VOLUME 87 • NUMBER 12 • DECEMBER 2020 • www.ccjm.org

CME MOC

Cleveland Clinic Journal of Medicine

Fever in a lung transplant recipient

Pancreatitis and high triglycerides

Does my patient need hip radiography?

Is oxygen always safe after surgery?

Air embolism after IV contrast

Hypothyroid and eyelash loss

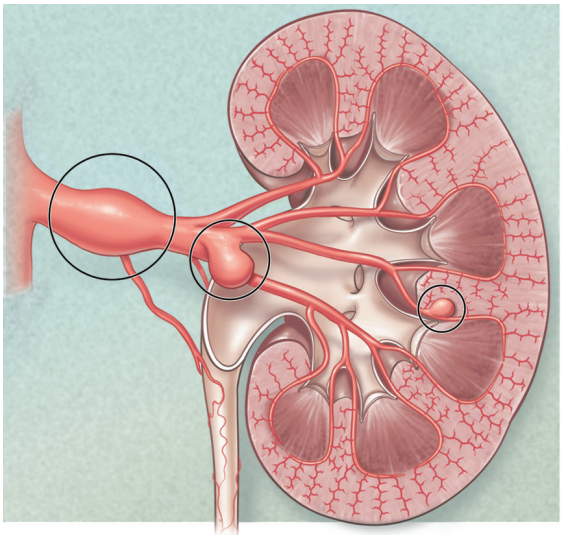
CT for coronary disease

COVID-19:
- Neurologic complications
- A year like no other
- Steroids, anticoagulation
- More at ccjm.org

Long-term effects of prematurity

ASMR: What your patients know

Aneurysm of the renal and splenic arteries



CLEVELAND CLINIC JOURNAL OF MEDICINE

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.

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 $155; institutional $183; single copy/back issue $20

Foreign: $200; 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

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
1950 Richmond Rd., TR404, Lyndhurst, OH 44124 • Phone (216) 444-2661 • Fax (216) 444-9385 • ccjm@ccf.org • www.ccjm.org

Cleveland Clinic Journal of Medicine [ISSN 0891-1150 (print), ISSN 1939-2869 (online)] is published monthly by Cleveland Clinic at 1950 Richmond Rd., TR404, Lyndhurst, OH 44124.

Table of Contents

CONTINUED ON PAGE 708

Cleveland Clinic | Comprehensive COVID Care

Participate in an interdisciplinary educational resource for the care of COVID-19 patients

Learn best practices in current therapy and rapidly evolving management strategies for COVID-19 patients

Review new safety protocols and procedures that ensure the safety of caregivers and patients in a COVID-19 environment

Attain key concepts pertinent to inpatient management of COVID and Non-COVID medical care for physicians preparing for redeployment

Access Just-in-Time care management guides for quick and easy referencesvon diagnosis and strategies for patient care treatment.

Participate Today! **healthcareedu.ccf.org**

These activities have been approved for *AMA PRA Category 1 Credit™*

CONTINUED FROM PAGE 706

2020

DECEMBER

LIVER UPDATE
December 4
LIVE STREAM

MASTERING THE TREATMENT OF MYELOID MALIGNANCIES IN THE ERA OF PERSONALIZED MEDICINE: VIRTUAL SYMPOSIUM
December 4
LIVE STREAM

A CASE-BASED APPROACH TO MASTERING THE MITRAL VALVE: IMAGING, INNOVATION, INTERVENTION
December 4–5
LIVE STREAM

DR. ROIZEN'S PREVENTIVE MEDICINE LONGEVITY CONFERENCE
December 5–6
LIVE STREAM

2021

JANUARY

SHAPING THE MANAGEMENT OF PARKINSON DISEASE: DEBATING THE MOST CONTROVERSIAL ISSUES AND DISCUSSING THE LATEST BREAKTHROUGHS
January 23–24
LIVE STREAM

FEBRUARY

VALVE DISEASE, STRUCTURAL INTERVENTIONS, AND DIASTOLOGY/IMAGING SUMMIT
February 5
LIVE STREAM

BASIC AND CLINICAL IMMUNOLOGY FOR THE BUSY CLINICIAN
February 5
LIVE STREAM

MARCH

MANAGEMENT OF CHECKPOINT INHIBITOR-RELATED TOXICITY
March 5
LIVE STREAM

INTERNATIONAL *PTEN* SYMPOSIUM: FROM PATIENT-CENTERED RESEARCH TO CLINICAL CARE
March 15
LIVE STREAM

CONTROVERSIES IN ENDOMETRIOSIS, ADENOMYOSIS, AND FIBROIDS
March 20
LIVE STREAM

PAIN MANAGEMENT SYMPOSIUM
March 27–31
Orlando, FL

JUNE

INTENSIVE REVIEW OF INTERNAL MEDICINE
June 7–11
LIVE STREAM

WASOG/AASOG 2021: MULTIDISCIPLINARY MEETING FOR SARCOIDOSIS AND ILD
June 21–24
Hollywood, FL

JULY

UPDATES IN MELANOMA AND HIGH-RISK SKIN CANCER MANAGEMENT
July 15–16
Cleveland, OH

CLEVELAND SPINE REVIEW: HANDS-ON 2021
July 28–August 2
Cleveland, OH

SEPTEMBER

PRIMARY CARE WOMEN'S HEALTH: ESSENTIALS AND BEYOND
September 9–10
Cleveland, OH

COMPREHENSIVE LIFELONG EXPEDITIOUS CARE OF AORTIC DISEASE
September 17–18
Cleveland, OH

INTENSIVE REVIEW FOR THE GI BOARDS
September 17–20
Las Vegas, NV

GENETICS EDUCATION SYMPOSIUM – GENETICS AND GENOMICS: APPLICATIONS FOR THE PREVENTION, DETECTION, AND TREATMENT OF CANCER
September 30
Cleveland, OH

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

2020: A year like no other

"Dawn is breaking everywhere, light a candle, curse the glare. Draw the curtains, I don't care, 'cause it's all right. I will get by… I will survive."
—Jerry Garcia and Robert Hunter. *Touch of Grey*. 1987.

History may repeat itself, but each year also brings something new, and this year it seems that we have rewritten the book. Historically, there likely have been times when a confluence of obstacles was equally daunting. But never has this happened in an environment when so much unfiltered information is available, while at the same time people are questioning the honesty of the organs responsible for the information transfer. Understandably, the various media outlets have defensively and aggressively responded to these challenges, but in doing so have morphed their perspective away from true objectivism and have added to the polarized environment in a way that has actually magnified the skepticism about what is factual and what is almost factual. Reflecting my age and the idealized and somewhat naive American world I grew up in, I ask, "Where is Walter Cronkite when we need him?"

Veracity and bias are issues that our editorial staff and I, as editor in chief of a medical journal, address on a daily basis. We live with and accept the concept that scientific "truths" are ephemeral, open for nuanced interpretation and situational exceptions. Clinical studies are always an approximation of reality; the hope is that the approximation is a good one. A policy of fact-checking is intrinsic to responsible medical publication. We call it peer review.

I want to offer my thanks to all our peer reviewers of the past year. We try to obtain 3 substantive peer reviews for each submitted manuscript. I ask our reviewers to focus on accuracy, to point out any nuances not indicated to be the authors' opinion that could be construed as unstated bias, and to offer suggestions as to how to improve the teaching value of each paper to our readership of practicing clinicians. This is no trivial request to our reviewers, all of whom are likely already overcommitted with their other responsibilities. Frequently, I also call upon our deputy editors Pelin Batur and Craig Nielsen to adjudicate mixed reviewer comments, to balance out or confirm concerns that I have, and particularly to provide insights for enhancing the practical clinical relevance of accepted manuscripts. Regarding our new online "COVID-19 Curbside Consults" section, this highly read addition to the *Journal* would not have been remotely possible without tireless input and review work from Kristin Highland, Mary Cusick, and many others. Thank you.

We are not immune to pointed questions about our process. I was recently challenged aggressively by an investigative reporter as to whether the reason that we published a paper discussing the potential role of anticytokine therapy in treating patients with COVID-19 was that I had previously received an honorarium for lecturing about the use of one of those drugs (for FDA-approved indications for other diseases). Naively, I initially didn't even realize the implication of this question—who in the medical community in the early throes of the pandemic was *not* interested in expert opinion regarding anticytokine therapy to address the cytokine storm associated with coronavirus infection? But his question did prompt me to reconsider the possibility of

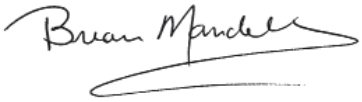
doi:10.3949/ccjm.87b.12020

intrinsic bias in editorial decision-making. While indeed the final decision to accept or reject a paper is mine, I very rarely make this decision in a vacuum without significant input from others. A preplanned updated version of that specific paper emphasized the failure of the mentioned therapy to significantly reverse the clinical course of treated patients. As above, apparent truth is ephemeral. We enhanced the visibility of author disclosures of potential or perceived conflicts of interest in our online postings to parallel our current practices in the printed version of the *Journal*.

As a country, we survived the overlapping impact of World War I and the H1N1 "Spanish Flu" epidemic, the latter of which strained the American health system and killed about 675,000 Americans. And we survived it despite President Woodrow Wilson's lack of visible leadership, as he was incapacitated by a major stroke in 1919.

The year 2020 is about over. It has been a year like no other in our memory. There have been demons and heroes. I feel proud to be part of our medical community. Despite fear and impediments, we have stood strong in the face of many adversities. I do not think that we have lost our way. Particularly, let me give an unrestrained shout-out to my colleagues staffing intensive care units, emergency rooms, and COVID wards. Despite flabbergasting public accusations from national leaders that you are fraudulently diagnosing COVID-19 for financial gain, and despite the irrational resistance by political "leaders" to mandated mask-wearing to help protect the entire population and ultimately healthcare providers, your efforts remain exemplary. You are the women and men of the year.

My personal wishes for a more civil, peaceful, and healthier 2021, for all of us.



Brian F. Mandell, MD, PhD
Editor In Chief

COVID-19 coagulopathy

To the Editor: I read with keen interest the article "Coagulopathy in COVID-19: Manifestations and management" in the August issue.[1] While I agree with the need for prophylaxis against venous thromboembolism (VTE) in patients admitted with COVID-19 and the need for therapeutic anticoagulation for confirmed VTE, I am skeptical of high-intensity prophylaxis for patients with D-dimer levels of 3.0 µg/mL or higher.

The American College of Chest Physicians, in their updated guidelines on prevention, diagnosis, and treatment of VTE in patients with COVID-19,[2] state, "In critically ill patients with COVID-19, we suggest current standard dose anticoagulant thromboprophylaxis over intermediate ([low-molecular-weight heparin twice a day] or increased weight-based dosing) or full treatment dosing, per existing guidelines."

Also, Al-Samkari et al[3] performed a retrospective analysis of 400 COVID-19 patients managed with prophylactic anticoagulation, in whom the rate of radiographically confirmed VTE was 4.8% and the overall bleeding rate was 4.8%. In 144 critically ill patients, the rate of radiographically confirmed VTE was 7.6%, and the bleeding rate was 5.6%. Elevated D-dimer levels predicted bleeding as well as thrombotic complications, suggesting one should exercise caution in using the higher VTE prophylaxis dose.

Randomized clinical trials are needed to determine the optimal dose and course of thromboprophylaxis in patients with COVID-19.

Anup Katyal, MD
St. Louis, MO

REFERENCES

1. **Mucha SR, Dugar S, McCrae K, Joseph D, Bartholomew J, Sacha GL, Militello M**. Coagulopathy in COVID-19: manifestations and management. Cleve Clin J Med 2020; 87(8):461–468, doi:10.3949/ccjm.87a.ccc024
2. **Moores LK, Tritschler T, Brosnahan S, et al**. Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019. Chest guideline and expert panel report. Chest 2020; 158(3):1143–1163. doi:10.1016/j.chest.2020.05.559
3. **Al-Samkari H, Leaf RSK, Dzik WH, et al**. Covid-19 and coagulation: bleeding and thrombotic manifestations of SARS-Cov-2 infection. Blood 2020; 136(4):489–500. doi:10.1182/blood.2020006520

doi:10.3949/ccjm.87c.12001

In Reply: We would like to thank Dr. Katyal for his interest in our article.[1] The comments highlight the ongoing uncertainties and urgent need for better data from prospective randomized controlled trials, such as those being developed under the National Heart, Lung, and Blood Institute's "Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)" program, to guide optimal management of COVID-19-associated coagulopathy.

As Dr. Katyal correctly points out, the current guidelines from the American College of Chest Physicians recommend standard venous thromboembolism prophylaxis.[2] In contrast, an expert panel of the American College of Cardiology failed to reach consensus on their recommendation for standard vs intensified prophylaxis or empiric therapeutic-dose anticoagulation,[3] while the authors of the interim guidance from the Anticoagulation Forum recommend high-intensity prophylactic dosing for all critically ill patients.[4]

Our approach represents an attempt to balance the potential risks and benefits of intensified prophylaxis by selecting patients at greatest risk of thrombosis for intensified prophylaxis, while we await the results of prospective randomized controlled trials. We are encouraged, however, by recent reports of low overall bleeding risk even with empiric therapeutic anticoagulation.[5]

Simon R. Mucha, MD
Cleveland Clinic

Siddharth Dugar, MD
Cleveland Clinic

Keith McCrae, MD
Cleveland Clinic

Douglas Joseph, DO
Cleveland Clinic

John Bartholomew, MD
Cleveland Clinic

Gretchen L. Sacha, PharmD, RPh, BCCCP
Cleveland Clinic

Michael Militello, PharmD, RPh, BCPS
Cleveland Clinic

■REFERENCES

1. **Mucha SR, Dugar S, McCrae K, Joseph D, Bartholomew J, Sacha GL, Militello M**. Coagulopathy in COVID-19: manifestations and management. Cleve Clin J Med 2020; 87(8):461–468, doi:10.3949/ccjm.87a.ccc024
2. **Moores LK, Tritschler T, Brosnahan S, et al**. Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019. Chest guideline and expert panel report. Chest 2020; 158(3):1143–1163. doi:10.1016/j.chest.2020.05.559
3. **Bikdeli B, Madhavan MV, Jimenez D, et al**. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol 2020; 75(23): 2950–2973. doi:10.1016/j.jacc.2020.04.031
4. **Barnes GD, Burnett A, Allen A, et al**. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the Anticoagulation Forum. J Thromb Thrombolysis 2020; 51(1):72–81. doi:10.1007/s11239-020-02138-z
5. **Nadkarni GN, Lala A, Bagiella E, et al**. Anticoagulation, mortality, bleeding and pathology among patients hospitalized with COVID-19: a single health system study. J Am Coll Cardiol 2020; Aug 24;S0735-1097(20)36408-1. doi: 10.1016/j.jacc.2020.08.041

doi:10.3949/ccjm.87c.12002

Assessing stable coronary artery disease

To the Editor: The article by Nagaraja and Lincoff[1] is an excellent review of the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches trial. It highlights the continuing evolution of patient-centered approaches in the management of stable coronary artery disease. Their algorithm contains the phrase "cardiac computed tomography to assess calcium score and exclude left main disease." Are the authors referring to the coronary artery calcium score (CACS) or coronary computed tomography angiography (CCTA)? I believe they mean the latter, but as both are computed tomographic modalities of the heart and the difference may not be readily appreciated by a general medicine audience, it may be helpful to clarify.

The CACS is most useful in risk assessment in primary prevention, particularly to improve specificity in older adults and allow for a personalized and risk-driven decision in use of lipid-lowering medications. For patients with established coronary artery disease and an abnormal stress test, it seems unlikely that the CACS will add any clinically useful information and may provide false reassurance, particularly in exclusion of disease. Noncalcified plaque, including that in the left main, would not be visible on CACS.

Further, it is noncalcified plaque that is the strongest risk-discriminator. The incidence of acute coronary syndrome is associated with fibrofatty plaques and plaques with necrotic cores (both generally low-density, noncalcified plaque types that are not visualized by CACS), but not calcified plaque burden.[2] Calcium development is a late-stage finding of a plaque, and high-risk atherosclerotic plaque features, such as rupture and erosion, are missed by CACS.[3] In fact, heavily calcified (stabilized) plaques appear to be protective.[4]

On the other hand, CCTA evaluates the entire spectrum of coronary artery disease and can identify noncalcified plaque. It would be the appropriate modality to exclude left main disease, as I believe the authors are proposing.

Taher Modarressi, MD
Diabetes & Endocrine Associates of Hunterdon
Hunterdon Medical Center
Flemington, NJ

■REFERENCES

1. **Nagaraja V, Lincoff AM**. Stable coronary artery disease: Intervene or not? Cleve Clin J Med 2020; 87(7):410–415. doi:10.3949/ccjm.87a.20048
2. **Chang HJ, Lin FY, Lee SE, et al**. Coronary atherosclerotic precursors of acute coronary syndromes. J Am Coll Cardiol 2018; 71(22):2511–2522. doi:10.1016/j.jacc.2018.02.079
3. **Mori H, Torii S, Kutyna M, et al**. Coronary artery calcification and its progression: what does it really mean? JACC Cardiovasc Imaging 2018; 11(1):127–142. doi:10.1016/j.jcmg.2017.10.012
4. **van Rosendael AR, Narula J, Lin FY, et al**. Association of high-density calcified 1K plaque with risk of acute coronary syndrome. JAMA Cardiol 2020; 5(3):282–290. doi:10.1001/jamacardio.2019.5315

doi:10.3949/ccjm.87c.12003

In Reply: We thank Dr. Modarressi for his interest in our article.[1] He astutely highlighted the issue in the algorithm proposed for the management of stable coronary artery disease. While coronary calcium scoring has utility for risk stratification in primary prevention, most patients being considered for coronary revascularization have established vascular disease, for which calcium scoring would be less useful.[2] We agree with Dr. Modarressi that coronary computed tomography angiography is the appropriate test in our algorithm for the management of stable angina to exclude left main disease,[3] and we have revised our algorithm to clarify this point.

Vinayak Nagaraja, MD
Department of Cardiovascular Medicine
Cleveland Clinic

A. Michael Lincoff, MD
Department of Cardiovascular Medicine
Cleveland Clinic

REFERENCES

1. **Nagaraja V, Lincoff AM**. Stable coronary artery disease: Intervene or not? Cleve Clin J Med 2020; 87(7):410–415. doi:10.3949/ccjm.87a.20048
2. **Mori H, Torii S, Kutyna M, et al**. Coronary artery calcification and its progression: what does it really mean? JACC: Cardiovascular Imaging 2018; 11:127–142. doi:10.1016/j.jcmg.2017.10.012
3. **Maron DJ, Hochman JS, Reynolds HR, et al**. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med 2020; 382(15):1395–1407. doi:10.1056/NEJMoa1915922

doi:10.3949/ccjm.87c.12004

Dexamethasone or hydrocortisone in COVID-19?

To the Editor: We read with interest the article by Chatterjee et al,[1] who provided an overview of the use of corticosteroids in patients with novel coronavirus disease 2019 (COVID-19). The authors discussed the best available evidence at the time of their writing regarding the outcomes in hospitalized patients with COVID-19 who received corticosteroids. However, with the publication of more randomized trials plus a meta-analysis by the World Health Organization (WHO)[2] on the use of corticosteroids in patients with COVID-19, we wish to complement the authors' discussion to elaborate on the relationship between pharmacodynamic profiles of hydrocortisone and dexamethasone and their respective efficacy in patients with COVID-19.

From the subgroup pooled analysis by WHO to determine the association between corticosteroid use and 28-day all-cause mortality rates in COVID-19 patients, there were no mortality benefits detected from the use of hydrocortisone, whereas dexamethasone significantly reduced the odds of all-cause death at 28 days.[2]

This is consistent with pharmacodynamic observations. Hydrocortisone has a lower affinity for the glucocorticoid receptor compared with dexamethasone. The reported log relative receptor affinities for hydrocortisone and dexamethasone were 0.95 and 2.0, respectively.[3] In addition, hydrocortisone demonstrates less inhibition of proinflammatory transcription factors than dexamethasone. For example, hydrocortisone inhibited tumor necrosis factor alpha-induced nuclear factor kappa B activation less than dexamethasone—the half-maximal inhibitory concentrations [IC50] for nuclear factor kappa inhibition were 15.52 nM and 2.93 nM, respectively.[4] The same is observed for nongenomic activity, for which hydrocortisone demonstrates lower potency: hydrocortisone had less inhibition of the release of prostaglandin E2 (PGE2) compared with dexamethasone (the IC50s for PGE2 release were 750 nM and 20 nM, respectively).[5] Both nuclear factor kappa B activation and PGE2 release play significant roles in the hyperinflammatory and immune responses in COVID-19.

For these reasons, along with its longer biological half-life and lesser mineralocorticoid activity, dexamethasone should be favored over hydrocortisone in patients with COVID-19 who need treatment with systemic corticosteroids.

