 2024 will incorporate the latest science, clinical evidence-base, a nd best-practices, to improve prevention, care delivery and outcomes for individuals at risk or with existing CVD. Attendees will receive essential educational content emphasizing cutting edge science, the implementation of evidence-based guidelines, and the promotion of health equity among diverse populations, ensuring improved cardiovascular outcomes for all patients.

Sessions

- Prevention and Management of CV Risk
- Special Populations
- Essentials of CVD
- Structural Heart Disease
- Heart Failure
- Heart Rhythm

Register Today!

www.ccfcme.org/cvupdate24

ABIM CME MOC ACCREDITED

Attend and Earn
ABIM MOC Points

CONTINUED FROM PAGE 454

CME CREDIT TEST

Visit WWW.CCJM.ORG
Test your knowledge
of clinical topics and earn
AMA PRA Category 1 Credit™
and *ABIM MOC points*

CLEVELAND CLINIC JOURNAL OF MEDICINE

Foxglove, not quite gone or forgotten

I have a true affection for the phenomenon of coincidence, so the timing of the submission of the Durán Crane et al[1] paper on the use and toxicity of digoxin in this issue of the *Journal* got my attention.

A somewhat fragile nonagenarian patient was struggling with her intermittently rapid atrial fibrillation. Although her baseline ejection fraction was normal, when her rate went up, she became dyspneic. She was intolerant to multiple medications prescribed for rate and rhythm control, including fatigue from beta-blockade, and at times she had low blood pressure with orthostatic symptoms (independent of her ventricular rate). There was an initial desire to avoid ablation, and in my discussion with her out-of-state cardiologist, I questioned whether there might be value in low-dose digoxin for symptom control. I think that he assumed I was calling from a rotary telephone. Ultimately, the patient developed an 8-second sinus pause, got a pacemaker and an ablation, and has done well on far fewer medications, not needing medications for rate control. But I nonetheless decided to explore the recent digoxin literature. I wanted to see where the drug that was popularized in 1785 by the English botanist and physician William Withering[2] and that had been a mainstay of cardiac treatment for many decades, including during my early medical career, had landed. That's when the paper by Durán Crane et al[1] was submitted—nice coincidence.

Granted that I now practice within a very specialized cardiovascular medicine community, but I couldn't recall the last patient I'd seen with digoxin on their list of medications. Nonetheless, it remains in clinical use. Digoxin has unique, if still not completely understood, pharmacodynamic effects. It has positive inotropic effects on cardiac myocytes, presumably due to increased intracellular calcium. It was initially used in treating "dropsy" (congestive heart failure), with subsequent documentation of its beneficial effect on ventricular function. It has vagomimetic effects that can slow the ventricular response in atrial fibrillation; these effects seem to require cardiac innervation, as they may not occur in transplanted hearts.[3] At higher serum levels, digoxin can increase myocyte automaticity and may increase the atrioventricular nodal refractory period. This combination accounts for some of the cardiac toxicity associated with its use, including the "classic" accelerated junctional tachycardia with conduction block. There is a narrow therapeutic window between efficacy and toxicity, with a lot of individual patient variability. Thus, it is not really surprising that use of the drug has waned dramatically over the past decades. Its use in treating patients with heart failure and atrial fibrillation has been supplanted by multiple medications, yet it still has a lower-tier place in the formal guidelines for the management of atrial fibrillation and heart failure.[1]

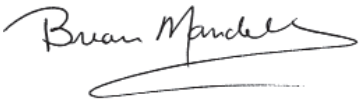
Back in the time of rotary telephones, when using digoxin for rate control in atrial fibrillation we dosed it by following the heart rate. We pushed it intravenously and expected a fairly rapid response over the course of hours as we fully "loaded" the patient. When treating patients with heart failure, we generally dosed digoxin paying attention to the patient's weight, kidney function, and concomitant medications. We were astute in asking about gastrointestinal symptoms and visual aberrations with chronic therapy, but there was little reliance on drug levels. And, as discussed in detail by Gona et al,[4] not routinely using drug levels to monitor for toxicity has likely been to patients' detriment and has appropriately contributed to the decreased use of digoxin. Do questions remain as to whether it still has a place at the therapeutic table?

doi:10.3949/ccjm.91b.08024

The use of digoxin for treatment of heart failure went out of fashion quickly after studies indicated a lack of effect on improving mortality and drugs with a marked positive effect on mortality became available. The landmark Digitalis Investigation Group study[5] in 1997 showed that patients with heart failure and reduced ejection fraction who received digoxin along with a diuretic and angiotensin-converting enzyme inhibitor had no reduction in overall mortality; *however*, digoxin reduced hospitalizations and death attributable to heart failure. Toxicity possibly attributable to digoxin was slightly increased in the digoxin-treated group compared with the placebo group. A number of studies have followed this, yielding mixed results, but with reduced digoxin toxicity when drug levels were monitored. As an indication that use of the drug for treating heart failure remains an open issue, a perusal of the clinical trial registration site ClinicalTrials.gov shows an active study on the effect of digoxin on heart failure.[6]

The value of digoxin in rate control in patients with "permanent" atrial fibrillation also remains an open question. Although rate control, as opposed to rhythm normalization, may not be the ideal approach for many with atrial fibrillation, digoxin for a select few may be a very reasonable option. Digoxin may not be as good as beta-blockade for rate management during exercise, but several studies have indicated that it may nonetheless improve patients' sense of exercise tolerance and well-being. This topic is nicely summarized in an editorial by Dorian and Angaran.[7]

So perhaps what Withering wrote about digoxin in 1776 is still correct: "It is certainly a very active medicine, and merits more attention than modern medicine bestows upon it."[7,8] We need to acknowledge its potential toxicity and utilize our clinical laboratory to minimize it. We are now fortunate to have a growing list of very effective treatment options for our patients with heart failure and atrial fibrillation, but digoxin may indeed still be a useful option for some patients.[1]



Brian F. Mandell, MD, PhD
Editor in Chief

1. **Durán Crane A, Militello M, Faulx MD.** Digoxin is still useful, but is still causing toxicity. Cleve Clin J Med 2024; 91(8):489–499. doi:10.3949/ccjm.91a.23105
2. **Withering W.** An Account of the Foxglove, and Some of its Medical Uses: with Practical Remarks on Dropsy, and Other Diseases. Birmingham: M. Swinney, 1785. Gutenberg.org/ebooks/24886. Accessed July 17, 2024.
3. **Joglar JA, Wan EY, Chung MK, et al.** Management of arrhythmias after heart transplant: current state and considerations for future research. Circ Arrhythm Electrophysiol 2021; 14(3):e007954. doi:10.1161/CIRCEP.120.007954
4. **Gona SR, Rosenberg J, Fyffe-Freil RC, Kozakiewicz JM, Money ME.** Review: failure of current digoxin monitoring for toxicity: new monitoring recommendations to maintain therapeutic levels for efficacy. Front Cardiovasc Med 2023; 10:1179892. doi:10.3389/fcvm.2023.1179892
5. **Digitalis Investigation Group.** The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997; 336(8):525–533. doi:10.1056/NEJM199702203360801
6. **US Department of Health and Human Services.** ClinicalTrials.gov. Digoxin evaluation in chronic heart failure: investigational study in outpatients in the Netherlands (DECISION). ID: NCT03783429. Updated December 12, 2023. https://clinicaltrials.gov/study/NCT03783429. Accessed July 17, 2024.
7. **Dorian P, Angaran P.** Beta-blockers and digoxin in atrial fibrillation: back to the future. Can J Cardiol 2023; 39(11):1594–1597. doi:10.1016/j.cjca.2023.07.013
8. **Aronson JK.** An Account of the Foxglove and Its Medical Uses 1785–1985. Oxford University Press; 1986.

CME MOC

2024

AUGUST

NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN
August 2–4
Washington, DC

STATE-OF-THE-ART TOPICS IN THE PREVENTION AND MANAGEMENT OF CARDIOVASCULAR DISEASE
August 2–4
Cleveland, OH

CLEVELAND BREAST CANCER SUMMIT: COLLABORATING FOR A CURE
August 9
Cleveland, OH

PEDIATRIC BOARD REVIEW
August 25–30
Cleveland, OH

SEPTEMBER

HOSPITAL MEDICINE 2024
September 5–6
Cleveland, OH, and Live stream

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: HEALTHCARE PROFESSIONALS COACH TRAINING
September 11
Live stream

GLOBAL EP 2024
September 20–21
Cleveland, OH

PRACTICAL MANAGEMENT OF STROKE
September 27
Independence, OH

SYMPOSIUM ON TRIGEMINAL NEURALGIA
September 27
Live stream

OCTOBER

OBESITY SUMMIT
October 6–8
Cleveland, OH, and Live stream

GENETICS EDUCATION SYMPOSIUM: MULTIDISCIPLINARY CARE IN CARDIOVASCULAR GENETICS
October 9
Cleveland, OH, and Live stream

CONTEMPORARY ISSUES IN PITUITARY DISEASE
October 17
Cleveland, OH

PREVENTION, DIAGNOSIS, AND MANAGEMENT OF CARDIOVASCULAR DISEASE: A CONTEMPORARY UPDATE
October 17–18
London, UK

INTENSIVE REVIEW OF ENDOCRINOLOGY AND METABOLISM
October 18–20
Cleveland, OH, and Live stream

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: HEALTHCARE PROFESSIONAL COACH TRAINING
October 23
Live stream

CARDIOVASCULAR UPDATE FOR PRIMARY CARE AND GENERAL CARDIOLOGY
October 31–November 1
Cleveland, OH

NOVEMBER

CLEVELAND CLINIC CANCER CONFERENCE: INNOVATIONS IN MULTIDISCIPLINARY CARE
November 1–3
Hollywood, FL

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: HEALTHCARE PROFESSIONALS COACH TRAINING
November 6
Live stream

ADVANCING CARDIOVASCULAR CARE
November 8
Columbus, OH

FUTURE OF STROKE CARE: STROKE AND CEREBROVASCULAR DISEASE CONFERENCE
November 9–10
Hollywood, FL, and
Hybrid (Encore)

DIMENSIONS IN CARDIAC CARE
November 10–12
Cleveland, OH

CALCIUM DAY
November 13
Cleveland, OH

PRIMARY CARE +: UPDATES IN PRIMARY CARE, WOMEN'S HEALTH, AND BEHAVIORAL MEDICINE
November 13–16
Beachwood, OH

COMPREHENSIVE NEUROTOXIN COURSE FOR NEUROLOGICAL CONDITIONS
November 16–17
Cleveland, OH

DECEMBER

CASE-BASED MANAGEMENT OF TRICUSPID AND MITRAL VALVE DISEASE
December 6–7
New York, NY

2025

JANUARY

PULMONARY HYPERTENSION SUMMIT
January 16–17
Hollywood, FL

BEST OF SAN ANTONIO BREAST CANCER SYMPOSIUM
January 18
Hollywood, FL

FEBRUARY

INTERNATIONAL COLORECTAL DISEASE SYMPOSIUM
February 13–15
Fort Lauderdale, FL

APRIL

UPDATES IN PRIMARY IMMUNODEFICIENCY
April 4–5
Cleveland, OH, and Live stream

MAY

BIOLOGIC THERAPIES SUMMIT AND VASCULITIS 2025
May 8–10
Cleveland, OH

JUNE

INTENSIVE REVIEW OF INTERNAL MEDICINE
June 9–13
Live stream

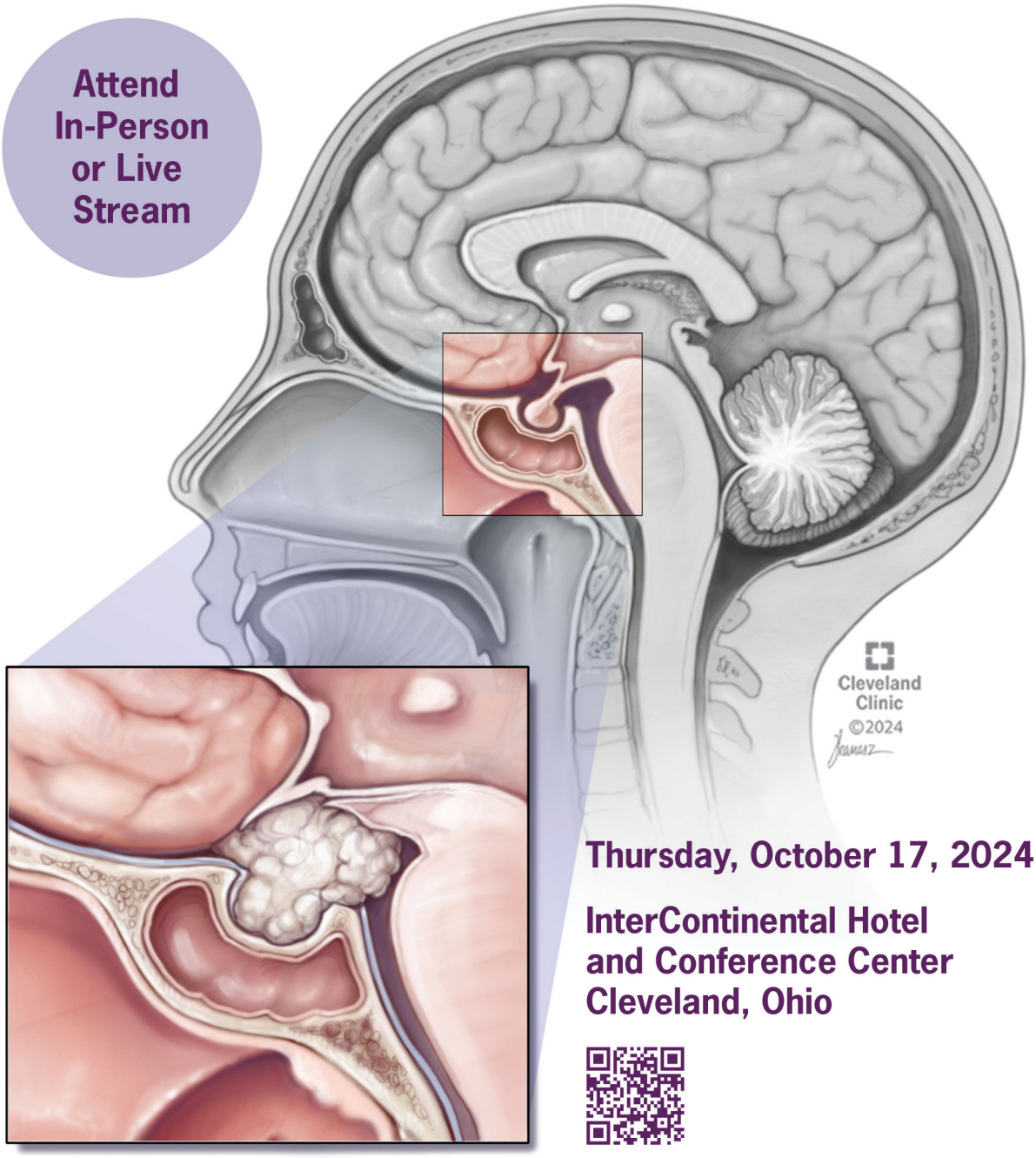
FOR SCHEDULE UPDATES AND TO REGISTER, VISIT: WWW.CCFCME.ORG/LIVE

Cleveland Clinic

15th Annual

Contemporary Issues in Pituitary Disease

Attend In-Person or Live Stream



Thursday, October 17, 2024

InterContinental Hotel and Conference Center Cleveland, Ohio

This activity has been approved for *AMA PRA Category 1 Credits,™*
ANCC Contact Hours, AAPA Category 1 CME Credits

Cleveland Clinic

Addressing the Impact of **RSV and Vaccine Hesitancy**

An Educational Resource for Providers

- Master the Latest in Adult & Pediatric RSV Prevention: Vaccines & Monoclonal Antibodies
- Discover RSV Prevention Solutions for Pregnant Women & Immunocompromised Patients
- Optimize RSV Immunization & Vaccination: From Storage to Administration
- Build Trust & Confidence: Addressing Vaccine Concerns in RSV Prevention

Free CME! Participate Today!
www.ccfcme.org/RSV

This activity has been approved for *AMA PRA Category 1 Credits*™, ANCC Contact Hours, AAPA Category 1 CME Credits, Continuing Pharmacy Education (CPE) Credits

Zheng Gu, MD
Beijing University of Chinese Medicine, Beijing, China; Department of Dermatology, China-Japan Friendship Hospital, Beijing, China

Dong-Lai Ma, MD, PhD
Department of Dermatology, Peking Union Medical College Hospital, Beijing, China; State Key Laboratory of Complex, Severe, and Rare Diseases, Beijing, China; Clinical Professor, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; National Clinical Research Center for Dermatologic and Immunologic Diseases, Beijing, China

Persistent erosions of the glans penis and foreskin

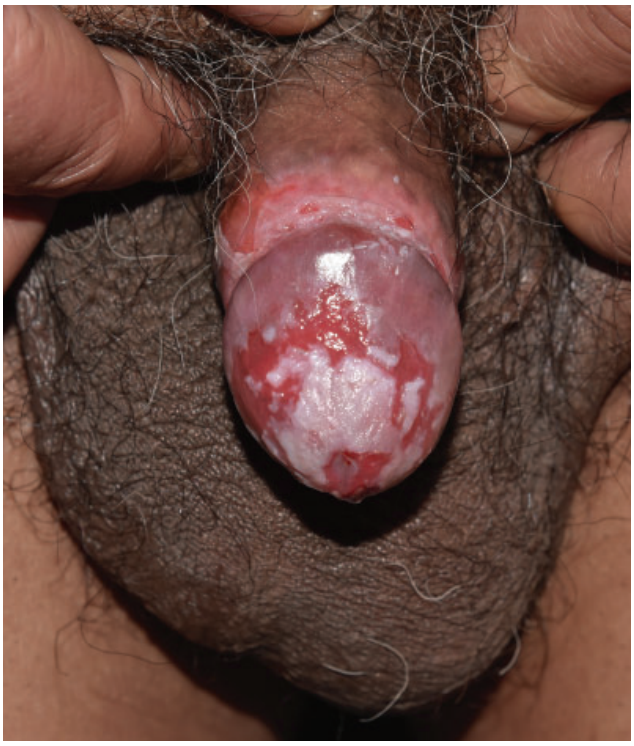


Figure 1. Erythema and superficial erosions on the glans penis and foreskin before treatment.

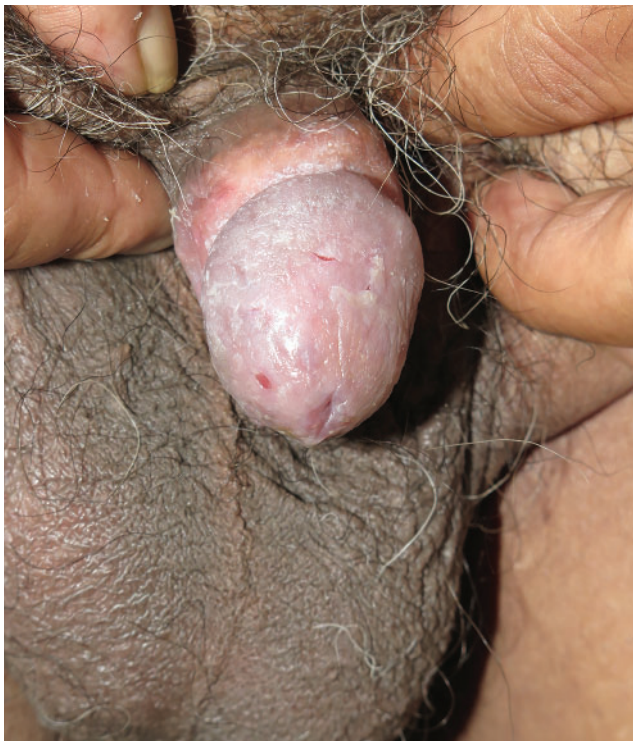


Figure 2. The erosions improved significantly after treatment.

A 66-year-old man presented with an 8-month history of persistent erosions of the glans penis and foreskin with slight itching and pain. Physical examination revealed erythema and superficial erosions on the glans penis and foreskin (**Figure 1**). Similar lesions were not found on the skin or oral mucosa elsewhere. Tests for syphilis were negative.

Biopsy taken from the foreskin showed suprabasal bullae with acantholysis. Direct immunofluorescence was negative for deposition of immunoglobulin (Ig) G, IgA, and IgM and complement C3 in the epidermal cells and basement membrane bands. However, indirect immunofluorescence tests showed that antispinous intercellular desmoglein antibodies were deposited in the interspinous cell reticulum (using monkey esophagus as a deposition substrate) at a titer of 1:320. No antibasement membrane zone antibodies (important autoantibodies in the diagnosis of bullous pemphigoid) were found.

doi:10.3949/ccjm.91a.23085

The patient was diagnosed with localized pemphigus vulgaris. The erosions improved significantly after 2 months of treatment with oral prednisolone at an initial dose of 30 mg daily (**Figure 2**).

PEMPHIGUS

Pemphigus encompasses a group of rare autoimmune disorders characterized by the development of flaccid blisters and erosions on the skin and mucous membranes.[1] These blisters are fragile and can easily rupture, leading to open sores and erosions. The majority of patients present with pemphigus vulgaris.[2] Pemphigus vulgaris can affect the skin or mucous membranes throughout the body, including the chest, back, head, and, in severe cases, the whole body, but oral involvement often occurs first. Lesions may localize to a single body site such as the nose, cheeks, or penis, which can easily lead to misdiagnosis.

Other subtypes of pemphigus include pemphigus foliaceus and rare pemphigus variants like paraneoplastic pemphigus and IgA pemphigus. Pemphigus foliaceus manifests with skin lesions, usually without mucosal involvement.[1] Patients with paraneoplastic pemphigus have known or potential tumors, usually of lymphoid tissue. Pain and severe oral and conjunctival erosions are the main features. The staining patterns on direct and indirect immunofluorescence differ in paraneoplastic pemphigus and classical pemphigus and can be used to distinguish between them.[2]

The differential diagnosis

Pemphigus should be distinguished from bullous pemphigoid, severe erythema multiforme, and drug-induced bullosa epidermolysis. Persistent erosions on the glans and foreskin of the penis are often encountered and have a wide differential, including syphilis, herpes simplex virus infection, candida balanitis, lichen planus, psoriasis, other autoimmune diseases, trauma, and skin cancer.[3] Pemphigus vulgaris can be differentiated from these diseases through histopathology, immunofluorescence, and autoimmune serum titers.[2,4]

Diagnosis and treatment

Diagnosis is based on clinical presentation, histopathology showing intraepidermal acantholysis, and either positive findings on direct immunofluorescence (ie, IgG or complement C3 deposits at the surface of keratinocytes) or detection of serum autoantibodies against epithelial cell surface.[4,5] Samples for biopsy should be taken from normal-appearing skin immediately adjacent to a lesion; sampling inflamed or blistered skin may lead to false-negative results on direct immunofluorescence[5] because the inflammatory process associated with pemphigus can damage immune deposits.[1]

First-line treatments are corticosteroids and anti-CD20 monoclonal antibodies.[4] In patients with moderate to severe disease, combination therapy may be used to improve efficacy and reduce the dose of glucocorticoids at the start of treatment or when the effect of glucocorticoids alone is not significant. First-line immunosuppressants are azathioprine and mycophenolate mofetil.