Chia Siang Kow
School of Postgraduate Studies
International Medical University
Kuala Lumpur, Malaysia

Syed Shahzad Hasan
School of Biomedical Sciences & Pharmacy
University of Newcastle
Callaghan, Australia

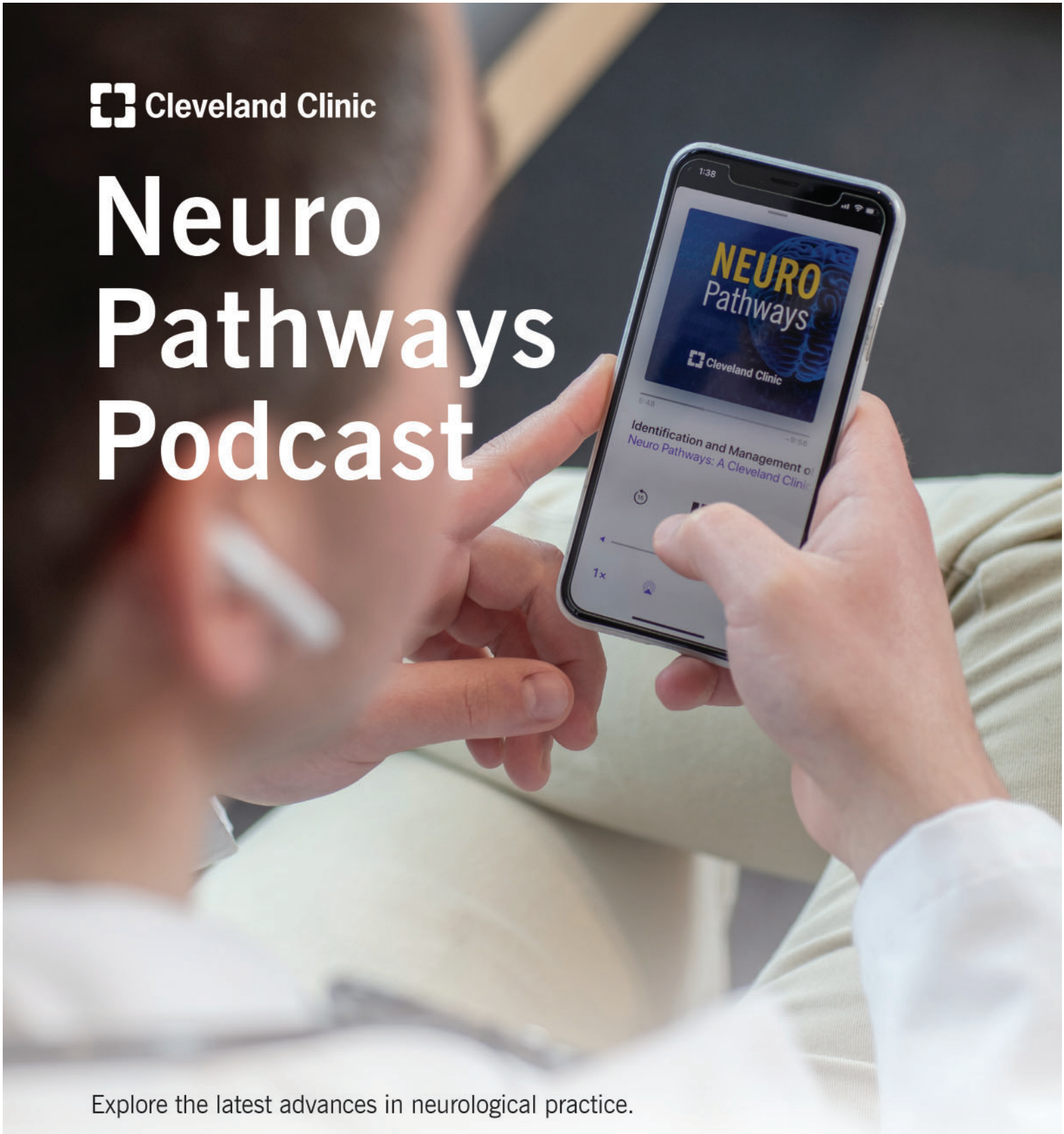
REFERENCES

1. **Chatterjee K, Wu CP, Bhardwaj A, Siuba M**. Steroids in COVID-19: an overview. Cleve Clin J Med 2020 Aug 20. doi:10.3949/ccjm.87a.ccc059
2. **The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group**. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA 2020 Sep 2. doi:10.1001/jama.2020.17023.
3. **Mager DE, Moledina N, Jusko WJ**. Relative immunosuppressive potency of therapeutic corticosteroids measured by whole blood lymphocyte proliferation. J Pharm Sci 2003; 92(7):1521–1525. doi:10.1002/jps.10402
4. **Cechin SR, Buchwald P**. Effects of representative glucocorticoids on TNFα- and CD40L-induced NF-κ activation in sensor cells. Steroids 2014; 85:36–43. doi:10.1016/j.steroids.2014.04.003
5. **Croxtall JD, van Hal PT, Choudhury Q, Gilroy DW, Flower RJ**. Different glucocorticoids vary in their genomic and non-genomic mechanism of action in A549 cells. Br J Pharmacol. 2002; 135(2):511–519. doi:10.1038/sj.bjp.0704474

doi:10.3949/ccjm.87c.12005

Cleveland Clinic

Neuro Pathways Podcast



Explore the latest advances in neurological practice.

A sampling of episode topics includes:

- Managing complex chronic back pain
- Diagnosing psychogenic non-epileptic seizures
- Evaluating Lewy body dementia
- Incorporating sleep management into routine care
- Managing patients in the opioid crisis era

Access these episodes and more at **clevelandclinic.org/neuropodcast**.

Hiroki Matsuura, MD
Department of General Internal Medicine, Okayama City Hospital, Okayama, Japan

Yu Suganami, MD, PhD
Department of General Internal Medicine, Okayama City Hospital, Okayama, Japan

Hypothyroidism, eyelash loss

A 77-year-old woman presented to our outpatient department with chronic general fatigue and peripheral edema. She had mild hypertension and diabetes but no significant cardiovascular or gastrointestinal problems.

Physical examination revealed nonpitting edema in the legs and loss of eyelashes (**Figure 1**) from all four eyelids. Her eyebrows were also thin, but she said she usually trims them for makeup. She denied rubbing the eyelid, pulling the eyelashes, or having experienced previous eyelid injuries.

Laboratory testing showed a high thyroid-stimulating hormone level of 33.7 µU/mL (reference range 0.35–4.94), a low serum thyroxine level, and the presence of antithyroid antibodies.

Based on the presentation and findings, the diagnosis was hypothyroidism with milphosis.

CAUSES OF MILPHOSIS

Terms used for hair loss include milphosis, madarosis, and alopecia. Milphosis is loss of eyelashes, madarosis is loss of eyelashes and eyebrow hairs, and alopecia is general loss of hair, but especially from the head.

Eyelashes and eyebrows have many roles such as protecting the eye (by preventing sweat and water from entering), cosmetic appearance, and social communication.

Typically, milphosis is caused by thyroid disorders, as in this case. Both insufficient and excessive levels of thyroid hormones are associated with hair growth and hair follicle cycling. In particular, hypothyroidism can cause telogen effluvium (thinning or shedding of hair resulting from the early entry of the hair follicle into the resting phase), early graying, and reduced tensile strength.

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

doi:10.3949/ccjm.87a.20009

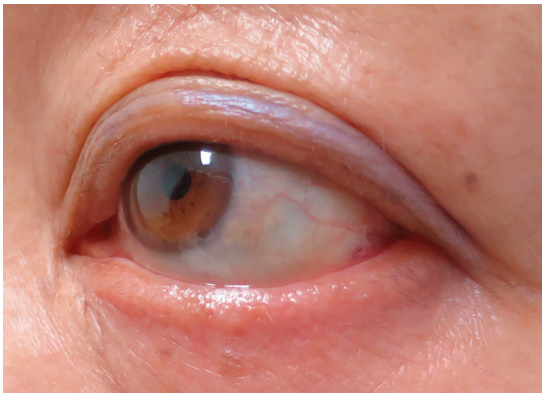


Figure 1.

Milphosis is also associated with a range of diseases from localized dermatologic disease to systemic disorders such as hypoparathyroidism, infection (herpes zoster, tuberculosis, syphilis, trachoma, Hansen disease), radiation, drug effects (heparin, androgens, retinoids, and angiotensin-converting enzyme inhibitors), injury, toxins (cocaine and thallium), zinc deficiency, biotin deficiency, psoriasis, systemic lupus erythematosus, discoid lupus, and neoplasm (basal cell carcinoma and squamous-cell carcinoma).[1]

Milphosis can sometimes be useful as a physical symptom when it helps detect underlying systemic disorders. However, clinicians should also consider trichotillomania in the differential diagnosis of patients with milphosis whose clinical history and laboratory findings are unclear. In nonscarring milphosis, hair can regrow after the primary disease is appropriately treated.

Our patient received supplemental thyroxine, but her eyelashes did not grow back. ■

Testing showed a high thyroid-stimulating hormone level, low serum thyroxine, and presence of antithyroid antibodies

REFERENCES

1. **Jordan DR**. Eyelash loss. Semin Plast Surg 2007; 21(1):32–36. doi:10.1055/s-2007-967745

***Address**: Hiroki Matsuura, MD, Department of General Internal Medicine, Okayama City Hospital, 3-20-1, Omote-cho, Kitanagase, Okayama-city, Okayama, 700-0962, Japan; superonewex0506@yahoo.co.jp*

Justin Goodwin, MS
Yale School of Medicine,
New Haven, CT

Karthik Gnanapandithan, MD, MS, FHM
Yale School of Medicine, New Haven, CT;
Department of Internal Medicine, Yale New Haven Hospital,
New Haven, CT

Air embolism after peripheral IV contrast injection

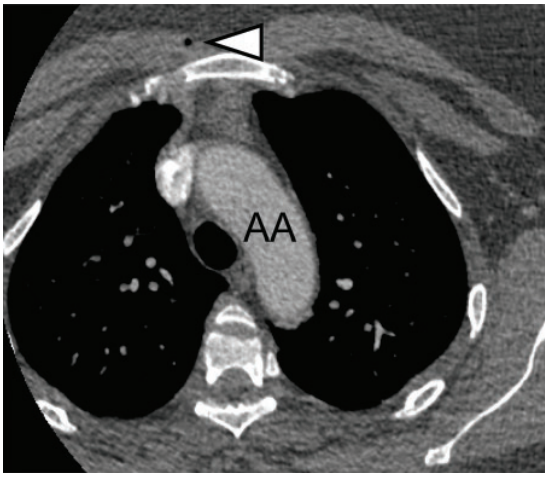


Figure 1. Computed tomography showed an air bubble (arrowhead) in the peripheral vasculature of the anterior chest wall at the level of the aortic arch (AA).

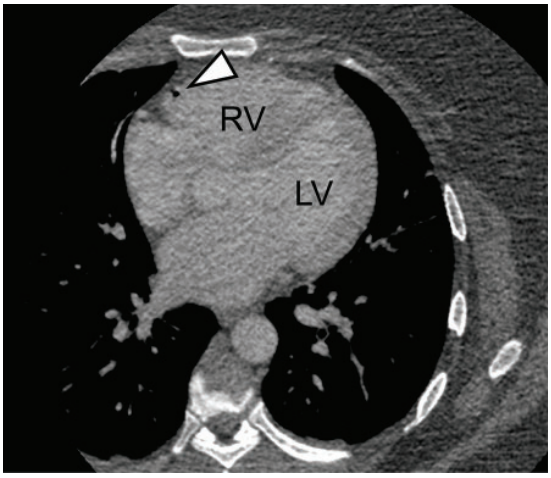


Figure 2. An air embolus (arrowhead) along the anterior wall of the right ventricle (RV).

As little as 0.5 mL of air in the coronary arteries can cause ventricular fibrillation; 2 to 3 mL of air in the cerebral circulation can be fatal

A 35-year-old woman with hypertension presented with acute intermittent abdominal pain radiating to her back.

Her blood pressure was 139/88 mm Hg in the right upper extremity and 133/80 mm Hg in the left upper extremity. Her heart rate was regular, and breath sounds were clear. She had mild abdominal tenderness in the umbilical and left lumbar regions.

Electrocardiography and laboratory testing, including troponins, showed no abnormalities. Computed tomography of the chest and abdomen with contrast enhancement showed no evidence of aortic dissection or pulmonary embolism. However, postcontrast images detected nonobstructing calculi in the left kidney and air emboli in the peripheral venous circulation (**Figure 1**), right ventricle (**Figure 2**), and pulmonary trunk (**Figure 3**). The air emboli were thought to be most likely from peripheral intravenous catheter placement or manipulation for contrast injection.

The patient remained hemodynamically stable, with no new-onset chest pain, shortness of breath, or neurologic signs. She was placed in the Trendelenburg position, and high-flow oxygen supplementation was started. Transthoracic echocardiography showed normal left ventricular systolic function with a 66% ejection fraction, and normal right ventricle size and function with an estimated systolic pressure of 26 mm Hg. The patient was maintained on supplemental oxygen and was encouraged to lie in the left lateral decubitus position. Her abdominal pain was likely due to nephrolithiasis, which improved with hydration and analgesia, and she was discharged home.

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

doi:10.3949/ccjm.87a.20001

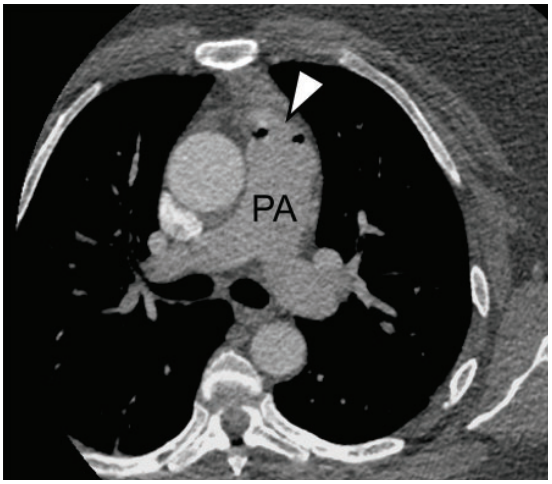


Figure 3. Multiple air emboli (arrowhead) in the proximal pulmonary artery (PA).

CAUSES OF VENOUS AIR EMBOLISM

Venous air embolism is a potentially catastrophic complication when it occludes blood flow to the pulmonary, cardiac, or cerebral circulation. It is most often associated with neurologic and otolaryngologic surgery, thoracic or abdominal trauma (including barotrauma from mechanical ventilation), and vascular interventions such as central and peripheral intravenous access.[1] It can also occur when central venous pressure is low, such as when a catheter is inserted during inspiration, when the patient is upright, or if the patient is hypovolemic.[1,2] Alternatively, incorrectly flushed lines or pressurized injection of fluids, such as contrast media, may force air into the vasculature.[3,4]

While venous air embolism is a known risk associated with intravenous access, many cases are asymptomatic and therefore go undetected, likely leading to an underestimation of the true incidence.[4] A study of more than 11,000 central venous catheter insertions using optimal positioning and technique found an incidence of 0.13%.[1] A study of 677 patients who underwent peripheral contrast injection observed an incidence of 11.7%.[4]

MANAGEMENT

Management of venous air embolism depends on the location and volume of the emboli. In most cases, the air is resorbed without complications. However, large emboli or those in patients with shunts that can result in paradoxical emboli may present with cardiopulmonary or neurologic symptoms.[1,2] As little as 0.5 mL of air in the coronary arteries can cause ventricular fibrillation, and 2 to 3 mL of air in the cerebral circulation can be fatal.[5]

High-flow oxygen therapy helps maintain adequate oxygenation and promotes air resorption.[1] Placing the patient in the Trendelenburg or left lateral decubitus position (Durant maneuver) encourages air emboli to migrate away from the right ventricular outflow tract and toward the right atrium, avoiding possible cardiopulmonary collapse.[1,6] If available, hyperbaric oxygen therapy is the definitive treatment for severe cases and has been shown to improve recovery when administered early.[1]

MINIMIZING THE RISK

The risk of venous air embolism can be minimized when inserting or removing a central venous catheter by placing the patient in the supine or Trendelenburg position and ensuring that the patient is hydrated. Catheter insertion should be avoided during inspiration, and removal should be performed while the patient performs a Valsalva maneuver or during exhalation.

Before contrast injection, the catheter lumen should be flushed, and components such as stopcocks and Luer locks should be inspected and secured.

Incidentally detected intracardiac air emboli rarely cause hemodynamic compromise. However, as in our patient, appropriate management is straightforward and effective in preventing potentially life-threatening cardiopulmonary and neurologic complications.

Incorrectly flushed lines or pressurized injection of fluids, such as contrast media, may force air into the vasculature

REFERENCES

1. **McCarthy CJ, Behravesh S, Naidu SG, Oklu R**. Air embolism: practical tips for prevention and treatment. J Clin Med 2016; 5(11):93. doi:10.3390/jcm5110093
2. **Gordy S, Rowell S**. Vascular air embolism. Int J Crit Illn Inj Sci 2013; 3(1):73–76. doi:10.4103/2229-5151.109428
3. **Ie SR, Rozans MH, Szerlip HM**. Air embolism after intravenous injection of contrast material. South Med J 1999; 92(9):930–933. doi:10.1097/00007611-199909000-00019
4. **Groell R, Schaffler GJ, Rienmueller R, Kern R**. Vascular air embolism: location, frequency, and cause on electron-beam CT studies of the chest. Radiology 1997; 202(2):459–462. doi:10.1148/radiology.202.2.9015074
5. **Ho AM**. Is emergency thoracotomy always the most appropriate immediate intervention for systemic air embolism after lung trauma? Chest 1999; 116(1):234–237. doi:10.1378/chest.116.1.234
6. **Ericsson JA, Gottlieb JD, Sweet RB**. Closed-chest cardiac massage in the treatment of venous air embolism. N Engl J Med 1964; 270:1353–1354. doi:10.1056/NEJM196406182702507

***Address**: Karthik Gnanapandithan, MD, MS, FHM, Yale School of Medicine, 333 Cedar St., New Haven, CT 06510; karthik.gnanapandithan@ynhh.org*

Christina Stull, MD, MBA
Department of Internal Medicine, University of Texas at Austin Dell Medical School, Austin, TX

Alejandro Moreno, MBBS, MPH, JD, MACP
Assistant Dean of Clinical Skills Integration and Director of Developing Outstanding Clinical Skills Course, Departments of Medical Education and Internal Medicine, University of Texas at Austin Dell Medical School, Austin, TX

ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Does this young adult patient need a hip radiograph?

A: A 41-year-old woman with chronic L3 radiculopathy and intermittent asthma controlled with as-needed short-acting beta-agonists presents after falling from standing. She reports no new pain or changes in her low-back pain. She has no history of systemic or inhaled steroid therapy, malignancy, osteoporosis, menopause, high-force trauma, smoking, substance abuse, or debilitating disease.

She has tenderness on her lower back, but not in the hip, and is able to bear weight. Her legs are symmetric and without deformities. Her left hip demonstrates full range of motion. A straight-leg test sharply increases her radiculopathic pain. Muscle strength is preserved, except for her left hip flexors and adductors, which have 4+ strength on a scale of 5.

HIP RADIOGRAPHY GUIDELINES LACKING FOR YOUNGER ADULTS

Between 21% and 35% of adults fall from standing every year, and internists will inevitably encounter such patients.[1] There are clinical guidelines on when a patient needs knee or ankle radiography after sustaining an injury,[2,3] but there are no similar high-value care guidelines for hip films. Consequently, clinicians routinely obtain hip radiographs regardless of the patient's age, the nature of the injury, the presence of risk factors, or the physical examination findings.[4]

RISK FACTORS FOR HIP FRACTURES

Age and sex, as markers for osteoporosis, are the strongest risk factors for hip fracture.[4,5] Hip fractures increase exponentially after age 60, with a 20% to 30% lifetime risk by age 90.[5,6] From age 60 to age 80, the hip fracture rate in women increases from 78 to 1,084 per 100,000, and in men from 56 to 658 per 100,000.[5]

On the other hand, hip fractures are uncommon in adults under age 50, even though this group has a high frequency of injuries. A study looking at 28 million emergency room visits found only 20,000 hip fractures in patients under age 50.[5]

High-energy trauma, eg, from a motor vehicle accident, a fall from a height, or a sports injury such as in bicycling or ice-skating, is another risk factor for hip fracture[4,7,8]; 56% of hip fractures in patients under age 50 are from high-energy trauma.[4,5,7,8]

Hip fractures are uncommon in adults under age 50

On the other hand, 90% of hip fractures in those age 60 and older occur after a fall from standing, ie, a low-energy trauma.[5,6] In contrast to fractures in patients age 60 and older, most hip fractures in people under 50 are in men (70%), reflecting the historical association between male sex and activities involving high-energy trauma.[6–8]

Debilitating diseases such as cancer, chronic systemic steroid therapy, heavy alcohol intake (> 10 drinks per week), smoking (> 1 pack per day), or substance use disorder are other important risk factors for hip fracture.[2–4] White people have a higher incidence of hip fracture than other racial groups, a factor that correlates with the higher incidence of osteoporosis in this group.[7,8]

SYMPTOMS, FINDINGS, AND INITIAL EVALUATION

Patients with hip fracture report pain in the groin that may radiate to the knee, a phenom-

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

doi:10.3949/ccjm.87a.20011

enon more commonly encountered in younger patients.[4] Pain in the low back, pelvis, or thigh or with a different radiation pattern indicates another process.[4] All patients report exquisite tenderness when pressure is applied to the affected hip.[4] Two-thirds of patients under age 50 present with a displaced fracture resulting in a shortened and externally rotated limb, inability to bear weight, and inability to move the joint in any direction actively or passively.[2]

Patients age 65 and older have a higher incidence of impacted hip fractures that permit joint range of motion, albeit with pain, and have no shortened, externally rotated limb, allowing for weight-bearing.[4] Between 40% and 75% of patients under 50 present with hypotension or have other injuries from high-energy trauma.[4]

DOES OUR 41-YEAR-OLD PATIENT NEED A HIP RADIOGRAPH?

Our patient has no factors that would place her at high risk for hip fracture. She is 41 and premenopausal, has no debilitating disease, is not on chronic systemic or inhaled corticosteroids, and does not smoke or drink alcohol heavily. Her trauma was low-energy. She reports no groin pain. On physical examination, the hip has normal range of motion, and the limb is not shortened, rotated, or deformed. She is able to bear weight. The subtle physical examination findings are consistent with the patient's chronic L3 radiculopathy.

Our patient had no factors that would place her at high risk for hip fracture

For a patient such as this, a physician would have to order at least 200,000 hip films (costing about $58 million) in order not to miss a hip fracture.[5–8] The number could be as high as 1 million hip films ($290 million) if the patient's lack of risk factors is fully accounted for.[5–8]

In summary, hip radiographs should not be routinely obtained for adults under age 50 who have low-energy trauma, have no risk factors for hip fracture, have a benign physical examination, and are able to bear weight. On the other hand, plain radiography should be strongly considered for patients age 60 and older, as 90% of hip fractures in this population occur after low-energy trauma, and they can present with impacted fractures with no evidence of limb-shortening or external rotation allowing joint movement and weight-bearing.[4]

***Acknowledgment**: Dr. Moreno would like to thank Timothy Weitz, JD, John Bedolla, MD, FACEP, and Patrick J. Crocker, DO, MS, FACEP, for their insights.*

REFERENCES

1. **Talbot LA, Musiol RJ, Witham EK, Metter EJ**. Falls in young, middle-aged and older community dwelling adults: perceived cause, environmental factors and injury. BMC Public Health 2005; 5:86. doi:10.1186/1471-2458-5-86
2. **Bachmann LM, Kolb E, Koller MT, Steurer J, ter Riet G**. Accuracy of Ottawa ankle rules to exclude fractures of the ankle and mid-foot: systematic review. BMJ 2003; 326(7386):417. doi:10.1136/bmj.326.7386.417
3. **Bachmann LM, Haberzeth S, Steurer J, ter Riet G**. The accuracy of the Ottawa knee rule to rule out knee fractures: a systematic review. Ann Intern Med 2004; 140(2):121–124. doi:10.7326/0003-4819-140-5-200403020-00013
4. **Walls RM, Hockberger RS, Gausche-Hill M**. Rosen's Emergency Medicine: Concepts and Clinical Practice. 9th ed. Philadelphia, PA: Elsevier; 2018.
5. **Kim SH, Meehan JP, Blumenfeld T, Szabo RM**. Hip fractures in the United States: 2008 nationwide emergency department sample. Arthritis Care Res (Hoboken) 2012; 64(5):751–757. doi:10.1002/acr.21580
6. **Al-Ani AN, Neander G, Samuelsson B, Blomfeldt R, Ekström W, Hedström M**. Risk factors for osteoporosis are common in young and middle-aged patients with femoral neck fractures regardless of trauma mechanism. Acta Orthop 2013; 84(1):54–59. doi:10.3109/17453674.2013.765639
7. **Karantana A, Boulton C, Bouliotis G, Shu KS, Scammell BE, Moran CG**. Epidemiology and outcome of fracture of the hip in women aged 65 years and under: a cohort study. J Bone Joint Surg Br 2011; 93(5):658–664. doi:10.1302/0301-620X.93B5.24536
8. **Boden SD, Labropoulos P, Saunders R**. Hip fractures in young patients: is this early osteoporosis?. Calcif Tissue Int 1990; 46(2):65–72. doi:10.1007/BF02556089

***Address**: Alejandro Moreno, MBBS, MPH, JD, MACP, University of Texas at Austin Dell Medical School, 1501 Red River Street, HLB 2.502, Austin, TX 78712; alejandro.moreno@austin.utexas.edu*

COMMENTARY

Roop Kaw, MD
Department of Hospital Medicine and Department of Outcomes Research, Cleveland Clinic; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Anthony G. Doufas, MD, PhD
Professor of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA

Is regular oxygen supplementation safe for obese postoperative patients?

Postoperative hypoxemia is common. A prospective blinded observational study[1] found that 21% of noncardiac postoperative patients had a pulse oxygen saturation less than 90% for at least 10 minutes per hour in the first 48 hours after surgery, and 3% had severe hypoxemia (pulse oxygen saturation < 80% for at least 30 minutes). Of note, most of the patients received supplemental oxygen for only a few hours after surgery, and standard observation by the nursing staff seriously underestimated the severity of hypoxemia.

Hypoxemia is more likely to occur in patients breathing room air as opposed to 35% oxygen.[2] The number of cases detected and treated might be higher if patients were monitored by pulse oximetry, but correcting hypoxemia has not been shown to improve morbidity and mortality rates, cognitive function, or length of stay.[3,4]

Hence, oxygen supplementation has become the default clinical standard, as opposed to the more cumbersome and expensive option of continuous pulse oximetry after surgery.

OBESITY, OBSTRUCTIVE SLEEP APNEA, AND CONTROL OF VENTILATION

Obese patients are more likely to need oxygen after surgery, possibly because they are more likely to have obstructive sleep apnea, obesity hypoventilation syndrome, or physiologic restrictive lung disease.[5] Patients with known obstructive sleep apnea are also more likely to receive supplemental oxygen postoperatively than to be resumed on continuous or bilevel positive airway pressure therapy.

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

doi:10.3949/ccjm.87a.19051

Complicating the picture, some patients with obstructive sleep apnea also have chronic obstructive pulmonary disease. Although supplemental oxygen may improve nocturnal oxygenation in patients with chronic obstructive pulmonary disease with only slight hypercapnia, hypercapnia may be more severe in patients who have both diseases, in which case giving oxygen may increase the duration of apnea episodes, leading to hypoventilation.

Asleep vs awake

Most patients with obstructive sleep apnea have enhanced chemoreflex sensitivity, and both obesity and metabolic syndrome have been shown to enhance ventilatory responses to hypoxia and hypercapnia—during wakefulness.[6–8] On the other hand, obstructive sleep apnea in obese patients was associated with a blunted response to hypercapnia during sleep in a study by Yuan et al.[9]

This finding has been supported by evidence that opioid-induced ventilatory depression in postoperative bariatric patients is greater during sleep.[10] Closer attention and ventilatory monitoring by the care staff in the immediate postoperative period, especially when patients are sedated or asleep, may help prevent the undesirable respiratory consequences of opioids.

Caution, but no evidence to support avoiding it altogether in obese patients

Supplemental oxygen in postoperative patients with obstructive sleep apnea

Giving oxygen to patients with obstructive sleep apnea while they are asleep has been associated with variable outcomes, partly reflecting underlying differences in the mechanisms of ventilatory control.[11]

Liao et al[12] performed a trial in postoperative obese patients with obstructive sleep apnea, randomizing them to receive either

supplemental oxygen at 3 L/min or room air. The mean oxygen saturation was 95.2% with oxygen vs 91.4% with room air ($P < .001$), and the median apnea-hypopnea index was 8.0 vs 15.6 ($P = .016$). The duration of apnea-hypopnea events was not increased, transcutaneous partial pressure of carbon dioxide increased significantly in only 11% of the patients on the first postoperative night, and no life-threatening events were reported. The total opioid requirement varied between 35 and 45 mg morphine equivalents over a 72-hour period and did not differ between the 2 groups. Of note, only 3% of the patients had a diagnosis of chronic obstructive pulmonary disease, and patients with presumed obesity hypoventilation syndrome (based on a serum bicarbonate level > 30 mmol/L) were excluded from the study.

Different phenotypes of obstructive sleep apnea?

Differences in response to supplemental oxygen in patients with obstructive sleep apnea have been attributed to differences in "loop gain," an engineering term that describes the gain of the negative feedback loop that regulates ventilation.[13] If loop gain is high, ventilatory control is relatively unstable, and vice versa. Giving oxygen lowers a high loop gain, hence leading to moderation (or elimination) of an excessive postobstruction hyperventilatory response that may have precipitated further hypocapnia-related cycles of airway obstruction.

Postoperative hypoxemia is common, and oxygen is the default clinical standard

Wellman et al[13] gave supplemental oxygen overnight to 12 patients with obstructive sleep apnea (not postoperative patients), of whom 6 had high loop gain and 6 had low. Oxygen lowered the apnea-hypopnea index in those with high loop gain but not in those with low loop gain.

At present, however, the extent to which certain phenotypes of obstructive sleep apnea influence the risk of adverse postoperative outcomes in obese patients remains unknown.

OPIOIDS AND OXYGEN

Postoperative patients experience a state of relative hypoventilation due to the residual effects of anesthesia and to opioid analgesics. Depending on the dose and route of administration, patient-related characteristics, the monitoring method, and the definition used, the incidence of postoperative opioid-induced ventilatory depression ranges from less than 1% to up to 40%.[1,14–16]

In a series of 92 cases of severe opioid-induced ventilatory depression associated with significant morbidity and mortality that were identified through insurance malpractice claims,[17] only a third of the patients were monitored with pulse oximetry, and only 15% were receiving supplemental oxygen; 42% of these events occurred within 2 hours of the last nursing check, and only a quarter of the patients either had a diagnosis of obstructive sleep apnea or were at high risk of it (with a STOP-BANG score ≥ 3). This evidence suggests that during hypoxemia, patients may benefit from closer monitoring, supplemental oxygen, or both to prevent hypoxic insults from escalating to more serious morbidity.

Similarly, a randomized trial[18] comparing supplemental oxygen at a regular flow rate (2–4 L/min to maintain pulse oxygen saturation ≥ 93%) vs a high flow rate (45 L/min) in postcardiac surgery patients did not show any advantage in postoperative oxygenation, but decreased the need for escalation of respiratory support.

Intermittent pulse oximetry has been shown to substantially underestimate ventilatory depression compared with continuous oximetry and capnography monitoring.[1,19]

Recently, investigators in an international prospective trial[16] (Prediction of Opioid-induced Respiratory Depression in Patients Monitored by Capnography; PRODIGY) developed a risk tool to predict opioid-induced respiratory depression. It is derived from data from 1,335 hospitalized patients on general medical-surgical floors who were monitored by continuous capnography and oximetry, of whom 614 (46%) had 1 or more episodes of respiratory depression. Points are awarded for age, male sex, no prior use of opioids, sleep disordered breathing, and chronic heart failure. Patients with a high PRODIGY score (≥ 15 of a possible 39) were more likely to develop respiratory depression than those with a score less than 8 (odds ratio 6.07, 95% confidence interval 4.44–8.30). The area under the receiver-operating curve was 0.74. Patients with respiratory depression were 2.5 times more

likely to need rescue action (including rapid-response-team activation) and 1.4 times more likely to need prolonged hospitalization.

Pharmacologic models need to be developed and validated for opioids in morbidly obese patients to link drug dose and effect and to interrogate the physiology behind the differential sensitivity of these patients for opioid-induced analgesia, sedation, and ventilatory depression.

DOES SUPPLEMENTAL OXYGEN MASK HYPOVENTILATION?

In spite of evidence that supplemental oxygen improves oxygenation in postoperative patients receiving opioids by patient-controlled devices, concern has been expressed that it could hamper our ability to promptly detect opioid-induced ventilatory depression and thus prevent morbid outcomes. This concern is based on experimental[20] and clinical[19,21,22] evidence that, in contrast to room air, oxygen supplementation may delay oxygen desaturation associated with ventilatory depression and associated hypercapnia.

Thus, some have suggested giving oxygen, but no more than 30% (which would increase arterial oxygen tension from 30 mm Hg to 94 mm Hg, with a carbon dioxide tension of 98 mm Hg), when a patient who is breathing room air (which contains 21% oxygen) becomes hypoxemic due to hypoventilation.[23]

On the other hand, Taenzer et al[24] demonstrated that, compared with room air, supplemental oxygen at 1 to 6 L/min neither influenced the magnitude or duration of desaturation events nor impaired the effectiveness of pulse oxygen saturation monitoring in detecting those events in postoperative patients.

The PRODIGY trial[16] reported a higher overall incidence of opioid-induced ventilatory depression (46%) than other studies, possibly because the patients underwent combined continuous capnography and oximetry monitoring, which detected more apneic and hypoventilation episodes. Notably, only 8% of the patients with episodes of opioid-induced ventilatory depression experienced hypoxemia. This low incidence was attributed to use of supplemental oxygen in most of the patients.

Current evidence does not agree as to the best monitoring method for promptly detecting a potentially serious respiratory event. An array of monitors may be the answer, to the extent that information they produce is both predictive and congruent between the instruments. Taenzer et al,[25,26] in an opportunity cost-based analysis modeled only on reduction of intensive care unit transfers and days spent in intensive care, reported that although universal continuous monitoring using a patient surveillance system would be cost-effective on certain units like the thoracovascular unit, it would be neutral or even more costly on medical units.

OBESITY HYPOVENTILATION SYNDROME AND 100% OXYGEN

A double-blind, randomized, placebo-controlled crossover study[27] concluded by advising extreme caution in giving 100% oxygen to patients with suspected but untreated obesity hypoventilation syndrome and reported a significant decrease in minute ventilation with consequent worsening of hypercapnia, as measured by transcutaneous carbon dioxide tension. The carbon dioxide tension rose by 5 mm Hg after 20 minutes, and a few patients showed a higher rate of rise, needing withdrawal from the study. However, there are no observations beyond 20 minutes to determine if carbon dioxide would continue to rise or respiratory acidosis ensue.

The PRODIGY risk tool predicts opioid-induced respiratory depression

Up to one-third of morbidly obese patients may have hypercapnia from presumed obesity hypoventilation syndrome, which is often unrecognized.[27] The lower the pulse oxygen saturation in obese patients, the more likely they are to receive a high fraction of inspired oxygen, potentially leading to a larger increase in hypercapnia. Also, up to 40% of patients with obesity hypoventilation syndrome may need additional oxygen in a nonsurgical environment, despite being adequately treated with positive airway pressure.[28] Interestingly, in patients who have obesity hypoventilation syndrome with hypoxia during sleep despite adequate long-term noninvasive positive-pressure ventilation therapy, supplemental oxygen therapy was found to be the only independent predictor of death.[29]

No studies to date have reported on the effect of supplemental oxygen in patients with

obesity hypoventilation syndrome while they are treated with intravenous opioids in the postoperative period, nor are there any data reporting the effect of high oxygen concentration or flow (> 3 L/min) in postoperative patients with obstructive sleep apnea receiving intravenous opioids for pain. Recently, however, it has been shown that patients with obstructive sleep apnea associated with hypercapnia had worse postoperative outcomes than those with obstructive sleep apnea alone, regardless of the severity of the sleep apnea or the body mass index.[30]

CONCLUSIONS

We advise caution in giving high-flow supplemental oxygen to obese postoperative patients who have known or suspected obstructive sleep apnea or obesity hypoventilation syndrome, especially when they are sedated, asleep, or receiving intravenous opioids. The concern is that giving high concentration oxygen could mask hypoventilation and hypoxemia, lead to greater hypercapnia, and delay needed treatment.

That said, there is no evidence to date to support withholding supplemental oxygen altogether in obese patients, even those with obesity hypoventilation syndrome, although evidence regarding the optimal fraction of inspired oxygen or target oxygen saturation in these patients is currently lacking.

Up to one-third of morbidly obese patients may have hypercapnia from presumed obesity hypoventilation syndrome

REFERENCES

1. **Sun Z, Sessler DI, Dalton JE, et al**. Postoperative hypoxemia is common and persistent: a prospective blinded observational study. Anesth Analg 2015; 121(3):709–715. doi:10.1213/ANE.0000000000000836
2. **Canet J, Ricos M, Vidal F**. Early postoperative arterial oxygen desaturation. Determining factors and response to oxygen therapy. Anesth Analg 1989; 69(2):207–212. pmid:2764289
3. **Pedersen T, Nicholson A, Hovhannisyan K, Møller AM, Smith AF, Lewis SR**. Pulse oximetry for perioperative monitoring. Cochrane Database Syst Rev 2014; 2014(3):CD002013. doi:10.1002/14651858.CD002013.pub3
4. **Moller JT, Johannessen NW, Espersen K, et al**. Randomized evaluation of pulse oximetry in 20,802 patients: II. Perioperative events and postoperative complications. Anesthesiology 1993; 78(3):445–453. doi:10.1097/00000542-199303000-00007
5. **American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea**. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. Anesthesiology 2014; 120(2):268–286. doi:10.1097/ALN.0000000000000053
6. **Narkiewicz K, Kato M, Pesek CA, Somers VK**. Human obesity is characterized by a selective potentiation of central chemoreflex sensitivity. Hypertension 1999; 33(5):1153–1158. doi:10.1161/01.hyp.33.5.1153
7. **Narkiewicz K, van de Borne PJ, Pesek CA, Dyken ME, Montano N, Somers VK**. Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. Circulation 1999; 99(9):1183–1189. doi:10.1161/01.cir.99.9.1183
8. **Trombetta IC, Maki-Nunes C, Toschi-Dias E, et al**. Obstructive sleep apnea is associated with increased chemoreflex sensitivity in patients with metabolic syndrome. Sleep 2013; 36(1):41–49. doi:10.5665/sleep.2298
9. **Yuan H, Pinto SJ, Huang J, et al**. Ventilatory responses to hypercapnia during wakefulness and sleep in obese adolescents with and without obstructive sleep apnea syndrome. Sleep 2012; 35(9):1257–1267. doi:10.5665/sleep.2082
10. **Zaremba S, Shin CH, Hutter MM, et al**. Continuous positive airway pressure mitigates opioid-induced worsening of sleep-disordered breathing early after bariatric surgery. Anesthesiology 2016; 125(1):92–104. doi:10.1097/ALN.0000000000001160
11. **Doufas AG**. Obstructive sleep apnea, pain, and opioid analgesia in the postoperative patient. Curr Anesthesiol Rep 2014; 4:1–9. doi:10.1007/s40140-013-0047-0
12. **Liao P, Wong J, Singh M, et al**. Postoperative oxygen therapy in patients with OSA: a randomized controlled trial. Chest 2017; 151(3):597–611. doi:10.1016/j.chest.2016.12.005
13. **Wellman A, Malhotra A, Jordan AS, Stevenson KE, Gautam S, White DP**. Effect of oxygen in obstructive sleep apnea: role of loop gain. Respir Physiol Neurobiol 2008; 162(2):144–151. doi:10.1016/j.resp.2008.05.019
14. **Cashman JN, Dolin SJ**. Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. Br J Anaesth 2004; 93(2):212–223. doi:10.1093/bja/aeh180
15. **Belcher AW, Khanna AK, Leung S, et al**. Long-acting patient-controlled opioids are not associated with more postoperative hypoxemia than short-acting patient-controlled opioids after noncardiac surgery: a cohort analysis. Anesth Analg 2016; 123(6):1471–1479. doi:10.1213/ANE.0000000000001534
16. **Khanna AK, Bergese SD, Jungquist CR, et al**. Prediction of opioid-induced respiratory depression on inpatient wards using continuous capnography and oximetry: an international prospective, observational trial. Anesth Analg 2020; April 16. doi:10.1213/ANE.0000000000004788
17. **Lee LA, Caplan RA, Stephens LS, et al**. Postoperative opioid-induced respiratory depression: a closed claims analysis. Anesthesiology 2015; 122(3):659–665. doi:10.1097/ALN.0000000000000564
18. **Parke R, McGuinness S, Dixon R, Jull A**. Open-label, phase II study of routine high-flow nasal oxygen therapy in cardiac surgical patients. Br J Anaesth 2013; 111(6):925–931. doi:10.1093/bja/aet262
19. **Lam T, Nagappa M, Wong J, Singh M, Wong D, Chung F**. Continuous pulse oximetry and capnography monitoring for postoperative respiratory depression and adverse events: a systematic review and meta-analysis. Anesth Analg 2017; 125(6):2019–2029. doi:10.1213/ANE.0000000000002557
20. **Niesters M, Mahajan RP, Aarts L, Dahan A**. High-inspired oxygen concentration further impairs opioid-induced respiratory depression. Br J Anaesth 2013; 110(5):837–841. doi:10.1093/bja/aes494
21. **Kopka A, Wallace E, Reilly G, Binning A**. Observational

study of perioperative PtcCO2 and SpO2 in non-ventilated patients receiving epidural infusion or patient-controlled analgesia using a single earlobe monitor (TOSCA). Br J Anaesth 2007; 99(4):567–571. doi:10.1093/bja/aem206
22. **Fu ES, Downs JB, Schweiger JW, Miguel RV, Smith RA**. Supplemental oxygen impairs detection of hypoventilation by pulse oximetry. Chest 2004; 126(5):1552–1558. doi:10.1378/chest.126.5.1552
23. **Lumb AB**. Oxygen. In: Lumb AB, ed. Nunn's Applied Respiratory Physiology. 6th ed. Elsevier; 2005:166–200.
24. **Taenzer AH, Perreard IM, MacKenzie T, McGrath SP**. Characteristics of desaturation and respiratory rate in postoperative patients breathing room air versus supplemental oxygen: are they different? Anesth Analg 2018; 126(3):826–832. doi:10.1213/ANE.0000000000002765
25. **Taenzer AH, Pyke JB, McGrath SP, Blike GT**. Impact of pulse oximetry surveillance on rescue events and intensive care unit transfers: a before-and-after concurrence study. Anesthesiology 2010; 112(2):282–287. doi:10.1097/ALN.0b013e3181ca7a9b
26. **Taenzer AH, Blike GT; APSF Newsletter**. Postoperative monitoring—the Dartmouth experience. https://www.apsf.org/article/postoperative-monitoring-the-dartmouth-experience/. Accessed November 5, 2020.
27. **Wijesinghe M, Williams M, Perrin K, Weatherall M, Beasley R**. The effect of supplemental oxygen on hypercapnia in subjects with obesity-associated hypoventilation: a randomized, crossover, clinical study. Chest 2011; 139(5):1018–1024. doi:10.1378/chest.10-1280
28. **Banerjee D, Yee BJ, Piper AJ, Zwillich CW, Grunstein RR**. Obesity hypoventilation syndrome: hypoxemia during continuous positive airway pressure. Chest 2007; 131(6):1678–1684. doi:10.1378/chest.06-2447
29. **Priou P, Hamel JF, Person C, et al**. Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. Chest 2010; 138(1):84–90. doi:10.1378/chest.09-2472
30. **Kaw R, Bhateja P, Paz Y Mar H, et al**. Postoperative complications in patients with unrecognized obesity hypoventilation syndrome undergoing elective noncardiac surgery. Chest 2016; 149(1):84–91. doi:10.1378/chest.14-3216

***Address**: Roop Kaw, MD, Department of Hospital Medicine, M2 Annex, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; kawr@ccf.org*

Catherine E. Hassett, DO
Cerebrovascular Center, Neurological Institute, Cleveland Clinic

Aron Gedansky, MD
Cerebrovascular Center, Neurological Institute, Cleveland Clinic

Ibrahim Migdady, MD
Division of Neurocritical Care, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Adarsh Bhimraj, MD
Section Head-Neuroinfections, Department of Infectious Disease and Department of Neurology, Cleveland Clinic; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Ken Uchino, MD
Cerebrovascular Center, Neurological Institute, Cleveland Clinic; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Sung-Min Cho, DO
Departments of Neurology, Neurological Intensive Care, Anesthesiology, and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Neurologic complications of COVID-19

ABSTRACT

Patients with COVID-19 have a fairly high risk of neurologic complications, including encephalopathy, stroke, central nervous system infection, seizures, and neuromuscular diseases. Many report losing their senses of smell and taste, and many survivors report lingering neurocognitive impairment. The diagnosis and treatment of these complications does not differ from that in other patients, although sophisticated testing may not be readily available for a patient in intensive care and respiratory isolation. Clinicians should therefore be alert to these complications.

KEY POINTS

Human coronaviruses, including SARS-CoV-2, can be neurotropic.

Commonly reported neurologic complications in patients infected with SARS-CoV-2 include encephalopathy, neuromuscular disorders, and acute cerebrovascular disorders.

Other complications such as postinfectious demyelination, encephalitis, and seizures are likely underreported given the inability to obtain further diagnostic information, such as cerebrospinal fluid sampling and electroencephalographic monitoring.

Long-term neurocognitive outcomes have yet to be established in COVID-19 survivors.

Clinicians should have a high clinical suspicion for associated neurologic complications in a COVID-19 patient.

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

doi:10.3949/ccjm.87a.ccc058

Like other members of the coronavirus family, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can infect the nervous system. Coronaviruses share several features, including the large spike glycoproteins that inspired their name *corona*, Latin for crown. These spike glycoproteins are essential for viral entry via the angiotensin-converting enzyme 2 (ACE2) receptor.[1,2] ACE2 receptors are expressed in many cell types, including the neurons and glial cells of the brainstem, raising suspicion of possible neurotropism of SARS-CoV-2. There is substantial evidence of SARS-CoV-2–related neurologic complications through direct and indirect neurotropism.

Below, we review common neurologic complications in patients with coronavirus disease 2019 (COVID-19) resulting from SARS-CoV-2 infection.

ACUTE ENCEPHALOPATHY

Presentation
Altered mental status

Supportive testing
Magnetic resonance imaging (MRI) normal
Electroencephalography abnormal (slowing)
Cerebrospinal fluid normal, negative for SARS-CoV-2

Treatment
Supportive, treat underlying COVID-19

Encephalopathy is a global cerebral dysfunction associated with infection, fever, drug exposure, and metabolic derangement. This altered functional state is a relatively common presenting symptom of severe COVID-19 disease.[3,4]

Careful examination and appropriate neu-

rologic workup are necessary in patients with acute encephalopathy that is not explained by their clinical condition. This was highlighted in a series of 13 patients with COVID-19 and unexplained encephalopathy, in whom brain MRI showed leptomeningeal enhancement in 8 patients and frontotemporal hypoperfusion in 11.[5]

ACUTE CEREBROVASCULAR DISEASES

Presentation
Acute presentation with focal motor, sensory, or speech disturbance

Supportive testing
MRI abnormal, lesion located in a vascular distribution

Treatment
No society guidelines for COVID-19–specific stroke treatment
Acute ischemic stroke
Consider thrombolytic and endovascular therapy
No society guidelines on stroke prevention
Consider therapeutic anticoagulation on a case-by-case basis
Acute hemorrhagic stroke (rare)
Standard treatment with blood pressure control
Cerebral venous sinus thrombosis
Standard treatment with full-dose therapeutic anticoagulation, evaluate for other thrombosis sites

ACE2 receptors are expressed in many cell types, including neurons and glial cells of the brainstem

Stroke has been reported in 2.5% to 6% of hospitalized patients with COVID-19.[4,6,7] In a study of 219 hospitalized patients with COVID-19 in Wuhan, China, those with acute stroke were more likely to be older, present with severe infection, and have cardiovascular risk factors, including a history of stroke.[6] Intracranial hemorrhage was much less common than acute ischemic strokes.

Acute ischemic stroke

Cases of acute ischemic strokes were reported during the SARS-CoV and MERS-CoV epidemics. In patients with COVID-19, a case series from New York City reported large-vessel ischemic stroke in 5 patients younger than 50 years.[7] Each presented with acute stroke symptoms with lymphopenia and elevated inflammatory markers on admission laboratory testing, but 2 had no COVID-19 symptoms.