The initial dose of glucocorticoids depends on the type and severity of disease. The absence of new blisters indicates that the dose is adequate. Conversely, the dosage should be increased or other immunosuppressive agents added if new blisters appear. Once disease control is observed, the dosage should be reduced slowly and gradually to prevent recurrence. Withdrawal of systemic corticosteroids may be proposed in patients in complete remission on minimal therapy.[2]

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

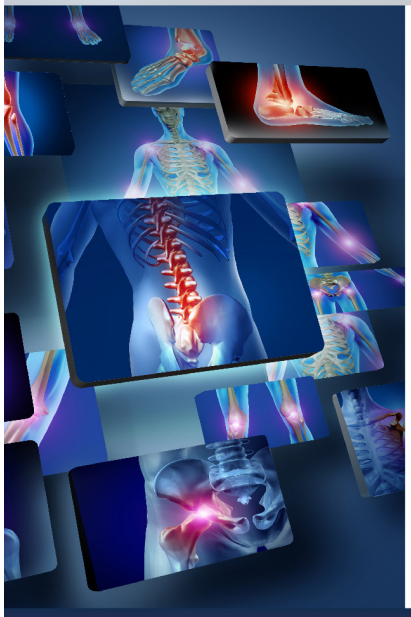
REFERENCES

1. **Malik AM, Tupchong S, Huang S, Are A, Hsu S, Motaparthi K.** An updated review of pemphigus diseases. Medicina (Kaunas) 2021; 57(10):1080. doi:10.3390/medicina57101080
2. **Schmidt E, Kasperkiewicz M, Joly P.** Pemphigus. Lancet 2019; 394(10201):882–894. doi:10.1016/S0140-6736(19)31778-7
3. **Su O, Dizman D, Ozkaya DB, Yildiz P, Demirkesen C, Onsun N.** Pemphigus vulgaris localised exclusively to the penis. Indian J Dermatol Venereol Leprol 2015; 81(3):298–299. doi:10.4103/0378-6323.154794
4. **Murrell DF, Peña S, Joly P, et al.** Diagnosis and management of pemphigus: recommendations of an international panel of experts. J Am Acad Dermatol 2020; 82(3):575–585.e1. doi:10.1016/j.jaad.2018.02.021
5. **Giurdanella F, Diercks GF, Jonkman MF, Pas HH.** Laboratory diagnosis of pemphigus: direct immunofluorescence remains the gold standard. Br J Dermatol 2016; 175(1):185–186. doi:10.1111/bjd.14408

Address: *Dong-Lai Ma, MD, PhD, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100730, China; mdonglai@sohu.com*

Cleveland Clinic
Florida

Save the Date!



3rd Advanced Practice Provider Conference

Clinical Updates for PA, APRN, AA and CRNA Practitioners

David G. Jagelman MD Conference Center
Cleveland Clinic Florida, Weston, Florida

October 19-20, 2024

www.ccfcme.org/APP2024

Cleveland Clinic

CREDITS
CME, MOC, AAPA, ANCC and CPE

Cleveland Clinic Cancer Conference

Innovations in Multidisciplinary Care

Register online: www.ccfcme.org/CCCC2024

November 1-3, 2024

Margaritaville Hollywood Beach Resort | Hollywood, Florida

Anusha Agarwal, MD
Department of Internal Medicine, Cleveland Clinic, Cleveland, OH

Arjun Chatterjee, MD
Department of Gastroenterology, Hepatology, and Nutrition, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH

Prabhleen Chahal, MD
Professor, Chief, Division of Gastroenterology, University of Texas Health, San Antonio, TX

ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: What fluids should I order for my patient with acute pancreatitis?

A 47-year-old female with a history of type 2 diabetes and hyperlipidemia presents to the emergency room with a 2-day history of nausea, vomiting, and severe epigastric pain radiating to the back. The patient is hemodynamically stable, though she appears fatigued and diaphoretic. Physical examination reveals dry mucous membranes and epigastric tenderness. No leukocytosis or electrolyte abnormalities are noted. Her blood urea nitrogen level is 24 mg/dL (reference range 5–20 mg/dL), and serum creatinine is 1.3 mg/dL (0.6–1.2 mg/dL); these values are mildly elevated from baseline. Lipase is elevated at 1,200 u/L (0–160 u/L). Bedside ultrasonography of the right upper quadrant reveals gallstones. The patient meets the diagnostic criteria for acute pancreatitis and is admitted to the hospital for further management. Nothing by mouth status is ordered along with appropriate analgesic agents for pain control. What fluids should be ordered in this patient with acute pancreatitis?

A: The cornerstone of acute pancreatitis treatment is fluid resuscitation, early enteral nutrition as tolerated, and analgesia. However, consensus for certain aspects of fluid resuscitation is lacking, especially regarding the type and volume of fluid. For years, early, aggressive fluid resuscitation was preferred. Limited, equivocal evidence supported the use of lactated Ringer's solution vs normal saline in acute pancreatitis management. Data from recent studies, however, show that moderate fluid resuscitation is associated with fewer adverse events[1] and that lactated Ringer's may be superior to normal saline in acute pancreatitis management.[2]

WHY IS FLUID RESUSCITATION IMPORTANT IN ACUTE PANCREATITIS?

Acute pancreatitis, an inflammatory condition of the pancreas, often precipitates a systemic inflammatory response, which can have a wide range of clinical consequences. More than 275,000 patients are hospitalized each year with acute pancreatitis, making it the third leading cause of hospitalization due to gastrointestinal disease in the United States and costing the US healthcare system more than $2.6 billion annually.[3]

Several factors predispose patients to develop hypovolemia in acute pancreatitis. Third-spacing coupled with classic symptoms of vomiting, reduced oral intake, and diaphoresis are frequent causes of hypovolemia in acute pancreatitis. Inflammation of the pancreatic parenchyma leads to recruitment of cytokines and other inflammatory molecules that increase vascular permeability, resulting in the movement of fluid from the intravascular space to the extravascular space. This inflammatory response activates numerous cascades, including pancreatic hypoperfusion, which, if persistent, can give rise to severe complications such as acinar cell death followed by pancreatic necrosis.[4] Studies have shown that persistent hypovolemia in acute pancreatitis is associated with pancreatic necrosis, organ failure, and poor outcomes. These findings correlate with data demonstrating improvement in morbidity and mortality with early fluid resuscitation.[4,5] It is posited that early fluid resuscitation provides macro- and microcirculatory support to reduce the risk of the aforementioned catastrophic consequences.[6]

HOW MUCH FLUID SHOULD I ORDER?

Early aggressive hydration in acute pancreatitis typically entails an initial fluid bolus followed by intravenous maintenance fluids at a rate of 250 to 500 mL/hour. This practice has been widely accepted in clinical settings, yet limited data exist to support it. Several randomized controlled trials, limited by small sample sizes and specific inclusion criteria, have demonstrated conflicting results for the role of aggressive fluid therapy in acute pancreatitis.[6]

doi:10.3949/ccjm.91a.24027

The landmark WATERFALL (Early Weight-Based Aggressive vs Nonaggressive Goal-Directed Fluid Resuscitation in the Early Phase of Acute Pancreatitis) trial,[1] published in 2022, sought to address this evidence gap by assessing the safety and efficacy of aggressive fluid resuscitation in patients with acute pancreatitis. In this multicenter, open-label, randomized controlled trial, aggressive fluid resuscitation consisted of a 20 mL/kg bolus followed by 3 mL/kg/hour maintenance, and moderate fluid resuscitation, a 10 mL/kg bolus, given only if patient was clinically hypovolemic, followed by 1.5 mL/kg/hour maintenance. Patients with moderately severe or severe pancreatitis with signs of organ failure were excluded.[1] Early aggressive fluid resuscitation led to a higher incidence of fluid overload (20.5% vs 6.3%) compared with moderate fluid resuscitation (adjusted relative risk 2.85, 95% confidence interval 1.36–5.94, $P = .004$), which notably led to early halting of the trial at the first safety checkpoint. The study also showed no significant difference in the overall health outcomes between the 2 fluid-resuscitation groups. Ultimately, the WATERFALL trial results favor the use of moderate fluid resuscitation in clinical practice, shifting the paradigm for early management of acute pancreatitis.

SHOULD I ORDER THE SAME AMOUNT OF FLUID FOR ALL PATIENTS?

There are some caveats regarding the WATERFALL trial[1] results. This trial excluded patients who are at higher risk for volume overload at baseline, such as patients with heart failure, cirrhosis, and chronic renal failure. Patients with moderately severe acute pancreatitis (organ failure that resolves within 48 hours or local or systemic complications without persistent organ failure) and severe acute pancreatitis (persistent organ failure [> 48 hours]), as defined by the revised Atlanta classification,[7] were also excluded. In patients who meet the exclusion criteria from the WATERFALL trial and are prone to volume overload, cautious use of fluids with close monitoring of volume status is needed to avoid progression of acute pancreatitis and worsening of their baseline comorbid conditions.

In patients with moderately severe or severe acute pancreatitis who may not be prone to volume overload at baseline, the optimal amount of fluid resuscitation remains unclear. As such, biomarkers such as blood urea nitrogen, creatinine, and hematocrit have been used as surrogate markers of successful hydration in patients with acute pancreatitis.[4,8] Absolute cutoffs for these biomarkers have not been defined, and thus clinical judgment is needed when assessing a patient's overall volume status during fluid resuscitation, especially within the first 48 hours.

LACTATED RINGER'S VS NORMAL SALINE: WHICH SHOULD I ORDER?

While the importance of fluid resuscitation in acute pancreatitis is well established, uncertainty remains regarding which type of intravenous fluid should be given. Pilot trials have shown potential benefit of lactated Ringer's over normal saline in achieving faster clinical recovery in mild acute pancreatitis[9] and reducing the risk of intensive care unit admission.[10] Studies have proposed that the perceived benefits of lactated Ringer's over normal saline may be due to superior pH homeostasis with lactated Ringer's infusion.[11] Normal saline infusion can lead to hyperchloremic metabolic acidosis. The creation of an acidic environment makes acinar cells more susceptible to injury and enables inappropriate trypsinogen activation, a key step in acute pancreatitis pathogenesis.[11] Nonetheless, these studies were limited by small sample size and lack of variation in disease severity, which impacted the generalizability of their results.[9,10]

To address this scarcity of data, Lee et al,[2] using data from 999 patients with acute pancreatitis, conducted an observational study looking at the relationship between the type of intravenous fluid (lactated Ringer's vs normal saline) administered within the first 24 hours and the development of moderately severe or severe acute pancreatitis. Analysis showed that lactated Ringer's administration within the first 24 hours was associated with reduced odds of developing moderately severe or severe acute pancreatitis, thereby improving acute pancreatitis outcomes (adjusted odds ratio 0.52, $P = .014$).[2] This well-powered study adds to the literature that supports lactated Ringer's over normal saline in acute pancreatitis management. Nevertheless, the limitations of an observational study must be kept in mind. An adequately powered randomized controlled trial is needed to establish stronger evidence for the perceived benefits of lactated Ringer's over normal saline in acute pancreatitis.

THE BOTTOM LINE

The hallmark for acute pancreatitis management remains early fluid resuscitation, analgesia, and nutritional support. The landmark WATERFALL trial[1] established that aggressive fluid resuscitation is associated with a higher incidence of volume overload with no significant improvement in health outcomes, favoring the strategy of moderate fluid resuscitation in

clinical practice. Emerging data suggest that lactated Ringer's is associated with improved health outcomes and hence may be superior to normal saline in acute pancreatitis management.[1,2]

REFERENCES

1. **de-Madaria E, Buxbaum JL, Maisonneuve P, et al.** Aggressive or moderate fluid resuscitation in acute pancreatitis. N Engl J Med 2022; 387(11):989–1000. doi:10.1056/NEJMoa2202884
2. **Lee PJ, Culp S, Kamal A, et al.** Lactated ringers use in the first 24 hours of hospitalization is associated with improved outcomes in 999 patients with acute pancreatitis. Am J Gastroenterol 2023; 118(12):2258–2266. doi:10.14309/ajg.0000000000002391
3. **Peery AF, Crockett SD, Barritt AS, et al.** Burden of gastrointestinal, liver, and pancreatic diseases in the United States. Gastroenterology 2015; 149(7):1731–1741.e3. doi:10.1053/j.gastro.2015.08.045
4. **Takeda K, Mikami Y, Fukuyama S, et al.** Pancreatic ischemia associated with vasospasm in the early phase of human acute necrotizing pancreatitis. Pancreas 2005; 30(1):40–49. pmid:15632698
5. **Wall I, Badalov N, Baradarian R, Iswara K, Li JJ, Tenner S.** Decreased mortality in acute pancreatitis related to early aggressive hydration. Pancreas 2011; 40(4):547–550. doi:10.1097/MPA.0b013e318215368d
6. **Gardner TB, Vege SS, Pearson RK, Chari ST.** Fluid resuscitation in acute pancreatitis. Clin Gastroenterol Hepatol 2008; 6(10): 1070–1076. doi:10.1016/j.cgh.2008.05.005
7. **Banks PA, Bollen TL, Dervenis C, et al.** Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013; 62(1):102–111. doi:10.1136/gutjnl-2012-302779
8. **Tenner S.** Initial management of acute pancreatitis: critical issues during the first 72 hours. Am J Gastroenterol 2004; 99(12): 2489–2494. doi:10.1111/j.1572-0241.2004.40329.x
9. **Buxbaum JL, Quezada M, Da B, et al.** Early aggressive hydration hastens clinical improvement in mild acute pancreatitis. Am J Gastroenterol 2017; 112(5):797–803. doi:10.1038/ajg.2017.40
10. **Lee A, Ko C, Buitrago C, et al.** Lactated ringers vs normal saline resuscitation for mild acute pancreatitis: a randomized trial. Gastroenterology 2021; 160(3):955–957.e4. doi:10.1053/j.gastro.2020.10.044
11. **Wu BU, Hwang JQ, Gardner TH, et al.** Lactated ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol 2011; 9(8):710–717. e1. doi:10.1016/j.cgh.2011.04.026

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

Address: *Prabhleen Chahal, MD, Division of Gastroenterology, University of Texas Health, 8300 Floyd Curl Drive, 4th Floor - 4A, San Antonio, TX 78229; chahalp@uthscsa.edu*

GREGORY W. RUTECKI, MD, Section Editor

Cindy Hsin-Ti Lin, MD
Department of Medicine, MetroHealth Medical Center, Cleveland, OH; Case Western Reserve University, Cleveland, OH

Michael Sheu, MD
Department of Internal Medicine, Cleveland Clinic, Cleveland, OH

Faiz Anwer, MD
Director, Inpatient Lymphoma Myeloma Service, Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Recurrent syncope in a 62-year-old man

A 62-year-old man with a medical history of hypertension and a family history of hypertrophic obstructive cardiomyopathy in his sister presented to the emergency room for a second episode of syncope in the previous few weeks.

The first episode occurred 4 weeks earlier. The patient had consumed a large amount of alcohol the day before the episode and had been working outside in the summer heat that morning. He experienced positional lightheadedness and, after taking a shower, noted a slow, thready pulse. Vital signs assessed by emergency medical services were within normal limits. He was taken to the emergency room by ambulance and admitted for syncope workup. Telemetry during admission was unremarkable. Echocardiography was obtained given the patient's family history of hypertrophic obstructive cardiomyopathy. It showed increased left ventricular septal wall thickness and impaired left ventricular diastolic function with no signs of obstruction. The patient was discharged with a working diagnosis of neurally mediated syncope.

Before the second episode, the patient was sitting in a chair visiting a family member at the hospital when he suddenly lost consciousness with no prodrome. No convulsions, urinary or fecal incontinence, or tongue biting were noted. He was taken to the emergency room in a wheelchair where he was initially noted to be confused. His only medication was finasteride.

Further review of the patient's history revealed that 7 years earlier he developed tingling and numbness of the first 3 digits of both hands. He was diagnosed with carpal tunnel syndrome and underwent 2 surgeries on each hand. Despite repeat interventions, carpal tunnel syndrome recurred in both hands.

doi:10.3949/ccjm.91a.24008

The patient also noted that he had ankle edema for the previous 18 months, which his primary care physician attributed to calcium channel blocker use. Amlodipine was discontinued, but the ankle swelling persisted.

DIFFERENTIAL DIAGNOSIS

1 Which underlying cause of this patient's episodes of syncope would be most consistent with his presentation?

- ☐ Neurally mediated syncope
- ☐ Orthostatic syncope
- ☐ Seizure
- ☐ Ventricular outflow obstruction from hypertrophic cardiomyopathy
- ☐ Arrhythmia

Neurally mediated syncope is the most common form of syncope[1] and could have been a cause of this patient's episodes, especially with the premonitory symptoms and history of exertion and dehydration during the first episode. However, the second syncopal episode lacked a prodrome or history suggestive of neurally mediated syncope. Orthostatic syncope can occur with volume depletion and finasteride use and is typically related to change in posture.[2,3] During his second episode, the patient had been sitting for some time before he lost consciousness.

He experienced some confusion immediately following the second episode, but seizure was less likely given that the episode was witnessed by multiple family members and no seizure-like activity was noted. His brief confusion could have been attributed to a slight delay in cerebral reperfusion as he was taken to the emergency room in a sitting (and therefore upright) position. And, though he had a family history of hypertrophic cardiomyopathy, which can be hereditary and

TABLE 1
Initial laboratory test results

Test	Result (reference range)[a]
Comprehensive metabolic panel	
Protein, total	**8.2 g/dL** (6.3–8.0)
Albumin	3.9 g/dL (3.9–4.9)
Calcium, total	10.1 mg/dL (8.5–10.2)
Bilirubin, total	0.4 mg/dL (0.2–1.3)
Alkaline phosphatase	72 U/L (38–113)
Aspartate aminotransferase	39 U/L (14–40)
Alanine transaminase	26 U/L (10–54)
Glucose	**117 mg/dL** (74–99)
Blood urea nitrogen	19 mg/dL (9–24)
Serum creatinine	**1.47 mg/dL** (0.73–1.22)
Sodium	**135 mmol/L** (136–144)
Potassium	4.0 mmol/L (3.7–5.1)
Chloride	102 mmol/L (97–102)
Carbon dioxide	23 mmol/L (22–30)
Anion gap	10 mmol/L (9–18)
Estimated glomerular filtration rate	**54 mL/minute/1.73 m^2** (≥ 60)
Complete blood cell count	
White blood cell count	5.47 x 10^9/L (3.70–11.00)
Red blood cell count	**3.46 x 10^9/L** (4.20–6.00)
Hemoglobin	**10.2 g/dL** (13–17)
Hematocrit	**32.4%** (39–51)
Mean corpuscular volume	93.6 fL (80.0–100.0)
Mean corpuscular hemoglobin	29.5 pg (26.0–34.0)
Mean corpuscular hemoglobin concentration	31.5 g/dL (30.5–36.0)
Red cell distribution width-coefficient of variation	14.5% (11.5–15.0)
Platelet count	250 x 10^9/L (150–400)
Mean platelet volume	9.5 fL (9.0–12.7)
Urine dipstick	
Protein	**2+** (negative)
Blood	**1+** (negative)
Miscellaneous	
Magnesium	2.3 mg/dL (1.7–2.3)
Ionized calcium	**1.31 mmol/L** (1.08–1.30)
High-sensitivity troponin T	**56 ng/L** (< 12)
N-terminal pro-brain natriuretic peptide	**2,397 pg/mL** (< 125)
D-dimer	**1,060 ng/mL** (< 500)

[a]Results outside of reference range are shown in bold.

cause left ventricular outflow obstruction, outflow obstruction is typically precipitated by factors that decrease preload or afterload, such as strenuous exertion, dehydration, or vasodilator use. The patient was dehydrated during his first syncope episode, but echocardiography at the time did not suggest obstruction, and hence syncope caused by hypertrophic cardiomyopathy was less likely. Also, the first episode happened after the patient had showered (and therefore occurred after and not during exertion), which is also less typical of syncope caused by ventricular outflow obstruction. The abrupt and unprovoked nature of this patient's second syncopal episode was most suspicious for arrhythmia, and further workup to rule out malignant arrhythmia was warranted.

INITIAL EVALUATION AND MANAGEMENT

The results of initial laboratory testing at the emergency room following the patient's second episode of syncope are presented in **Table 1**.

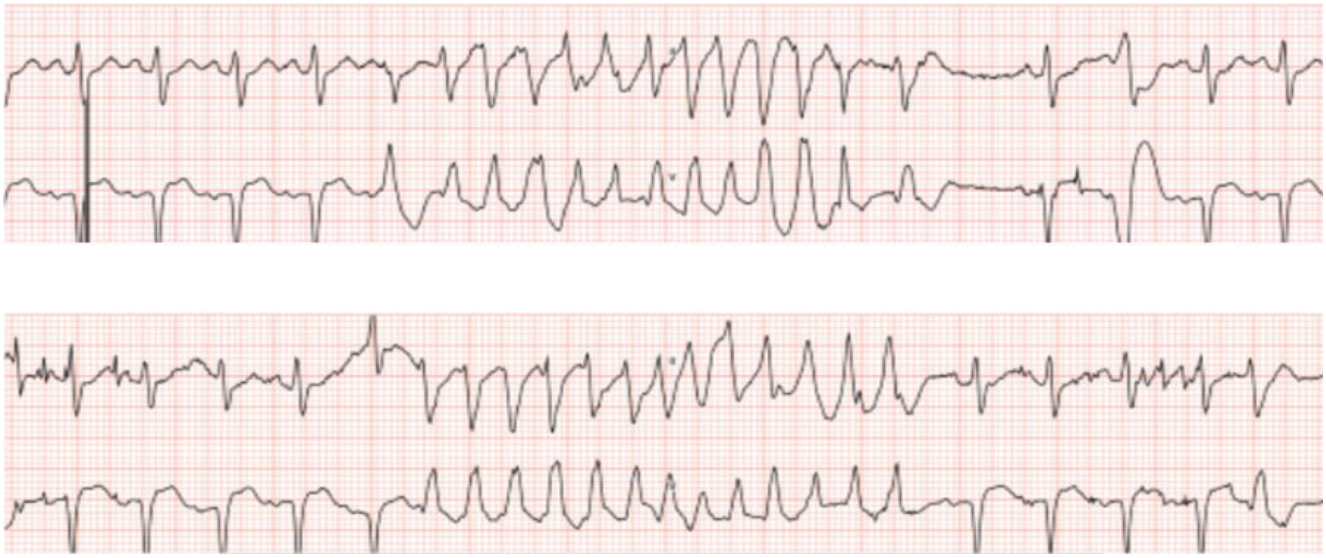


Figure 1. Polymorphic ventricular tachycardia episodes captured on continuous telemetry.

Orthostatic vital signs were negative for orthostatic hypotension (blood pressure with the patient in the supine position was 121/71 mm Hg with a heart rate of 68 beats per minute vs 124/74 mm Hg and 78 beats per minute while standing). No bruits were noted on physical examination.

Electrocardiography showed sinus rhythm with normal voltage. Computed tomography of the brain showed no acute intracranial process. Due to the presence of bilateral lower extremity edema noted on examination, elevated D-dimer, and unexplained syncope, computed tomography of the chest with pulmonary embolism protocol was done. It showed mild mediastinal and bilateral hilar adenopathy (< 1 cm) and no evidence of pulmonary embolism. Bilateral lower extremity ultrasonography was negative for thrombosis.

Repeat echocardiography findings were similar to those from echocardiography done at the time of the first syncope epidsode, with mild left ventricular septum hypertrophy and a dilated left atrium. Nonsustained polymorphic ventricular tachycardia was noted on telemetry (**Figure 1**).

Left heart catheterization was done due to concern for myocardial ischemia given the patient's chest pain, shortness of breath on exertion, and persistently elevated high-sensitivity troponin (56 ng/mL in the emergency room and 68 ng/mL on repeat laboratory evaluation). The results showed no coronary artery stenosis.