Lupus anticoagulants and prolonged activated partial thromboplastin time have also been frequently reported among hospitalized COVID-19 patients, with a prevalence of 45% to 91% for lupus anticoagulants.[8,9] While there is no clear association between lupus anticoagulants and thrombosis in these studies, a case series reported antiphospholipid antibodies in 3 critically ill COVID-19 patients with bilateral cerebral infarcts in multiple vascular territories.[10] This suggests that an acquired antiphospholipid syndrome was the underlying cause, but unlike the 5 young patients who had large-artery strokes,[7] the patients with antiphospholipid antibodies were over 60 years of age.

These reports show that the prevalence of antiphospholipid antibodies varies in patients with COVID-19, but it is likely higher than expected in the general population. As the clinical significance is not yet known, these laboratory values should not be routinely checked in COVID-19 patients without thrombosis.

Other causes of ischemic stroke, such as viral-induced central nervous system vasculitis, have been considered in COVID-19 patients with brain lesions in vascular patterns but without clear cerebrovascular etiology. A postmortem histologic analysis of 3 patients with COVID-19 revealed lymphocytic endotheliitis within the endothelial cells of multiple organs, including the lungs, heart, kidneys, small intestine, and liver.[11] Endotheliitis can cause microcirculatory vasoconstriction and endothelial dysfunction with consequent ischemia and apoptosis. However, histopathologic analyses of the central nervous system have been limited, and it remains unclear if lymphocytic endotheliitis has been established in COVID-related central nervous system vasculitis.

Venous thromboembolism

Patients with severe COVID-19 also may be at risk of thromboembolic events from COVID-19–associated coagulopathy.[12,13] In hospitalized patients with COVID-19, the increased coagulation activity is marked by elevated D-dimer concentrations.[3,12,13] Further, patients with COVID-19 and cerebrovascular disease had higher D-dimer levels than those without cerebrovascular disease (6.9 mg/L vs 0.5 mg/L, $P < .001$).[6] At this

time, however, it is unclear if elevated D-dimer levels in patients with COVID-19 are directly associated with either arterial or venous ischemic stroke.

A case series and systematic review[14] reported 14 cases of cerebral venous sinus thrombosis, with a median of 7 days from initial COVID-19 symptoms to diagnosis of the thrombosis. Initial imaging revealed cerebral venous sinus thrombosis-related intracranial hemorrhage with involvement of the transverse (75%), sigmoid (50%), and deep venous sinuses (33%) at presentation. The mortality rate was high despite therapeutic anticoagulation.

Overall, the incidence of COVID-19-related cerebral venous sinus thrombosis remains much lower than that of acute ischemic stroke.[15]

CENTRAL NERVOUS SYSTEM INFECTIONS

Encephalitis, meningitis

Presentation
Headache, nuchal rigidity, seizures, focal neurologic deficits, plus altered mental status in encephalitis

Supportive testing
MRI abnormal, white matter changes
Electroencephalography normal to abnormal (slow, with or without focal epileptiform discharges)
Cerebrospinal fluid normal to lymphocytic pleocytosis with or without elevated protein; SARs-CoV-2–positive

Treatment
Remains unclear
Role for high-dose corticosteroids?

Encephalitis is characterized by brain inflammation that can cause morbidity and death if left untreated.[16] In acute viral encephalitis, the virus replicates in brain tissue, leading to significant central nervous system insults. Studies in mice have shown that the human coronavirus can infect neurons and subsequently cause persistent infection in human neural-cell lines.[17]

Ellul et al[18] tallied 8 cases of encephalitis from various sources. These patients presented with a range of symptoms, including irritability, confusion, seizures, and nuchal rigidity. Cerebrospinal fluid analysis in 5 patients detected lymphocytic pleocytosis. Most brain imaging was normal, but electroencephalography completed in 5 patients showed generalized slowing, focal epileptiform discharges, and 1 case of nonconvulsive status epilepticus. No specific treatment was noted in these patients; however, 1 patient responded quickly to high-dose steroids.

The low reported rate of central nervous system infection in patients with COVID-19 is likely an underestimation, as the subtle symptoms of encephalitis may be missed, and performing a lumbar puncture in patients with severe COVID-19 infection requires a substantial risk-benefit consideration.

Postinfectious demyelination

Presentation
Headache, acute neurologic symptoms

Supportive testing
MRI shows hyperintense fluid-attenuated inversion recovery (FLAIR) lesions with variable enhancement

Treatment
2 case reports showed improvement with:
5 days of intravenous immunoglobulin 0.4 g/kg/day[19]
5 days of intravenous dexamethasone 20 mg/day with a 10-day taper[20]

Acute disseminated encephalomyelitis is a monophasic, demyelinating disease of the central nervous system characterized by multifocal white matter demyelination in the setting of a rapidly progressive encephalopathy. An antecedent infectious process before the onset of central nervous system symptoms is common; however, the cause is typically only found in a small percentage of cases.

Two cases of probable acute disseminated encephalomyelitis have been reported in the COVID-19 population, with bilateral, extensive, nonenhancing T2-FLAIR signal changes noted in the cerebral white matter, involving the subcortical brain parenchyma and cervical spinal cord.[19,20] The cerebrospinal fluid was negative for SARS-CoV-2 by polymerase chain reaction testing in both cases. One patient was treated with intravenous immunoglobulin and the other with a 5-day course of a high-dose cortico-

The increased coagulation activity is marked by elevated D-dimer concentrations

steroid with a 10-day taper. Neurologic improvement was noted in both patients.

Acute necrotizing hemorrhagic encephalopathy

A case report presented details of a SARS-CoV-2–infected woman in her late 50s who presented with fever, cough, and altered mental status.[21] Computed tomography (CT) without contrast depicted symmetric hypoattenuation in the bilateral medial thalami with a normal CT angiogram and venogram. MRI demonstrated hemorrhagic, enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions. Cerebrospinal fluid analysis revealed negative bacterial cultures and viral testing. The reason for not testing the cerebrospinal fluid for SARS-CoV-2 was not reported. Based on imaging and clinical context, she was given a diagnosis of probable acute necrotizing hemorrhagic encephalopathy and started on intravenous immunoglobulin therapy. No further information is available on her clinical course.

Acute necrotizing hemorrhagic encephalopathy in children with virulent influenza infections has been well described.[22] This complication is pathologically distinguished from acute disseminated encephalomyelitis by causing blood-brain barrier breakdown without direct viral invasion or demyelination.[23]

The low reported rate of central nervous system infection in COVID-19 is likely an underestimation

SEIZURES

Although new-onset seizures in patients who have COVID-19 are rare, 2 cases were reported of acute symptomatic seizures in nonepileptic patients with COVID-19 at Cleveland Clinic.[24]

Two retrospective studies have described electroencephalographic patterns seen in patients with acute COVID-19.[25,26] One study reported frequent sporadic interictal epileptiform discharges in 22 patients with COVID-19, using mostly continuous 8-channel electroencephography.[25]

However, this finding was not supported by the other study, which used standard 21-channel recordings.[26] This study also reported a variety of other electroencephographic findings, including continuous slowing, generalized rhythmic activity, and generalized periodic discharges.[26]

These studies support the high incidence of encephalopathy in hospitalized patients with COVID-19 and the presence of acute symptomatic seizures from an underlying metabolic or toxic process or primary central nervous system insult as a complication of COVID-19.

NEUROMUSCULAR DISORDERS

Presentation
Myalgias

Supportive testing
Creatine kinase elevated
Muscle biopsy shows necrosis

Treatment
Supportive; remains unclear
Role for corticosteroids?
Physical therapy

Critical illness polyneuropathy and myopathy

Patients in the intensive care unit are at risk of developing severe weakness secondary to critical illness polyneuropathy, critical illness myopathy, or both, with a reported incidence of up to 33%.[27] To date, there have been no definitive reports of either disorder in patients with COVID-19. However, a study from Wuhan, China, reported 23 COVID-19 patients with acute muscle injury (defined as myalgia and serum creatine kinase level above 200 U/L).[4]

Thus, clinicians should suspect critical illness polyneuropathy or critical illness myopathy in patients with COVID-19 presenting with sepsis or complications leading to prolonged mechanical ventilation and intensive care unit length of stay.

Acute inflammatory demyelinating polyneuropathy

Presentation
Flaccid paralysis with or without respiratory compromise, cranial nerve deficits

Supportive testing
Cerebrospinal fluid has increased protein, normal white blood cell count
Nerve conduction study abnormal; axonal and demyelinating variants noted

Treatment
Standard Guillain-Barré treatment with 5 days of intravenous immunoglobulin (0.4 g/kg/day)
Case series noted only minimal improvement in 2 of 5 patients after treatment[28]

Acute inflammatory demyelinating polyneuropathy (more commonly known as Guillain-Barré syndrome), is an autoimmune demyelinating disorder of the peripheral nervous system usually following an antecedent infection. It is characterized by parathesias, areflexia, and ascending weakness that may lead to respiratory failure.

There are several cases of patients developing acute inflammatory demyelinating polyneuropathy after the onset of COVID-19 symptoms.[28–30] A case series from Italy described 5 patients presenting with paraplegia, facial muscle weakness, and areflexia 5 to 10 days after the onset of COVID-19 symptoms.[28] Of those, 3 patients had pathognomonic cerebrospinal fluid findings of albuminocytologic dissociation consistent with acute inflammatory demyelinating polyneuropathy. All 5 patients were treated with intravenous immunoglobulins, but after 4 weeks only 1 had been discharged and was able to walk independently.

Although it is important to recognize the classic symptoms of acute inflammatory demyelinating polyneuropathy, a case series from Spain reported 2 rare variants of it, ie, Miller Fisher syndrome and polyneuritis cranialis.[30]

CRANIAL NEUROPATHY

Olfactory neuropathy

Presentation
Olfactory or taste dysfunction

Supportive testing
Abnormal smell and taste evaluation

Treatment
Supportive; improvement noted by 2 weeks after symptom onset

Anosmia and dysgeusia are common symptoms associated with COVID-19, and are likely due to the virus directly accessing the olfactory bulb.[31]

A study of 417 patients with mild to moderate COVID-19 symptoms in 12 European hospitals reported sudden-onset olfactory dysfunction in 86%, and gustatory dysfunction in 88%.[32] At 2 weeks, 25% of the patients had recovered both their sense of smell and their sense of taste.

Anosmia and dysgeusia are now recognized as presenting COVID-19 symptoms by the US Centers for Disease Control and Prevention.

NEUROCOGNITIVE IMPAIRMENT

Presentation
Neurocognitive impairments in at least 1 domain after COVID-19

Supportive testing
Formal neurocognitive assessment

Treatment
Consideration for neurorehabilitation programs

At 2 weeks, 25% had recovered both their sense of smell and of taste

Mental fatigue and mild inattention has been frequently reported in patients with COVID-19.[33] In 1 series, 179 hospitalized COVID-19 survivors underwent a battery of telephone-administered, standardized neurocognitive, psychiatric morbidity, and quality of life assessments within 2 months of hospital discharge.[33] Of these, 59% had neurocognitive impairment in at least 1 function, with moderate impairment of immediate verbal memory and learning in 38%, of verbal fluency in 35%,

and of executive function in 6.1%.[33] Risk factors for neurocognitive impairment included severe COVID-19 infection, hypoxemia requiring mechanical ventilation, hypoperfusion, and increased inflammatory response. Delirium and stress-related symptoms also increased the odds of developing neurocognitive symptoms.

Neurorehabilitation programs have been anecdotally reported to improve neurocognitive symptoms by targeting alertness, sleep problems, and behavior disturbances.[34] Ongoing monitoring is needed to fully understand the long-term prognosis and psychologic impact of COVID-19.

REFERENCES

1. **Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E**. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res 2020; 176:104742. doi:10.1016/j.antiviral.2020.104742
2. **Letko M, Marzi A, Munster V**. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B beta-coronaviruses. Nat Microbiol 2020; 5(4):562–569. doi:10.1038/s41564-020-0688-y
3. **Guan W-J, NI Z-Y, Hu Y, et al**. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382(18):1708–1720. doi:10.1056/NEJMoa2002032
4. **Mao L, Jin H, Wang M, et al**. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020; 77(6):1–9. doi:10.1001/jamaneurol.2020.1127
5. **Helms J, Kremer S, Merdji H, et al**. Neurologic features in severe SARS-CoV-2 infection [letter]. N Engl J Med 2020; 382(23):2268–2270. doi:10.1056/NEJMc2008597
6. **Li Y, Li M, Wang M, et al**. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 2020; 5(3):279–284. doi:10.1136/svn-2020-000431
7. **Oxley TJ, Mocco J, Majidi S, et al**. Large vessel stroke as a presenting feature of COVID-19 in the young [letter]. N Engl J Med 2020; 382(20):e60. doi:10.1056/NEJMc2009787
8. **Bowles L, Platton S, Yartey N, et al**. Lupus anticoagulant and abnormal coagulation tests in patients with Covid-19 [letter]. N Engl J Med 2020; 383(3):288–290. doi:10.1056/NEJMc2013656
9. **Harzallah I, Debliquis A, Drénou B**. Lupus anticoagulant is frequent in patients with Covid-19 [letter]. J Thromb Haemost 2020; Apr 23. doi:10.1111/jth.14867
10. **Zhang Y, Xiao M, Zhang S, et al**. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020; 382(17):e38. doi:10.1056/NEJMc2007575
11. **Varga Z, Flammer AJ, Steiger P, et al**. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020; 395(10234):1417–1418. doi:10.1016/S0140-6736(20)30937-5
12. **Lodigiani C, Iapichino G, Carenzo L, et al**. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020; 191:9–14. doi:10.1016/j.thromres.2020.04.024
13. **Klok FA, Kruip MJ, van der Meer NJ, et al**. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191:145–147. doi:10.1016/j.thromres.2020.04.013
14. **Tu TM, Goh C, Tan YK, et al**. Cerebral venous thrombosis in patients with COVID-19 infection: a case series and systematic review. J Stroke Cerebrovasc Dis 2020; 29(12):105379. doi:10.1016/j.jstrokecerebrovasdis.2020.105379
15. **Asadi-Pooya AA, Simani L**. Central nervous system manifestations of COVID-19: a systematic review. J Neurol Sci 2020; 413:116832. doi:10.1016/j.jns.2020.116832
16. **Swanson PA 2nd, McGavern DB**. Viral diseases of the central nervous system. Curr Opin Virol 2015; 11:44–54. doi:10.1016/j.coviro.2014.12.009
17. **Arbour N, Côté G, Lachance C, Tardieu M, Cashman NR, Talbot PJ**. Acute and persistent infection of human neural cell lines by human coronavirus OC43. J Virol 1999; 73(4):3338–3350. doi:10.1128/JVI.73.4.3338-3350.1999
18. **Ellul MA, Benjamin L, Singh B, et al**. Neurological associations of COVID-19. Lancet Neurol 2020; 19:767–783. doi:10.1016/S1474-4422(20)30221-0
19. **Zhang T, Rodricks MB, Hirsh E**. COVID-19-associated acute disseminated encephalomyelitis: a case report. medRxiv 2020. https://doi.org/10.1101/2020.04.16.20068148. Accessed November 17, 2020.
20. **Zanin L, Saraceno G, Panciani PP, et al**. SARS-CoV-2 can induce brain and spine demyelinating lesions. Acta Neurochir (Wien) 2020; 162(7):1491–1494. doi:10.1007/s00701-020-04374-x
21. **Poyiadji N, Shahin G, Noujam D, et al**. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. Radiology 2020; 296(2):E119-E120. doi:10.1148/radiol.2020201187
22. **Wong AM, Simon EM, Zimmerman RA, Wang HS, Toh CH, Ng SH**. Acute necrotizing encephalopathy of childhood: correlation of MR findings and clinical outcome. AJNR Am J Neuroradiol 2006; 27(9):1919–1923. pmid:17032866
23. **Rossi A**. Imaging of acute disseminated encephalomyelitis. Neuroimaging Clin N Am 2008; 18(1):149–161. doi:10.1016/j.nic.2007.12.007
24. **Hepburn M, Mullaguri N, George P, et al**. Acute symptomatic seizures in critically ill patients with COVID-19: is there an association? Neurocrit Care 2020; May 28:1–5. doi:10.1007/s12028-020-01006-1
25. **Galanopoulou AS, Ferastraoaru V, Correa DJ, et al**. EEG findings in acutely ill patients investigated for SARS CoV2/COVID 19: a small case series preliminary report. Epilepsia Open 2020; 5(2):314–324. doi:10.1002/epi4.12399
26. **Louis S, Dhawan A, Newey C, et al**. Continuous electroencephalopathy (cEEG) characteristics and acute symptomatic seizures in COVID-19 patients. medRxiv 2020. https://doi.org/10.1101/2020.05.26.20114033. Accessed November 17, 2020.
27. **de Letter MA, Schmitz PI, Visser LH, et al**. Risk factors for the development of polyneuropathy and myopathy in critically ill patients. Crit Care Med 2001; 29(12):2281–2286. doi:10.1097/00003246-200112000-00008
28. **Toscano G, Palmerini F, Ravaglia S, et al**. Guillain-Barré syndrome associated with SARS-CoV-2. N Engl J Med 2020; 382(26):2574–2576. doi:10.1056/NEJMc2009191
29. **Zhao H, Shen D, Zhou H, et al**. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol 2020; 19(5):383–384. doi:10.1016/s1474-4422(20)30109-5
30. **Gutierrez-Ortiz C, Mendez-Guerrero A, Rodrigo-Rey S, et al**. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. Neurology 2020; 95(5):e601-e605. doi:10.1212/WNL.0000000000009619
31. **Desforges M, Le Coupanec A, Dubeau P, et al**. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? Viruses 2019; 12(1):14. doi:10.3390/v12010014
32. **Lechien JR, Chiesa-Estomba CM, De Siati DR, et al**. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020; 277(8):2251–2261. doi:10.1007/s00405-020-05965-1
33. **Méndez R, Balanza-Martinez V, Luperdi SC, et al**. Short-term neuropsychiatric outcomes and quality of life in COVID-19 survivors. MedRxiv. doi:10.1101/2020.09.23.20190090
34. **Devita M, Bordignon A, Sergi G, et al**. The psychological and cognitive impact of Covid-19 on individuals with neurocognitive impairments: research topics and remote intervention proposals. Aging Clin Exp Res 2020. doi:10.1007/s40520-020-01637-6

***Address**: Sung-Min Cho, DO, Department of Neurology, Neurosurgery, Anesthesiology and Critical Care Medicine, Division of NCCU, Johns Hopkins Medical Institutions, 600 N. Wolfe Street, Phipps 455, Baltimore, MD 21287; csungmi1@jhmi.edu*

GREGORY W. RUTECKI, MD, Section Editor

Graham Walter, MD
Department of Internal Medicine,
Max Rady College of Medicine,
University of Manitoba,
Winnipeg, Canada

Hanna Lyubetska, MD, MSc
Department of Internal Medicine,
Max Rady College of Medicine,
University of Manitoba,
Winnipeg, Canada

Aditya Sharma, MD, FRCPC
Department of Internal Medicine,
Section of General Internal Medicine,
Max Rady College of Medicine,
University of Manitoba,
Winnipeg, Canada

Fever in a lung transplant recipient

A 36-year-old woman presented to the emergency department in June 2019 after experiencing high fevers, chills, nausea, decreased oral intake, and diarrhea for 4 days. Her medical history included cystic fibrosis with resultant exocrine insufficiency, and type 2 diabetes mellitus.

In addition, she had received a double lung transplant 9 years earlier, for which she was on a long-term immunosuppressive regimen. The donor had been positive for cytomegalovirus (CMV), whereas the patient had been negative for both CMV and Epstein-Barr virus (EBV). The EBV status of her donor was unavailable. However, the patient's EBV serology was negative when tested 6 months before this presentation, and she was also known to be negative for both hepatitis B and hepatitis C.

She also had a history of stage 3a proteinuric chronic kidney disease with a baseline serum creatinine level of 1.2 mg/dL, hypertension, and an episode of acute transplant rejection in 2014, which resolved with conservative treatment with glucocorticoids. Her home medications were azathioprine, calcium carbonate, cholecalciferol, ferrous sulfate, insulin neutral protamine Hagedorn, insulin aspart with meals, labetalol, a daily multivitamin, prednisone, tacrolimus, ranitidine, and pancreatic enzyme replacement with meals.

She was a lifelong nonsmoker with little alcohol intake, and she said she does not use illicit drugs. She had no recent sick contacts, though she had been hospitalized 4 months earlier for *Pseudomonas aeruginosa* pneumonia, from which she had fully recovered.

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

doi:10.3949/ccjm.87a.19132

INITIAL EVALUATION

Physical examination

On presentation to the emergency department, she was normotensive, febrile with a temperature of 39.5°C (103.1°F), and tachycardic with a heart rate of 133 beats per minute.

Jugular venous pulsation was visible 1 cm above the sternal angle, and respiratory examination revealed fine crackles in the right upper lobe. There was a soft systolic ejection murmur, grade 2 on a scale of 6, heard best at the right upper sternal border.

Her abdomen was nontender on palpation, but her liver could be felt 3 cm below the right costal margin and the spleen at 7 cm below the left costal margin.

Palpation of the head and neck revealed small diffuse lymphadenopathy. The patient also had prominent right axillary and inguinal lymphadenopathy.

A 36-year-old woman presents with high fevers, chills, nausea, decreased oral intake, and diarrhea

Initial investigations

On initial testing (**Table 1**), her serum sodium concentration was 131 mmol/L and her potassium level was 5.6 mmol/L. Her creatinine level was 2.5 mg/dL, up from a baseline of 1.24 mg/dL, consistent with an "acute-on-chronic" kidney injury. She had elevated liver enzymes and bilirubin, as well as neutropenia with an absolute neutrophil count of 0.57×10^9/L.

Urinalysis was negative for nitrites, leukocytes, glucose, bilirubin, and protein, with a nonactive sediment on microscopy.

Liver enzyme analysis revealed the following levels: aspartate aminotransferase 43 U/L, alanine aminotransferase 33 U/L, lactate dehydrogenase 563 U/L, gamma-glutamyl transferase 342 U/L, and alkaline phosphatase 888 U/L.

Ferritin was elevated at 1,983 ng/mL (normal 20–200 ng/mL), and her nonfasting

TABLE 1

The patient's initial laboratory values

Substance	Value[a]	Reference range
Sodium	**131** mmol/L	135–147
Potassium	**5.6** mmol/L	3.5–5.1
Chloride	98 mmol/L	97–106
Carbon dioxide	**17** mmol/L	22–33
Creatinine	**2.5** mg/dL	0.40–1.09
Blood urea nitrogen	**77** mg/dL	5.9–19.9
Corrected calcium	2.41 mmol/L	2.1–2.6
Magnesium	**1.03** mmol/L	0.7–0.96
Bilirubin, total	**1.35** mg/dL	0.29–1.23
Bilirubin, direct	**0.53** mg/dL	0–0.41
Aspartate aminotransferase	**43** U/L	10–32
Alanine aminotransferase	**33** U/L	< 25
Lactate dehydrogenase	**563** U/L	63–200
Gamma glutamyl transferase	**342** U/L	5–29
Alkaline phosphatase	**888** U/L	30–120
White blood cell count	**3.8** × 10^9/L	4.5–11
Absolute neutrophil count	**0.57** × 10^9/L	1.8–5.4
Hemoglobin	**8.8** g/dL	12.0–16.0
Platelets	143 × 10^9/L	140–440
Human chorionic gonadotropin	< 1 mIU/mL	0–5
Random cortisol	20.3 µg/dL	AM 5.1–25.0 PM 2.9–16.0
Tacrolimus level[b]	10.5 ug/L	0–15 ug/L

[a]Abnormal levels are in boldface type.
[b]Level taken on the second day of admission.

triglycerides were minimally elevated at 3.2 mmol/L (< 2 mmol/L). Further results of laboratory testing can be found in **Table 1**.