Cardiac magnetic resonance imaging (MRI) showed subendocardial to mid-myocardial delayed gadolinium enhancement with multiple foci, predominantly within the basal inferolateral and basal septum. A dual-chamber implantable cardioverter-defibrillator was placed before the patient was discharged.

CASE CONTINUED

Because the patient's cardiac MRI report suggested that the imaging findings were most consistent with cardiac sarcoidosis, the patient was referred to the sarcoidosis clinic after discharge. Bronchoscopy was offered to evaluate for cardiac sarcoidosis, but the patient declined. Additional testing was ordered:

- Positron emission tomography (PET) and computed tomography of the whole body showed no evidence of focal uptake to suggest a fluorodeoxyglucose F18 (FDG)–avid neoplastic process or active granuloma disease such as sarcoidosis
- Cardiac PET showed evidence of active inflammation with a large amount (> 5 segments) of inflamed myocardium with focal-on-diffuse myocardial FDG uptake.

Further testing and results

Given the patient's history of recurrent bilateral carpal tunnel syndrome, unexplained anemia, proteinuria with edema, and renal insufficiency, workup to rule out cardiac amyloidosis was done:

- Kappa free light chains: 1,099.7 mg/L (reference range 3.3–19.4)
- Lambda free light chains: 2.3 mg/L (5.7–26.3)
- Kappa-to-lambda free light chain ratio: 478.13 (0.26–1.65)

- Serum protein electrophoresis monoclonal (M) protein concentration: 1.99 g/dL (0)
- 24-hour urine protein: 4.11 g (< 0.15), M protein present
- Lactate dehydrogenase: 282 U/L (135–225)
- Beta-2 microglobulin: 3.4 mg/L (< 3.1)

LABORATORY WORKUP INTERPRETATION

2 For which type of disorder do these laboratory results raise suspicion?

☐ Hypergammaglobulinemia (polyclonal gammopathy)
☐ Plasma cell dyscrasia
☐ T-cell lymphoma

This patient's laboratory results showed significantly elevated kappa free light chains, an abnormal kappa-to-lambda ratio, and paraproteinemia. These findings were most suspicious for a plasma cell dyscrasia. The presence of M-protein confirmed that a monoclonal gammopathy was present. The extremely elevated (≥ 100) ratio of involved to uninvolved serum free light chains was also indicative of an underlying plasma cell disorder, and combined with 10% or greater clonal bone marrow plasma cells or biopsy-proven plasmacytoma, would be diagnostic for multiple myeloma.[4]

Though an elevated lactate dehydrogenase level, free light chains, and M-spike can sometimes be seen in B-cell lymphomas, T-cell lymphomas are not typically associated with monoclonal gammopathies.[5]

3 Which type of amyloidosis does this patient most likely have?

☐ Immunoglobulin light chain (AL) amyloidosis
☐ Serum amyloid A (AA) amyloidosis
☐ Transthyretin (ATTR) amyloidosis

AL amyloidosis, or primary amyloidosis, occurs when misfolded immunoglobulin light chains are deposited in tissues of patients with an underlying plasma cell dyscrasia.[6] As this patient had an underlying plasma cell dyscrasia, AL amyloidosis was most likely.

In AA amyloidosis, the deposited protein is derived from the acute-phase reactant serum AA protein. This condition is commonly found with long-standing inflammatory disorders such as autoimmune disease or chronic infection.[7]

ATTR amyloidosis results from the misfolding of transthyretin, a protein involved in transporting thyroxine- and retinol-binding protein.[8] ATTR amyloidosis can occur due to pathologic deposits of transthyretin protein in patients with hereditary mutations in the transthyretin gene (hereditary ATTR amyloidosis) or with no known mutation (wild-type ATTR amyloidosis).

DIAGNOSTIC TESTING

4 Which diagnostic modality is the gold standard test for differentiating cardiac sarcoidosis and cardiac amyloidosis?

☐ Echocardiography
☐ Cardiovascular MRI
☐ FDG-PET
☐ Myocardial biopsy

Amyloidosis and sarcoidosis are both infiltrative cardiomyopathies caused by interstitial deposition of pathological tissue.[9] Cardiac amyloidosis can present with ventricular wall thickening and a granular sparkling appearance of the septum on echocardiography.[10] The granulomatous lesions and thinning from fibrous scars seen in cardiac sarcoidosis can cause wall motion abnormalities, diastolic dysfunction, and abnormal myocardial wall thickness in a noncoronary distribution.[11] Cardiovascular MRI also can be useful for differentiating amyloidosis and sarcoidosis: amyloidosis more often presents with global subendocardial late gadolinium enhancement, while a wider variety of late gadolinium enhancement distributions is seen in sarcoidosis (eg, nodular, circumferential, subepicardial, or subendocardial types). However, amyloidosis and sarcoidosis can mimic each other on both echocardiography and cardiovascular MRI, and neither test can definitively diagnose either condition.[12]

FDG-PET in cardiac sarcoidosis shows focal areas of increased FDG uptake corresponding to the increased glucose consumption of macrophages within granulomatous lesions or resting perfusion defects from compression of the microvasculature due to inflammation or fibrosis.[11] Amyloidosis, on the other hand, can have variable FDG avidity, and FDG-PET is not routinely used for diagnosis.[13]

Myocardial biopsy is the gold standard for establishing a diagnosis and should be pursued when the diagnosis cannot be fully substantiated through other modalities.[14]

FURTHER INVESTIGATIONS AND FINAL DIAGNOSIS

Cardiovascular technetium-99m pyrophosphate scintigraphy was obtained and was negative for ATTR amyloidosis. Bone marrow biopsy showed 30% plasma cells, and Congo red staining was positive for amyloid

deposition in the periosteal soft tissue. Flow cytometry of marrow aspirate showed an abnormal plasma cell population with trisomy 9, gain at the *CCND1* locus, and deletion at the *RB1* locus.

Atypical presentation of AL cardiac amyloidosis was suspected, and cardiac biopsy was pursued. Biopsy of the right ventricle showed no sarcoplasmic inclusions or vascularizations but was positive for amyloid on thioflavin S stain examined under fluorescence microscopy. Immunohistochemical staining performed for amyloid typing showed amyloid deposits positive for kappa light chain and negative for lambda light chain and transthyretin.

A dual diagnosis of systemic AL amyloidosis with cardiac involvement (Mayo 2012 stage 3; European modification Mayo 2004 stage IIIa)[15,16] and Revised International Staging System[17] stage 2, standard-risk immunoglobulin G kappa multiple myeloma was made. The patient was started on induction therapy with daratumumab, cyclophosphamide, bortezomib, and dexamethasone. He has not had any further episodes of ventricular tachycardia.

AL AMYLOIDOSIS

AL amyloidosis is a rare disease with an estimated global incidence of 10 cases per million population.[18] AL amyloidosis occurs when soluble light chains are misfolded and convert into insoluble fibrillar aggregates that deposit in tissues throughout the body.[19] The most commonly affected organs in AL amyloidosis include the heart, kidney, nervous system, gastrointestinal tract, liver, spleen, and lungs as well as soft tissue. Clinical manifestations vary widely depending on organ involvement and can include shortness of breath, orthopnea, peripheral edema, arrhythmia, peripheral neuropathy, autonomic dysfunction, macroglossia, carpal tunnel syndrome, waxy skin, easy bruising, hepatomegaly, fatigue, weight loss, and early satiety.[20]

Diagnosis of amyloidosis is often delayed due to the nonspecific presentation of the disease.[21] Clinicians may erroneously attribute early signs and symptoms to other, more common pathologies. However, features that should trigger suspicion of amyloidosis include nephrotic-range proteinuria not attributable to diabetes, heart failure and left ventricular hypertrophy in the absence of aortic stenosis or hypertension, peripheral or autonomic neuropathy of unclear etiology, hepatomegaly with increased alkaline phosphatase, macroglossia, bilateral carpal tunnel syndrome, and periorbital purpura.[20]

Effective therapies for AL amyloidosis are becoming available, with a recent trial showing improved rates of complete hematologic response and survival free from major organ deterioration or hematologic progression with the addition of daratumumab to bortezomib, cyclophosphamide, and dexamethasone.[22] Early diagnosis of AL amyloidosis is essential to halt disease progression and maximize patients' chances of longer survival and recovery of organ function.

TAKE-HOME POINTS

Cardiac AL amyloidosis is a rare disease with varying presentations that can mimic other pathologies on imaging. Early recognition of the clinical manifestations of amyloidosis is crucial for facilitating timely intervention and preventing complications such as life-threatening arrhythmic events and advanced heart failure.

DISCLOSURES

Dr. Anwer disclosed consulting, teaching and speaking, and acting as principal investigator and co-principal investigator for Bristol-Myers Squibb Co. and consulting for Caribou Bio. Dr. Lin and Dr. Sheu report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Writing Committee Members, Shen WK, Sheldon RS, et al.** 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm 2017; 14(8):e155–e217. doi:10.1016/j.hrthm.2017.03.004
2. **Nestor MS, Ablon G, Gade A, Han H, Fischer DL.** Treatment options for androgenetic alopecia: efficacy, side effects, compliance, financial considerations, and ethics. J Cosmet Dermatol 2021; 20(12):3759-3781. doi:10.1111/jocd.14537
3. **Joseph A, Wanono R, Flamant M, Vidal-Petiot E.** Orthostatic hypotension: a review. Nephrol Ther 2017; 13 Suppl 1:S55–S67. doi:10.1016/j.nephro.2017.01.003
4. **Cowan AJ, Green DJ, Kwok M, et al.** Diagnosis and management of multiple myeloma: a review. JAMA 2022; 327(5):464–477. doi:10.1001/jama.2022.0003
5. **Economopoulos T, Papageorgiou S, Pappa V, et al.** Monoclonal gammopathies in B-cell non-Hodgkin's lymphomas. Leuk Res 2003; 27(6):505–508. doi:10.1016/s0145-2126(02)00277-1
6. **Al Hamed R, Bazarbachi AH, Bazarbachi A, Malard F, Harousseau JL, Mohty M.** Comprehensive review of AL amyloidosis: some practical recommendations. Blood Cancer J 2021; 11(5):97. doi:10.1038/s41408-021-00486-4
7. **Westermark GT, Fändrich M, Westermark P.** AA amyloidosis: pathogenesis and targeted therapy. Annu Rev Pathol 2015; 10:321–344. doi:10.1146/annurev-pathol-020712-163913
8. **Raz A, Goodman DS.** The interaction of thyroxine with human plasma prealbumin and with the prealbumin-retinol-binding protein complex. J Biol Chem 1969; 244(12):3230–3237.

9. **Fuchs TA, Gaemperli O.** Infiltrative disease (amyloidosis/sarcoidosis). In: Camm AJ, Lüscher TF, Maurer G, Serruys PW, eds. The ESC Textbook of Cardiovascular Medicine. 3rd ed. New York, NY: Oxford University Press; 2018:608.
10. **Koyama J, Ikeda S, Ikeda U.** Echocardiographic assessment of the cardiac amyloidoses. Circ J 2015; 79(4):721–734. doi:10.1253/circj.CJ-14-1425
11. **Blankstein R, Waller AH.** Evaluation of known or suspected cardiac sarcoidosis. Circ Cardiovasc Imaging 2016; 9(3):e000867. doi:10.1161/CIRCIMAGING.113.000867
12. **Takemura K, Nakamura R, Shimazu K, et al.** A case of cardiac sarcoidosis mimicking cardiac amyloidosis on cardiovascular magnetic resonance. ESC Heart Fail 2018; 5(2):306–310. doi:10.1002/ehf2.12263
13. **Lee JH, Lee GY, Kim SJ, et al.** Imaging findings and literature review of (18)F-FDG PET/CT in primary systemic AL amyloidosis. Nucl Med Mol Imaging 2015; 49(3):182–190. doi:10.1007/s13139-015-0338-0
14. **Briasoulis A, Bampatsias D, Papamichail A, et al.** Invasive and non-invasive diagnostic pathways in the diagnosis of cardiac amyloidosis. J Cardiovasc Dev Dis 2023; 10(6):256. doi:10.3390/jcdd10060256
15. **Kumar S, Dispenzieri A, Lacy MQ, et al.** Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol 2012; 30(9):989–995. doi:10.1200/JCO.2011.38.5724
16. **Wechalekar AD, Schonland SO, Kastritis E, et al.** A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood 2013; 121(17):3420–3427. doi:10.1182/blood-2012-12-473066
17. **Palumbo A, Avet-Loiseau H, Oliva S, et al.** Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol 2015; 33(26):2863–2869. doi:10.1200/JCO.2015.61.2267
18. **Kumar N, Zhang NJ, Cherepanov D, Romanus D, Hughes M, Faller DV.** Global epidemiology of amyloid light-chain amyloidosis. Orphanet J Rare Dis 2022; 17(1):278. doi:10.1186/s13023-022-02414-6
19. **Merlini G, Dispenzieri A, Sanchorawala V, et al.** Systemic immunoglobulin light chain amyloidosis. Nat Rev Dis Primers 2018; 4(1):38. doi:10.1038/s41572-018-0034-3
20. **Vaxman I, Gertz M.** When to suspect a diagnosis of amyloidosis. Acta Haematol 2020; 143(4):304–311. doi:10.1159/000506617
21. **Hester LL, Gifkins DM, M Bellew K, et al.** Diagnostic delay and characterization of the clinical prodrome in AL amyloidosis among 1523 US adults diagnosed between 2001 and 2019. Eur J Haematol 2021; 107(4):428–435. doi:10.1111/ejh.13679
22. **Kastritis E, Palladini G, Minnema MC, et al.** Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. N Engl J Med 2021; 385(1):46–58. doi:10.1056/NEJMoa2028631

Address: *Faiz Anwer, MD, Department of Hematology and Medical Oncology, CA 60, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; anwerf@ccf.org*

Cleveland Clinic

BEYOND THE PAGES:

Cleve Clin J Med Podcast

"Beyond the Pages: Cleve Clin J Med Podcasts" explore C*leveland Clinic Journal of Medicine* articles in depth through interviews with authors and experts in the field. Clinicians will learn more about clinical breakthroughs in medicine and how to practically apply them in patient care.

Listen today!

www.ccfcme.org/CCJMpodcast

Podcasts include

- Management of benign prostatic hyperplasia
- Treatments for obstructive sleep apnea: CPAP and beyond
- Metformin therapy for weight loss in patients without diabetes
- Antibiotics to prevent infective endocarditis before dental procedures

This activity has been approved for *AMA PRA Category 1 Credit*™.

Cleveland Clinic

ABC
Association of Black Cardiologists, Inc.
Saving the Hearts and Minds of a Diverse America

Cardiovascular Update 2024 for Primary Care and General Cardiology

October 31-November 1, 2024
Hilton Cleveland Downtown | Cleveland, OH

Register Today!
www.ccfcme.org/cvupdate24

ABIM CME MOC ACCREDITED
Attend and Earn ABIM MOC Points

Join us at Cardiovascular Update for Primary Care and General Cardiology

Cardiovascular disease (CVD) is the world's leading cause of death, underscoring the priority to develop and deliver education to improve care and outcome for individuals with CVD. Cardiovascular Update 2024 will incorporate the latest science, clinical evidence-base, and best-practices, to improve prevention, care delivery and outcomes for individuals at risk or with existing CVD. Attendees will receive essential educational content emphasizing cutting edge science, the implementation of evidence-based guidelines, and the promotion of health equity among diverse populations, ensuring improved cardiovascular outcomes for all patients.

Sessions

- Prevention and Management of CV Risk
- Special Populations
- Essentials of CVD
- Structural Heart Disease
- Heart Failure
- Heart Rhythm

Cleveland Clinic

Primary Care +

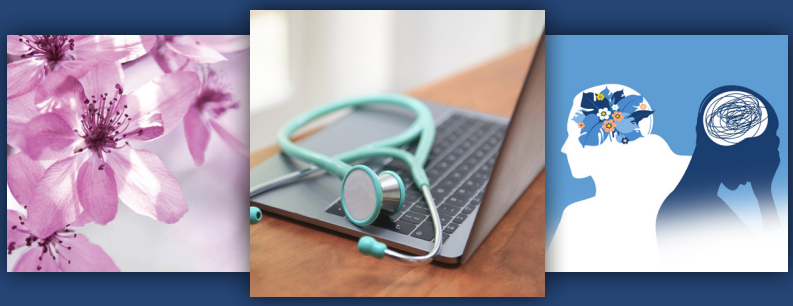
Updates in Primary Care, Women's Health and Behavioral Medicine

Featuring evidence-based update on marijuana use

November 13-16, 2024
Cleveland Clinic Administrative Campus
3175 Science Park Drive, Building #4, 4th Floor | Beachwood, OH

Register Today!
ccfcme.org/PCP24

Register today for a review of best practices that highlight the latest therapies, procedures, and diagnostics in primary care, women's health and behavioral medicine.



Wafa A. Aldhaleei, MBBCh, MSc, MPH
Assistant Professor, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN

Michael B. Wallace, MD, MPH
Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL

Dana M. Harris, MD
Division of Internal Medicine, Mayo Clinic, Jacksonville, FL

Yan Bi, MD, PhD
Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL

Helicobacter pylori: A concise review of the latest treatments against an old foe

ABSTRACT

Helicobacter pylori is a significant public health concern given its high prevalence, growing rates of antibiotic resistance, and carcinogenic effect, all of which create management challenges for internists, gastroenterologists, and other specialty physicians. With almost half of the world's human population harboring *H pylori*, carcinogenic sequelae are a concern to many practitioners. Recent guidelines recommend testing high-risk populations for *H pylori* using noninvasive or invasive methods. *H pylori* eradication regimens are tailored based on the presence of effective empiric therapy (local cure rates ≥ 90% for a given regimen) or antimicrobial susceptibility testing. When empiric therapy cure rates are not optimal, guidelines recommend antimicrobial susceptibility testing to improve eradication rates and reduce the progression of antibiotic resistance.

KEY POINTS

- *H pylori* infection is a major health concern and is the most common carcinogenic infection worldwide.
- Antimicrobial susceptibility testing is recommended when the cure rate of empiric therapy is less than 90%.
- The choice of *H pylori* eradication therapy depends on antimicrobial susceptibility testing, the local antibiogram, cost, pill burden, and patient-related factors.

doi:10.3949/ccjm.91a.24031

HELICOBACTER PYLORI is a gram-negative spiral microaerophilic bacterium that infects and colonizes the stomach mucosa.[1,2] Nearly 50% of the world's human population harbor *H pylori*,[2] while the overall prevalence in the United States is less than 50%, with notable racial and ethnic disparities.[1,3] *H pylori* infection has been linked with low socioeconomic status, poor hygiene, close interpersonal contact, and old age.[1,2,4]

About 10% to 20% of persons with *H pylori* infection will develop duodenal or gastric ulcer disease, and around 80% of non-cardia–type gastric cancers are caused by *H pylori*.[2,5] In 1994, the World Health Organization and International Agency for Research on Cancer consensus group designated *H pylori* as a group 1 carcinogenic organism.[2]

Although antibiotic regimens to treat *H pylori* infection are available, disease related to *H pylori* remains a socioeconomic burden and a significant health concern. In 2018, *H pylori* was the primary cause of cancer in 37% (810,000 cases) of new infection-attributable cancer cases, making it the most common carcinogenic infection worldwide.[5] *H pylori* eradication therapy reduces the risk of gastric cancer by about 34%.[5,6]

This review summarizes current evidence and guidelines on *H pylori* testing and management.

WHO SHOULD BE TESTED?

In 2017, the American College of Gastroenterology (ACG)[4] strongly recommended *H pylori* testing for patients with active or past peptic ulcer

TABLE 1
Noninvasive and invasive testing methods for *Helicobacter pylori*

Testing method	Pros	Cons	Cost (approximate)	Sensitivity	Specificity
Invasive tests					
Endoscopic biopsy	Allows direct visualization of *H pylori* infection Allows for histological evaluation	Discomfort and risk of complications	$$–$$$	95%–98%	95%–98%
Rapid urease test	Quick results (usually within minutes) Relatively low cost	False negatives can occur with recent proton pump inhibitor use or active bleeding	$–$$	90%–95%	95%–98%
H pylori culture	Allows for antibiotic susceptibility testing	Time-consuming and labor-intensive	$$–$$$	Variable[a]	Variable[a]
Molecular testing (gastric tissue)	High sensitivity and specificity Can detect resistance mutations	Requires specialized equipment and expertise	$$–$$$	90%–95%	90%–95%
Noninvasive tests					
Stool antigen test	Easy to collect specimens	May yield false negatives if antigen levels are low	$–$$	90%–95%	90%–95%
Molecular testing (stool)	Easy to collect specimens High sensitivity and specificity	Requires specialized equipment and expertise	$$–$$$	Variable	Variable
Serology (blood test)	Easy to perform	Cannot distinguish current infection from past exposure False positives can occur	$–$$	80%–85%	80%–85%
Urea breath test	Well tolerated High sensitivity and specificity	Requires abstaining from certain medications (eg, antibiotics, proton pump inhibitors) before the test False positives can occur in the presence of urease-producing bacteria other than *H pylori*	$$–$$$	95%–98%	95%–98%
GastroPanel[b]	Provides comprehensive information on gastric health	Limited availability Interpretation may be complex	$$$	Variable	Variable

[a]Depending on DNA extraction method.
[b]Combination of immunoglobulin G serology coupled with pepsinogen I and II testing.

Based on information from references 8 and 9.

disease (unless a cure is documented), low-grade gastric mucosa–associated lymphoid tissue lymphoma, or a history of early endoscopic resection of gastric cancer, and conditionally recommended nonendoscopic testing for patients under age 60 with uninvestigated dyspepsia who do not have alarm symptoms. Other scenarios in which *H pylori* testing is conditionally recommended include long-term nonsteroidal anti-inflammatory drug therapy, low-dose aspirin use, and unexplained iron deficiency anemia or idiopathic thrombocytopenic purpura.[4]

TABLE 2
Recommended susceptibility-based *Helicobacter pylori* eradication therapy after failure of empiric therapy

Susceptibility testing results	Recommended regimen
Clarithromycin-susceptible	Clarithromycin triple therapy for 14 days
Clarithromycin-resistant, metronidazole-susceptible	Metronidazole triple therapy for 14 days
Clarithromycin- and metronidazole-resistant, levofloxacin-susceptible	Preferred: empiric therapy with bismuth quadruple therapy for 14 days Alternative: levofloxacin triple therapy for 14 days[a]

[a]If levofloxacin triple therapy is selected and fails, bismuth quadruple therapy is the next step.

Based on information from reference 15.

In 2018, 11 *H pylori* management experts suggested additional indications for *H pylori* testing, such as patients with a family history of gastric cancer, first-generation immigrants from high-prevalence areas, and patients of Latino or African American ethnic or racial groups.[7]

Table 1 summarizes key aspects of noninvasive and invasive *H pylori* testing.[8,9] The noninvasive urea breath test and stool antigen test are highly specific and sensitive, and are widely available for use in clinical practice in the United States. Invasive molecular testing can be considered to detect infection and assess antibiotic susceptibility.

WHAT IS STANDARD TREATMENT FOR *H PYLORI*?

The ACG guidelines[4] recommend treating all patients with positive tests for active *H pylori* infection. The recommended standard therapy is a combination of a proton pump inhibitor with or without a bismuth-containing product and 1 or more of the following antibiotics: clarithromycin, metronidazole, amoxicillin, or tetracycline, given for 10 to 14 days.[10,11] Clarithromycin-based regimens generally should not be offered where *H pylori* clarithromycin resistance exceeds 15%.[4,10,11] Clarithromycin resistance is determined through antimicrobial susceptibility testing and local patterns of resistance, ie, the local antibiogram.

The overall eradication success rate with standard therapy is around 75%, with bismuth quadruple therapy having a higher success rate (about 90%) than other therapies.[12] Hence, current guidelines recommend bismuth quadruple (proton pump inhibitor, bismuth, metronidazole, tetracycline) or nonbismuth quadruple (proton pump inhibitor, amoxicillin, metronidazole, clarithromycin) therapies for 10 to 14 days as first-line treatments.[4,10]

Treatment failure and antibiotic resistance

H pylori treatment failure can be due to many factors, including systems-, host-, and microbial-related factors.[13] Systems-related factors include a lack of surveillance registries and supportive modalities for increasing medication adherence. Host factors include age, smoking history, medication nonadherence, host genetics, drug- or food-drug interaction, and insufficient dose and frequency of proton pump inhibitor or antibiotic therapy. Medication nonadherence is a common and modifiable host risk factor for eradication failure. Nonadherence can be caused by high pill burden, complicated regimens, intolerance, lack of understanding of the impact of treatment on health, and patient-clinician miscommunication. Microbial factors include primary or secondary resistance, *H pylori* load, and virulence through vacuolating cytotoxin A and cytotoxin-associated antigen A.[13]

A recent systematic review and meta-analysis showed that in the United States the prevalence of *H pylori* resistance to clarithromycin is 31%, metronidazole 42%, and levofloxacin 38%; the pooled resistance rates are higher than 30%.[14] Resistance rates to amoxicillin, tetracycline, and rifabutin remain low.[14] Metronidazole resistance may be overcome by using higher doses.[13,14]

WHEN IS ANTIMICROBIAL SUSCEPTIBILITY TESTING RECOMMENDED?

Antimicrobial susceptibility testing examines *H pylori* cultures against several antibiotics to determine sensitivity.[15] Susceptibility testing is an underlying principle of antimicrobial stewardship programs that have been developed to guide treatment and limit antibiotic resistance. Such programs focus on:

- Restricting empiric therapy and tailoring antibiotic choice to locally effective therapy based on the local antibiogram

TABLE 3
Effective *Helicobacter pylori* regimens available in the United States

Regimen	Drug and dosing	Duration
Empiric therapy		
Bismuth quadruple therapy	Bismuth subsalicylate 300 mg 4 times daily, 30 minutes before meals Tetracycline 500 mg 4 times daily, 30 minutes after meals Metronidazole 500 mg 4 times daily, 30 minutes after meals Proton pump inhibitor (standard dose) twice daily, 30 minutes before meals and at bedtime, or before morning and evening meals	14 days
Bismuth quadruple therapy (Pylera)	Combination pill containing bismuth, tetracycline, and metronidazole 4 times daily with meals and at bedtime Proton pump inhibitor (standard dose) twice daily, 30 minutes before meals and at bedtime	14 days
Susceptibility-based therapy		
Clarithromycin triple therapy	Clarithromycin 500 mg twice daily, 30 minutes after meals Amoxicillin 1 g twice daily, 30 minutes after meals Proton pump inhibitor (standard dose) twice daily, 30 minutes before meals	14 days
Metronidazole triple therapy	Metronidazole 500 mg twice daily, 30 minutes after meals Amoxicillin 1 g twice daily, 30 minutes after meals Proton pump inhibitor (standard dose) 3 times daily, 30 minutes before meals	14 days
Levofloxacin triple therapy	Levofloxacin 500 mg daily, 30 minutes after meal Amoxicillin 1 g twice daily, 30 minutes after meals Proton pump inhibitor (standard dose) twice daily, 30 minutes before meals	14 days

Based on information from reference 15.

- Assessing treatment effectiveness using a test of cure
- Evaluating treatment outcomes
- Sharing test-of-cure data with local and regional clinicians, to be integrated into their antimicrobial stewardship programs.[16]

In general, antimicrobial susceptibility testing is recommended when empiric therapy cure rates fall below 90% or after a failed treatment attempt.[15] Gastric biopsy culture with drug sensitivity testing is considered the gold standard for antibiotic susceptibility evaluation, with 100% specificity; however, it is difficult and time-consuming to perform, and requires a special medium for transportation and culture.[15,17] Molecular-based testing such as polymerase chain reaction or next-generation sequencing is sensitive and specific and offers several other advantages: it can be done using stool samples and fresh or formalin-fixed, paraffin-embedded histological samples; can detect active infection and provide drug resistance information; has a rapid turnaround time (around 5 business days); and does not require special handling and transportation. However, only a limited number of laboratories can perform molecular-based testing, and it may not be covered by health insurance.[17]

HOW SHOULD *H PYLORI* ERADICATION THERAPY REGIMENS BE TAILORED?

If highly effective empiric therapy is available based on local resistance profiles, empiric treatment with bismuth quadruple therapy is recommended (**Table 2**).[15] If empiric therapy fails, antimicrobial susceptibility testing is indicated, with treatment selection based on the results (**Table 3**).[15]

Penicillin allergy may hinder *H pylori* eradication therapy because most treatment regimens contain amoxicillin.[4,18] Even though up to 20% of the general population is labeled as having a penicillin allergy, most can safely take amoxicillin after a thorough history or allergy testing.[18] The ACG guidelines recommend allergy testing in individuals with a history of penicillin allergy or failed first-line therapy.[4]

PROTON PUMP INHIBITOR OR POTASSIUM-COMPETITIVE ACID BLOCKERS

The ability of *H pylori* to survive in an acidic environment necessitates the use of a proton pump inhibitor to maintain the intragastric pH above 6 and enhance the bioavailability of the antibiotics.[19,20] Several proton

TABLE 4
Proposed approach for *Helicobacter pylori* eradication therapy incorporating vonoprazan

		Preferred regimens	Alternative regimens
Antimicrobial susceptibility information not available	Clarithromycin resistance < 15%	Vonoprazan triple therapy[a]	Vonoprazan dual therapy[b] Clarithromycin triple therapy Bismuth quadruple therapy
	Clarithromycin resistance ≥ 15%	Bismuth quadruple therapy	Vonoprazan dual therapy[b]
Antimicrobial susceptibility information available	Clarithromycin susceptible	Clarithromycin or vonoprazan triple therapy[a]	Vonoprazan dual therapy[b]
	Metronidazole susceptible	Metronidazole triple therapy	Vonoprazan dual therapy[b]
	Levofloxacin susceptible	Levofloxacin triple therapy	Vonoprazan dual therapy[b] Bismuth quadruple therapy

[a]Vonoprazan plus amoxicillin and clarithromycin.
[b]Vonoprazan plus amoxicillin.

Based on information from reference 29.

pump inhibitor agents are available, but rabeprazole or esomeprazole 20 to 40 mg twice daily is preferable. Unlike omeprazole, lansoprazole, esomeprazole, and pantoprazole, which are mainly metabolized in the liver by CYP2C19, rabeprazole is mainly metabolized by a nonenzymatic pathway and to a lesser extent by CYP2C19.[21] CYP2C19 metabolism is based on genetic predisposition (normal, intermediate, poor, rapid or ultra-rapid metabolizer), resulting in more or less acid suppression, depending on the patient. Information on the type of metabolism is only available with genetic testing. Because rabeprazole metabolism is not dependent on enzyme CYP2C19 metabolism, acid suppression is more consistent and not patient dependent.[22] Esomeprazole exhibits potent inhibition of the proton pump.[15]

Potassium-competitive acid blockers (P-CAB) directly compete with potassium, which in turn directly inhibits hydrogen-potassium adenosine triphosphatase (proton pump).[23] P-CAB agents have the following advantages over proton pump inhibitors:

- Have direct action on the proton pump
- Reversibly bind to the proton pump
- Achieve full effect from the first dose
- Are not affected by CYP2C19 genetic polymorphism
- Have a potent antisecretory effect and a longer half-life.[23,24]

The US Food and Drug Administration recently approved the P-CAB vonoprazan for treating *H pylori* infection.[25] Vonoprazan is reversible and fast-acting, has a prolonged half-life, and is not affected by diet or genetic polymorphism in drug-metabolizing enzymes.[24,26]

Studies of P-CAB–based regimens

A recent systematic review and meta-analysis of 8 studies focused on first-line *H pylori* eradication regimens found that vonoprazan-based regimens were superior to proton pump inhibitor–based therapy.[26] Another systematic review and meta-analysis showed that vonoprazan-based regimens were superior to proton pump inhibitor–based therapy as second-line therapy.[27] A systematic review and meta-analysis[28] that comparing vonoprazan dual (with amoxicillin) therapy with vonoprazan triple (with amoxicillin and clarithromycin) therapy concluded that vonoprazan dual therapy is as effective as vonoprazan triple therapy. More interestingly, a recent systematic review and meta-analysis of randomized controlled trials[29] showed eradication rates exceeding 90% in clarithromycin-sensitive strains using P-CAB–based regimens. Notably, the majority of evidence supporting the superiority of vonoprazan-based treatment was from studies conducted outside the United States.

As noted, clarithromycin-based regimens can be used when clarithromycin resistance does not exceed 15%, but with higher resistance rates, bismuth-based quadruple therapy regimens guided by susceptibility testing are preferred.[4,10,11] In a multicenter, randomized controlled trial conducted in the United States and Europe, vonoprazan regimens were noninferior to standard therapy

(proton pump inhibitor triple therapy).[30] Eradication success rates among patients with clarithromycin- and amoxicillin-susceptible organisms were 78.5% for vonoprazan dual therapy and 84.7% for vonoprazan triple therapy, compared with 78.8% for standard therapy. In cases involving clarithromycin-resistant organisms, both vonoprazan regimens (69.6% for dual therapy and 65.8% for triple therapy) showed superiority over standard therapy (31.9%). Despite the superiority of vonoprazan regimens, eradication rates with these regimens remained below the desirable threshold of 70% when used against clarithromycin-resistant organisms. As long as clarithromycin resistance rates in the United States exceed 30%,[14] vonoprazan-based regimens may not be optimal. Further studies are warranted to evaluate vonoprazan-based regimens in settings where clarithromycin resistance exceeds 15%.

Table 4 summarizes a proposed treatment approach for *H pylori* infection based on susceptibility testing and incorporating vonoprazan-based regimens.[31]

CONCLUSION

H pylori infection is the most common carcinogenic infection worldwide. Eradication therapy is indicated for all individuals who test positive for active infection. Due to the rising burden of antibiotic resistance, susceptibility testing for *H pylori* infection is recommended when local empiric therapy cure rates are less than 90%; testing is also recommended after a failed first treatment attempt. Several *H pylori* eradication therapies, including vonoprazan-based regimens, are available. Clinicians should tailor the therapy according to antimicrobial susceptibility testing results, the local antibiogram, cost, pill burden, and patient-related factors.

Acknowledgment: *The authors thank Dr. Ahmed Salih for his valuable support throughout the writing of this manuscript.*

DISCLOSURES

Dr. Wallace has disclosed consulting for Boston Scientific Corporation, Cosmo Pharmaceuticals, and Fujifilm, and ownership interest (stock, stock options in a publicly traded company) in Verily. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Hooi JKY, Lai WY, Ng WK, et al.** Global prevalence of *Helicobacter pylori* Infection: systematic review and meta-analysis. Gastroenterology 2017; 153(2):420–429. doi:10.1053/j.gastro.2017.04.022
2. **Robinson K, Atherton JC.** The spectrum of *Helicobacter*-mediated diseases. Annu Rev Pathol 2021; 16:123–144. doi:10.1146/annurev-pathol-032520-024949
3. **Shah SC, Halvorson AE, Lee D, et al.** *Helicobacter pylori* burden in the United States according to individual demographics and geography: a nationwide analysis of the Veterans healthcare system. Clin Gastroenterol Hepatol 2024; 22(1):42–50.e26. doi:10.1016/j.cgh.2023.05.016
4. **Chey WD, Leontiadis GI, Howden CW, Moss SF.** ACG clinical guideline: treatment of *Helicobacter pylori* Infection [published correction appears in Am J Gastroenterol 2018; 113(7):1102]. Am J Gastroenterol 2017; 112(2):212–239. doi:10.1038/ajg.2016.563
5. **de Martel C, Georges D, Bray F, Ferlay J, Clifford GM.** Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health 2020; 8(2):e180–e190. doi:10.1016/S2214-109X(19)30488-7
6. **Herrero R, Park JY, Forman D.** The fight against gastric cancer—the IARC Working Group report. Best Pract Res Clin Gastroenterol 2014; 28(6):1107-1114. doi:10.1016/j.bpg.2014.10.003
7. **El-Serag HB, Kao JY, Kanwal F, et al.** Houston consensus conference on testing for *Helicobacter pylori* infection in the United States [published correction appears in Clin Gastroenterol Hepatol 2019; 17(4):801]. Clin Gastroenterol Hepatol 2018; 16(7):992–1002.e6. doi:10.1016/j.cgh.2018.03.013
8. **Kamboj AK, Cotter TG, Oxentenko AS.** *Helicobacter pylori*: the past, present, and future in management. Mayo Clin Proc 2017; 92(4):599–604. doi:10.1016/j.mayocp.2016.11.017
9. **Bordin DS, Voynovan IN, Andreev DN, Maev IV.** Current *Helicobacter pylori* diagnostics. Diagnostics (Basel) 2021; 11(8):1458. doi:10.3390/diagnostics11081458
10. **Malfertheiner P, Megraud F, O'Morain CA, et al.** Management of *Helicobacter pylori* infection-the Maastricht V/Florence consensus report. Gut 2017; 66(1):6–30. doi:10.1136/gutjnl-2016-312288
11. **Fallone CA, Moss SF, Malfertheiner P.** Reconciliation of recent *Helicobacter pylori* treatment guidelines in a time of increasing resistance to antibiotics. Gastroenterology 2019; 157(1):44–53. doi:10.1053/j.gastro.2019.04.011
12. **Argueta EA, Alsamman MA, Moss SF, D'Agata EMC.** Impact of antimicrobial resistance rates on eradication of *Helicobacter pylori* in a US population. Gastroenterology 2021; 160(6):2181–2183.e1. doi:10.1053/j.gastro.2021.02.014
13. **Shah SC, Iyer PG, Moss SF.** AGA clinical practice update on the management of refractory *Helicobacter pylori* Infection: expert review. Gastroenterology 2021; 160(5):1831–1841. doi:10.1053/j.gastro.2020.11.059
14. **Ho JJC, Navarro M, Sawyer K, Elfanagely Y, Moss SF.** *Helicobacter pylori* antibiotic resistance in the United States between 2011 and 2021: a systematic review and meta-analysis. Am J Gastroenterol 2022; 117(8):1221–1230. doi:10.14309/ajg.0000000000001828
15. **Graham DY, Moss SF.** Antimicrobial susceptibility testing for *Helicobacter pylori* is now widely available: when, how, why. Am J Gastroenterol 2022; 117(4):524–528. doi:10.14309/ajg.0000000000001659
16. **Graham DY, Liou JM.** Primer for development of guidelines for *Helicobacter pylori* therapy using antimicrobial stewardship. Clin Gastroenterol Hepatol 2022; 20(5):973–983.e1. doi:10.1016/j.cgh.2021.03.026
17. **Dore MP, Graham DY.** Modern approach to the diagnosis of *Helicobacter pylori* infection. Aliment Pharmacol Ther 2022; 55(suppl 1):S14–S21. doi:10.1111/apt.16566
18. **Saleem N, Howden CW.** Update on the management of *Helicobacter pylori* infection. Curr Treat Options Gastroenterol 2020; 18(3):476–487. doi:10.1007/s11938-020-00300-3
19. **Scott D, Weeks D, Melchers K, Sachs G.** The life and death of *Helicobacter pylori.* Gut 1998; (suppl 1):S56–S60. doi:10.1136/gut.43.2008.s56
20. **Graham DY, Fischbach L.** *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. Gut 2010; 59(8):1143–1153. doi:10.1136/gut.2009.192757
21. **Bakheit AH, Al-Kahtani HM, Albraiki S.** Rabeprazole: A comprehensive profile. Profiles Drug Subst Excip Relat Methodol 2021; 46:137-183. doi:10.1016/bs.podrm.2020.07.003
22. **Harris DM, Stancampiano FF, Burton MC, et al.** Use of pharmacogenomics to guide proton pump inhibitor therapy in clinical practice. Dig Dis Sci 2021; 66(12):4120–4127. doi:10.1007/s10620-020-06814-1

23. **Leowattana W, Leowattana T.** Potassium-competitive acid blockers and gastroesophageal reflux disease. World J Gastroenterol 2022; 28(28):3608–3619. doi:10.3748/wjg.v28.i28.3608
24. **Miftahussurur M, Pratama Putra B, Yamaoka Y.** The potential benefits of vonoprazan as *Helicobacter pylori* infection therapy. Pharmaceuticals (Basel) 2020; 13(10):276. doi:10.3390/ph13100276
25. **Gatta L, Scarpignato C.** S1368 vonoprazan-based dual therapy and FDA-approved *H pylori* eradication regimens: a comparison of the available pooled data [abstract]. Am J Gastroenterol 2020; 115:S690–691.
26. **Sun Y, Yue L, Hu W.** Effectiveness and safety of vonoprazan-based regimens compared with those of proton pump inhibitor ['p'[-based regimens as first-line agents for *Helicobacter pylori*: a meta-analysis of randomized clinical trials. Eur J Clin Pharmacol 2023; 79(2): 279–288. doi:10.1007/s00228-022-03430-y
27. **Shinozaki S, Kobayashi Y, Osawa H, et al.** Effectiveness and safety of vonoprazan versus proton pump inhibitors for second-line *Helicobacter pylori* eradication therapy: systematic review and meta-analysis. Digestion 2021; 102(3):319–325. doi:10.1159/000504939
28. **Ouyang Y, Wang M, Xu YL, Zhu Y, Lu NH, Hu Y.** Amoxicillin-vonoprazan dual therapy for *Helicobacter pylori* eradication: a systematic review and meta-analysis. J Gastroenterol Hepatol 2022; 37(9):1666–1672. doi:10.1111/jgh.15917
29. **Chen PY, Tsai FP, Chen MJ, Yang HY, Wu MS, Liou JM.** Vonoprazan-based versus proton pump inhibitor-based therapy in *Helicobacter pylori* eradication: an updated systematic review and meta-analysis of randomised trials. Gut 2024; 73(5):872–874. doi:10.1136/gutjnl-2023-329826
30. **Chey WD, Mégraud F, Laine L, López LJ, Hunt BJ, Howden CW.** Vonoprazan triple and dual therapy for *Helicobacter pylori* infection in the United States and Europe: randomized clinical trial. Gastroenterology 2022; 163(3):608–619. doi:10.1053/j.gastro.2022.05.055
31. **Fallone CA.** The current role of vonoprazan in *Helicobacter pylori* treatment. Gastroenterology 2022; 163(3):572–574. doi:10.1053/j.gastro.2022.06.076

Address: Wafa A. Aldhaleei, MBBCh, MSc, MPH, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905; Aldhaleei.Wafa@mayo.edu

The Role of Behavioral Medicine in Reducing OPIOID USE

Provided by Cleveland Clinic | The France Foundation

Complimentary, CE-certified Online Education

Participate in education that focuses on utilizing behavioral medicine to reduce opioid use and covers all aspects of the core content outlined in the revised FDA Blueprint, with an emphasis on behavioral health and how the application of behavioral methods can help control pain.

The content in this complimentary, CE-certified online education is broken down into four modules: The Basics of Pain Management, Creating the Pain Treatment Plan, Managing Patients with Pain on Opioid Analgesics, and Addiction Medicine Primer. This is a FDA REMS-compliant accredited CE activity.

Hosted by Cleveland Clinic

Robert Bales, MD
Department of Family Medicine, Primary Care Institute
Center for Behavioral Health, Neurological Institute

Richard W. Rosenquist, MD
Chairman, Pain Management Department

Pavan Tankha, DO
Medical Director, Center for Comprehensive Pain Recovery

Amy Zack, MD
Vice Chair of Education, Primary Care Institute

Participate today!

ccfcme.org/opioid-use-cme

This activity has been approved for *AMA PRA Category 1 Credit*™, ANCC contact hours, and AAPA Category 1 CME credits.

Alejandro Durán Crane, MD
Cardiovascular Medicine Fellow,
Cleveland Clinic, Cleveland, OH

Michael Militello, PharmD, BCPS
Cardiology Clinical Pharmacist,
Pharmacotherapy Residency Program Director,
Cleveland Clinic, Cleveland, OH

Michael D. Faulx, MD
Department of Cardiovascular Medicine,
Cleveland Clinic, Cleveland, OH; Professor,
Cleveland Clinic Lerner College of Medicine
of Case Western Reserve University,
Cleveland, OH

Digoxin is still useful, but is still causing toxicity

ABSTRACT

Digoxin, the oldest known cardiovascular drug, is still used today to treat heart failure and atrial fibrillation. Because it has a narrow therapeutic index and multiple interactions, it frequently causes toxicity with a wide range of symptoms and cardiac arrhythmias. More importantly, elevated serum digoxin levels have been linked to a higher risk of death in patients with heart failure or atrial fibrillation, even without signs or symptoms of toxicity. This article reviews the current state of digoxin use, its pharmacologic principles, and the mechanisms, clinical presentation, and management of toxicity.

KEY POINTS

Digoxin, a reversible sodium-potassium adenosine triphosphatase inhibitor, has inotropic and vagomimetic properties that make it useful for treating refractory heart failure with reduced ejection fraction and for controlling the heart rate in atrial fibrillation.

The drug has a narrow therapeutic index, and toxicity is common, especially in patients with impaired kidney function, polypharmacy, or electrolyte derangements.

Digoxin toxicity can present with a wide range of nonspecific gastrointestinal and central nervous system symptoms and several cardiac arrhythmias. Hence, it can be difficult to diagnose and easy to miss.

Treatment of digoxin toxicity includes supportive management and digoxin-specific antibody fragments that can be used if the patient has life-threatening cardiac arrhythmias or electrolyte abnormalities.

doi:10.3949/ccjm.91a.23105

Digoxin, extracted from the foxglove plant (*Digitalis purpurea* and *Digitalis lanata*), is the oldest cardiovascular drug still used today. As far back as 1785, when Dr. William Withering reported using foxglove to treat edematous states ("dropsy"), physicians have known about its beneficial effects—and its toxicity.[1] Here is Dr. Withering:

"The Foxglove when given in very large and quickly-repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow; increased secretion of urine, with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death."

For more than 2 centuries, the drug was the mainstay of treatment for heart failure, as it increases both the force of the heart's contractions and the urine volume. It also has a parasympathetic effect, giving it a role in controlling the ventricular rate in patients with atrial fibrillation. Although digoxin use is decreasing (prescriptions for it dropped by 46.4% in the United States from 2007 to 2014, for example[2]), it is still widely used.

Before laboratory assays were widely available to measure the serum digoxin concentration, physicians would titrate the drug to clinical response (increase in urine output or reduction of cardiac silhouette in the chest radiograph) or until side effects such as nausea, altered color perception, or electrocardiographic changes ensued. Digoxin toxicity was therefore common, and its presentation was widely taught in medical schools. Not until the 1970s, when a radioimmunoassay to measure serum digoxin concentrations became

TABLE 1
Dosing recommendations for digoxin therapy

Indication	Dosing	Desired serum concentration	Comments
Symptomatic heart failure with reduced ejection fraction despite guideline-directed medical therapy	0.125–0.25 mg daily, modified according to nomogram of Jelliffe and Brooker[6]	0.5–0.9 ng/mL	No need for loading dose Low doses (0.125 mg daily or every other day) should be used initially if the patient is > 70 years, has impaired renal function, or has a low lean body mass
Rate control in atrial fibrillation with decreased left ventricular function or hemodynamic instability	Loading dose: 0.25 mg intravenously with repeat dosing every 6 hours to a maximum of 1.5 mg over 24 hours Maintenance dose: 0.125–0.25 mg daily	0.5–1.2 ng/mL	For individuals with low body weight (45–70 kg) and renal dysfunction, loading doses should be reduced to 0.7 to 1.0 mg in the first 24 hours

Based on information from references 3–5.

available, were doses titrated to a target therapeutic range, and thereafter toxicity became less frequent.