Chest radiography performed in the emergency department did not show any acute processes.

DIFFERENTIAL DIAGNOSIS

1 Which of the following is the least likely cause of the patient's symptoms?

☐ Hemophagocytic lymphohistiocytosis (HLH)

☐ Bacterial sepsis in an immunocompromised host

☐ Acute viral infection

☐ Posttransplant lymphoproliferative disease (PTLD)

Hemophagocytic lymphohistiocytosis

HLH is primarily a pediatric syndrome, although it can occur in adults in a sporadic fashion, particularly in those with an infectious trigger. It also more commonly arises in older patients (age > 49),[1] whereas our patient was 36.

HLH is characterized by extensive tissue inflammation and destruction, the result of abnormal activation of the immune system. In support of this diagnosis in our patient, HLH has been associated with EBV virus infection as a trigger,[2] and hepatosplenomegaly may be seen.[1] Lactate dehydrogenase is also often quite elevated in HLH,[2] and HLH can be seen in patients with lymphoma, or in those who are immunosuppressed.[3] When cytopenias are seen in HLH, however, they are typically represented by anemia and thrombocytopenia (although any cell line can be depressed).[1–3]

Although our patient had anemia, it was long-standing, and thrombocytopenia was absent. Given the entirety of her presentation, HLH was judged to be less likely than the other possible diagnoses.

Bacterial sepsis

The possibility of bacterial sepsis was strongly considered, as the patient was immunosuppressed, febrile, and tachycardic, and eventually met the diagnostic criteria for febrile neutropenia. In addition, she fulfilled several criteria of the Sequential Organ Failure Assessment, including elevated bilirubin and creatinine,[4] and bacterial sepsis is the most prevalent of all options presented.

Therefore, her neutropenia could have been related to sepsis through marrow suppression, but this was clearly confounded by the multiple immunosuppressive drugs she was taking. Given the known mortality risk associated with sepsis in general—and particularly in a patient on chronic tacrolimus and prednisone—treating this case as bacterial sepsis was the correct first step. However, bacterial sepsis does not explain her new hepatosplenomegaly and lymphadenopathy.

Acute viral infection

An acute EBV or CMV illness could result in high fevers, fatigue, weakness, and hepatosplenomegaly with diffuse lymphadenopathy. Acute CMV and EBV infection or reactivation were strongly considered, given the patient's posttransplant status and symptoms.[5,6] However, while CMV infection can present with acute hepatitis, it does not characteristically present with splenomegaly, which is more typical of a congenital CMV infection.[7]

Regarding other possible viral etiologies, acute viral pneumonia was an initial consideration, given the physical examination findings. However, commonly implicated viruses such as the respiratory syncytial virus, adenovirus, rhinovirus, and influenza[8] do not typically cause splenomegaly.[9]

Additionally, in a posttransplant patient on an immunosuppressive regimen, it is important to consider multiple co-occurring pathologies as the etiologic entity. These include viral or bacterial co-infection, multiple viral co-infection, or viral pneumonia resulting in lung allograft dysfunction,[10] a combination of which could theoretically explain the constellation of findings.

Posttransplant lymphoproliferative disease

PTLD comprises a heterogeneous group of immunosuppression-associated lymphomas that occur after organ transplant.[11] It can present in a variety of ways, often subtly and even as an asymptomatic incidental finding, but occasionally as extensive disseminated disease and even as tumor lysis syndrome.[11,12]

Our patient's main presenting signs and symptoms were nonspecific and included malaise, high fevers, and neutropenia. She had hepatosplenomegaly, which can often be seen with EBV-related PTLD.[11] Further, lactate dehydrogenase is often elevated in patients with PTLD,[13] as was seen here.

Unfortunately, because of the nature of this disease and the fact that it can present in a subtle fashion, PTLD is often a difficult diagnosis to make upon initial evaluation. Certain risk factors, such as older age at presentation, EBV positivity, EBV seronegativity at time of transplant, hepatitis C positivity, as well as type of organ transplant (such as lung and heart) result in increased risk of PTLD.[13–15]

PTLD can develop either early after solid-organ transplant, with approximately 30% of cases being diagnosed within the first year,[16] or in subsequent years posttransplant. The onset of PTLD is thought to be related to the immunosuppressive regimen,[4,16] and it is thought that induction therapy plays a major role in the development of early-onset PTLD. There is some evidence that the use of muromonab-CD3 and antithymocyte globulin may increase the risk of development of PTLD earlier posttransplant.[4,17]

The current understanding of late-onset PTLD is that it is a reflection of the cumulative effect of immunosuppression over time, rather than of a particular immunosuppressant.[4] Therefore, it is important to maintain a high level of suspicion in a transplant recipient with significant immunosuppression, irrespective of time from transplant.

CASE CONTINUED: SPLENOMEGALY, PERSISTENT CYTOPENIAS

The patient was admitted to the hospital and blood and urine cultures were obtained, as well as extensive viral serologic tests. She was empirically treated for presumed bacterial sepsis with piperacillin-tazobactam and vancomycin. She received corticosteroids in stress doses for 1 day, and her prednisone dosing was subsequently increased from 5 mg to 10 mg daily. She received intravenous fluids for her acute kidney injury, and her serum creatinine level declined to its baseline value, consistent with the diagnosis of hypovolemic prerenal acute kidney injury.

The lung donor had been CMV-positive; EBV status unknown

Despite broad-spectrum antibiotics, the patient remained febrile and her neutrophil count continued to decline. Nausea and general malaise continued. Blood cultures and urine culture were negative. Testing of stool for *Clostridioides difficile* was also negative.

Echocardiography showed no valvular vegetation and a normal ejection fraction. Ultrasonography of the abdomen revealed the spleen to be enlarged at 19.2 cm with diffuse retroperitoneal and porta hepatis lymphadenopathy.

At this time, due to ongoing cytopenias, fevers, and in particular, posttransplant status, we strongly suspected PTLD. Thus, serologic

tests for EBV, CMV, human T-cell lymphotropic virus (HTLV), and human immunodeficiency virus (HIV) were sent, and hepatitis B and hepatitis C serologies repeated. The patient's azathioprine and tacrolimus were held, and a dose of basiliximab 20 mg intravenously was given subsequently in an attempt to prevent a recurrent episode of acute rejection in the setting of cytopenias and acute kidney injury.[18]

FURTHER INVESTIGATION AND MANAGEMENT

2 Once acute bacterial infectious causes are reasonably accounted for, what is the best next step in the management and diagnosis of this patient?

- ☐ EBV and CMV serology
- ☐ Addition of antifungal therapy
- ☐ Splenic biopsy
- ☐ Long-term antimicrobial therapy
- ☐ Bone marrow biopsy

Serology in the immunocompromised

Ordering EBV and CMV serology is the correct next step and should include both immunoglobulin G (IgG) and immunoglobulin M (IgM) tests.

The patient was empirically treated for presumed bacterial sepsis, but she remained febrile

Although CMV serology has long been demonstrated to be of little utility in these patients,[19] this is not necessarily true of EBV serology.[20] IgG and IgM against EBV viral capsid antigen (VCA) can be used to preliminarily diagnose acute vs prior infection, although polymerase chain reaction confirmation is still recommended.[20] Acute infection with either CMV or EBV can result in a sepsis-like syndrome, but EBV infection or reactivation is closely related to the development of PTLD, and as such, the case described provides an intriguing illustration regarding the pathophysiology of this association in real time.

In a general sense, EBV-associated malignancies are a well-studied phenomenon, dating back to the discovery of the virus itself in Burkitt lymphoma patients through excisional node biopsies by Drs. Burkitt, Epstein, and Barr in their seminal 1964 article.[21] However, it took until the late 1960s for EBV's role in PTLD to be formally documented, and until 1969 for Penn et al to recognize a pattern and compile a small series of seemingly related cases.[22–24]

Since this time, the understanding of this disease process as being purely EBV-mediated has shifted and changed as knowledge has grown and immunosuppressive regimens have changed. This being said, EBV-positive disease still composes the backbone of the understanding of PTLD pathophysiology, and positive EBV IgM serology can clinch this diagnosis in the right clinical setting. Further detail on this phenomenon can be found below.

Other possible steps

Although it would not be unreasonable to consider adding antifungal therapy in this case, local practice as well as North American guidelines recommend empiric antifungal therapy only in a patient who remains febrile despite 7 days of broad-spectrum antibacterial therapy, whose neutrophil nadir is not expected to resolve by this time, and when the patient is known to be colonized by fungi.[25–27]

Long-term antibacterial therapy is not indicated here, as we had not identified an infectious nidus. Thus, further investigation would be warranted before committing this patient to long-term antimicrobial therapy and its possible adverse effects.

A splenic biopsy would be wrong in this case because this test is much more invasive than the others listed and would be unlikely to yield a diagnostic answer.

THE ROLE OF EBV IN PTLD

3 What is the significance of EBV in PTLD?

- ☐ EBV is the causative agent behind all cases of PTLD
- ☐ EBV causes PTLD only in solid organ transplant recipients
- ☐ Tacrolimus reactivates EBV, which results in PTLD
- ☐ EBV can evade immune detection in the immunosuppressed by incorporating itself into B cells and transforming them

EBV: Cause and effect

EBV can evade immune detection in the immunosuppressed by incorporating itself into B cells and transforming them. The best un-

derstood model of the development of EBV-associated malignancy involves differential expression of surface antigens expressed on host B cells, which is the hematologic cell line most typically affected.[28] These antigens characterize the malignancies they can potentially cause into the subtypes I through III, each progressively more immunogenic than the one prior. EBV-related PTLD is represented by subtype III,[8] because EBV-infected host B cells express a large range of antigens such as LMP1, LMP2, RFO, EBNA1, EBNA2, EBNA3a,b,c, and LP.[29] Consequently, these cells remain quite immunogenic when present in the immunocompetent host by cytotoxic T-cell–mediated immunity and do not lead to the pathophysiology seen in PTLD.[29] This issue becomes important when a person becomes immunosuppressed, however, and it plays a major role in B-cell immune evasion which subsequently sows the seeds for PTLD to proceed unchecked.[15] EBV-positive PTLD is classified as a type III EBV-associated malignancy by the aforementioned schema, based on the surface antigens and immunogenicity of the resultant B-cell.

EBV-negative PTLD

While EBV was initially hypothesized as the driver behind all cases of PTLD, the proportion of EBV-positive PTLD has more recently been evaluated to be approximately 50% when contemporary data were examined, with cases of EBV-negative PTLD growing in proportion in recent decades.[16] Thus, all cases of PTLD are not caused by EBV.

PTLD by transplant type

Although the relative risk of PTLD in lung-transplant recipients is reportedly as high as 58.6—in keeping with one of the highest rates of PTLD outside of multiorgan transplant recipients at 3.0% to 10.0%—there have been many documented cases of PTLD in those receiving bone-marrow transplants.[11,17] Thus, EBV does not cause PTLD *only* in solid-organ transplant recipients.

The role of tacrolimus

Tacrolimus has been implicated as one of the causative agents of EBV-negative PTLD.[16] The proportion of EBV-negative disease has grown in recent decades, and it is generally hypothesized to be related to the transition from cyclosporine to tacrolimus and from azathioprine to mycophenolate as immunosuppressive agents for single-organ transplant recipients.

Tacrolimus has been demonstrated to increase the risk of PTLD,[17] although the same studies that demonstrated this finding also had a greater proportion of EBV-negative patients on tacrolimus, which somewhat clouds this signal. Despite these possible differences, there doesn't seem to be any difference when it comes to outcomes or mortality between EBV-associated and nonassociated disease.[16] Thus, although tacrolimus may play some role in PTLD itself, it has not been shown to "reactivate EBV."

DEFINITIVE MANAGEMENT

4 What is the initial management of PTLD?

- ☐ Reduction in immunosuppression
- ☐ Rituximab alone
- ☐ Combination drug regimen
- ☐ Immunotherapy

Reduction in immunosuppression

Reduction in immunosuppression is correct. Initial management of PTLD is to hold or largely reduce the immunosuppressive regimen.[11,30] Preferably this includes reducing the calcineurin inhibitor by at least 50% and completely discontinuing the antimetabolite.[11] The rationale for reducing immunosuppression is that the immune system may be able to recover functionality of cytotoxic T cells and thus be able to fend off the EBV-infected self-cells.[30] Unfortunately, while this step makes intuitive sense for PTLD management, there is a clear risk to patients in the form of organ transplant rejection.[31]

Her azathioprine and tacrolimus were held, and basiliximab was given

The role of chemotherapy

As a monotherapy, rituximab has demonstrated significant benefit with regard to PTLD management.[11,32] On its own it has induced remission for patients[32] and is often the next step when response to reduction in immunosuppression is suboptimal, or immunosuppression cannot be tapered due to high risk of rejection.[11]

Despite the success of single-agent ritux-

imab therapy, the most commonly used regimen is the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[11,33,34] Treatment depends largely on the histology of the lymphoma and whether it is monomorphic or polymorphic PTLD. In addition, the EBV status of each patient is paramount in determining the optimal treatment type and duration.[11,33] Thus, rituximab or R-CHOP would not be the initial management for most patients with PTLD.

Immunotherapy

While immunotherapy is promising in that it may eventually be used to treat patients with PTLD without requiring reduction in immunosuppression, it is still a developing treatment and would not yet be considered first-line therapy.[11,31]

CASE CONCLUSION

Returning to the case, our patient's EBV anti-VCA IgG and IgM as well as CMV IgG and IgM were both subsequently found to be positive, while her HTLV 1+2, HIV, and hepatitis B and C serology were found to be negative. Her CMV positivity was presumed to be secondary to nonspecific binding during the assay, and this was corroborated by the finding of no detectable CMV DNA on nucleic acid amplification testing.[15] This is a common and understood phenomenon with viral serology, particularly in transplant recipients and the immune-compromised.[19]

Fine needle aspiration and core biopsy of the right axillary and inguinal lymph nodes was done under ultrasonographic guidance

The hematology service was consulted and recommended a bone marrow biopsy, which was performed on the fifth day of admission. Fine needle aspiration and core biopsy of the right axillary and inguinal lymph nodes were performed on the same day under ultrasonographic guidance.

Preliminary results of the bone marrow biopsy as well as the fine needle aspiration demonstrated findings consistent with a B-cell lymphoma. The results from the fine needle aspiration showed 94% lymphocytes, of which 62% were T cells and 1% natural killer cells. There was a significant monoclonal plasma-cell vs a B-cell population, and this was interpreted as either a B-cell lymphoma undergoing plasma-cell transformation or a plasma-cell neoplasm. There was no evidence of a hemophagocytic process.

In the right axillary node, plasma cells and B cells were MUM1-positive, and plasma cells took up the CD138 stain. CD30 staining showed scattered groups of atypical lymphocytes. All of the lymphocytes were positive for CD45. Plasma cells and immunoblasts were positive for lambda light chain restriction with diffusely positive Epstein-Barr virus-encoded small RNAs (EBV in situ hybridization).

These results were definitive for PTLD. Given the consistency with this diagnosis, further nucleic acid testing for EBV was not sought, as the primary management for PTLD (as outlined above), does not involve treatment of this viral reactivation. Despite the aforementioned concerns with viral serology, we believe this to be consistent with EBV reactivation leading to PTLD, especially given the high sensitivity and specificity of anti-VCA serology compared with older methods of viral serologic testing, but optimally PCR would have clinched this diagnosis beyond a reasonable doubt.[20]

Other donor-derived infectious diseases (aside from the already ruled-out hepatitis B, hepatitis C, HIV, and HTLV) were thought to be less likely with the given presentation and timeline. These include less-common pathogens such as lymphocytic choriomeningitis virus, rabies, and *Mycobacterium tuberculosis*.[35]

The patient was subsequently transferred to a quaternary care hospital possessing a dedicated medical unit staffed by lung transplantation physicians. Computed tomography of the chest, abdomen, and pelvis was performed there and found widely disseminated lymphadenopathy in the chest, neck, and abdomen. Thus, the Ann Arbor stage was IV. The patient has thus far received 2 cycles of R-CHOP and is recovering from her acute illness.

SALIENT POINTS

It is important to remain suspicious of PTLD when solid-organ transplant recipients present with subtle findings. Making the connection between elevated LDH, cytopenias, and constitutional symptoms in patients who have undergone solid organ transplantation is essential in the diagnosis of PTLD.

Further, it is important to thoroughly examine the patient for lymphadenopathy and

organomegaly and to pursue appropriate imaging studies and biopsy for patients in whom you suspect this diagnosis.

EBV serology and PCR are essential in understanding how the patient developed PTLD and in dictating further treatment.

The first step in treatment is still to reduce immunosuppression and maintain a high clinical suspicion for PTLD in patients presenting post solid organ transplantation, as well as to involve respective medical subspecialties early, particularly hematology.

REFERENCES

1. **Skinner J, Yankey B, Shelton BK**. Hemophagocytic lymphohistiocytosis. AACN Adv Crit Care 2019; 30(2):151–164. doi:10.4037/aacnacc2019463
2. **Boisseau M, Lambotte O, Galicier L, et al**. Epstein-Barr virus viral load in human immunodeficiency virus-positive patients with reactive hemophagocytic syndrome. Infect Dis (Lond) 2015; 47(6):423–427. doi:10.3109/00365548.2015.1007475
3. **Rivière S, Galicier L, Coppo P, et al**. Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. Am J Med 2014; 127(11):1118–1125. doi:10.1016/j.amjmed.2014.04.034
4. **Marik PE, Taeb AM**. SIRS, qSOFA and new sepsis definition. J Thorac Dis 2017; 9(4):943–945. doi:10.21037/jtd.2017.03.125
5. **Dioverti MV, Razonable RR**. Cytomegalovirus. Microbiol Spectr 2016; 4(4). doi:10.1128/microbiolspec.DMIH2-0022-2015
6. **Ljungman P, Griffiths P, Paya C**. Definitions of cytomegalovirus infection and disease in transplant recipients. Clin Infect Dis 2002; 34(8):1094–1097. doi:10.1086/339329
7. **Verbeeck J, Van Kerschaver E, Wollants E, Beuselinck K, Stappaerts L, Van Ranst M**. Detection of perinatal cytomegalovirus infection and sensorineural hearing loss in Belgian infants by measurement of automated auditory brainstem response. J Clin Microbiol 2008; 46(11):3564–3568. doi:10.1128/JCM.00757-08
8. **Ruuskanen O, Lahti E, Jennings LC, Murdoch DR**. Viral pneumonia. Lancet 2011; 377(9773):1264–1275. doi:10.1016/S0140-6736(10)61459-6
9. **Nakanishi M, Yoshida Y, Takeda N, et al**. Community-acquired pneumonia distinguished from influenza infection based on clinical signs and symptoms during a novel (swine) influenza A/H1N1 pandemic. Prim Care Respir J 2011; 20(4):421–426. doi:10.4104/pcrj.2011.00067
10. **Allyn PR, Duffy EL, Humphries RM, et al**. Graft loss and CLAD-onset is hastened by viral pneumonia after lung transplantation. Transplantation 2016; 100(11):2424–2431. doi:10.1097/TP.0000000000001346
11. **Dierickx D, Habermann TM**. Post-transplantation lymphoproliferative disorders in adults. N Engl J Med 2018; 378(6):549–562. doi:10.1056/NEJMra1702693
12. **Kremer BE, Reshef R, Misleh JG, et al**. Post-transplant lymphoproliferative disorder after lung transplantation: a review of 35 cases. J Heart Lung Transplant 2012; 31(3):296–304. doi:10.1016/j.healun.2011.10.013
13. **Kumarasinghe G, Lavee O, Parker A, et al**. Post-transplant lymphoproliferative disease in heart and lung transplantation: defining risk and prognostic factors. J Heart Lung Transplant 2015; 34(11):1406–1414. doi:10.1016/j.healun.2015.05.021
14. **Cockfield SM**. Identifying the patient at risk for post-transplant lymphoproliferative disorder. Transpl Infect Dis 2001; 3(2):70–78. doi:10.1034/j.1399-3062.2001.003002070.x
15. **Minárovits J, Niller H**. Epstein Barr Virus: Methods and Protocols. Totowa, NJ: Humana Press; 2016.
16. **Luskin MR, Heil DS, Tan KS, et al**. The impact of EBV status on characteristics and outcomes of posttransplantation lymphoproliferative disorder. Am J Transplant 2015; 15(10):2665–2673. doi:10.1111/ajt.13324
17. **Cao S, Cox KL, Berquist W, et al**. Long-term outcomes in pediatric liver recipients: comparison between cyclosporin A and tacrolimus. Pediatr Transplant 1999; 3(1):22–26. doi:10.1034/j.1399-3046.1999.00002.x
18. **McKeage K, McCormack PL**. Basiliximab: a review of its use as induction therapy in renal transplantation. BioDrugs 2010; 24(1):55–76. doi:10.2165/11203990-000000000-00000
19. **Humar A, Mazzulli T, Moussa G, et al**. Clinical utility of cytomegalovirus (CMV) serology testing in high-risk CMV D+/R- transplant recipients. Am J Transplant 2005; 5(5):1065–1070. doi:10.1111/j.1600-6143.2005.00797.x
20. **Maylin S, Feghoul L, Salmona M, et al**. Evaluation the Architect EBV VCA IgM, VCA IgG, and EBNA-1 IgG chemiluminescent immunoassays to assess EBV serostatus prior transplantation. J Med Virol 2017; 89(11):2003–2010. doi:10.1002/jmv.24889
21. **Epstein MA, Achong BG, Barr YM**. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. Lancet 1964; 1(7335):702–703. doi:10.1016/s0140-6736(64)91524-7
22. **Crawford D, Johannessen I, Rickinson AB**. Cancer Virus: The Story of Epstein-Barr Virus. New York, NY: Oxford University Press; 2014.
23. **Pope JH, Horne MK, Scott W**. Transformation of foetal human keukocytes in vitro by filtrates of a human leukaemic cell line containing herpes-like virus. Int J Cancer 1968; 3(6):857–866. doi:10.1002/ijc.2910030619
24. **Penn I, Hammond W, Brettschneider L, Starzl TE**. Malignant lymphomas in transplantation patients. Transplant Proc 1969; 1(1):106–112. pmid:4944206
25. **Bow EJ, Evans G, Fuller J, et al**. Canadian clinical practice guidelines for invasive candidiasis in adults. Can J Infect Dis Med Microbiol 2010; 21(4):e122–e150. doi:10.1155/2010/357076
26. **Marchetti O, Cordonnier C, Calandra T**. Empirical antifungal therapy in neutropaenic cancer patients with persistent fever. Eur J Cancer Suppl 2007; 5(2):32–42. doi:10.1016/j.ejcsup.2007.06.005
27. **Taplitz RA, Kennedy EB, Bow EJ, et al**. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol 2018; 36(14):1443–1453. doi:10.1200/JCO.2017.77.6211
28. **Green M, Michaels MG**. Epstein-Barr virus infection and posttransplant lymphoproliferative disorder. Am J Transplant 2013; 13(suppl 3):41–54. doi:10.1111/ajt.12004
29. **Span AH, van Dam-Mieras MC, Mullers W, Endert J, Muller AD, Bruggeman CA**. The effect of virus infection on the adherence of leukocytes or platelets to endothelial cells. Eur J Clin Invest 1991; 21(3):331–338. doi:10.1111/j.1365-2362.1991.tb01378.x
30. **Tsai DE, Hardy CL, Tomaszewski JE, et al**. Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients. Transplantation 2001; 71(8):1076–1088. doi:10.1097/00007890-200104270-00012
31. **Dharnidharka VR, Mohanakumar T**. New approaches to treating B-cell cancers induced by Epstein-Barr virus. N Engl J Med 2015; 372(6):569–571. doi:10.1056/NEJMcibr1415117
32. **Oertel SH, Verschuuren E, Reinke P, et al**. Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). Am J Transplant 2005; 5(12):2901–2906. doi:10.1111/j.1600-6143.2005.01098.x
33. **Mendogni P, Henchi S, Morlacchi LC, et al**. Epstein-Barr virus-related post-transplant lymphoproliferative disorders in cystic fibrosis lung transplant recipients: a case series. Transplant Proc 2019; 51(1):194–197. doi:10.1016/j.transproceed.2018.05.032
34. **Kinch A, Baecklund E, Backlin C, et al**. A population-based study of 135 lymphomas after solid organ transplantation: the role of Epstein-Barr virus, hepatitis C and diffuse large B-cell lymphoma subtype in clinical presentation and survival. Acta Oncol 2014; 53(5):669–679. doi:10.3109/0284186X.2013.844853
35. **Ison MG, Grossi P; AST Infectious Diseases Community of Practice**. Donor-derived infections in solid organ transplantation. Am J Transplant 2013; 13(suppl 4):22–30. doi:10.1111/ajt.12095

***Address**: Hanna Lyubetska, MD, Department of Internal Medicine, University of Manitoba Faculty of Health Sciences, 820 Sherbrook Street, Winnipeg, MB R3A 1R9, Canada; lyubetsh@myumanitoba.ca*

GREGORY W. RUTECKI, MD, Section Editor

Michael A. Munoz, MD
Pediatric Department, Monmouth Medical Center, Monmouth, NJ

Kaviya Sathyakumar, MD
Department of Family Medicine, University of Central Florida Ocala Regional Medical Center, Ocala FL

Benson A. Babu, MD, MBA
Department of Internal Medicine, Northwell Health, Plainview, NY

Acute pancreatitis secondary to hypertriglyceridemia

A man presents with acute severe abdominal pain and triglycerides 5,250 mg/dL

A 42-year-old man with obesity, type 2 diabetes mellitus, hyperlipidemia, depression, asthma, and obstructive sleep apnea presents with severe abdominal pain, nausea, and vomiting. He says the pain started 18 hours ago and has steadily worsened. He describes the pain as 8 on a scale of 10, intermittent, aching, and mainly localized to his epigastric area. It does not radiate and is relieved with simethicone. He also has had some nonbloody diarrhea since the pain started. He recalls a similar episode 2 years ago and was told it was pancreatitis, and it resolved.