Nonetheless, digoxin is still causing toxicity, having a narrow therapeutic index, multiple interactions, and variability of serum levels with changes in renal clearance. And not only does digoxin toxicity produce a wide range of morbidity, but, more importantly, elevated serum levels are associated with increased mortality. Therefore, cardiovascular and internal medicine physicians still need to be familiar with the presentation of digoxin toxicity, its mechanisms and predisposing factors, and its medical management.

DIGOXIN'S CLINICAL USES

Digoxin is approved by the US Food and Drug Administration for treating heart failure with reduced ejection fraction (HFrEF) and for rate control in atrial fibrillation. **Table 1** shows the dosing recommendations for digoxin based on the American Heart Association (AHA) and American College of Cardiology (ACC) guidelines.[3–6]

Heart failure with reduced ejection fraction

The 2022 AHA/ACC guidelines[4] recommend digoxin for patients with HFrEF who have symptoms despite guideline-directed medical therapy and for patients who cannot tolerate guideline-directed medical therapy, to decrease hospitalizations for decompensated heart failure. However, digoxin gets only a class 2b (weak) recommendation, based on level B-R evidence (moderate quality, based on randomized trials or meta-analysis of such trials). With its inotropic properties, digoxin is useful specifically for patients with end-stage HFrEF who cannot tolerate afterload-reduction agents because of hypotension. In this population, digoxin can increase the cardiac index and offset neurohormonal imbalances present in heart failure.

Data on digoxin in heart failure

The DIG trial. The AHA/ACC recommendation is based on results from the Digitalis Investigation Group (DIG) trial,[7] published in 1997. Patients in this trial had left ventricular ejection fractions of 45% or less and normal sinus rhythm, and were already on diuretics and angiotensin-converting enzyme inhibitors (the mainstay of heart failure therapy in 1997). They were randomized in a double-blind fashion to receive digoxin or placebo. The digoxin group did not have a lower mortality rate, but they did have a lower rate of hospitalizations for heart failure (risk ratio [RR] 0.72, 95% confidence interval [CI] 0.66–0.79, $P < .001$).

Of note, 11.9% of the patients in the digoxin group developed suspected digoxin toxicity vs 7.9% in the placebo group, representing a number needed to harm of 25. Of those in the digoxin group with suspected toxicity, 16.5% were hospitalized. There was no difference in the rate of ventricular arrhythmias between groups, but the digoxin group did have higher rates of supraventricular tachyarrhythmias (2.5% vs 1.2%, RR 2.10, 95% CI 1.45–3.07, $P < .001$) and second- or third-degree atrioventricular block (1.2% vs 0.4%, RR 2.87, 95% CI 1.56–5.28, $P < .001$).[7]

A post hoc analysis of the DIG trial[8] suggested that patients with higher serum digoxin concentrations (≥ 1 ng/mL) had higher rates of cardiovascular mortality (hazard ratio [HR] 1.26, $P < .001$) and all-cause mortality (HR 1.23, $P < .002$) compared with patients with lower concentrations and those on placebo. In contrast, patients with low concentrations had lower mortality rates compared with those on placebo; hence the dosing recommendations in current guidelines.

Get with the Guidelines. With the advent over the past 3 decades of multiple drugs that reduce mortality, digoxin use for heart failure has decreased significantly. Data from more than 117,000 patients with HFrEF enrolled in the Get with the Guidelines registry between 2005 and 2014 showed that, over time, prescriptions for digoxin decreased substantially, from 33.1% of all patients with HFrEF in 2005 to 10.7% in 2014 ($P < .0001$), a 68% relative reduction.[9]

Goldberger and Alexander[10] similarly showed that office visits for digoxin therapy for heart failure in the United States declined by 91%, from more than 2.5 million visits in 1997 to fewer than 500,000 in 2012.

Atrial fibrillation

The 2023 AHA/ACC and Heart Rhythm Society guidelines for the management of patients with atrial fibrillation[5] state that digoxin can be considered as a rate-control agent, albeit not as a first-line agent and usually in conjunction with beta-blockers or nondihydropyridine calcium channel blockers. The class of recommendation is 2a (moderate), level of evidence B-R.

Digoxin can be particularly helpful in patients with atrial fibrillation associated with severe left ventricular dysfunction and heart failure. Likewise, it is helpful in patients who cannot tolerate other rate-control drugs, patients with hypotension or borderline low blood pressure who cannot tolerate beta-blockers or calcium channel blockers for rate control, or patients in whom cardioversion is contraindicated due to risk of stroke. It is not recommended in patients with preexcitation and atrial fibrillation.[5]

Data on digoxin in atrial fibrillation

In several studies conducted over the past decade, 23%[11] to 33%[12] of patients with atrial fibrillation were receiving digoxin at baseline, and several suggested that digoxin may be associated with higher mortality rates. For example:

TREAT-AF (The Retrospective Evaluation and Assessment of Therapies in Atrial Fibrillation),[11] using data from more than 100,000 patients with atrial fibrillation in the Veterans Health Administration healthcare system between 2003 and 2008, showed that those treated with digoxin had higher mortality rates than those not treated with digoxin, even after adjusting for drug adherence:

- After multivariate adjustment: HR 1.26, 95% CI 1.23–1.29, $P < .001$
- After propensity matching: HR 1.21, 95% CI 1.17–1.25, $P < .001$.

The ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation)[13] similarly showed that patients with digoxin levels of 1.2 ng/mL or greater had a higher risk of death (adjusted HR 1.56, 95% CI 1.20–2.04, $P < .001$) compared with those not on digoxin. For sudden cardiac death, the number needed to harm was 180 for the first year of use and 56 at 2 years.

Vamos et al[14] performed a meta-analysis of 37 trials of digoxin therapy for both heart failure and atrial fibrillation and found a higher risk of death in patients taking digoxin (HR 1.17, 95% CI 1.05–1.29, $P < .01$). The increase was higher in patients taking digoxin for atrial fibrillation (HR 1.23) than in those taking it for heart failure (HR 1.11).

DIGOXIN HAS INOTROPIC AND OTHER EFFECTS

Embedded in the cell membrane of cardiac myocytes is an important molecule: sodium-potassium adenosine triphosphatase (ATPase). This molecule pumps sodium ions out of the cell and potassium ions in, so that there is more sodium outside than in the cell, and more potassium inside than out. At the same time, another pump, the sodium-calcium exchanger, takes advantage of this sodium gradient to let sodium ions back into the cell while pumping calcium out.

Digoxin inhibits sodium-potassium ATPase, so that there is more sodium inside the cell and therefore less of a sodium gradient. In turn, the sodium-calcium exchanger cannot pump as much calcium out of the cell, resulting in higher intracellular concentrations of calcium. The excess calcium binds with troponin C and other contractile proteins that rely on calcium coupling, thus leading to an enhanced myocardial inotropic response and increased force of contraction.

Digoxin's effect on cardiac contractility is seen primarily in patients with decreased left ventricular function, in whom digoxin improves left ventricular ejection fraction and decreases pulmonary capillary wedge pressure. These effects are not seen in patients with normal left ventricular ejection fraction.[15]

TABLE 2
Drug interactions that increase the risk of digoxin toxicity

Medication	Mechanism of interaction	Comments
Amiodarone, quinidine, dronedarone, nondihydropyridine calcium channel blockers (diltiazem and verapamil), propafenone, flecainide, clarithromycin, cyclosporine, itraconazole	Inhibition of P-glycoprotein, a drug efflux pump that mediates secretion of digoxin in the kidney, liver, and gut	Digoxin dose may have to be decreased to half when starting any of these medications Check digoxin levels 1 week after starting any P-glycoprotein inhibitor
Macrolides (azithromycin, clarithromycin, erythromycin) and tetracycline	Decreased initial degradation of digoxin by gut microflora, leading to increased drug absorption	Monitor levels closely when co-administering digoxin with these antibiotics
Diuretics, amphotericin B	Decreased glomerular filtration rate and hypokalemia can increase digoxin toxicity	Monitor potassium levels to avoid hypokalemia
Nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, cyclosporine	Decreased glomerular filtration rate and acute kidney injury	Telmisartan increases digoxin concentration by about 50%
Beta-blockers, nondihydropyridine calcium channel blockers	Slowing of atrioventricular conduction can lead to bradycardia compounding on digoxin's vagotonic effects	Increased risk of bradycardia; carvedilol can increase digoxin concentration
Amiodarone, sotalol, quinidine, procainamide, dofetilide, ibutilide, quinolones, macrolides, azole antifungals, tricyclic antidepressants, antipsychotics, methadone	QT-prolonging agents increase risk of life-threatening arrhythmias as digoxin increases early afterdepolarizations, which can lead to R-on-T phenomenon and torsade de pointes	Monitor QT closely when adding any of these medications

Based on information from references 17 and 18.

But there are dangers. More calcium inside the cell leads to inactivation of L-type calcium channels (the main route for calcium entry into cardiomyocytes), which shortens the duration of the action potential and refractory period of cardiomyocytes, a mechanism that favors reentry arrhythmias. Less potassium and more sodium in the cell lead to increased diastolic repolarization and automaticity, which may favor supraventricular arrhythmias and lead to rapid spontaneous rhythms of Purkinje fibers.[15] At higher digoxin concentrations, the sarcoplasmic reticulum becomes overloaded with calcium and can spontaneously release enough calcium to depolarize the cell, resulting in extrasystoles, bigeminy, and a higher risk of ventricular fibrillation.

In the autonomic nervous system, digoxin decreases the sympathetic response and increases the parasympathetic response, mainly by stimulating the central vagal nucleus. It also restores baroreceptor sensitivity, which is attenuated in low-output heart failure, and as such improves heart rate variability and decreases catecholamine release.

In conjuction with digoxin's inotropic effect, these neurohormonal changes lead to favorable hemodynamic changes in heart failure. Decreased preload and afterload with increased contractility lead to reduced chamber dilation and wall stress, thereby reducing myocardial oxygen consumption. The vagal (parasympathetic) effects of digoxin result in a lower sinus rate, decreased automaticity and conduction velocity, and a prolonged refractory period of the atrioventricular node, which makes it effective for rate control in atrial fibrillation.[15]

PHARMACOKINETICS AND DOSING

Digoxin has an oral bioavailability of about 70%. In some individuals, gut microflora can metabolize digoxin and decrease its bioavailability. Twenty-five percent of serum digoxin is albumin-bound, and its volume of distribution is large (5–10 L/kg) due to extensive binding to muscle tissue. The drug penetrates the blood-brain and placental barriers and cannot be removed from plasma with dialysis. Serum digoxin levels are typically checked at least 6 hours after an oral dose.[16]

TABLE 3
Risk factors for digoxin toxicity

Risk factor	Comments
Advanced age	Reduced volume of distribution due to lower muscle mass and reduced renal drug clearance can lead to higher serum concentrations of digoxin in the elderly Digoxin use has been linked to higher mortality in patients age 65 and older with atrial fibrillation and heart failure[19]
Renal dysfunction	Digoxin is primarily excreted by the kidneys and its clearance is directly proportional to the glomerular filtration rate Reduced renal clearance results in higher serum digoxin concentration, and dose should be reduced in patients with renal dysfunction Any condition that leads to acute renal injury (eg, dehydration, sepsis, glomerular or tubular disease, or decompensated heart failure) can predispose to toxicity Digoxin use in patients with end-stage kidney disease undergoing hemodialysis is associated with a 28% increase in mortality and is therefore not recommended[20] If needed in end-stage kidney disease, a loading dose of 3 to 5 µg/kg (0.25–0.375 mg) is recommended, followed by a maintenance dose of 0.0625 mg every 48 hours
Hypokalemia	Decreased potassium levels result in decreased competition for the binding spot of digoxin in sodium-potassium adenosine triphosphatase, favoring binding of digoxin to the ionic pump[17]
Drug interactions	Diuretics, antiarrhythmic drugs, and antibiotics can increase serum digoxin concentration or enhance digoxin action[17,18]

The onset of action after an oral dose is at about 2 hours, and the peak effect is at 6 hours. Given intravenously, the onset of action is within 5 to 30 minutes, with maximum effect within 1.5 to 4 hours. Digoxin is excreted primarily by the kidneys; its half-life is 36 to 48 hours in patients with normal kidney function, but up to 6 to 8 days in anuric patients.[16]

When used for heart failure, digoxin is given in daily oral doses, without the need for a loading dose, and it reaches a steady-state plateau concentration after 4 to 5 half-lives, roughly 6 to 8 days.[16]

When digoxin is used for rate control in atrial fibrillation, intravenous loading is usually required for faster onset of action. In this setting, an initial intravenous dose of 0.25 to 0.5 mg is given over several minutes, followed by 0.25 mg every 6 hours for a total of 0.75 to 1.5 mg over 24 hours (10–12 µg/kg of lean body weight). For patients with low body weight (ie, 45–70 kg), digoxin loading should be limited to 0.75 to 1.0 mg in the first 24 hours.[5,16]

MANY DRUGS INCREASE DIGOXIN LEVELS

Digoxin has several drug interactions that can predispose to toxicity (**Table 2**).[17,18]

P-glycoprotein inhibitors. P-glycoprotein is a drug efflux pump that mediates secretion of digoxin in the kidney, liver, and gut. Drugs that inhibit P-glycoprotein raise the serum level of digoxin and can lead to toxicity. These include several antiarrhythmics such as amiodarone, quinidine, dronedarone, nondihydropyridine calcium channel blockers, propafenone, and flecainide, as well as other drugs such as clarithromycin, cyclosporine, and itraconazole.[17,18] Quinidine can double the serum digoxin concentration, and amiodarone increases it by 60%.

Digoxin dosing should be reduced, typically to half of the previous dose, when it is given concomitantly with most P-glycoprotein inhibitors. Digoxin levels should be checked 1 week after starting these drugs.

Some antibiotics can decrease initial degradation of digoxin by gut microflora and thereby increase its absorption. In about 10% of patients, digoxin undergoes sequential hydrolysis in the proximal gastrointestinal tract. Macrolides and tetracycline increase serum digoxin levels by inhibiting this mechanism, and digoxin levels should be closely monitored when giving these antibiotics.

Diuretics can increase serum digoxin concentrations by decreasing the glomerular filtration rate and causing hypokalemia, which increases digoxin's potential for arrhythmias.

TABLE 4
Clinical manifestations of digoxin toxicity

Cardiac
Tachyarrhythmias
Bidirectional ventricular tachycardia
Ventricular tachycardia
Ventricular fibrillation
Atrial fibrillation
Supraventricular tachycardia
Bradyarrhythmias
Sinus bradycardia
Atrioventricular block
Asystole
Increased ectopy
Atrial ectopy
Ventricular ectopy
Ventricular bigeminy
Gastrointestinal
Nausea
Vomiting
Abdominal pain
Mesenteric ischemia and diarrhea (rare)
Central nervous system
Color perception disturbances (xanthochromia)
Visual disturbances (halos)
Headaches
Confusion
Apathy
Electrolyte abnormalities
Hyperkalemia
Constitutional
Fatigue
Anorexia

Based on information from references 15,19,20,22,23.

INTERACTIONS WITH CATIONS

Hyperkalemia reduces digoxin's binding affinity for sodium-potassium ATPase. On the other hand, *hypokalemia* reduces repolarizing potassium currents in the action potential, leading to increased diastolic depolarizations and automaticity and thus enhancing the arrhythmogenic effects of digoxin.

Hypercalcemia and hypomagnesemia contribute to calcium overload in the sarcoplasmic reticulum and therefore promote spontaneous depolarizations.[17]

CLINICAL PRESENTATION OF TOXICITY

The annual incidence of digoxin toxicity is difficult to accurately define, but older reports claim it to be as high as 13% to 25% of all patients who are prescribed the drug.[17] Risk factors for digoxin toxicity have been widely studied (**Table 3**).[17–20] Because it produces a wide variety of symptoms, digoxin toxicity is easy to suspect, but proving that the symptoms are due to digoxin toxicity is harder. Toxicity is more common with levels higher than 2.0 ng/mL.

A study of all patients who were admitted to a Boston hospital who were taking digoxin during an 8-month period in 1969–1970 reported a prevalence of toxicity of 23%.[21] In patients with confirmed toxicity, the mean serum digoxin concentration was 2.3 ng/mL (± 1.6 ng/mL standard deviation), compared with 1.0 ± 0.5 ng/mL in patients without toxicity. Of note, there was significant overlap in serum levels between patients with or without toxicity, as some patients are unusually sensitive to the drug.

Digoxin toxicity has a variety of symptoms (**Table 4**).[15,19,20,22,23] Cardiac arrhythmias are the most frequent side effect (90% of patients), followed by gastrointestinal symptoms (55%) and central nervous system symptoms (12%).[21]

Cardiac manifestations of digoxin toxicity include virtually any type of arrhythmia and are the most serious and potentially lethal complications of toxicity. Digoxin toxicity can lead to all degrees of atrioventricular block and result in clinically significant bradycardia that can be refractory to pacing, as well as sinus arrest and sinus exit block through its action on the sinus node. Ventricular ectopy is an early sign of digoxin toxicity but is not always present. Bidirectional ventricular tachycardia (**Figure 1**) and nonparoxysmal junctional tachycardia (> 80 beats per minute) are suggestive of but not specific to digoxin toxicity.[22] Enhanced automaticity can lead to supraventricular tachycardia as well as ventricular tachycardia and fibrillation.[17,23]

Other electrocardiographic changes of digoxin toxicity include PR prolongation, shortening of the QT and QTc intervals, and a change in ventricular repolarization resulting in nonspecific ST-segment depressions classically described as "sagging" depressions (**Figure 2**). These changes do not imply toxicity and can be present with therapeutic drug levels.[17]

Gastrointestinal. Nausea, anorexia, and fatigue are common, with anorexia present in up to 61% of individuals.[21] In rare instances, excessive smooth muscle contraction of visceral arteries can lead to mesenteric ischemia manifested with abdominal pain, diarrhea, and gastrointestinal bleeding.

Central nervous system. Visual disturbances can be present and are described as flashing lights, halos, and green-yellow perception impairment. Mental status

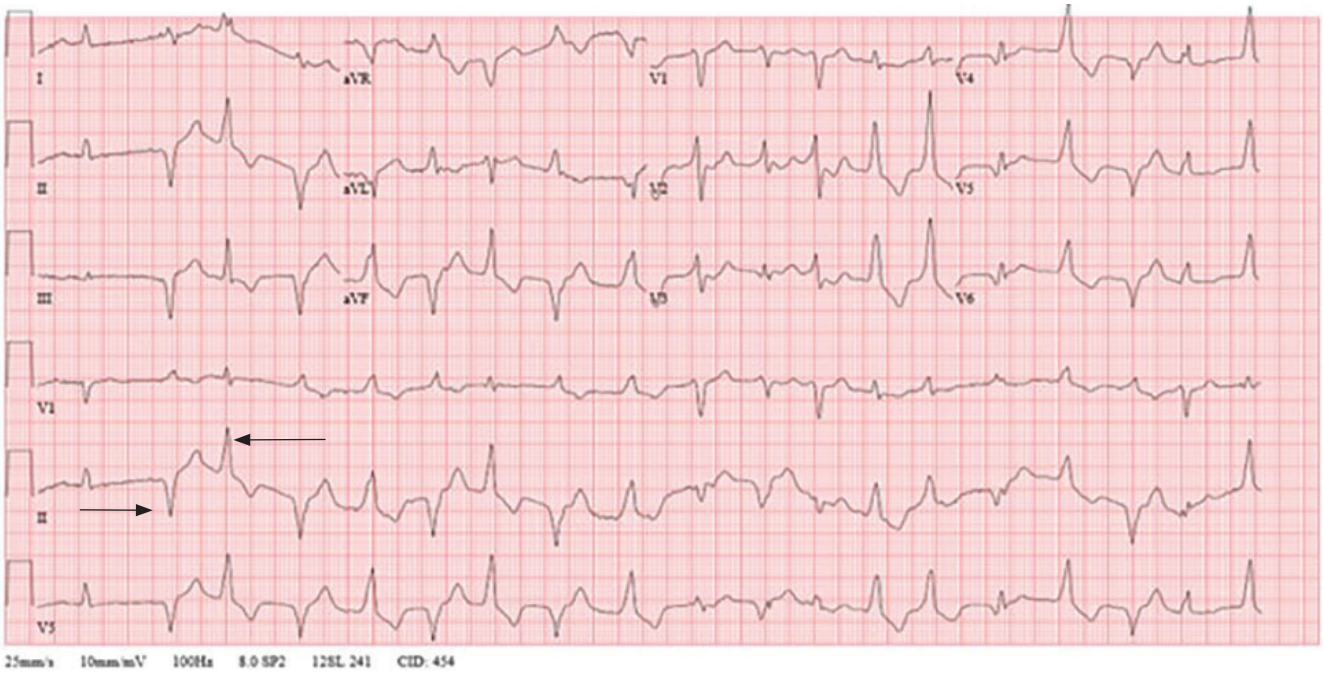


Figure 1. Bidirectional ventricular tachycardia in a patient with digoxin toxicity. The QRS axis alternates with each QRS complex (see rhythm strip for lead II).

changes such as confusion, hallucinations, or apathy can be present, especially in the elderly.[15]

Toxicity can also manifest with hyperkalemia (because less potassium is being pumped into the cells via sodium-potassium ATPase, resulting in elevated extracellular potassium).[15] Attributing these symptoms to digoxin toxicity is often difficult, as some of them are also commonly attributed to cardiovascular disease.

The evaluation of a patient with suspected digoxin toxicity should include an electrocardiogram to assess for arrhythmias and changes associated with digoxin toxicity. Laboratory evaluation should include measurement of digoxin levels as well as renal function and electrolyte disturbances such as hypokalemia, hypercalcemia, and hypomagnesemia, as these are often predisposing factors for toxicity.

MEASURING DIGOXIN LEVELS

Serum digoxin levels are usually measured with immunoassays that measure total digoxin levels, including bound and unbound molecules. When starting therapy, measuring the digoxin level is usually recommended after achieving a steady state, 1 to 2 weeks after initiating therapy.

Because patients with elevated digoxin concentrations (> 1.2 ng/mL) may have no signs of toxicity, and because elevated levels have been linked to increased mortality, measuring serum digoxin levels is recommended to titrate dosing to a goal therapeutic range (**Table 1**). Serum levels should ideally be obtained at least 6 hours after the last dose to avoid falsely elevated results, as complete redistribution of digoxin into body tissues takes several hours.

Immunoassays also identify digoxin-like immunoreactive substances, endogenous molecules equivalent to digitalis that cross-react with many of the older available immunoassays. Digoxin-like immunoreactive substances have been found in neonates and older children, adults with renal insufficiency, hepatic disease, and hypertension, transplant recipients, and pregnant women, increasing the risk for falsely positive results in these populations.[24] Older immunoassays for digoxin have also been known to interact with spironolactone, digoxin-fab, the Chinese medicine *Chan Shu*, and herbal supplements with oleander and lily of the valley extracts.[24] The presence of any of these substances in serum can cause falsely elevated levels of serum digoxin when using available immunoassays.