He has had no recent trauma and has not traveled or started new medications. He says he does not use tobacco or illicit drugs, and he consumes alcohol occasionally, the last time 3 days ago, when he had approximately 3 glasses of wine.

He says he has recently started eating more fried and unhealthy foods. He admits to not complying with his medications, which include metformin, albuterol, simvastatin, and escitalopram. His diabetes is not under control, but he has not been hospitalized in the last 2 years for hyperglycemia. His family history is significant for hyperlipidemia and diabetes in his father and brother.

INITIAL EVALUATION

The patient's body mass index is 36.5 kg/m^2 and his waist circumference is 44 inches. His temperature is 98.1 °F (36.7 °C), heart rate 90 beats per minute, blood pressure 148/92 mm Hg, respiratory rate 20 breaths per minute, and oxygen saturation 98% on room air.

On physical examination, he has mild discomfort because of the pain, and his abdomen is mildly tender to palpation near the epigastric region. Bowel sounds are diminished in all 4 quadrants. The abdomen is not visibly distended, and the skin is without jaundice, pruritus, or xanthomas.

Laboratory test results

- Hematocrit 45% (reference range 41–53)
- Glucose 347 mg/dL (70–110)
- Lipase 19,889 U/L (31–186)
- Triglycerides 5,250 mg/dL (35–160)
- White blood cell count 9.8 × 10^9/L (4.5–11)
- Bicarbonate 28 mmol/L (21–28)
- Sodium 138 mmol/L (136–142)
- Potassium 4.2 mmol/L (3.5–5)
- Blood urea nitrogen 16 mg/dL (6–24)
- Serum creatinine 1.1 mg/dL (0.6–1.2).

Imaging and electrocardiography results

Abdominal ultrasonography shows an enlarged fatty liver and a heterogeneous pancreas with some mild peripancreatic fluid surrounding it. His gallbladder has a wall thickness of less than 3 mm and no cholelithiasis.

Computed tomography (CT) shows hepatomegaly with fatty liver and moderate pancreatitis.

Electrocardiography shows normal sinus rhythm.

DIAGNOSING ACUTE PANCREATITIS

Acute pancreatitis is one of the more common diagnoses in patients hospitalized for epigastric abdominal pain. It is an inflammatory process that begins with the acinar cells in the pancreas, initiating a systemic inflammatory

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

doi:10.3949/ccjm.87a.19156

response. In severe cases, this inflammatory process can lead to necrosis of the pancreas and multisystem organ failure, resulting in a high risk of death. To help reduce the risks, it is essential to recognize acute pancreatitis early and initiate timely treatment.

Guidelines recommend abdominal CT if the diagnosis is unclear or if the patient's symptoms have not improved after 2 or 3 days of treatment.[1] Thus, this patient underwent CT to confirm the cause of his pain, and it showed moderate pancreatitis. He now fulfilled all 3 of the diagnostic criteria for acute pancreatitis (**Table 1**)—abdominal pain in the epigastric region, significantly elevated serum lipase, and pancreatitis on imaging.

The severity of his acute pancreatitis and the risk of complications is assessed using the Bedside Index for Severity in Acute Pancreatitis (**Table 2**).[2] Our patient's score is 0, indicating a low mortality risk—less than 1%.

TABLE 1

Diagnostic criteria for acute pancreatitis

Must have at least 2 of these 3 criteria:

Abdominal pain

Serum amylase or lipase level at least 3 times the upper limit of normal

Ultrasonography, computed tomography, or magnetic resonance imaging that shows irritation of the pancreas

Based on information in reference 8.

NEXT STEP: IDENTIFY THE CAUSE OF ACUTE PANCREATITIS

1 What is the most likely cause of this patient's acute pancreatitis?

- ☐ Cholelithiasis
- ☐ Alcohol use
- ☐ Hypertriglyceridemia
- ☐ Hereditary pancreatitis
- ☐ Pancreatic duct variants or anomalies
- ☐ Autoimmune pancreatitis
- ☐ Pharmaceutical agents

Cholelithiasis

Cholelithiasis is one of the most common causes of acute pancreatitis in the United States and needs to be looked for in patients with acute pancreatitis. To identify it as the instigating factor, there has to be cholelithiasis or choledocholithiasis on radiologic imaging with no signs of other risk factors.[3] The patient's liver enzyme panel also must be assessed. Small stones and sludge have been hypothesized to irritate the wall of the gallbladder and contribute to causing some cases of idiopathic acute pancreatitis. This patient's history of diabetes also increases his risk of biliary sludge.[4]

Patients with signs of ductal obstruction secondary to cholelithiasis should undergo endoscopic retrograde cholangiopancreatography (ERCP), which has been shown to decrease overall morbidity and mortality in patients with ductal obstruction.[5] It is warranted if acute pancreatitis worsens or there are clinical signs of ductal obstruction, including an increase in total bilirubin, aspartate aminotransferase, alanine aminotransferase, or ductal dilation on imaging.[1,5,6]

Magnetic resonance cholangiopancreatography (MRCP) has been shown to be a helpful tool to diagnose acute pancreatitis, but it has no benefit in the clinical management of acute pancreatitis because it is an imaging modality only; it does not support treatment. The advantage of MRCP is its low risk of adverse effects compared with ERCP, which has been associated with inducing acute pancreatitis, bleeding, and pain. However, MRCP is purely diagnostic, whereas ERCP can be both diagnostic and therapeutic.[6]

Endoscopic ultrasonography also has been proposed as a standard in approaching acute pancreatitis secondary to biliary issues. One of its main benefits is it can be performed at the bedside to evaluate the size of the obstruction to determine if ERCP is warranted.[7]

Patients with acute pancreatitis secondary to gallstones should undergo cholecystectomy to prevent future occurrences. This surgery should be performed during the same hospitalization unless the patient develops severe acute pancreatitis with complications such as pancreatic necrosis. Patients who do not qualify for surgery because of age or comorbidities may undergo biliary sphincterotomy, which can help reduce the frequency of acute pancreatitis.[1]

Common causes of pancreatitis: gallstones, alcohol use, hypertriglyceridemia

TABLE 2

Bedside Index of Severity in Acute Pancreatitis

Clinical factor	Score Yes = 1 point No = 0 points
Blood urea nitrogen > 25 mg/dL	
Abnormal mental status (Glasgow Coma Score < 15)	
Evidence of systemic inflammatory response syndrome[a]	
Over age 60	
Imaging tests showing pleural effusion	
Total points[b]	

[a]Requires at least 2 of the following: temperature < 36°C or > 38°C, respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mm Hg, pulse > 90 beats per minute, and white blood cell count < 2.0 or > 12.0 × 10^9/L or > 10% immature bands.
[b]0–2 points = low mortality risk (< 2%); ≥ 3 points = high mortality risk (> 15%).

Reprinted from Hagjer S, Kumar N. Evaluation of the BISAP scoring system in prognostication of acute pancreatitis—A prospective observational study. Int J Surg 2018; 54(Pt A):76–81 doi:10.1016/j.ijsu.2018.04.026 with permission from Elsevier. https://www.journals.elsevier.com/international-journal-of-surgery

Our patient did not display any signs of cholelithiasis or choledocholithiasis in any of the abdominal imaging studies. However, that does not rule out the possibility of microlithiasis or biliary sludge, and it requires further investigation with a liver enzyme panel and, possibly, endoscopic ultrasonography.

Triglycerides > 1,000 mg/dL typically cause pancreatitis symptoms

Alcohol use

Alcohol is another major cause of acute pancreatitis. Alcohol-induced acute pancreatitis occurs with frequent intake of alcohol or episodes of heavy drinking (> 80 mL of alcohol in 24 hours).[8]

Even though the patient admitted to drinking 3 days before his symptoms started, he denied daily alcohol use or binges, making alcohol use less likely to be the main cause of his acute pancreatitis.

Hypertriglyceridemia

Pancreatitis induced by hypertriglyceridemia is a well-known phenomenon that typically goes underreported. It is the third most common cause of acute pancreatitis, but is relatively rare, accounting for 7% of cases.[9]

Establishing hypertriglyceridemia as the cause of acute pancreatitis can be challenging because most cases of acute pancreatitis have other causes. Moreover, triglyceride levels can be mildly or moderately elevated with these other causes as well: the 2 main causes of acute pancreatitis, alcohol and gallstones, can both cause acquired hypertriglyceridemia.

Both biliary obstruction by gallstones and alcohol consumption increase the levels of triglycerides because of their secondary effects on fatty metabolism. Biliary obstruction from gallstones increases the trapping of triglycerides in the serum, causing a rise in their levels. Alcohol increases very low-density lipoprotein (VLDL), which causes an increase in the release of fatty acids from both the liver and adipose tissue, also causing a rise in triglycerides in the serum. Hypertriglyceridemia should therefore be considered only after heavy alcohol consumption and gallstones have been ruled out due to the false rise that can be seen in the other 2 primary causes of acute pancreatitis.

Serum triglyceride levels need to be evaluated early in the disease in these patients because levels can fall drastically with fasting, and hypertriglyceridemia can be missed. Patients with hypertriglyceridemia-induced pancreatitis typically have serum triglyceride levels above 1,000 mg/dL and no signs of gallstones or alcohol-induced acute pancreatitis.

Compared with the common causes of acute pancreatitis, hypertriglyceridemia has a more complicated and severe medical course with a higher mortality rate.[10]

This patient's triglyceride level in the emergency department was 5,250 mg/dL, which supports the diagnosis of hypertriglyceridemia as the instigating factor for his acute pancreatitis.

Hereditary pancreatitis

Hereditary pancreatitis is an uncommon cause of acute pancreatitis, but it must be considered in patients who have multiple episodes of acute pancreatitis. Patients with hereditary pancreatitis-induced acute pancreatitis typically present with multiple episodes by age 30. They have a higher risk of pancreatic adenocarcinoma and require surveillance for it.

Hereditary pancreatitis also increases a patient's risk of developing chronic pancreatitis, which can cause fibrosis and strictures in the pancreatic ducts that can lead to pancreatic

TABLE 3

Revised Atlanta classification of severity of acute pancreatitis

Mild	Moderate to severe	Severe
Absence of organ failure	Organ failure for < 48 hours	Persistent organ failure for > 48 hours
Absence of local complications[a]	Local complications[a]	

[a]Local complications: interstitial edematous pancreatitis, necrotizing pancreatitis, pancreatic pseudocyst, necrotic collection, and pleural effusion.

Based on information in references 8 and 14.

exocrine and endocrine insufficiency. Genetic testing and visualization of the pancreas for signs of acute or chronic pancreatitis can help identify patients with hereditary pancreatitis.[11]

This patient had no knowledge of a family history of pancreatitis or of having pancreatitis before age 30, making hereditary pancreatitis less likely.

Pancreatic duct variants or anomalies

Abnormalities in the pancreatic duct can lead to recurring acute pancreatitis that usually requires surgical management. Many times, congenital abnormalities in the pancreatic duct can go undetected until adulthood, when they are incidentally found during abdominal imaging. If pancreatic duct abnormalities are suspected, the best initial test is MRCP.[12]

In our patient, no abnormalities were seen on CT of the abdomen or ultrasonography, but those results did not rule out the possibility of an abnormality in the pancreatic duct.

Autoimmune pancreatitis

Autoimmune pancreatitis, also known as idiopathic duct-destructive pancreatitis, is being clinically recognized more often because of technologic advances in imaging, which may reveal an enlarged pancreas, often with a hypoattenuated rim or narrowing of the main pancreatic duct.

To differentiate autoimmune pancreatitis from a malignancy, a fine-needle biopsy is required. The symptoms most associated with autoimmune pancreatitis are jaundice, weight loss, and epigastric pain. It can also present alongside other autoimmune diseases.[13]

Even though this patient has epigastric pain, he does not have jaundice or weight loss. On imaging, the pancreas appeared to be irritated but not enlarged.

Drugs

Certain medications can cause acute pancreatitis, including statins, selective serotonin-reuptake inhibitors, and metformin. Medication-induced pancreatitis tends to be mild to moderate but it can be severe.

The diagnosis of medication-induced pancreatitis depends on ruling out the more common causes such as biliary stones or obstructions, alcohol use, and hypertriglyceridemia. The best course of action if medication-induced pancreatitis is suspected is to stop the offending drug and see if the symptoms of acute pancreatitis resolve.

Our patient admits to not taking his medications for the last 2 months. Also, 2 of the more common causes of acute pancreatitis have not been ruled out yet, which make this diagnosis less likely.

Triglycerides > 2,000 mg/dL are classified as very severe hypertriglyceridemia

THE NEXT STEP

2 What is the most appropriate next step in this patient's workup?

- ☐ Assess his risk of complications of acute pancreatitis
- ☐ Determine if there is a possibility of biliary sludge or microlithiasis
- ☐ Identify the cause of his hypertriglyceridemia

The revised Atlanta classification for acute pancreatitis provides guidance for determining its severity and identifying complications attributed to it (**Table 3**).[14] Organ failure, a key component of the classification criteria, is assessed using the modified Marshall scoring system (**Table 4**).

TABLE 4

Modified Marshall scoring system for organ failure

	Respiratory	Renal	Cardiovascular
Score[a]	Pao_2/Fio_2[b]	Serum creatinine (mg/dL)	Systolic blood pressure (mm Hg)
0	> 400	≤ 1.4	> 90
1	301–400	1.5–1.8	< 90 and responding to fluid resuscitation
2	201–300	1.9–3.5	< 90 and not responding to fluid resuscitation
3	101–200	3.6–4.9	< 90 with pH < 7.3
4	≤ 100	≥ 5	< 90 with pH < 7.2

[a]A score of 2 or more indicates organ failure. Persistent failure is considered organ failure lasting longer than 48 hours.
[b]Ratio of partial pressure of arterial oxygen to fractional inspired oxygen.

Based on information in references 8 and 14.

TABLE 5

Criteria for clinical diagnosis of hypertriglyceridemia

Degree of hypertriglyceridemia	Serum triglycerides (mg/dL)
Mild	150–199
Moderate	200–999
Severe	1,000–1,999
Very severe	≥ 2,000

Based on Endocrine Society clinical practice guidelines, reference 18.

During the second week after the onset of acute pancreatitis symptoms, patients may develop local complications that can manifest clinically as unremitting pain, sepsis, elevation in pancreatic enzymes for a second time, or organ dysfunction. These patients should undergo contrast-enhanced CT, contrast-enhanced magnetic resonance imaging (MRI), or non-enhanced MRI to identify the local complications. Imaging done during the first 5 to 7 days of symptom onset does not help detect necrosis in the pancreas or local complications because these complications don't typically arise, or are undetectable, until the second week.[14,15]

Correctly identifying the trigger for the acute pancreatitis is important for long-term management of the patient, in order to prevent future episodes of acute pancreatitis. Unfortunately, some cases might remain as idiopathic acute pancreatitis, in which case the patient should be advised of the most common causes of acute pancreatitis and certain risk factors that can potentiate another episode of it.

CASE CONTINUED

The patient is admitted to the intensive care unit, where he is placed on nothing-by-mouth orders and given intravenous fluids. Laboratory tests are ordered.

Laboratory test results

- Low-density lipoprotein cholesterol (LDL-C) 170 mg/dL (reference range 50–130)
- High-density lipoprotein cholesterol (HDL-C) 31 mg/dL (40–75)
- Aspartate aminotransferase 34 U/L (10–40)
- Alanine aminotransferase 18 U/L (9–46)
- Alkaline phosphatase 80 U/L (40–115)
- Total bilirubin 0.7 mg/dL (0.2–1.2)
- Indirect bilirubin 0.6 mg/dL (0.2–1.2)
- Direct bilirubin 0.1 mg/dL (< 0.2)
- Total protein 6.9 g/dL (6.1–8.1)
- Albumin 4.2 g/dL (3.6–5.1)
- Globulin 2.7 g/dL (1.9–3.7)
- Hemoglobin A_{1c} 9.1% (4–5.6).

MANAGING HYPERTRIGLYCERIDEMIA-INDUCED ACUTE PANCREATITIS

The higher the triglyceride level, the greater the risk of acute pancreatitis and secondary cardiovascular complications.[16,17] Patients who display signs of acute pancreatitis caused by hypertriglyceridemia typically have serum triglyceride levels above 1,000 mg/dL, classified as severe hypertriglyceridemia by the Endocrine Society (**Table 5**).[18]

There are primary and secondary causes of hypertriglyceridemia (**Table 6**). Identifying the cause can help practitioners select appropriate long-term management strategies and address specific risk factors associated with the causes.

This patient's hypertriglyceridemia was most likely caused by metabolic syndrome. He fulfilled all 5 criteria for metabolic syndrome (of which only 3 are needed):

- Waist circumference significantly greater than 40 inches

- Fasting glucose level higher than 110 mg/dL
- Triglyceride level higher than 150 mg/dL
- HDL-C level less than 40 mg/dL
- Systolic blood pressure higher than 130 mm Hg.

Patients with the metabolic syndrome have an excess of visceral adipose tissue, which contributes to the increase in triglyceride levels. Many also develop insulin-resistant diabetes, resulting in increased concentrations of VLDLs and an influx of free fatty acids to the liver, which can contribute to fatty liver disease in this patient population. Having the metabolic syndrome, insulin-resistant diabetes, and elevated apolipoprotein B level can increase a patient's cardiovascular risk by up to 20 times. This risk can be reduced by lowering the triglyceride level through glycemic control and weight loss.

TREATMENT FOR ACUTE PANCREATITIS

3 What is the best treatment for this patient's acute pancreatitis?

☐ Insulin drip
☐ Heparin
☐ Plasmapheresis

Acute pancreatitis secondary to hypertriglyceridemia is initially managed by giving aggressive intravenous hydration, limiting food intake, and managing pain. Further management of the elevated triglycerides includes an insulin drip, plasmapheresis, or heparin.[19] There are no formal guidelines to advise the best treatment regimen, so the decision is left to practitioners' discretion, considering the risks and benefits as well as the availability of resources.

Insulin drip

Insulin drip therapy for hypertriglyceridemia has been shown to be effective in lowering triglycerides to less than 500 mg/dL.[20] It also increases the level of peripheral lipoprotein lipase, which helps process the excess triglycerides. The dosage is 0.1 to 0.3 U/kg/hour by continuous infusion, with glucose monitoring every 30 minutes to every hour. In patients whose glucose levels are below 200 mg/dL, a separate 5% dextrose infusion can help prevent hypoglycemia. Insulin increases the metabolism of low-density lipoprotein and also accelerates chylomicron formation.[9,19,20]

TABLE 6

Causes of hypertriglyceridemia

Primary causes
Familial hypertriglyceridemia
Apolipoprotein C-II deficiency
Familial combined hyperlipidemia
Secondary causes (acquired)
Diseases
Hypothyroidism
Diabetes mellitus
Renal disease
Human immunodeficiency virus-associated dyslipidemia
Systemic lupus erythematosus
Nephrotic syndrome
Pregnancy
Medications
Beta-blockers
Corticosteroids
Thiazides
Protease inhibitors
Second-generation antipsychotics
Estrogen-based oral contraceptives
Diet
Excessive alcohol intake
High-fat diet

Based on information in reference 16.

Heparin

Heparin has potential benefits in that it increases lipoprotein lipase, which helps break down triglycerides. However, although heparin, like insulin, causes an initial increase in lipoprotein lipase, in the long term it reduces the activity of this enzyme. Some studies have found that the initial benefits are not worth the long-term risks, which can include an increase in the release of toxic components from triglycerides, decreased metabolism of triglycerides, and storage of triglycerides in the liver. In turn, this can cause a net increase in triglyceride levels and also increase the risk of bleeding.

Pancreatitis caused by hypertriglyceridemia has a more complicated and severe medical course

Plasmapheresis

Plasmapheresis physically removes triglycerides from the blood, leading to faster lowering of levels to below 500 mg/dL.[19,21] It consists of removing some of the patient's plasma with the elevated triglycerides and replacing it with a colloid solution.

The main advantage of plasmapheresis over insulin in correcting hypertriglyceridemia is its speed. However, it is more expensive and also requires the insertion of a central line. It can be considered for patients who are at high risk of complications or have signs of organ failure and necrosis.[19,21] Our patient had no signs of organ failure nor necrosis in the pancreas on his abdominal CT.

CASE CONTINUED

The patient is started on an insulin drip at a rate of 0.1 U/kg/hour. Because he now requires hourly glucose checks, he is kept in the intensive care unit. His triglyceride levels begin to show a downward trend, although they remain significantly above the normal range. The patient also receives heparin.

Insulin drip lowers triglycerides in acute pancreatitis

Discussion

Untreated acute pancreatitis increases the risk of serious complications and death. The most commonly noted complications are pancreatic pseudocyst, peripancreatic fluid collections, and necrotic collections. In necrotizing pancreatitis, there is a collection of necrosis and fluids that can become walled off and encapsulate the material, enabling bacteria to colonize. Patients who are left untreated are also at risk for developing systemic inflammatory response syndrome and multiorgan failure.

An insulin drip has the most evidence of a true therapeutic benefit in acute pancreatitis secondary to hypertriglyceridemia. However, the evidence is inconclusive regarding its effects on mortality and in the long term.

LONG-TERM MANAGEMENT OF HYPERTRIGLYCERIDEMIA

Treatment of hypertriglyceridemia focuses on preventing cardiovascular complications and managing its cause. For patients with a nonfasting triglyceride level above 200 mg/dL, a full lipid panel is recommended to help assess their cardiovascular risk.[18]

The initial management of hypertriglyceridemia focuses on lifestyle changes, which include losing weight, reducing alcohol consumption, increasing physical activity, and avoiding refined carbohydrates and sweetened substances with high levels of fructose.[19] Fructose increases VLDL cholesterol production and promotes triglyceride formation in the liver, which increases the serum triglyceride levels.

The American Heart Association recommends using triglyceride-lowering medications if a patient's level is above 500 mg/dL.[22] Fibrates are the first-line treatment for patients at risk for developing acute pancreatitis.[18] Fibrates can reduce triglycerides by 30% to 50% and also increase HDL, which has cardiovascular protective factors. When using fibrates, one must be cautious with the increased risk of developing cholesterol-based gallstones, which can also trigger acute pancreatitis.[18] In combination therapy with statins, fenofibrate is the preferred fibrate, owing to its low interference with the metabolism of statins.[16] Recent studies also have found that ezetimibe in combination with fibrates helps lower triglyceride and LDL levels.[18]

Niacin can also be used as a monotherapy or in combination with statins to prevent cardiovascular events due to hypertriglyceridemia.[17] Patients taking niacin should have routine liver enzyme panel testing because of the hepatotoxicity risk with niacin. The more common side effects associated with niacin include cutaneous flushing, which can be minimized with aspirin therapy. Niacin should be used with caution in patients with diabetes or a history of gout, owing to its impairment of glucose tolerance and promotion of hyperuricemia.

Omega-3 fatty acids have been shown to lower triglyceride levels by 20% to 50% at doses of 3 to 4 g/day.[23] Even with this decrease in triglyceride levels, no studies have shown a decrease in cardiovascular risk when they are used as monotherapy. When omega-3 fatty acids are combined with statins, studies have shown a 19% decrease in cardiovascular events.

Statins should not be used as monotherapy in severe hypertriglyceridemia because they lack efficacy in lowering triglyceride levels, but

a statin can be used in combination therapies, especially to reduce the cardiovascular risk.[18,23]

Rimonabant is a hunger-reducing medication that assists in weight loss and lowering triglyceride levels.[24] It has been approved by several countries but was rejected by the US Food and Drug Administration because of associated increases in suicidal ideation.

For patients with familial lipoprotein lipase deficiency, alipogene tiparvovec is a gene therapy geared to reverse this deficiency. It has been shown to help increase the production of lipoprotein lipase, which is used to break down triglycerides.[25] It is approved for use in the European Union but not in the United States.

Apolipoprotein C-III (apoC3) has a major influence on triglyceride metabolism. An increase in its function has been associated with hypertriglyceridemia, but loss of function is associated with lower triglyceride levels and fewer cardiovascular events. ApoC3 inhibits lipoprotein lipase from breaking down triglycerides. Antisense oligonucleotide is currently being investigated in clinical trials to function against apoC3 mRNA by inhibiting its translation to decrease the production of apoC3 and inherently lower triglyceride levels.[26]

CASE CONTINUED

Our patient's long-term treatment is aimed at managing the metabolic syndrome effects by addressing his triglycerides, glucose, and weight. Fenofibrate therapy is initiated with atorvastatin to help lower his triglyceride levels and reduce his cardiovascular risk. He is also prescribed long-acting insulin to better manage his diabetes.

TAKE-HOME POINTS

- In patients with acute pancreatitis, test for hypertriglyceridemia and manage it appropriately.
- The severity of hypertriglyceridemia is a clinical indicator of the patient's risk for cardiovascular complications and pancreatitis.
- Hypertriglyceridemia-induced acute pancreatitis has a more complicated and severe medical course than acute pancreatitis due to other causes such as alcohol use or biliary obstruction.
- Determine the cause of hypertriglyceridemia and direct long-term treatment to address it.
- Prevent and manage secondary cardiovascular risks related to hypertriglyceridemia. ■

REFERENCES

1. **Tenner S, Baillie J, DeWitt J, Vege SS; American College of Gastroenterology**. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013; 108(9):1400–1416. doi:10.1038/ajg.2013.218
2. **Hagjer S, Kumar N**. Evaluation of the BISAP scoring system in prognostication of acute pancreatitis—A prospective observational study. Int J Surg 2018; 54(pt A):76–81. doi:10.1016/j.ijsu.2018.04.026
3. **Jin M, Bai X, Chen X, et al**. A 16-year trend of etiology in acute pancreatitis: the increasing proportion of hypertriglyceridemia-associated acute pancreatitis and its adverse effect on prognosis. J Clin Lipidol 2019; 13(6):947–953.e1. doi:10.1016/j.jacl.2019.09.005
4. **Grover BT, Kothari SN**. Biliary issues in the bariatric population. Surg Clin North Am 2014; 94(2):413–425. doi:10.1016/j.suc.2014.01.003
5. **Gabbrielli A, Pezzilli R, Uomo G, et al**. ERCP in acute pancreatitis: what takes place in routine clinical practice? World J Gastrointest Endosc 2010; 2(9):308–313. doi:10.4253/wjge.v2.i9.308
6. **Kaltenthaler EC, Walters SJ, Chilcott J, Blakeborough A, Vergel YB, Thomas S**. MRCP compared to diagnostic ERCP for diagnosis when biliary obstruction is suspected: a systematic review. BMC Med Imaging 2006; 6:9. doi:10.1186/1471-2342-6-9
7. **Anderloni A, Repici A**. Role and timing of endoscopy in acute biliary pancreatitis. World J Gastroenterol 2015; 21(40):11205–11208. doi:10.3748/wjg.v21.i40.11205
8. **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
9. **Weston N, Fernando U, Baskar V**. Hypertriglyceridaemia-induced pancreatitis. BMJ Case Rep 2013; 2013:bcr2013008722. doi:10.1136/bcr-2013-008722
10. **Carr RA, Rejowski BJ, Cote GA, Pitt HA, Zyromski NJ**. Systematic review of hypertriglyceridemia-induced acute pancreatitis: a more virulent etiology? Pancreatology 2016; 16(4):469–476. doi:10.1016/j.pan.2016.02.011
11. **Raphael KL, Willingham FF**. Hereditary pancreatitis: current perspectives. Clin Exp Gastroenterol 2016; 9:197–207. doi:10.2147/CEG.S84358
12. **Türkvatan A, Erden A, Türkoglu MA, Yener Ö**. Congenital variants and anomalies of the pancreas and pancreatic duct: imaging by magnetic resonance cholangiopancreaticography and multidetector computed tomography. Korean J Radiol 2013; 14(6):905–913. doi:10.3348/kjr.2013.14.6.905
13. **Fan BG, Andrén-Sandberg A**. Autoimmune pancreatitis. N Am J Med Sci 2009; 1(4):148–151. pmid:22666688
14. **Foster BR, Jensen KK, Bakis G, Shaaban AM, Coakley FV**. Revised Atlanta classification for acute pancreatitis: a pictorial essay. Radiographics 2016; 36(3):675–687. doi:10.1148/rg.2016150097
15. **Chatila AT, Bilal M, Guturu P**. Evaluation and management of acute pancreatitis. World J Clin Cases 2019; 7(9):1006–1020. doi:10.12998/wjcc.v7.i9.1006
16. **Rygiel K**. Hypertriglyceridemia—common causes, prevention and treatment strategies. Curr Cardiol Rev 2018; 14(1):67–76. doi:10.2174/1573403X14666180123165542
17. **Yuan G, Al-Shali KZ, Hegele RA**. Hypertriglyceridemia: its etiology, effects and treatment. CMAJ 2007; 176(8):1113–1120. doi:10.1503/cmaj.060963
18. **Berglund L, Brunzell JD, Goldberg AC, et al**. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical

practice guideline. J Clin Endocrinol Metab 2012; 97(9):2969–2989. doi:10.1210/jc.2011-3213
19. **Rawla P, Sunkara T, Thandra KC, Gaduputi V**. Hypertriglyceridemia-induced pancreatitis: updated review of current treatment and preventive strategies. Clin J Gastroenterol 2018; 11(6):441–448. doi:10.1007/s12328-018-0881-1
20. **Scherer J, Singh VP, Pitchumoni CS, Yadav D**. Issues in hypertriglyceridemic pancreatitis: an update. J Clin Gastroenterol 2014; 48(3):195–203. doi:10.1097/01.mcg.0000436438.60145.5a
21. **Joglekar K, Brannick B, Kadaria D, Sodhi A**. Therapeutic plasmapheresis for hypertriglyceridemia-associated acute pancreatitis: case series and review of the literature. Ther Adv Endocrinol Metab 2017; 8(4):59–65. doi:10.1177/2042018817695449
22. **Grundy SM, Stone NJ, Bailey AL, et al**. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73(24):e285-e350. doi:10.1016/j.jacc.2018.11.003
23. **Karalis DG**. A review of clinical practice guidelines for the management of hypertriglyceridemia: a focus on high dose omega-3 fatty acids. Adv Ther 2017; 34(2):300–323. doi:10.1007/s12325-016-0462-y
24. **National Library of Medicine**. National Center for Biotechnology Information. Rimonabant. https://pubchem.ncbi.nlm.nih.gov/compound/Rimonabant. Accessed October 14, 2020.
25. **Scott LJ**. Alipogene tiparvovec: a review of its use in adults with familial lipoprotein lipase deficiency. Drugs 2015; 75(2):175–182. doi:10.1007/s40265-014-0339-9
26. **Schmitz J, Gouni-Berthold I**. APOC-III antisense oligonucleotides: a new option for the treatment of hypertriglyceridemia. Curr Med Chem 2018; 25(13):1567–1576. doi:10.2174/0929867324666170609081612

***Address**: Michael A. Munoz, MD, Department of Medicine, Ross Medical Education Center, 2300 SW 145th Avenue #200, Miramar, FL 33027; michaelmunoz515@gmail.com*

Neha V. Reddy
Brown University, Providence, RI

Arya B. Mohabbat, MD, FACP
Division of General Internal Medicine,
Mayo Clinic, Rochester, MN

Autonomous sensory meridian response: Your patients already know, do you?

ABSTRACT

Public interest in autonomous sensory meridian response (ASMR) is growing on digital media platforms. Some people can elicit the response by watching videos containing triggering sounds and images. People susceptible to ASMR's effects report tingling sensations on the head and neck, as well as feelings of euphoria, relaxation, and mood elevation. Underlying mechanisms of the phenomenon are not well understood, but physiologic evidence corroborates some of the self-reported positive effects. Healthcare professionals should be aware of this emerging topic, and the potential for therapeutic applications should be investigated.

KEY POINTS

ASMR involves pleasurable feelings resulting from audiovisual stimuli, such as tapping sounds, watching someone brush their hair, or having something explained in detail in a whisper.

Differences between people capable of the ASMR response and controls have been detected in personality traits, neural activity, and functional brain connectivity.

ASMR has been anecdotally reported to improve symptoms of anxiety, depression, insomnia, and chronic pain.

Many videos designed to elicit ASMR are freely available on YouTube and other platforms.

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

doi:10.3949/ccjm.87a.20005

AUTONOMOUS SENSORY MERIDIAN RESPONSE (ASMR) is an atypical sensory-emotional phenomenon triggered in some people by specific audiovisual stimuli. It is characterized as a pleasant, tingling sensation of the head or neck, and is accompanied by positive feelings, such as relaxation, a sense of well-being, euphoria, and mood elevation. Common triggers include watching someone whispering, engaging in repetitive rhythmic motions, and exploring an object.[1]

Although our understanding of the mechanisms behind ASMR and its potential clinical implications are in early stages, public interest in the phenomenon is growing and people are actively seeking it out as a type of complementary therapy. As in other complementary therapies such as acupuncture and massage, patients may be ahead of the evidence-based literature in their interest and use of ASMR. Many use it to help alleviate stress or pain or promote sleep as an alternative to conventional therapies,[1] and they may seek information from their healthcare professionals about its use.

This article describes ASMR and summarizes published research investigating its underlying mechanisms and effects.

POPULARITY OUTSIDE OF THE MEDICAL COMMUNITY

ASMR has had a presence in Internet culture for nearly a decade. It is becoming more commonly recognized and has recently been referenced in conventional media outlets, including *Good Morning America* and the Netflix

series *Follow This*. Despite being relatively unstudied, it has garnered a large following on digital platforms such as Reddit and YouTube, where ASMR videos are freely available.

CHARACTERISTICS OF ASMR-CAPABLE PEOPLE

Specific personality traits have been ascribed to people who are capable of ASMR. A study evaluating the Big Five Personality Inventory of 290 ASMR-capable people and 290 matched controls determined that the capable cohort scored significantly higher on openness-to-experience and neuroticism personality scales, and significantly lower on personality scales of conscientiousness, extraversion, and agreeableness.[2] A positive correlation was also found between the degree of openness-to-experience and neuroticism personality dimensions and intensity of ASMR experiences.

Another study found that ASMR-capable people scored significantly higher on the mindful attention and awareness scale and the curiosity subscale of the Toronto Mindfulness Scale than matched controls,[3] suggesting that ASMR-capable people tend to be more mindful than those who do not experience ASMR. These findings suggest that certain personality characteristics (and likely other unstudied factors) may contribute to the ability to experience the phenomenon.

Many use ASMR to help alleviate stress or pain or promote sleep as an alternative to conventional therapies

WHAT ASMR IS NOT

ASMR is sometimes confused with other sensory-emotional phenomena such as misophonia, synesthesia, and frisson. These are distinct, although sometimes overlapping, conditions.

Misophonia is an aversion to sounds such as chewing, coughing, or loud breathing. While misophonia and ASMR appear to lie on opposite ends of a spectrum,[1] a study found that ASMR-capable people scored higher on the Misophonia Questionnaire than matched controls, indicating that they may be more likely to have misophonia than the general population.[4]

Synesthesia involves external sensory stimuli triggering the internal experience of a different sensory modality. Commonly experienced synesthetic associations include perceiving color in response to seeing a letter of the alphabet or sensing a taste when hearing a specific word.[5] Unlike ASMR, synesthesia can be regarded as a blending of senses.

Frisson, also known as musical or aesthetic chills, is the sensation of chills down the spine when listening to peak emotional moments in music.[6] This positive sensation resembles those of ASMR. Neuroimaging in a small sample of ASMR-capable participants (n = 10) found that ASMR and frisson follow similar neurofunctional patterns of activation in areas of reward and emotion, such as the nucleus accumbens, dorsal anterior cingulate cortex, supplementary motor area, and insula.[7–9] However, people with ASMR had increased activation of the medial prefrontal cortex, an area associated with social cognition, social behaviors (eg, grooming), and self-awareness, while people with frisson had reduced activation of this area.[7–11]

KEY FEATURES ELICIT ASMR

Although ASMR triggers can be found in daily life, many people seek online videos designed to elicit ASMR, with the most popular amassing millions of views.[1] Their focus varies widely and includes personal attention, grooming, spa treatments (eg, massage, aromatherapy, haircut, make-up application), eating, cleaning, and exploring household objects. Many videos feature specific trigger sounds, such as whispering, rustling of metallic foil, tapping fingernails, scratching, crisp sounds, keyboard typing, chewing, and lip-smacking. A category of ASMR videos is dedicated to clinical role-playing, which may include whispered narration during simulated medical history-taking and physical examinations.[12] Some simulate an "authentic" experience by using props such as penlights, stethoscopes, ophthalmoscopes, and otoscopes.

ASMR intensity depends on various characteristics of the stimuli.[13] The most effective triggers are about 1 to 5 minutes long, are viewed in a pleasant environment, contain subject matter that is perceived as realistic, and involve diligent exploration of an object. Low-pitched audio triggers may be more reliable at inducing ASMR than visual stimuli.

NEUROLOGIC BASIS STUDIED

Preliminary studies have largely focused on understanding mechanisms by which ASMR elicits positive sensations in capable individuals. Functional magnetic resonance imaging-based investigations suggest that exposure to ASMR media evokes activation in certain brain areas associated with attention, social cognition, and sensory processing.[7,9,14] One study performed with ASMR-capable participants revealed significant activation of the nucleus accumbens (a reward area).[7] A subsequent study compared ASMR-capable participants with controls but did not identify this effect.[14] The dissimilar results could be due to differences in study methods: the former study measured brain activity during the self-reported tingling sensations and the latter measured brain activity throughout the entire ASMR media viewing session.

Other studies have found that ASMR-capable people have significantly less functional connectivity between frontal lobes and sensory-attentional areas compared with controls, suggesting that ASMR-capable people have a reduced capacity to inhibit sensory-emotional experiences.[15,16]

Another study found that ASMR may interfere with certain aspects of executive function, suggesting that people should not engage in ASMR before performing tasks that require focused attention.[17]

PAIN AND MOOD IMPROVEMENTS

Some authors have suggested that ASMR can temporarily improve symptoms of depression,[18] stress,[19,20] and chronic pain[21,22] in a manner similar to meditation and mindfulness.[1]

A study conducted in ASMR-capable individuals found that 80% of participants self-reported in an online questionnaire that ASMR had a positive effect on their mood.[1] Among participants who scored moderate to severe on the Beck Depression Inventory, 69% reported using ASMR to ease symptoms of depression, with many reporting mood improvement. Among respondents with chronic pain, 42% reported that ASMR improved their pain symptoms, and the reduction in pain symptoms was significant ($P < .0005$); the pain-relieving effect was maintained for 3 hours after ASMR ($P = .014$).

ASMR-capable study participants felt significantly more excited ($P = .048$), more calm ($P < .001$), less stressed ($P < .001$), less sad ($P < .001$), and more socially connected ($P < .001$) than non-ASMR participants after watching ASMR media, as measured by the Multi-Affect Indicator scale.[23]

Evidence indicates that ASMR can not only induce subjective positive emotions but also objective physiologic responses. It has been found to decrease heart rate by an average of 3.41 beats per minute ($P = .028$) and increase skin conductance (commonly used to measure emotional arousal)[24] by an average of 0.30 microsiemens ($P = .017$).[25]

Although the anecdotal benefits of improved pain and mood symptoms are promising, further investigation in clinical and laboratory settings is important before ASMR can be considered a therapeutic option.

PLACEBO EFFECT INVESTIGATED

Some researchers have raised the concern that the expectation of positive effects from ASMR media could act as a placebo, causing or enhancing the response. Cash et al[26] investigated this possibility by showing ASMR videos and first telling viewers that they either did or did not contain ASMR triggers. Experienced ASMR users were not only able to identify the presence of ASMR triggers, but they experienced the response only when a true trigger was present. In contrast, ASMR-naive participants were more likely to be influenced by the instructions. The authors concluded that an expectancy effect exists, which may translate to a placebo effect in ASMR-naive people but not in experienced users.

Multiple ASMR videos are available for free

Soon after the release of this study,[26] Hostler et al[27] rebutted some of the conclusions, arguing that the finding that ASMR-capable people reported feeling the response only when genuine triggers were present, regardless of instructions, means that ASMR is not driven by expectancy or placebo effects but is a genuine phenomenon for those able to experience it. They also pointed out that the study was unclear about the differences between ASMR-experienced and ASMR-naive groups; because the ASMR-naive group contained people with no previous exposure to ASMR videos, at least some might have

been capable of experiencing the response associated with triggers. They argued that future research should use standardized tools such as the ASMR checklist[2] to better define study groups of ASMR-capable and noncapable participants.

In a related study, Keizer et al[28] found that people who experience ASMR are more likely than controls to experience other illusory sensory events based on verbal suggestion. Suggestibility is thought to be a factor contributing to the placebo effect,[29] and the finding that ASMR-capable people may be inherently more suggestible merits further research into the potential role of placebo.