MANAGEMENT OF DIGOXIN TOXICITY

Digoxin-specific antibody fragments (digoxin-fab) were first developed in 1967 for immunoassays to measure

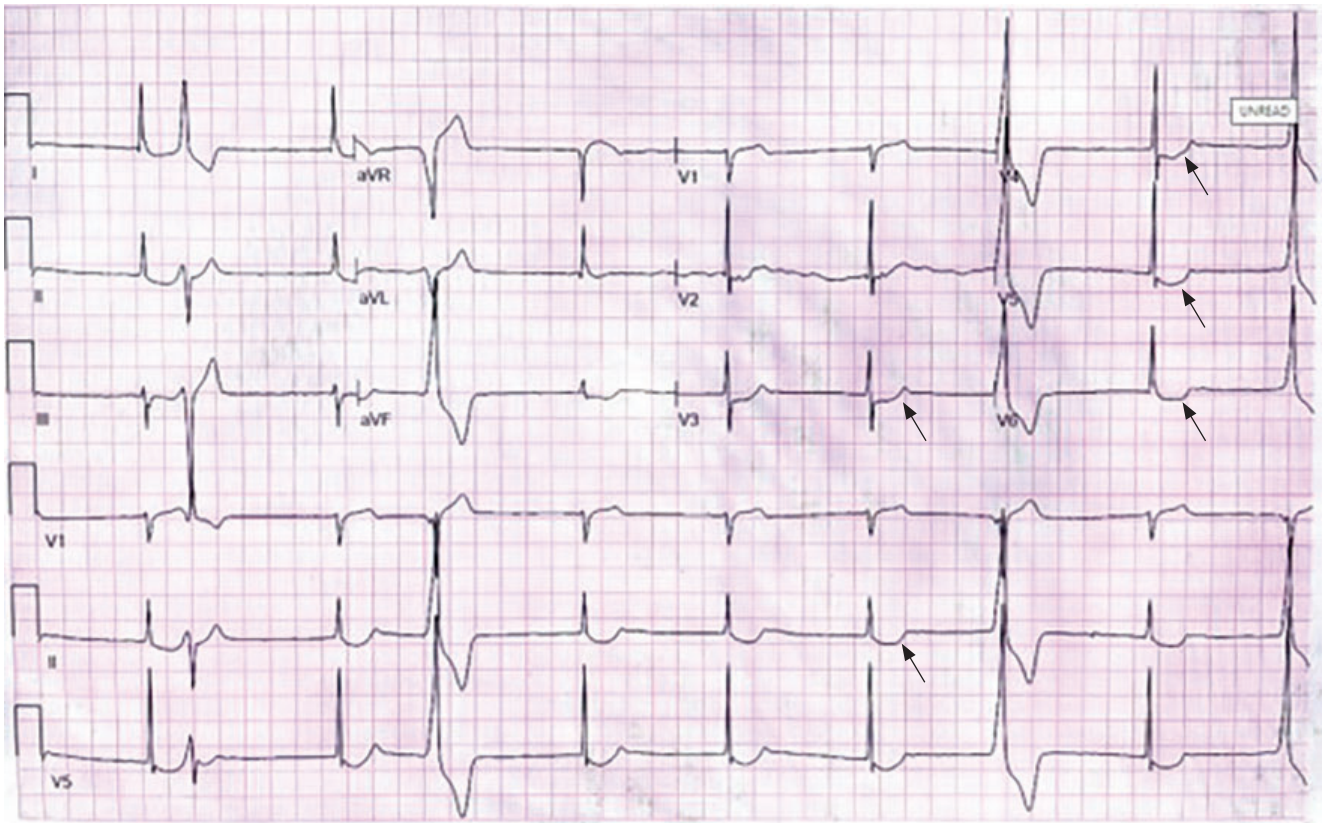


Figure 2. Electrocardiogram showing "sagging" ST depressions, most notably in leads V3–V6 and lead II, and ventricular ectopy in a patient with digoxin toxicity with a serum level of 8.0 ng/mL (normal range 0.6–1.2).

digoxin levels, and were first used to treat acute digoxin toxicity in 1976. Before they became readily available in the 1980s, treatment of digitalis toxicity included stopping the drug and giving supportive therapy with hydration, correcting electrolyte abnormalities, and treating cardiac arrhythmias; mortality rates were as high as 20% to 30%.[25] Quantitative serum digoxin measurements and antibodies to treat digoxin toxicity have reduced the digoxin-associated mortality rate to 3.7% (in-hospital) to 10% (30-day) in the past decade.[2]

Supportive therapy

Supportive therapy with intravenous fluids should be given if the patient has dehydration due to nausea and vomiting. Activated charcoal can be used for patients with acute intoxication if digoxin was ingested less than 2 hours before presentation.

If symptomatic bradycardia is present, atropine can help improve the heart rate temporarily by decreasing vagal tone, but its effects are usually transitory. Transvenous pacing can often result in iatrogenic arrhythmias in the setting of digoxin toxicity and therefore should be avoided unless bradycardia is refractory to atropine.[26]

Electrolyte abnormalities such as hypokalemia and hypomagnesemia should be corrected, as these can potentiate toxicity. Hyperkalemia should be corrected without using calcium salts, as these can worsen intracellular hypercalcemia and worsen spontaneous cardiac depolarizations.

Digoxin-fab

Mild cases of toxicity might resolve if digoxin therapy is simply stopped, but severe cases with bradycardia or ventricular arrhythmias generally require the use of digoxin-fab. It is indicated in patients with life-threatening tachy- or bradyarrhythmias, hyperkalemia (serum potassium > 6 mmol/L), or hemodynamic instability with end-organ dysfunction with elevated serum digoxin concentrations (> 2 ng/mL) that suggest digoxin is the cause.[27]

Digoxin-fab is an ovine (sheep) monovalent immunoglobulin with 100 to 1,000 times more affinity for digoxin than digoxin's binding site in sodium-potassium ATPase.[27] It rapidly binds free digoxin in the serum and creates a gradient for intracellular digoxin to move into the serum, where it is subsequently bound by antibodies.

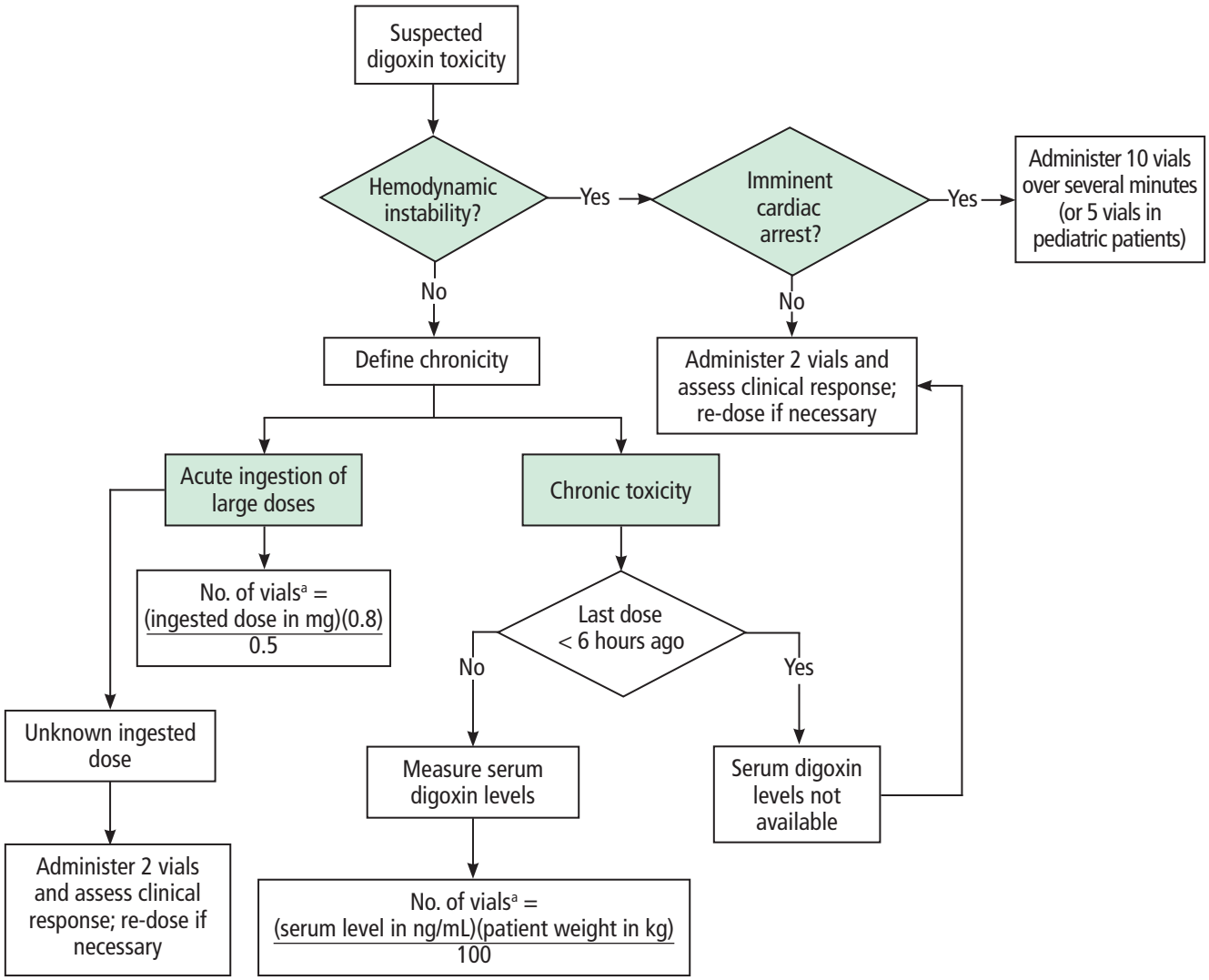


Figure 3. Treatment of severe digoxin toxicity with digoxin-fab.

[a]The calculated number of vials should be rounded up to the nearest digit. Each vial contains 38 to 40 mg of digoxin-fab.

Based on information from reference 29.

Digoxin-fab is eliminated by the kidneys and liver; it has a half-life of 19 to 30 hours, but this can increase up to 10 times in patients with renal dysfunction. The onset of action to reversal of digoxin toxicity after acute ingestion is around 30 to 45 minutes.[27] The main adverse effect is a hypersensitivity reaction to sheep protein.

Dosage and administration. One vial contains 38 to 40 mg of digoxin-fab, which binds approximately 0.5 mg of digoxin. In the case of acute ingestion in which the total ingested dose is known, the number of required vials is calculated by dividing the total body load (ingested dose × 0.8) by 0.5 and rounding up to the nearest digit.[28] If steady-state serum digoxin levels are known in a stable patient with chronic toxicity, the dose of vials can be calculated by dividing the product of the serum concentration (in ng/mL) and the patient's weight (in kg) by 100 and rounding up to the nearest digit (**Figure 3**).[29]

If the digoxin level is not known or cannot be accurately measured due to recent ingestion (< 6 hours), 2 vials can be given, with repeated dosing if there is no apparent clinical response.[29] This approach can also be used if a patient has relative hemodynamic instability and waiting for serum digoxin levels is impractical.

The use of digoxin-fab can precipitate rebound heart failure or atrial fibrillation due to the sudden binding of free serum digoxin. If this is a clinical concern, half of the calculated dose can be given instead.

In general, vials should be administered over 30 minutes, unless a patient is in imminent cardiac arrest, in which case 10 vials (or 5 vials for pediatric patients) can be given empirically over several minutes.

Digoxin-fab causes redistribution of digoxin from tissues into serum, and digoxin bound to antibodies is also recognized by immunoassays, both of which can result in rising levels of serum digoxin if these are checked after digoxin-fab administration. In general, digoxin levels should not be used for clinical decision-making up to 3 weeks after using digoxin-fab, since assays will measure antibody-bound digoxin as well as unbound digoxin in serum. Because antibody half-life increases up to 10-fold in patients with renal dysfunction, these patients might require closer monitoring and even measurement of digoxin-binding antibodies before digoxin therapy is restarted.[27]

A significant limitation of digoxin-fab is its cost. Although the direct cost to patients varies widely based on insurance coverage,[30] the only commercially available digoxin-fab in the United States (DigiFab, BTG Pharmaceuticals, Conshohocken, PA) currently costs about $5,000 per 40-mg vial of intravenous powder for injection.

Digoxin-fab is used in about 20% of cases of reported digoxin toxicity.[31] Its utility has been elucidated mostly by case series, which report a response rate of 50% to 90%.[32,33] While its use may show a nonsignificant trend toward lower rates of mortality at 30 days and overall, the efficacy of digoxin-fab is unclear due to the lack of high-quality evidence and the fact that it is used more frequently in patients with underlying comorbidities (mainly heart failure) or with acute intoxication, likely representing a sicker population. Nonetheless, and despite its declining use over several decades, digoxin-fab is the mainstay of treatment for severe digoxin toxicity. Further research into the appropriate dosing and administration of these antibodies is required, given the paucity of high-quality evidence on the management of digoxin toxicity.

A CHANGING LANDSCAPE

The landscape of digoxin use has changed over the past decades. Multiple associations with digoxin use and increased mortality in heart failure and atrial fibrillation, especially with higher serum concentrations, have raised concerns about the use of this medication. Due to digoxin's narrow therapeutic window, dependence on renal clearance, and multiple drug interactions, digoxin toxicity occurs often and remains an important clinical entity despite a decreasing trend in digoxin use.

Toxicity has a wide range of symptoms and cardiovascular effects that can result in potentially fatal arrhythmias and death, and therefore digoxin use must be monitored carefully, with knowledge of the drug's pharmacokinetic profile. The availability of digoxin-specific antibody fragments has allowed prompt treatment of severe cases of digoxin toxicity associated with life-threatening arrhythmias.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Withering W.** An Account of the Foxglove, and Some of its Medical Uses: With Practical Remarks on Dropsy, and Other Diseases. Birmingham: M. Swinney, 1785. Gutenberg.org/ebooks/24886. Accessed July 19, 2024.
2. **Angraal S, Nuti SV, Masoudi FA, et al.** Digoxin use and associated adverse events among older adults. Am J Med 2019; 132(10): 1191–1198. doi:10.1016/j.amjmed.2019.04.022
3. **January CT, Wann LS, Calkins H, et al.** 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration with the Society of Thoracic Surgeons [published correction appears in Circulation 2019; 140(6):e285]. Circulation 2019; 140(2):e125–e151. doi:10.1161/CIR.0000000000000665
4. **Heidenreich PA, Bozkurt B, Aguilar D, et al.** 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022; 145:e895–e1032. doi:10.1161/CIR.0000000000001063
5. **Joglar JA, Chung MK, Armbruster AL, et al.** 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2024; 149(1):e1–e156. doi: 10.1161/CIR.0000000000001193
6. **Jelliffe RW, Brooker G.** A nomogram for digoxin therapy. Am J Med 1974; 57(1):63–68. doi:10.1016/0002-9343(74)90769-4
7. **Digitalis Investigation Group.** The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997; 336(8):525–533. doi:10.1056/NEJM199702203360801
8. **Ahmed A, Rich MW, Love TE, et al.** Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. Eur Heart J 2006; 27(2):178–186. doi:10.1093/eurheartj/ehi687
9. **Patel N, Ju C, Macon C, et al.** Temporal trends of digoxin use in patients hospitalized with heart failure: analysis from the American Heart Association Get with the Guidelines-Heart Failure registry. JACC Heart Fail 2016; 4(5):348–356. doi:10.1016/j.jchf.2015.12.003
10. **Goldberger ZD, Alexander GC.** Digitalis use in contemporary clinical practice: refitting the foxglove. JAMA Intern Med 2014; 174(1): 151–154. doi:10.1001/jamainternmed.2013.10432

11. **Turakhia MP, Santangeli P, Winkelmayer WC, et al.** Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF study. J Am Coll Cardiol 2014; 64(7):660–668. doi:10.1016/j.jacc.2014.03.060
12. **Granger CB, Alexander JH, McMurray JJ, et al.** Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365(11):981–992. doi:10.1056/NEJMoa1107039
13. **Lopes RD, Rordorf R, De Ferrari GM, et al.** Digoxin and mortality in patients with atrial fibrillation. J Am Coll Cardiol 2018; 71(10): 1063–1074. doi:10.1016/j.jacc.2017.12.060
14. **Vamos M, Erath JW, Benz AP, Lopes RD, Hohnloser SH.** Meta-analysis of effects of digoxin on survival in patients with atrial fibrillation or heart failure: an update. Am J Cardiol 2019; 123(1):69–74. doi:10.1016/j.amjcard.2018.09.036
15. **Eichhorn EJ, Gheorghiade M.** Digoxin. Prog Cardiovasc Dis 2002; 44(4):251–266. doi:10.1053/pcad.2002.31591
16. **GlaxoSmithKline.** Prescribing information. Lanoxin (digoxin) tablets, USP. 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020405s004lbl.pdf. Accessed July 19, 2024.
17. **Smith TW, Antman EM, Friedman PL, Blatt CM, Marsh JD.** Digitalis glycosides: mechanisms and manifestations of toxicity. Part I. Prog Cardiovasc Dis 1984; 26(5):413–458. doi:10.1016/0033-0620(84)90012-4
18. **Fromm MF, Kim RB, Stein CM, Wilkinson GR, Roden DM.** Inhibition of P-glycoprotein-mediated drug transport: a unifying mechanism to explain the interaction between digoxin and quinidine [see comments]. Circulation 1999; 99(4):552–557. doi:10.1161/01.cir.99.4.552
19. **Shah M, Avgil Tsadok M, Jackevicius CA, Essebag V, Behlouli H, Pilote L.** Relation of digoxin use in atrial fibrillation and the risk of all-cause mortality in patients ≥ 65 years of age with versus without heart failure. Am J Cardiol 2014; 114(3):401–406. doi:10.1016/j.amjcard.2014.05.013
20. **Chan KE, Lazarus JM, Hakim RM.** Digoxin associates with mortality in ESRD. J Am Soc Nephrol 2010; 21(9):1550–1559. doi:10.1681/ASN.2009101047
21. **Beller GA, Smith TW, Abelmann WH, Haber E, Hood WB Jr.** Digitalis intoxication. A prospective clinical study with serum level correlations. N Engl J Med 1971; 284(18):989–997. doi:10.1056/NEJM197105062841801
22. **Almarzuqi A, Kimber S, Quadros K, Senaratne J.** Bidirectional ventricular tachycardia: challenges and solutions. Vasc Health Risk Manag 2022; 18:397–406. doi:10.2147/VHRM.S274857
23. **Saner HE, Lange HW, Pierach CA, Aeppli DM.** Relation between serum digoxin concentration and the electrocardiogram. Clin Cardiol 1988; 11(11):752–756. doi:10.1002/clc.4960111106
24. **Dasgupta A.** Significant improvement in digoxin immunoassays over four decades: newer assays are less affected by interferences. Ther Drug Monit 2023; 45(1):26–34. doi:10.1097/FTD.0000000000001005
25. **Williamson KM, Thrasher KA, Fulton KB, et al.** Digoxin toxicity: an evaluation in current clinical practice. Arch Intern Med 1998; 158(22):2444–2449. doi:10.1001/archinte.158.22.2444
26. **Taboulet P, Baud FJ, Bismuth C, Vicaut E.** Acute digitalis intoxication—is pacing still appropriate? J Toxicol Clin Toxicol 1993; 31(2):261–273. doi:10.3109/15563659309000393
27. **Chan BS, Buckley NA.** Digoxin-specific antibody fragments in the treatment of digoxin toxicity. Clin Toxicol (Phila) 2014; 52(8): 824–836. doi:10.3109/15563650.2014.943907
28. **Digifab digoxin immune fab (ovine).** Full prescribing information. West Conshohocken, PA; BTG International Inc, 2001. https://digifab.health/getmedia/f821face-fe6e-4105-8090-5b81816942f0/DigiFab-PI_P12011E_A4-Updated-June2017.pdf. Accessed July 19, 2024.
29. **Levine MD, O'Connor A.** Dosing regimen for digoxin-specific antibody (Fab) fragments in patients with cardiac glycoside (digoxin) toxicity. UpToDate. Updated May 22, 2024. https://www-uptodate-com.ccmain.ohionet.org/contents/dosing-regimen-for-digoxin-specific-antibody-fab-fragments-in-patients-with-cardiac-glycoside-digoxin-toxicity?topicRef=319&source=see_link. Accessed July 19, 2024.
30. **Johnson AR, Crouch B, Horowitz BZ.** Discrepancies in reported US pricing information for digoxin-Fab. Clin Toxicol (Phila) 2015; 53(1):71. doi:10.3109/15563650.2014.994065
31. **Hauptman PJ, Blume SW, Lewis EF, Ward S.** Digoxin toxicity and use of digoxin immune Fab: insights from a national hospital database. JACC Heart Fail 2016; 4(5):357–364. doi:10.1016/j.jchf.2016.01.011
32. **Antman EM, Wenger TL, Butler VP Jr, Haber E, Smith TW.** Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. Circulation 1990; 81(6):1744–1752. doi:10.1161/01.cir.81.6.1744
33. **Hickey AR, Wenger TL, Carpenter VP, et al.** Digoxin immune Fab therapy in the management of digitalis intoxication: safety and efficacy results of an observational surveillance study. J Am Coll Cardiol 1991; 17(3):590–598. doi:10.1016/s0735-1097(10)80170-6

Address: *Michael D. Faulx, MD, Department of Cardiovascular Medicine, J2-4, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; faulxm@ccf.org*

Cleveland Clinic

Endorsed by:

ACP American College of Physicians Leading Internal Medicine, Improving Lives | Ohio Chapter

Hospital Medicine 2024

September 5-6, 2024
InterContinental Hotel & Conference Center
Cleveland, OH and Live stream

Register now! ccfcme.org/HospitalMedicine

Why attend the Hospital Medicine 2024 Symposium?

- Hear from expert faculty addressing the most common inpatient conditions
- Learn best practices for improving the care of hospitalized patients
- Q&A panel discussions to supplement the presentations
- Earn CME and ABIM MOC points
- Choose the format that works best for you - in-person or live stream
- Network with colleagues and exhibitors

This activity has been approved for *AMA PRA Category 1 Credit™*, American Nurses Credentialing Center (ANCC) Contact Hours, American Academy of PAs (AAPA) Category 1 CME, IPCE credits, and ABIM MOC Points.

Cleveland Clinic Florida

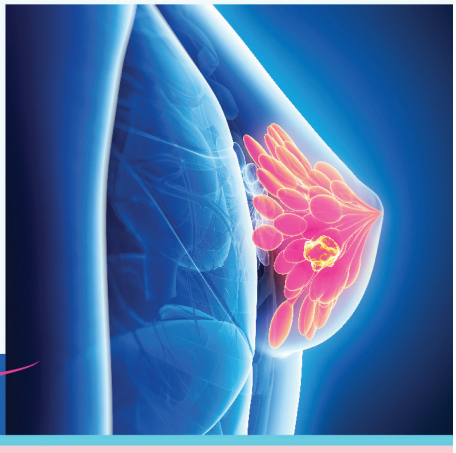
SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center | AACR American Association for Cancer Research

LICENSED BY ENCORE MEDICAL EDUCATION

CME & MOC Credits Available

7th Annual

Best of San Antonio Breast Cancer Symposium® (SABCS®)



Saturday, January 18, 2025

Margaritaville Beach Resort
Hollywood Beach, Florida

www.ccfcme.org/SABCS2025

Cleveland Clinic

Improve Your Virtual Patient Visit Skills

Many patients are eager to visit their physicians virtually, but not all physicians are comfortable conducting virtual visits.

You can take advantage of a free series of self-directed online modules to help you build your virtual patient visit skills.

The free course offers:

- brief introduction to virtual visits
- guidance for demonstrating communication and empathy
- best practices for taking a patient history
- instructions for conducting a physical examination, based on organ system

To help you master the content, the free course includes many video demonstrations and knowledge checks throughout.

Visit clevelandclinic.org/virtual-training

With the exception of the physical examination module, these activities have been approved for *AMA PRA Category 1 Credit™*.

Cleveland Clinic
Sydell and Arnold Miller Family
Heart, Vascular and Thoracic Institute

Tall Rounds®

Fast-paced, case-based online learning with the No. 1 hospital for heart care. Complimentary CME credit available.

clevelandclinic.org/tallrounds

@TallRoundsTM

This activity has been approved for AMA PRA Category 1 Credit™.

David D. Chong, BA
Case Western Reserve University School of Medicine, Cleveland, OH

Nikhil Das, MD
Center for Ophthalmic Bioinformatics, Cole Eye Institute, Cleveland Clinic, Cleveland, OH

Rishi P. Singh, MD
Vice President, Chief Medical Officer, Cleveland Clinic Martin Hospitals, Cleveland Clinic Florida, Stuart, FL; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Diabetic retinopathy: Screening, prevention, and treatment

ABSTRACT

Internists are integral in the multidisciplinary approach to diabetic retinopathy, contributing significantly to the management of diabetes and diabetes-related complications. Effective screening processes, timely referrals, and strategic diabetes management are imperative to prevent and mitigate the consequences of diabetic retinopathy. The evolution of treatments for diabetic retinopathy has markedly improved vision outcomes and reduced the burden on patients. Despite these advances, a collaborative approach to care is essential to prevent the progression of vision impairment and manage associated complications.

KEY POINTS

Primary care physicians should implement the American Diabetes Association screening guidelines and consider leveraging new technologies to ensure patients who require ophthalmologic care are effectively referred to an ophthalmologist.

Glycemic control is crucial for preventing progression of diabetic retinopathy and can be more easily achieved using new diabetes therapies.

Diabetic retinopathy and diabetic macular edema are primarily treated with anti-vascular endothelial growth factors that are administered based on diabetic retinopathy staging and the presence of center-involved diabetic macular edema, as determined by optical coherence tomography.

doi:10.3949/ccjm.91a.24028

Diabetic retinopathy is the leading cause of new cases of blindness in patients with diabetes mellitus.[1–4] In 2020, more than 103 million individuals with diabetes mellitus worldwide were affected by diabetic retinopathy, and estimates suggest this number will increase to 160 million by 2045.[5] Compared with all other leading causes of blindness, diabetic retinopathy is the only condition that has not experienced a decrease in age-standardized prevalence between 1990 and 2020.[6] Without proper prevention and management, the burden of diabetic retinopathy will continue to grow, placing more patients at risk for complications that can cause severe vision loss, such as diabetic macular edema (DME) and proliferative diabetic retinopathy. This article reviews the principles of screening for diabetic retinopathy, measures for preventing its development and progression, and current treatment options.

DIABETIC RETINOPATHY CLASSIFICATIONS

Diabetic retinopathy is classified as nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy based on the absence or presence of abnormal new blood vessels growing in the retina. The nonproliferative and proliferative stages are sequential. NPDR is further classified by severity as mild, moderate, or severe, and proliferative diabetic retinopathy as early or high-risk.[7] DME, defined as thickening of the retina, can occur in any stage of diabetic retinopathy and is the most common complication of diabetic retinopathy that causes vision loss (**Figure 1**).[7,8] DME can be divided into center-involved DME, which is

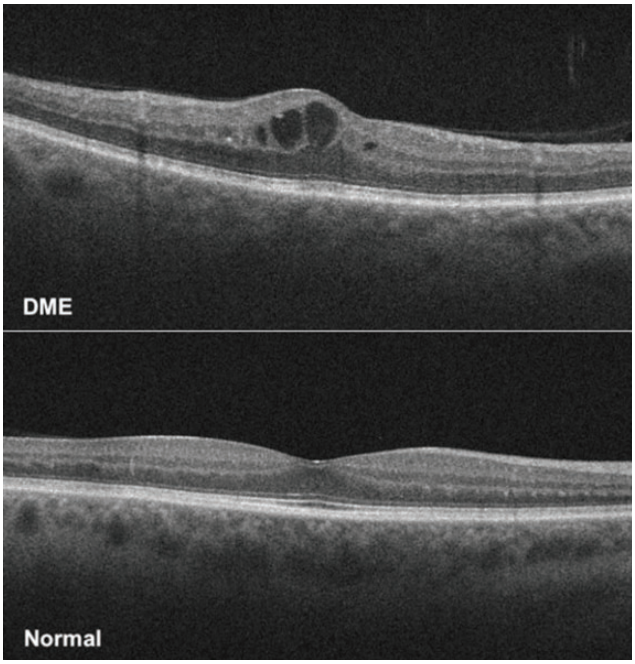


Figure 1. Optical coherence tomography images demonstrating center-involved diabetic macular edema (DME) and a normal retina with no edema.

thickening in the center of the macula and has greater risk for vision loss, or noncenter-involved DME.[8]

SCREENING

Patients with type 1 and type 2 diabetes, including children, are at increased risk for diabetic retinopathy. These patients should be screened regularly with a comprehensive eye examination because symptoms may not occur until the disease has advanced and sight is threatened.[2,9,10] Although there are effective treatments to prevent progression to sight-threatening diabetic retinopathy, management is not possible until diabetic retinopathy has been detected. Unfortunately, screening rates remain low, with less than 50% of patients with diabetes mellitus receiving appropriate ophthalmic care through referrals from primary care physicians.[3,11]

Who to screen, and how often

The American Diabetes Association recommends referring patients with type 1 diabetes to an ophthalmologist or optometrist for an initial dilated and comprehensive eye examination within 5 years of onset; patients with type 2 diabetes should be referred at the time of diagnosis.[2,8] If any level of diabetic retinopathy is present on eye examination, the patient should receive dilated retinal examinations by an ophthalmologist or optometrist at least annually.[2,8] If symptoms progress or sight is threatened, more frequent examinations are required. Conversely, if 1 or more annual eye examinations show no evidence of diabetic retinopathy and glycemic indicators are within goal range, eye examinations can take place every 1 to 2 years.[2]

Patients who have lowered their hemoglobin A1c (HbA1c) to less than 6.5% for at least 3 months while off glucose-lowering medications would be considered in remission for diabetes mellitus.[12] With these patients, extending the screening intervals is acceptable, but it is important to adjust intervals based on the presence of other risk factors such as progression of diabetic retinopathy, advanced baseline retinopathy, uncontrolled hyperglycemia, or diabetic macular edema.[2]

Pregnancy increases the risk for the development and progression of diabetic retinopathy. Patients with preexisting type 1 diabetes or type 2 diabetes who are planning pregnancy should undergo an eye examination before pregnancy, early in the first trimester and in the following trimesters, and up to 1 year post partum, depending on the degree of diabetic retinopathy (**Table 1**).[2,11–13] According to the American Academy of Ophthalmology and the American Diabetes Association, patients who develop gestational diabetes mellitus do not require eye examinations.[2,8]

Retinal photography with remote interpretation

Retinal photography in the primary care setting with remote reading by an ophthalmologist, optometrist, or artificial intelligence algorithms approved by the US Food and Drug Administration can be used in patients without a history of diabetic retinopathy.[2,14–16] This approach can increase access to diabetic retinopathy screening. However, retinal images must be of sufficient quality, and retinal photographs cannot substitute for follow-up eye examinations once abnormalities are detected.[2]

Artificial intelligence algorithms have specific exclusion criteria and provide limited results. The algorithms have not been used to screen patients with diabetes mellitus who are pregnant or who have blurred vision or floaters. Also, artificial intelligence algorithms are limited to detecting whether the eye is negative or positive for "more than mild" diabetic retinopathy.[17,18] Consequently, if the screening is positive, an in-person eye examination by an ophthalmologist is required.

Sensitivity of artificial intelligence platforms for detecting diabetic retinopathy is greater than 87%, and specificity is greater than 88%.[15,17,19] With high sensitivity and greater convenience, artificial intelligence

TABLE 1
American Diabetes Association screening recommendations for diabetic retinopathy in different patient populations

Patient population	Initial eye examination	Follow-up eye examination interval
Type 1 diabetes	Within 5 years after onset of type 1 diabetes	At least annually[a]
Type 2 diabetes	At time of diagnosis of type 2 diabetes	At least annually[a]
Preexisting diabetes and planning on pregnancy	Before pregnancy	Every trimester and up to 1 year post partum
Gestational diabetes	Not required[b]	Not required[b]

[a]If diabetic retinopathy is symptomatic or sight-threatening, examinations should be more frequent. If ≥ 1 annual eye examination shows no evidence of diabetic retinopathy, examinations can occur every 1 to 2 years.
[b]Individuals who develop gestational diabetes do not appear to be at increased risk of developing diabetic retinopathy during pregnancy.

Based on information from references 2,11–13.

platforms can increase the likelihood that patients with signs of diabetic retinopathy will receive a referral to ophthalmology, reducing the screening burden. The cost of hardware and services that come with these platforms is a consideration for primary care practices, and may be a barrier to implementing these systems.[18] However, remote interpretation by ophthalmologists, optometrists, or an artificial intelligence algorithm increases screening rates and provides higher sensitivity and accuracy in detecting diabetic retinopathy than fundoscopic examination done in the primary care setting.[11,20,21]

Retinopathy predicts diabetes outcomes

Diabetic retinopathy is associated with major systemic complications of diabetes. Its presence and severity have been shown to predict stroke, myocardial infarction, and death.[22–25] Diabetic retinopathy is associated with the risk of diabetic nephropathy and diabetic neuropathy as well, and hence can be used to predict the development and progression of these conditions.[26,27] Primary care physicians can help decrease the risk of diabetes complications by referring patients for comprehensive eye examinations and managing associated comorbidities.

PREVENTION

Risk factors associated with diabetic retinopathy development and progression include hyperglycemia, dyslipidemia, and high blood pressure. Strict glycemic control has been established as absolutely key in preventing diabetic retinopathy progression, but evidence is mixed for targeting dyslipidemia and high blood pressure as measures specifically to prevent or slow the progression of diabetic retinopathy.

Hyperglycemia

Strict control of hyperglycemia is essential in minimizing the risk of diabetic retinopathy development or progression.[1,28] The Diabetes Control and Complications Trial reported a strong relationship between risk of diabetic retinopathy and mean HbA1c: a decrease of about 10% in HbA1c resulted in a 39% decrease in risk of diabetic retinopathy progression.[8] Long-term follow-up also showed that strict blood glucose control decreased the incidence of progression in severe NPDR, proliferative diabetic retinopathy, and clinically significant macular edema.[29]

Dyslipidemia

Elevated serum cholesterol and triglyceride levels have been implicated as risk factors for diabetic retinopathy. However, studies of the effect of statin and fibrate treatment specifically on diabetic retinopathy development and progression have produced mixed results.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[30] investigated intensive glycemic control and treatment of dyslipidemia in patients with type 2 diabetes (median baseline values for the dyslipidemia group were high-density lipoprotein cholesterol of 38 mg/dL, low-density lipoprotein cholesterol 93 mg/dL, and triglycerides 162 mg/dL). After 4 years of follow-up, the study reported reduced rates of diabetic retinopathy progression with intensive glycemic control combined with fenofibrate and simvastatin treatment vs simvastatin plus placebo. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[31] reported a decreased need for laser treatment in patients with diabetic retinopathy treated with fenofibrate. Other studies reported that statin therapy decreased the risk and incidence of diabetic

retinopathy,[4,32] while others found that statins do not protect against diabetic retinopathy progression.[33–35]

Despite the uncertainty about the effect of statin and fibrate therapy on diabetic retinopathy outcomes, multiple trials have shown the benefits of statin therapy and lipid control for overall management of diabetes mellitus, including a decreased risk for atherosclerotic cardiovascular disease events, coronary heart disease deaths, and all-cause mortality.[36]

Blood pressure

The role of blood pressure management in the prevention of diabetic retinopathy has been explored. A Cochrane review showed that although intensive blood pressure control was associated with a reduced risk of diabetic retinopathy development, it did not significantly impact progression of existing diabetic retinopathy compared with less stringent measures of blood pressure control.[37]

Glucagon-like peptide-1 receptor agonists, rapid HbA1c reduction, and retinopathy

Although glycemic control with insulin or pharmacologic therapies is critical, the evidence is mixed on the effect of glucagon-like peptide-1 (GLP-1) receptor agonists on risk for diabetic retinopathy. Some meta-analyses and trials reported an increased risk of diabetic retinopathy with certain GLP-1 receptor agonists,[38–44] while others reported no significant difference.[45–49] Interestingly, many trials that reported an increased risk included or exclusively studied semaglutide, and many of the studies that found no significant difference reported on other GLP-1 receptor agonists. Furthermore, the increased risk for diabetic retinopathy seems to occur early in treatment and be transient, ranging from 3 months to 3 years after starting a GLP-1 receptor agonist, while the duration of improvement in retinopathy attributable to glycemic control ranges from about 3 years to more than 5 years.[42,50]

A plausible explanation for the potential early increased risk of diabetic retinopathy with GLP-1 receptor agonists is the drastic decrease in HbA1c that occurs when intensively managing diabetes mellitus, a phenomenon that may not necessarily be intrinsic to GLP-1 receptor agonists.[50–52] In a multicenter, randomized clinical trial (Diabetes Control and Complications Trial), the risk of early worsening of diabetic retinopathy was greater in the intensive insulin treatment group compared with the conventional insulin treatment group among patients with type 1 diabetes.[50] Interestingly, statistical analysis showed that the magnitude—but not the rapidity—of reduction in HbA1c was a significant risk factor for early worsening of diabetic retinopathy in the first 6 months of intensive treatment.[50] A retrospective case-control study reported similar results, with a significant association between large reductions in HbA1c and worsening diabetic retinopathy in patients with uncontrolled type 2 diabetes.[53] Further investigations of drastic reductions in HbA1c, specific pharmacotherapies, and other glucose-lowering treatments such as bariatric surgery are needed to characterize early worsening of diabetic retinopathy and guide the safe management of diabetic retinopathy.

Nevertheless, GLP-1 receptor agonists have clear benefits in weight loss and cardiovascular risk, hypoglycemic risk, and kidney risk management for patients with diabetes mellitus.[38] When weighing the risks and benefits of a GLP-1 receptor agonist, the possible increased risk of development or progression of diabetic retinopathy should be carefully considered, especially if patients have a history of diabetic retinopathy or are already taking other diabetes medications that lower blood glucose. Primary care physicians should prioritize management of diabetes mellitus with a target HbA1c of 7% or lower while being mindful of large reductions of HbA1c when starting diabetes medications such as GLP-1 receptor agonists.[8] Additional studies of GLP-1 receptor agonists with longer follow-up and primary end points for diabetic retinopathy risk assessment are needed. When considering GLP-1 receptor agonists, retinopathy status should be assessed by an ophthalmologist because of the potential initial worsening of retinopathy.

As with any progression of diabetic retinopathy, patients who experience worsening symptoms or signs of diabetic retinopathy in the context of rapid HbA1c reduction from diabetes medications such as GLP-1 receptor agonists should be seen by an ophthalmologist as soon as possible to assess the severity of progression and presence of any complications.[2,8] These complications should be evaluated to determine their impact on next possible steps in management, such as observation, discontinuation of medications, antivascular endothelial growth factor (VEGF) injections, intravitreal corticosteroid injections, or surgery.

MANAGEMENT

Management of patients with diabetic retinopathy depends on the severity of the retinopathy and whether DME is present.[8] Patients with mild, moderate, or severe NPDR have a 15.6%, 44.6%, and 62.6% chance of developing DME, respectively.[54] Owing to the risk of developing complications, follow-up examinations are recommended every 6 to 12 months for those with mild to moderate NPDR and every 2 to 4 months for

patients with severe NPDR and non-high-risk proliferative diabetic retinopathy.[8]

VEGF injections

Standard treatment of diabetic retinopathy is anti-VEGF injections, which are used as off-label or US Food and Drug Administration–approved treatment for all stages of diabetic retinopathy.[8,55]

NPDR. The American Academy of Ophthalmology Preferred Practice Pattern regarding patients with diabetic retinopathy and no DME recommends considering anti-VEGF only in patients with severe NPDR.[8] However, recent studies have shown benefit in patients with milder disease. PANORAMA (Study of the Efficacy and Safety of Intravitreal Aflibercept for the Improvement of Moderately Severe to Severe Nonproliferative Diabetic Retinopathy)[56] and the Diabetic Retinopathy Clinical Research Retina Network Protocol W[57] looked at patients with moderate to severe NPDR and moderately severe to severe NPDR, respectively, both without DME. In these studies, patients treated with anti-VEGF injections had similar vision acuity outcomes compared with sham but a reduced risk of progression to proliferative diabetic retinopathy and development of center-involved DME.

Of US retina specialists treating very severe NPDR without DME, 60% closely monitor the condition and encourage systemic glycemic control, 25% consider anti-VEGF therapy in some patients with poor glycemic control, around 8% consider it in all or most patients, and 3% consider it in some patients with good glucose control and compliance.[58,59] Additionally, among those treating patients with severe NPDR without clinically significant DME, 52% do not recommend anti-VEGF therapy; 39.1% said they would recommend it if extensive peripheral nonperfusion was present on fluorescein angiography, and 27.5% would recommend it if fellow eye pathology were present.[60]

Proliferative diabetic retinopathy. Clinical trials have evaluated visual acuity outcomes in patients with proliferative diabetic retinopathy treated with ranibizumab vs panretinal photocoagulation. Gross et al[61] showed that anti-VEGF treatment is noninferior to photocoagulation in patients with and without DME, and Sivaprasad et al[62] showed that anti-VEGF treatment is superior in patients without DME. However, physicians should assess patient adherence, as patients with proliferative diabetic retinopathy treated with panretinal photocoagulation who were lost to follow-up longer than 6 months had better anatomic and functional outcomes compared with those treated with anti-VEGF therapy.[63]

Most ophthalmologists treat patients with high-risk proliferative diabetic retinopathy and center-involved DME with both anti-VEGF therapy and laser. In a survey of US retina specialists, 69.9% of respondents said that they would start anti-VEGF therapy and plan for concurrent or future panretinal photocoagulation; 26% said they would treat with anti-VEGF injections and later assess the need for panretinal photocoagulation.[59]

DME. First-line therapy for patients with DME is intravitreal anti-VEGF injections.[8] The RISE and RIDE (Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus) trials showed that ranibizumab significantly improved vision in patients with DME and reduced diabetic retinopathy severity across all stages.[64] Anti-VEGF treatment is initiated with monthly injections for 3 to 6 months.[65] The Diabetic Retinopathy Clinical Research Retina Network Protocol V evaluated patients with center-involved DME and visual acuity of 20/25 or better. It found that these patients should be observed with follow-up every 2 to 4 months, as initial treatment with either aflibercept or laser did not result in significant vision improvements compared with observation.[66]

Owing to insurance and costs, most patients are first treated with bevacizumab and, after treatment failure is demonstrated, are switched to another anti-VEGF therapy.[67] However, in the Diabetic Retinopathy Clinical Research Retina Network Protocol T trial comparing the efficacy of intravitreal aflibercept, bevacizumab, and ranibizumab in center-involved DME, patients with a visual acuity of 20/50 or worse receiving bevacizumab had worse 2-year visual acuity outcomes compared with those taking aflibercept.[8] Protocol AC, a multicenter, randomized clinical trial at 54 US clinical sites, showed that patients who first received bevacizumab and then switched to aflibercept due to nonresponse had noninferior 2-year vision outcomes compared with those taking aflibercept only.[67,68]

The efficacy of fixed-dose anti-VEGF regimens has been shown in clinical trials, but most clinicians use an as-needed or treat-and-extend approach to reduce treatment burden.[69] Patients on the treat-and-extend treatment regimen are administered anti-VEGF at each visit, and the intervals between appointments are extended, maintained, or decreased based on the presence of macular edema, as determined by optical coherence tomography imaging.[70] Treat-and-extend has been shown to have similar vision and anatomic outcomes compared with as-needed or fixed-dose regimens in patients with center-involved DME, with treat-and-extend requiring significantly fewer injections compared with fixed dosing.[70,71]

Extended treatment intervals can be used with other anti-VEGF agents that have received US Food and Drug Administration approval for treatment of center-involved DME.[72,73] In the double-masked 96-week PHOTON (Study of a High-Dose Aflibercept in Participants With Diabetic Eye Disease) trial,[74] patients with center-involved DME were randomized to receive aflibercept 8 mg every 12 or 16 weeks after 3 monthly doses or aflibercept 2 mg every 8 weeks after 5 monthly doses. Aflibercept 8 mg provided noninferior outcomes with fewer injections. In the YOSEMITE and RHINE (Efficacy and Safety of Faricimab in Participants With Diabetic Macular Edema) trials, faricimab also had extended durability in treating patients with center-involved DME.[75]

Laser surgery

Laser is used as both primary and adjunctive treatment of diabetic retinopathy and DME. Multiple studies have demonstrated anti-VEGFs to be more effective than focal laser photocoagulation in improving visual acuity in patients with center-involved DME.[8,76–79] In a survey of US retina specialists treating patients with clinically significant DME on anti-VEGF therapy, 59.2% treated less than 5% of patients with focal or grid laser, and 21.7% treated 5% to 10% of patients with focal or grid laser.[76] The American Academy of Ophthalmology Preferred Practice Pattern clinical guidelines advocate for focal or grid laser as the preferred treatment modality for noncenter-involved DME, citing lack of research on this specific pathology.[8] Despite these guidelines, ongoing debate continues regarding the role of laser therapy in preventing vision loss.[77,78]

Intravitreal steroids

Intravitreally injected steroids are effective in treating DME, with visual acuity gains similar to anti-VEGF treatment.[79] However, because of the risk of elevated intraocular pressure and cataract progression, intravitreal steroids are second-line therapies.[8,79]

CONCLUSION

Clinicians managing patients with diabetes mellitus must recognize the risks and complications associated with diabetic retinopathy and ensure that proper screening and referral processes are in place. Technological advancements like retinal photography with remote interpretation can reduce the burden of screening for diabetic retinopathy, but there are device and service costs. Furthermore, awareness of advances in diabetes medications, which effectively control blood glucose levels and subsequently prevent diabetic retinopathy and its direct and related complications, is essential. The treatment of diabetic retinopathy and DME primarily involves anti-VEGF therapy. This therapy, while being the standard of care, may impose a significant treatment burden on patients. Therefore, it is imperative for clinicians to leverage new tools for early detection and new medications for effective management of diabetes and diabetic retinopathy.

DISCLOSURES

Dr Singh has disclosed consulting for Alcon Lab, Apellis Pharmaceuticals, EyePoint Pharmaceuticals, Genentech/Roche, Iveric Bio, Regeneron, and Zeiss Meditech, and conducting research as a primary investigator for Janssen Pharmaceuticals. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Khalil H.** Diabetes microvascular complications—a clinical update. Diabetes Metab Syndr 2017; 11(suppl 1):S133–S139. doi:10.1016/j.dsx.2016.12.022
2. **American Diabetes Association Professional Practice Committee.** 12. Retinopathy, neuropathy, and foot care: standards of care in diabetes—2024. Diabetes Care 2024; 47(suppl 1):S231–S243. doi:10.2337/dc24-S012
3. **Centers for Disease Control and Prevention.** National Diabetes Fact Sheet, 2011. https://stacks.cdc.gov/view/cdc/13329. Accessed July 19, 2024.
4. **Kang EY, Chen TH, Garg SJ, et al.** Association of statin therapy with prevention of vision-threatening diabetic retinopathy. JAMA Ophthalmol 2019; 137(4):363–371. doi:10.1001/jamaophthalmol.2018.6399
5. **Teo ZL, Tham YC, Yu M, et al.** Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. Ophthalmology 2021; 128(11):1580–1591. doi:10.1016/j.ophtha.2021.04.027
6. **Global Burden of Disease 2019 Blindness and Vision Impairment Collaborators.** Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the right to sight: an analysis for the Global Burden of Disease study [published correction appears in Lancet Glob Health 2021; 9(4):e408]. Lancet Glob Health 2021; 9(2): e144–e160. doi:10.1016/S2214-109X(20)30489-7
7. **Reddy NG, Venkatesh R, Jayadev C, et al.** Diabetic retinopathy and diabetic macular edema in people with early-onset diabetes. Clin Diabetes 2022; 40(2):222–232. doi:10.2337/cd21-0110
8. **Flaxel CJ, Adelman RA, Bailey ST, et al.** Diabetic retinopathy Preferred Practice Pattern® [published correction appears in Ophthalmology 2020; 127(9):1279]. Ophthalmology 2020; 127(1):P66–P145. doi:10.1016/j.ophtha.2019.09.025
9. **Jampol LM, Glassman AR, Sun J.** Evaluation and care of patients with diabetic retinopathy. N Engl J Med 2020; 382(17):1629–1637. doi:10.1056/NEJMra1909637
10. **Lascar N, Brown J, Pattison H, Barnett AH, Bailey CJ, Bellary S.** Type 2 diabetes in adolescents and young adults. Lancet Diabetes Endocrinol 2018; 6(1):69–80. doi:10.1016/S2213-8587(17)30186-9
11. **Jani PD, Forbes L, Choudhury A, Preisser JS, Viera AJ, Garg S.** Evaluation of diabetic retinal screening and factors for ophthalmology referral in a telemedicine network. JAMA Ophthalmol 2017; 135(7):706–714. doi:10.1001/jamaophthalmol.2017.1150
12. **Taheri S.** Type 2 diabetes remission: a new mission in diabetes care. Diabetes Care 2024; 47(1):47–49. doi:10.2337/dci23-0062

13. **Widyaputri F, Rogers SL, Kandasamy R, Shub A, Symons RCA, Lim LL.** Global estimates of diabetic retinopathy prevalence and progression in pregnant women with preexisting diabetes: a systematic review and meta-analysis. JAMA Ophthalmol 2022; 140(5):486–494. doi:10.1001/jamaophthalmol.2022.0050
14. **US Food and Drug Administration.** FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems. https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-artificial-intelligence-based-device-detect-certain-diabetes-related-eye. Accessed July 19, 2024.
15. **US Department of Health and Human Services; ClinicalTrials.**gov. Efficacy and safety of AEYE-DS software device for automated detection of diabetic retinopathy from digital fundus images. Updated August 1, 2023. https://clinicaltrials.gov/study/NCT04612868. Accessed July 19, 2024.
16. **US Department of Health and Human Services; ClinicalTrials.** gov. Assessment of EyeArt as an automated diabetic retinopathy screening tool. Updated July 30, 2018. https://clinicaltrials.gov/study/NCT03112005. Accessed July 19, 2024.
17. **Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC.** Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. NPJ Digit Med 2018; 1:39. doi:10.1038/s41746-018-0040-6
18. **Savoy M.** IDx-DR for diabetic retinopathy screening. Am Fam Physician 2020; 101(5):307–308. pmid:32109029
19. **Lim JI, Regillo CD, Sadda SR, et al.** Artificial intelligence detection of diabetic retinopathy: subgroup comparison of the EyeArt system with ophthalmologists' dilated examinations. Ophthalmol Sci 2022; 3(1):100228. doi:10.1016/j.xops.2022.100228
20. **Shah AR, Wu R.** Disparities in diabetes-related retinal disease and approaches to improve screening rates. In: A Practical Guide to Diabetes-Related Eye Care. Arlington,VA: American Diabetes Association; 2022:16–19.
21. **Song A, Lusk JB, Roh KM, et al.** Practice patterns of fundoscopic examination for diabetic retinopathy screening in primary care. JAMA Netw Open 2022; 5(6):e2218753. doi:10.1001/jamanetworkopen.2022.18753
22. **Wang Z, Cao D, Zhuang X, et al.** Diabetic retinopathy may be a predictor of stroke in patients with diabetes mellitus. J Endocr Soc 2022; 6(8):bvac097. doi:10.1210/jendso/bvac097
23. **Hu K, Jiang M, Zhou Q, et al.** Association of diabetic retinopathy with stroke: a systematic review and meta-analysis. Front Neurol 2021; 12:626996. doi:10.3389/fneur.2021.626996
24. **Hsu CY, Lee CM, Chou KY, et al.** The association of diabetic retinopathy and cardiovascular disease: a 13-year nationwide population-based cohort study. Int J Environ Res Public Health 2021; 18(15):8106. doi:10.3390/ijerph18158106
25. **Modjtahedi BS, Wu J, Luong TQ, Gandhi NK, Fong DS, Chen W.** Severity of diabetic retinopathy and the risk of future cerebrovascular disease, cardiovascular disease, and all-cause mortality. Ophthalmology 2021; 128(8):1169–1179. doi:10.1016/j.ophtha.2020.12.019
26. **Saini DC, Kochar A, Poonia R.** Clinical correlation of diabetic retinopathy with nephropathy and neuropathy. Indian J Ophthalmol 2021; 69(11):3364–3368. doi:10.4103/ijo.IJO_1237_21
27. **Joshi D, Khan MA, Singh A.** A clinical study of the association and risk factors for lower limb neuropathy in patients with diabetic retinopathy. J Family Med Prim Care 2020; 9(4):1891–1895. doi:10.4103/jfmpc.jfmpc_231_20
28. **Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al.** The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329(14):977–986. doi:10.1056/NEJM199309303291401
29. **Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM.** Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy [published correction appears in N Engl J Med 2000; 342(18):1376]. N Engl J Med 2000; 342(6):381–389. doi:10.1056/NEJM200002103420603
30. **ACCORD Study Group; ACCORD Eye Study Group, Chew EY, et al.** Effects of medical therapies on retinopathy progression in type 2 diabetes [published correction appears in N Engl J Med 2011; 364(2):190] [published correction appears in N Engl J Med 2012; 367(25):2458]. N Engl J Med 2010; 363(3):233–244. doi:10.1056/NEJMoa1001288
31. **Keech A, Simes RJ, Barter P, et al.** Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial [published correction appears in Lancet 2006; 368(9545):1420] [published correction appears in Lancet 2006; 368(9545):1415]. Lancet 2005; 366(9500):1849–1861. doi:10.1016/S0140-6736(05)67667-2
32. **Liu J, Wu YP, Qi JJ, Yue ZP, Hu CD.** Effect of statin therapy on diabetes retinopathy in people with type 2 diabetes mellitus: a meta-analysis. Clin Appl Thromb Hemost 2021; 27:10760296211040109. doi:10.1177/10760296211040109
33. **Mozetic V, Pacheco RL, Latorraca COC, Riera R.** Statins and/or fibrates for diabetic retinopathy: a systematic review and meta-analysis. Diabetol Metab Syndr 2019; 11:92. doi:10.1186/s13098-019-0488-9
34. **Chung YR, Park SW, Choi SY, et al.** Association of statin use and hypertriglyceridemia with diabetic macular edema in patients with type 2 diabetes and diabetic retinopathy. Cardiovasc Diabetol 2017; 16(1):4. doi:10.1186/s12933-016-0486-2
35. **Klein BE, Myers CE, Howard KP, Klein R.** Serum lipids and proliferative diabetic retinopathy and macular edema in persons with long-term type 1 diabetes mellitus: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. JAMA Ophthalmol 2015; 133(5):503–510. doi:10.1001/jamaophthalmol.2014.5108
36. **American Diabetes Association.** 10. Cardiovascular disease and risk management: standards of medical care in diabetes-2021 [published correction appears in Diabetes Care 2021; 44(9):2183–2185]. Diabetes Care 2021; 44(suppl 1):S125–S150. doi:10.2337/dc21-S010
37. **Do DV, Han G, Abariga SA, Sleilati G, Vedula SS, Hawkins BS.** Blood pressure control for diabetic retinopathy. Cochrane Database Syst Rev 2023; 3(3):CD006127. doi:10.1002/14651858.CD006127.pub3
38. **Marso SP, Bain SC, Consoli A, et al.** Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016; 375(19):1834–1844. doi:10.1056/NEJMoa1607141
39. **Wang F, Mao Y, Wang H, Liu Y, Huang P.** Semaglutide and diabetic retinopathy risk in patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. Clin Drug Investig 2022; 42(1):17–28. doi:10.1007/s40261-021-01110-w
40. **Albert SG, Wood EM, Ahir V.** Glucagon-like peptide 1-receptor agonists and A1c: Good for the heart but less so for the eyes? Diabetes Metab Syndr 2023; 17(1):102696. doi:10.1016/j.dsx.2022.102696
41. **Tsapas A, Avgerinos I, Karagiannis T, et al.** Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. Ann Intern Med 2020; 173(4): 278–286. doi:10.7326/M20-0864
42. **Bethel MA, Diaz R, Castellana N, Bhattacharya I, Gerstein HC, Lakshmanan MC.** HbA1c change and diabetic retinopathy during GLP-1 receptor agonist cardiovascular outcome trials: a meta-analysis and meta-regression. Diabetes Care 2021; 44(1):290–296. doi:10.2337/dc20-1815
43. **Husain M, Birkenfeld AL, Donsmark M, et al.** Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019; 381(9):841–851. doi:10.1056/NEJMoa1901118
44. **Yoshida Y, Joshi P, Barri S, et al.** Progression of retinopathy with glucagon-like peptide-1 receptor agonists with cardiovascular benefits in type 2 diabetes—a systematic review and meta-analysis. J Diabetes Complications 2022; 36(8):108255. doi:10.1016/j.jdiacomp.2022.108255
45. **Marso SP, Daniels GH, Brown-Frandsen K, et al.** Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375(4):311–322. doi:10.1056/NEJMoa1603827
46. **Bethel MA, Mentz RJ, Merrill P, et al.** Microvascular and cardiovascular outcomes according to renal function in patients treated with once-weekly exenatide: insights from the EXSCEL Trial. Diabetes Care 2020; 43(2):446–452. doi:10.2337/dc19-1065

47. **Wei J, Yang B, Wang R, et al.** Risk of stroke and retinopathy during GLP-1 receptor agonist cardiovascular outcome trials: an eight RCTs meta-analysis. Front Endocrinol (Lausanne) 2022; 13:1007980. doi:10.3389/fendo.2022.1007980
48. **Zhang X, Shao F, Zhu L, Ze Y, Zhu D, Bi Y.** Cardiovascular and microvascular outcomes of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized controlled cardiovascular outcome trials with trial sequential analysis. BMC Pharmacol Toxicol 2018; 19(1):58. doi:10.1186/s40360-018-0246-x
49. **Gerstein HC, Colhoun HM, Dagenais GR, et al.** Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019; 394(10193): 121–130. doi:10.1016/S0140-6736(19)31149-3
50. **Bain SC, Klufas MA, Ho A, Matthews DR.** Worsening of diabetic retinopathy with rapid improvement in systemic glucose control: a review. Diabetes Obes Metab 2019; 21(3):454–466. doi:10.1111/dom.13538
51. **Vilsbøll T, Bain SC, Leiter LA, et al.** Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. Diabetes Obes Metab 2018; 20(4):889–897. doi:10.1111/dom.13172
52. **Poonoosamy J, Lopes P, Huret P, et al.** Impact of intensive glycemic treatment on diabetes complications-a systematic review. Pharmaceutics 2023; 15(7):1791. doi:10.3390/pharmaceutics15071791
53. **Shurter A, Genter P, Ouyang D, Ipp E.** Euglycemic progression: worsening of diabetic retinopathy in poorly controlled type 2 diabetes in minorities. Diabetes Res Clin Pract 2013; 100(3):362–367. doi:10.1016/j.diabres.2013.03.018
54. **Moshfeghi A, Garmo V, Sheinson D, Ghanekar A, Abbass I.** Five-year patterns of diabetic retinopathy progression in US clinical practice. Clin Ophthalmol 2020; 14:3651–3659. doi:10.2147/OPTH.S275968
55. **Bahr TA, Bakri SJ.** Update on the management of diabetic retinopathy: anti-VEGF agents for the prevention of complications and progression of nonproliferative and proliferative retinopathy. Life (Basel) 2023; 13(5):1098. doi:10.3390/life13051098
56. **Brown DM, Wykoff CC, Boyer D, et al.** Evaluation of intravitreal aflibercept for the treatment of severe nonproliferative diabetic retinopathy: results from the PANORAMA randomized clinical trial. JAMA Ophthalmol 2021; 139(9):946–955. doi:10.1001/jamaophthalmol.2021.2809
57. **Maturi RK, Glassman AR, Josic K, et al.** Four-year visual outcomes in the Protocol W randomized trial of intravitreous aflibercept for prevention of vision-threatening complications of diabetic retinopathy [published correction appears in JAMA 2023; 28;329(12):1034]. JAMA 2023; 329(5):376–385. doi:10.1001/jama.2022.25029
58. **Tieger MG, Baumal CR.** Severe diabetic retinopathy without diabetic macular edema. Retinal Physician 2022; 19:18–21.
59. **American Society of Retina Specialists.** ASRS 2021 Global Trends in Retina. https://www.asrs.org/content/documents/2021-global-trends-survey-highlights.pdf Accessed July 19, 2024.
60. **Hahn P, ed.** ASRS 2023 Preferences and Trends Membership Survey. Chicago, IL: American Society of Retina Specialists; 2023.
61. **Writing Committee for the Diabetic Retinopathy Clinical Research Network, Gross JG, Glassman AR, et al.** Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial [published correction appears in JAMA 2016; 315(9):944] [published correction appears in JAMA 2019; 321(10):1008]. JAMA 2015; 314(20):2137–2146. doi:10.1001/jama.2015.15217
62. **Sivaprasad S, Prevost AT, Vasconcelos JC, et al.** Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. Lancet 2017; 389(10085):2193–2203. doi:10.1016/S0140-6736(17)31193-5
63. **Obeid A, Su D, Patel SN, et al.** Outcomes of eyes lost to follow-up with proliferative diabetic retinopathy that received panretinal photocoagulation versus intravitreal anti-vascular endothelial growth factor. Ophthalmology 2019; 126(3):407–413. doi:10.1016/j.ophtha.2018.07.027
64. **Wykoff CC, Eichenbaum DA, Roth DB, Hill L, Fung AE, Haskova Z.** Ranibizumab induces regression of diabetic retinopathy in most patients at high risk of progression to proliferative diabetic retinopathy. Ophthalmol Retina 2018; 2(10):997–1009. doi:10.1016/j.oret.2018.06.005
65. **Figueira J, Henriques J, Carneiro Â, et al.** Guidelines for the management of center-involving diabetic macular edema: treatment options and patient monitorization. Clin Ophthalmol 2021; 15:3221–3230. doi:10.2147/OPTH.S318026
66. **Baker CW, Glassman AR, Beaulieu WT, et al.** Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. JAMA 2019; 321(19):1880–1894. doi:10.1001/jama.2019.5790
67. **Jhaveri CD, Glassman AR, Ferris FL 3rd, et al.** Aflibercept monotherapy or bevacizumab first for diabetic macular edema. N Engl J Med 2022; 387(8):692–703. doi:10.1056/NEJMoa2204225
68. **Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al.** Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015; 372(13):1193–1203. doi:10.1056/NEJMoa1414264
69. **Chaudhary V; Retina Evidence and Trials INternational Alliance (RETINA) Study Group.** The need for a pragmatic, individualized treat-and-extend (T&E) treatment paradigm for centre-involving diabetic macular oedema. Eye (Lond) 2023; 37(12):2431–2433. doi:10.1038/s41433-023-02455-6
70. **Sarohia GS, Nanji K, Khan M, et al.** Treat-and-extend versus alternate dosing strategies with anti-vascular endothelial growth factor agents to treat center involving diabetic macular edema: a systematic review and meta-analysis of 2,346 eyes. Surv Ophthalmol 2022; 67(5):1346–1363. doi:10.1016/j.survophthal.2022.04.003
71. **Payne JF, Wykoff CC, Clark WL, et al.** Randomized trial of treat and extend ranibizumab with and without navigated laser versus monthly dosing for diabetic macular edema: TREX-DME 2-year outcomes. Am J Ophthalmol 2019; 202:91–99. doi:10.1016/j.ajo.2019.02.005
72. **Regeneron Pharmaceuticals, Inc.** Eylea. Highlights of prescribing information. https://www.regeneron.com/downloads/eylea_fpi.pdf. Accessed July 19, 2024.
73. **Genentech, Inc.** Vabysmo. Highlights of prescribing information. https://www.gene.com/download/pdf/vabysmo_prescribing.pdf. Accessed July 19, 2024.
74. **Do DV.** Aflibercept 8 mg for diabetic macular edema: 48-week results from the phase 2/3 PHOTON Trial. Invest Ophthalmol Vis Sci 2023; 64(8):2814 (abstract). https://iovs.arvojournals.org/article.aspx?articleid=2787521&resultClick=1. Accessed July 19, 2024.
75. **Wykoff CC, Abreu F, Adamis AP, et al.** Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. Lancet 2022; 399(10326):741–755. doi:10.1016/S0140-6736(22)00018-6
76. **American Society of Retina Specialists.** ASRS 2022 Global Trends in Retina. https://www.asrs.org/content/documents/2022-asrs-global-trends-in-retina-survey.pdf. Accessed July 19, 2024.
77. **Zur D, Loewenstein A.** Should we still be performing macular laser for non-centre involving diabetic macular oedema? Yes. Eye (Lond) 2022; 36(3):483–484. doi:10.1038/s41433-021-01793-7
78. **Mueller I, Talks JS.** Should we still be performing macular laser for non-centre involving diabetic macular oedema? No. Eye (Lond) 2022; 36(3):485–486. doi:10.1038/s41433-021-01787-5
79. **Patil NS, Mihalache A, Hatamnejad A, Popovic MM, Kertes PJ, Muni RH.** Intravitreal steroids compared with anti-VEGF treatment for diabetic macular edema: a meta-analysis. Ophthalmol Retina 2023; 7(4):289–299. doi:10.1016/j.oret.2022.10.008

Address: *Rishi P. Singh, MD, Cole Eye Institute, i-32, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; singhr@ccf.org*

Cleveland Clinic

Featuring evidence-based update on marijuana use

Primary Care +
Updates in Primary Care, Women's Health and Behavioral Medicine

November 13-16, 2024

Cleveland Clinic Administrative Campus
3175 Science Park Drive, Building #4 | Beachwood, OH

Why Attend?

- Stay up-to-date on common chronic disease management
- Review most salient research publications for Primary Care
- Learn new medical management and clinical skills

Highlights for 2024!

Pre-Conference Dermatology Workshop (optional)

- Review indications for and evaluation of skin lesions
- Learn and practice procedural skills including dermoscopy, shave and punch biopsy, lesion resection, cyst removal, skin closures and cryotherapy

Primary Care

- Updates in research, prostate cancer, cardiovascular disease, diabetes management and more!
- Hands-on workshop featuring ambulatory cardiac monitors and interpretation

Women's Health

- Case-based management of menopause therapy, updates in female sexual dysfunction, vaginal and vulvar conditions, and bone health, among others!

Behavioral Medicine

- Medical marijuana primer starting with the basics and including pharmacotherapy, clinical utility, physiology and management ***featuring a national guest speaker***
- Updates on alcohol use disorder treatment, Adult ADHD and integrative treatment regimens for behavioral health disorders

Who Should Attend?

- This activity is designed for family physicians, general internists, nurses, nurse practitioners, physician assistants, pharmacists, pharmacy technicians, fellows, residents, and other health care professionals who have an interest in primary care, women's health and behavioral medicine.

Register Today! **ccfcme.org/PCP24**

This activity has been approved for *AMA PRA Category 1 Credit*™ ANCC Contact Hours, AAPA Category 1 CME Credits, APCE Hours, and ABIM MOC Points.

How to earn *AMA PRA Category 1 Credit*™ and ABIM MOC points

AMA/PRA Category 1 Credit™

To read articles as CME activities and claim credit, go to www.ccjm.org, click on the "CME/MOC" menu, and then "Articles." Find the articles that you want to read as CME activities and click on the appropriate links. After reading an article, click on the link to complete the activity. You will be asked to log in to your MyCME account (or to create an account). Upon logging in, select "CME," complete the activity evaluation, and print your certificate.

Call 216-444-2661 or e-mail ccjm@ccf.org with questions.

Maintenance of Certification (MOC) Points

All *Cleveland Clinic Journal of Medicine* CME activities are eligible for ABIM MOC points. Physicians may claim MOC points in addition to CME credit.

Follow the instructions for completing and claiming credit for CME activities.

When you log into your MyCME account, select "CME & MOC" and enter your ABIM identification number and your date of birth. The system will store this information after you enter it the first time.

Complete the quiz and evaluation and print your CME certificate.

August 2024 CME/MOC activity:

Estimated time to complete the activity: up to 1 hour

Digoxin is still useful, but is still causing toxicity

Release date: August 1, 2024
Expiration date: July 31, 2025

FINANCIAL DISCLOSURES: In accordance with the Standards for Integrity and Independence issued by the Accreditation Council for Continuing Medical Education (ACCME), The Cleveland Clinic Center for Continuing Education mitigates all relevant conflicts of interest to ensure CE activities are free of commercial bias.

AUTHOR AND STAFF DISCLOSURES: Authors' potential conflicts of interest are disclosed within their articles. *Cleveland Clinic Journal of Medicine's* staff disclose the following financial relationships that may be relevant to their editorial roles: Dr. Brian F. Mandell (Editor in Chief) reports teaching and speaking for Genentech; and consulting for Horizon Pharma. Dr. Kristin Highland (Associate Editor) has disclosed financial interests (consulting, research, teaching, and speaking) with Actelion Pharmaceuticals, Bayer Healthcare, Boehringer Ingelheim, Eiger Biopharmaceuticals, Gententech, Gossamer Bio, Lilly, Reata Pharmaceuticals, United Therapeutics, and Viela Bio. Dr. Christian Nasr (Associate Editor) reports service on advisory committees or review panels for Exelixis, Horizon Pharma, Neurogastrx, and Nevro Corp.; and consulting for Siemens.

DISCLAIMER: The information in these educational activities is provided for general medical education purposes only and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options of a specific patient's medical condition. The viewpoints expressed in these CME activities are those of the authors. They do not represent an endorsement by The Cleveland Clinic Foundation. In no event will The Cleveland Clinic Foundation be liable for any decision made or action taken in reliance upon the information provided through these CME activities.

CME ACCREDITATION:
In support of improving patient care, Cleveland Clinic Center for Continuing Education is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The Cleveland Clinic Center for Continuing Education designates this journal-based CME activity for a maximum of *1.0 AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Participants claiming CME credit from this activity may submit the credit hours to the American Osteopathic Association for Category 2 credit.

AMERICAN BOARD OF INTERNAL MEDICINE (ABIM):
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Please Note: To receive MOC you must select the MOC option during the online credit claiming process and complete the required steps. ABIM MOC points will be reported within 30 days of claiming credit.