REFERENCES

1. **Barratt EL, Davis NJ**. Autonomous sensory meridian response (ASMR): a flow-like mental state. PeerJ 2015; 3:e851. doi:10.7717/peerj.851
2. **Fredborg B, Clark J, Smith SD**. An examination of personality traits associated with autonomous sensory meridian response (ASMR). Front Psychol 2017; 8:247. doi:10.3389/fpsyg.2017.00247
3. **Fredborg BK, Clark JM, Smith SD**. Mindfulness and autonomous sensory meridian response (ASMR). PeerJ 2018; 6:e5414. doi:10.7717/peerj.5414
4. **Janik McErlean AB, Banissy MJ**. Increased misophonia in self-reported autonomous sensory meridian response. PeerJ 2018; 6:e5351. doi:10.7717/peerj.5351
5. **Ward J**. Synesthesia. Annu Rev Psychol 2013; 64:49–75. doi:10.1146/annurev-psych-113011-143840
6. **Harrison L, Loui P**. Thrills, chills, frissons, and skin orgasms: toward an integrative model of transcendent psychophysiological experiences in music. Front Psychol 2014; 5:790. doi:10.3389/fpsyg.2014.00790
7. **Lochte BC, Guillory SA, Richard CAH, Kelley WM**. An fMRI investigation of the neural correlates underlying the autonomous sensory meridian response (ASMR). Bioimpacts 2018; 8(4):295–304. doi:10.15171/bi.2018.32
8. **Blood AJ, Zatorre RJ**. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. Proc Natl Acad Sci USA 2001; 98(20):11818–11823. doi:10.1073/pnas.191355898
9. **del Campo MA, Kehle TJ**. Autonomous sensory meridian response (ASMR) and frisson: mindfully induced sensory phenomena that promote happiness. Int J Sch Educ Psychol 2016; 4(2):99–105. doi:10.1080/21683603.2016.1130582
10. **Mitchell JP, Banaji MR, Macrae CN**. The link between social cognition and self-referential thought in the medial prefrontal cortex. J Cogn Neurosci 2005; 17(8):1306–1315. doi:10.1162/0898929055002418
11. **Grossmann T**. The role of medial prefrontal cortex in early social cognition. Front Hum Neurosci 2013; 7:340. doi:10.3389/fnhum.2013.00340
12. **Ahuja A, Ahuja NK**. Clinical role-play in autonomous sensory meridian response (ASMR) videos: performance and placebo in the digital era. JAMA 2019; 321(14):1336–1337. doi:10.1001/jama.2019.2302
13. **Barratt EL, Spence C, Davis NJ**. Sensory determinants of the autonomous sensory meridian response (ASMR): understanding the triggers. PeerJ 2017 ;5:e3846. doi:10.7717/peerj.3846
14. **Smith SD, Fredborg BK, Kornelsen J**. A functional magnetic resonance imaging investigation of the autonomous sensory meridian response. PeerJ 2019; 7:e7122. doi:10.7717/peerj.7122
15. **Smith SD, Katherine Fredborg B, Kornelsen J**. An examination of the default mode network in individuals with autonomous sensory meridian response (ASMR). Soc Neurosci 2017; 12(4):361–365. doi:10.1080/17470919.2016.1188851
16. **Smith SD, Fredborg BK, Kornelsen J**. Atypical functional connectivity associated with autonomous sensory meridian response: an examination of five resting-state networks. Brain Connect 2019; 9(6):508–518. doi:10.1089/brain.2018.0618
17. **Wang X, Yang X, Sun Y, Su Y**. The influence of autonomous sensory meridian response on individual's executive function. Q J Exp Psychol (Hove) 2020; 73(10):1587-1595. doi:10.1177/1747021820922954
18. **Beck AT, Steer RA, Brown GK**. Manual for the Beck depression inventory–II. San Antonio, TX: Psychological Corporation; 1996.
19. **Beck AT, Epstein N, Brown G, Steer RA**. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988; 56(6):893–897. doi:10.1037//0022-006x.56.6.893
20. **Hofmann SG, Gómez AF**. Mindfulness-based interventions for anxiety and depression. Psychiatr Clin North Am 2017; 40(4):739–749. doi:10.1016/j.psc.2017.08.008
21. **Kabat-Zinn J, Lipworth L, Burney R**. The clinical use of mindfulness meditation for the self-regulation of chronic pain. J Behav Med 1985; 8(2):163–190. doi:10.1007/BF00845519
22. **Hilton L, Hempel S, Ewing BA, et al**. Mindfulness meditation for chronic pain: systematic review and meta-analysis. Ann Behav Med 2017; 51(2):199–213. doi:10.1007/s12160-016-9844-2
23. **Warr P, Bindl UK, Parker SK, Inceoglu I**. Four-quadrant investigation of job-related affects and behaviours. Eur J Work Organ Psychol 2014; 23(3):342–363. doi:10.1080/1359432X.2012.744449
24. **Gatti E, Calzolari E, Maggioni E, Obrist M**. Emotional ratings and skin conductance response to visual, auditory and haptic stimuli. Sci Data 2018; 5:180120. doi:10.1038/sdata.2018.120
25. **Poerio GL, Blakey E, Hostler TJ, Veltri T**. More than a feeling: autonomous sensory meridian response (ASMR) is characterized by reliable changes in affect and physiology. PLoS One 2018; 13(6):e0196645. doi:10.1371/journal.pone.0196645
26. **Cash DK, Heisick LL, Papesh MH**. Expectancy effects in the autonomous sensory meridian response. PeerJ 2018; 6:e5229. doi:10.7717/peerj.5229
27. **Hostler TJ, Poerio GL, Blakey E**. Still more than a feeling: commentary on Cash et al, "Expectancy effects in the autonomous sensory meridian response" and recommendations for measurement in future ASMR research. Multisens Res 2019; 32(6):521–531. doi:10.1163/22134808-20191366
28. **Keizer A, Chang THR, O'Mahony CJ, Schaap NS, Stone KD**. Individuals who experience autonomous sensory meridian response have higher levels of sensory suggestibility. Perception 2020; 49(1):113–116. doi:10.1177/0301006619891913
29. **De Pascalis V, Chiaradia C, Carotenuto E**. The contribution of suggestibility and expectation to placebo analgesia phenomenon in an experimental setting. Pain 2002; 96(3):393–402. doi:10.1016/s0304-3959(01)00485-7

***Address**: Arya B. Mohabbat, MD, Division of General Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905; mohabbat.arya@mayo.edu*

CME MOC

Tom Kai Ming Wang, MBCHB, MD(res), FRACP
Advanced Cardiac Imaging Fellow, Section of Cardiovascular Imaging, Heart Vascular, and Thoracic Institute, Cleveland Clinic

Milind Y. Desai, MD
Staff Cardiologist, Section of Cardiovascular Imaging and Medical Director, Aorta Center, Heart, Vascular, and Thoracic Institute, Cleveland Clinic; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Optimal surveillance and treatment of renal and splenic artery aneurysms

ABSTRACT

Aneurysms of the renal artery and splenic artery are uncommon but clinically important, as they pose a risk of rupture with a high fatality rate. Indications for surgical or endovascular repair are based on aneurysm location and risk factors for rupture, such as aneurysm size, growth, and associated conditions, while medical management is also important. Regular surveillance with imaging is critical before and after intervention to guide treatment.

KEY POINTS

Renal and splenic artery aneurysms are often detected incidentally but can present acutely with dissection, rupture, or both, which are associated with high risk of death and morbidities.

Computed tomographic and magnetic resonance angiography are key to diagnosing and characterizing the aneurysm and the remaining vasculature, while ultrasonography helps in assessment and surveillance. Catheter angiography is the gold standard for diagnosis and allows the opportunity for intervention.

The individual's risk for rupture or dissection determines the need for prophylactic intervention and is based on aneurysm size, location, growth, and other associated conditions and risk factors.

Management strategies include open and laparoscopic surgery and endovascular procedures. Regular imaging surveillance is critical after both diagnosis and interventions.

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

doi:10.3949/ccjm.87a.19140-2

Although aneurysms of the abdominal and thoracic aorta are more common, visceral aneurysms such as those of the renal artery and splenic artery can also form.

In a previous article,[1] we discussed the optimal surveillance strategies and treatment for aneurysm of the thoracic aorta. Here, we address the diagnosis, surveillance, and treatment of renal artery and splenic artery aneurysms.

RENAL ARTERY ANEURYSM

What is the clinical importance of renal artery aneurysm?

Renal artery aneurysms are rare, found in about 0.1% of the population in autopsy studies, although significantly more in cross-sectional imaging or angiography studies.[2] They are categorized by location and morphology into 3 types (**Figure 1**), with important management implications:

- Type 1—saccular aneurysm from the main renal artery or large segmental branch
- Type 2—fusiform aneurysm
- Type 3—intralobar artery aneurysm.[3]

Renal artery aneurysms often present in the sixth decade. Up to 90% of patients have hypertension, and a minority have arterial aneurysms elsewhere.[4] Most younger patients with renal artery aneurysms are women, and about two-thirds have fibromuscular dysplasia.

Symptoms are rare but can include hypertensive crisis, shock, hematuria, flank and abdominal pain, and urinary obstruction, with signs of a palpable abdominal mass and a renal bruit.[2] The natural history is slow growth at 0.06 to 0.09 mm per year. The clinical concern is rupture, which occurs in 3% to 5%, with mortality rates near 10%, although these figures are lower than with other types of visceral aneurysms.[2,5]

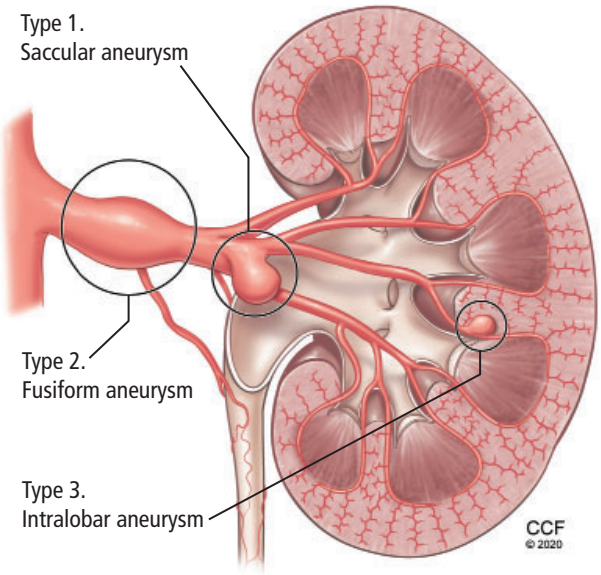


Figure 1. Three types of renal artery aneurysms.

How is renal artery aneurysm assessed?

Renal artery aneurysms are often diagnosed incidentally either during investigation of resistant hypertension or during angiography for another indication. They are detected more often now than in the past because of improvements in imaging.[2]

Up to 90% of patients with a renal artery aneurysm have hypertension

Blood pressure and renal function should be routinely assessed. Accurate measurement is important, as size is directly associated with risk of rupture and need for intervention. Circumferential calcification may be protective.[2]

Duplex ultrasonography is the least expensive imaging modality. Further, it does not expose the patient to radiation, and it can show a dilated vessel with turbulent flow. On the other hand, it has the lowest sensitivity and specificity, and its accuracy depends on operator experience and the patient's body habitus.[6]

Multidetector computed tomographic angiography (CTA) is the most commonly used modality for assessing renal artery aneurysms. Its superior resolution can characterize anatomy using multiplanar reconstructions and volume-rendered imaging (**Figure 2**). On the negative side, it entails the use of nephrotoxic contrast media and radiation exposure.[7]

Magnetic resonance angiography (MRA) has become an alternative to CTA, with comparable accuracy and without radiation, but it is less available and costs more.[6,7]

Catheter angiography remains the gold standard invasive option for diagnosing renal artery aneurysm, allowing assessment of proximal and distal aneurysms, and providing the opportunity for percutaneous interventions.[2]

If a renal artery aneurysm is found but does not meet the criteria for intervention (see below), repeat imaging at 1, 6, and 12 months and then annually has been recommended by some experts, although guidelines are lacking.[2] Ultrasonography can be used for surveillance, and abnormalities can be confirmed by any of the other 3 modalities. Annual surveillance should also be considered after surgery at least initially, and long-term after endovascular therapy.[2,8]

How should renal artery aneurysm be treated?

There are no guidelines for treatment of renal artery aneurysm, and if the aneurysm has not ruptured, indications for prophylactic surgery are based on rupture risk.[2] These include any of the following[4]:

- Large size (> 2 cm)
- Symptoms
- Refractory hypertension with significant renal artery stenosis or thromboembolism
- Childbearing age, for women.

The two main intervention options are surgical and endovascular repair. Acute rupture calls for emergency surgical repair of the aneurysm with renal artery reconstruction or with nephrectomy if the kidneys are not salvageable. For elective management, surgical primary repair or endovascular repair with stents or coil occlusions can be performed for type 1 aneurysm; surgical reconstruction with a vein graft or aortorenal bypass graft typically for type 2 aneurysm; and embolization coils for type 3 aneurysm, with renal preservation whenever possible.[2,9]

Mortality rates during elective interventions have been less than 5% in recent studies, but up to 50% in pregnancy. Surgical complications include occlusion of the renal artery, branch, or graft; renal ischemia; and cardiac events. Endovascular complications include failed procedure (< 10%), thrombosis, embolization, and postembolization syndrome.[2,10] "Postembolization syndrome" refers to a constellation of symptoms including abdominal pain, fever, and at times ileus and pancreatitis that occur in up to 30% of patients after ab-

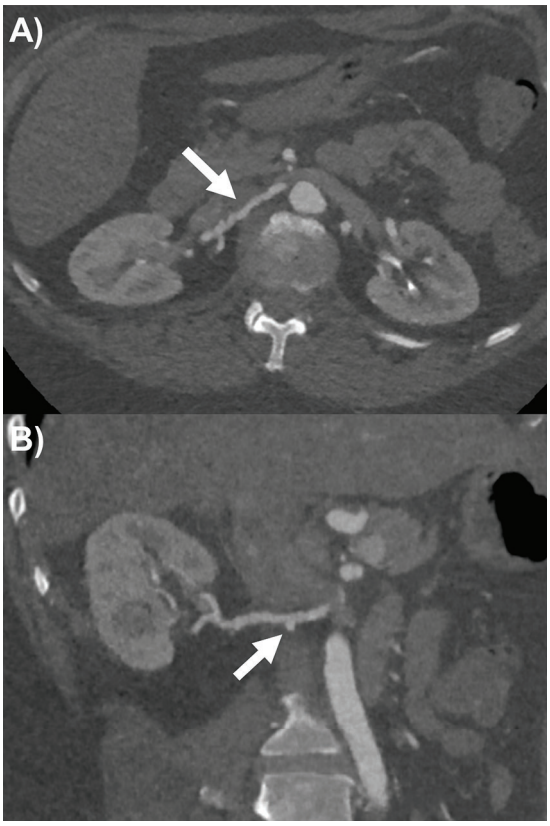


Figure 2. Right renal artery ectasia and beading with focal aneurysm (arrows) by computed tomography angiography in patient with fibromuscular dysplasia on (A) axial slice and (B) double oblique multiplanar reconstruction.

dominal visceral arterial embolization.[11]

Overall, outcomes have improved significantly over time with earlier detection and better planning and interventional techniques.[2,4]

SPLENIC ARTERY ANEURYSM

What is the clinical importance of splenic artery aneurysm?

The prevalence of splenic artery aneurysm is 0.04% to 0.10% at arteriography and autopsy. It is often found incidentally, but accounts for about 60% of visceral arterial aneurysms.[12]

The main risk factors or causes include portal hypertension, liver transplant, pregnancy, pancreatitis, atherosclerosis, hypertension, connective tissue disease (eg, Marfan syndrome), vasculitis, endocarditis, fibromuscular dysplasia, trauma, congenital anomalies, infection, older age, and female sex (especially multiparous women).[11,12]

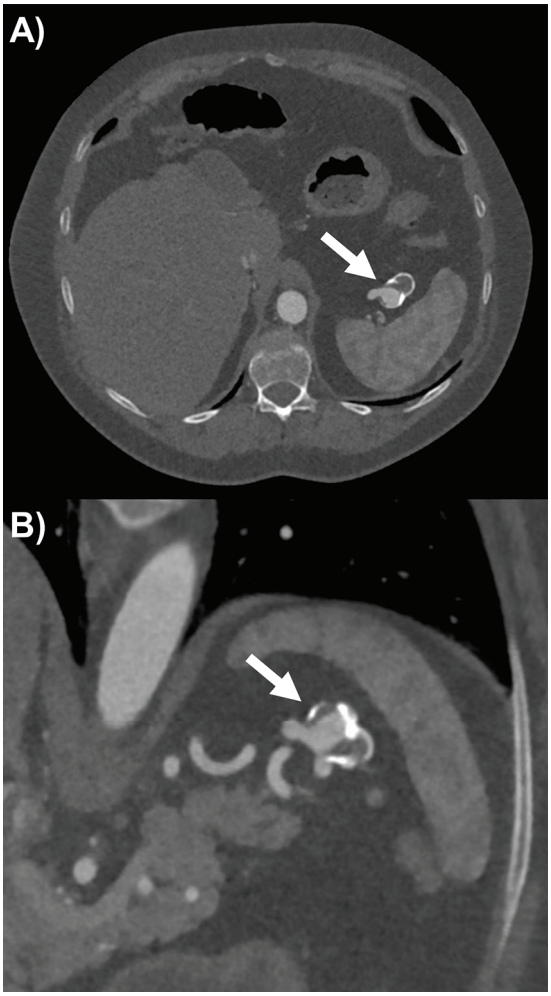


Figure 3. Splenic artery aneurysm (arrows) partially calcified and thrombosed by computed tomography angiography on (A) axial slice and (B) double oblique multiplanar reconstruction showing proximal and distal end of vessel.

Symptoms occur in up to 20% of cases and include upper abdominal pain that can radiate to the shoulder, nausea, vomiting, anorexia, and gastrointestinal bleeding. Rupture presents with acute abdomen, peritoneal bleeding, and shock.[12,13] The risk of rupture is 2% to 10%, with a mortality rate of 25%, and both figures are markedly higher in pregnancy.[12,14]

How should splenic artery aneurysm be evaluated?

Abdominal radiographs rarely detect splenic artery aneurysm. Ultrasonography has some utility as an accessible, low-cost, and radi-

Outcomes have improved with earlier detection and better planning and interventional techniques

ation-free tool, with varying sensitivity for splenic artery aneurysm depending on the operator's experience and the patient's body habitus.[12] Therefore, CTA (**Figure 3**) and MRA are again the preferred imaging modalities for diagnosing splenic artery aneurysms. Both can provide 3-dimensional reconstruction for accurately assessing the aneurysm's dimensions, the neighboring vasculature, and other abdominal pathologies that could contribute to its cause.[12,13] Endoscopic ultrasonography can also assist in the diagnosis and differentiate splenic artery aneurysm from nearby splenic and pancreatic pathology, such as pancreatic pseudocyst.[13,15] Catheter angiography, although invasive, continues to be the gold standard for characterizing the aneurysm's location, size, and extent.[12,13]

If intervention is not planned, surveillance is recommended at 6 months after diagnosis and then annually. Ultrasonography is suitable for surveillance if it can adequately characterize the aneurysm. CTA is also an option.[12]

How should splenic artery aneurysm be managed?

In the absence of guidelines, the main recommended indications for intervention of splenic artery aneurysm are rupture, aneurysm size larger than 2 or 2.5 cm, growth of the aneurysm by 3 to 5 mm or more during surveillance regardless of initial size, symptoms, women of childbearing age, portal hypertension, and planned liver transplant.[11,12]

The treatment options again are open surgery (mandatory in the setting of rupture), endovascular procedures, and laparoscopic surgery.

Open surgical procedures include ligation of the splenic artery or aneurysm and aneurysmectomy with or without splenectomy. Mortality rates are around 1%.

Endovascular options include transcatheter embolization, covered stent-graft insertion, and coil or thrombin injection or both, and these have now become first-line for elective management when anatomically feasible because of lower mortality and complication rates than with open surgery.[16]

Minimally invasive laparoscopic surgery has become an alternative. It is associated with less pain and shorter length of stay compared with open surgery, and it allows splenectomy and distal pancreatectomy to be performed if needed.[13]

Potential complications of intervention include postembolization syndrome, splenic infarction or abscess, and pancreatitis. Therefore, follow-up imaging with CTA or ultrasonography is recommended.[12]

REFERENCES

1. **Wang TKM, Desai MY**. Thoracic aortic aneurysm: optimal surveillance and treatment. Cleve Clin J Med 2020; 87(9):557–568. doi:10.3949/ccjm.87a.19140-1
2. **González J, Esteban M, Andrés G, Linares E, Martínez-Salamanca JI**. Renal artery aneurysms. Curr Urol Rep 2014; 15(1):376. doi:10.1007/s11934-013-0376-z
3. **Rundback JH, Rizvi A, Rozenblit GN, et al**. Percutaneous stent-graft management of renal artery aneurysms. J Vasc Interv Radiol 2000; 11(9):1189–1193. doi:10.1016/s1051-0443(07)61362-1
4. **Coleman DM, Stanley JC**. Renal artery aneurysms. J Vasc Surg 2015; 62(3):779–785. doi:10.1016/j.jvs.2015.05.034
5. **Wayne EJ, Edwards MS, Stafford JM, Hansen KJ, Corriere MA**. Anatomic characteristics and natural history of renal artery aneurysms during longitudinal imaging surveillance. J Vasc Surg 2014; 60(2):448–452. doi:10.1016/j.jvs.2014.03.006
6. **Chadha M, Ahuja C**. Visceral artery aneurysms: diagnosis and percutaneous management. Semin Intervent Radiol 2009; 26(3):196–206. doi:10.1055/s-0029-1225670
7. **Chimpiri AR, Natarajan B**. Renal vascular lesions: diagnosis and endovascular management. Semin Intervent Radiol 2009; 26(3):253–261. doi:10.1055/s-0029-1225665
8. **Gandini R, Morosetti D, Chiocchi M, et al**. Long-term follow-up of endovascular treatment of renal artery aneurysms with covered stent deployment. J Cardiovasc Surg (Torino) 2016;57(5):625–633. pmid:25475915
9. **English WP, Pearce JD, Craven TE, et al**. Surgical management of renal artery aneurysms. J Vasc Surg 2004; 40(1):53–60. doi:10.1016/j.jvs.2004.03.024
10. **Cochennec F, Riga CV, Allaire E, et al**. Contemporary management of splanchnic and renal artery aneurysms: results of endovascular compared with open surgery from two European vascular centers. Eur J Vasc Endovasc Surg 2011; 42(3):340–346. doi:10.1016/j.ejvs.2011.04.033
11. **Al-Habbal Y, Christophi C, Muralidharan V**. Aneurysms of the splenic artery—a review. Surgeon 2010; 8(4):223–231. doi:10.1016/j.surge.2009.11.011
12. **Madoff DC, Denys A, Wallace MJ, et al**. Splenic arterial interventions: anatomy, indications, technical considerations, and potential complications. Radiographics 2005; 25(suppl 1):S191–S211. doi:10.1148/rg.25si055504
13. **Kassem MM, Gonzalez L**. Splenic artery aneurysm. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2020.
14. **Mattar SG, Lumsden AB**. The management of splenic artery aneurysms: experience with 23 cases. Am J Surg 1995; 169(6):580–584. doi:10.1016/s0002-9610(99)80225-6
15. **Fang G, Chen B, Fu W, et al**. Strategies for endovascular treatment of complicated splenic artery aneurysms. J Vasc Surg 2018; 68(3):787–794. doi:10.1016/j.jvs.2017.12.053
16. **Hogendoorn W, Lavida A, Hunink MG, et al**. Open repair, endovascular repair, and conservative management of true splenic artery aneurysms. J Vasc Surg 2014; 60(6):1667–1676.e1. doi:10.1016/j.jvs.2014.08.067

***Address**: Tom Kai Ming Wang, MD, Section of Cardiovascular Imaging, J1-5, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; wangt2@ccf.org*

REVIEW

Cristina I. Pravia, MD
Assistant Professor, Department of Internal Medicine
University of Miami Miller School of Medicine,
Miami, FL

Merline Benny, MD
Assistant Professor, Department of Pediatrics,
University of Miami Miller School of Medicine,
Miami, FL

Long-term consequences of prematurity

ABSTRACT

Due to a shortened period of in utero organ development, premature infants are at higher risk of chronic respiratory, cardiac, renal, and endocrine system disorders later in life. With more premature babies being born and more of them surviving, internists and primary care practitioners should be aware of their patient's birth history and of the potential long-term effects of prematurity. Such understanding can lead to early detection of disease and targeted lifestyle modifications.

KEY POINTS

About 10% of live births are premature, and rates are increasing.

Survivors of premature birth may have later adverse health effects related to organs failing to achieve optimal development.

Increased risk of cardiovascular, metabolic, and kidney diseases suggest that risk factors should be monitored and patients counseled on maintaining a healthy lifestyle.

Pulmonary vulnerabilities warrant asthma control as needed, keeping current on influenza and *Pneumococcus* vaccinations, and avoiding smoking.

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

doi:10.3949/ccjm.87a.19108

Medical attention to premature babies usually focuses exclusively on immediate survival and monitoring of problems in early childhood. As advancing technology has allowed more early neonates to survive with apparently good outcomes, long-term health consequences of prematurity are less often considered, although evidence indicates that they can be significant.

This article reviews lifelong pulmonary, renal, cardiac, neurologic, and endocrine vulnerabilities associated with prematurity and suggests recommendations for routine management of adults who were born premature.

PREMATURITY: DEFINITIONS AND EPIDEMIOLOGY

Prematurity is defined by the World Health Organization[1] as birth occurring before 37 weeks of gestation, with the following categories:

- Extremely preterm (< 28 weeks)
- Very preterm (28–32 weeks)
- Moderate to late preterm (32–36 weeks).

Prematurity is the main cause of neonatal death globally, accounting for 16% of deaths of children under age 5 in 2014. That year, the worldwide preterm birth rate was 10.6%, or nearly 15 million infants.[1]

US figures are as follows:

- 10.0% of live births occurred before 37 weeks of gestation (2018 data)[2]
- Preterm birth rates (< 37 weeks of gestation) were 13.6% in Black women, 9.5% in Hispanic women, and 9.1% in non-Hispanic White women (2016 data)[3]
- 2.8% of live births occurred before 34 weeks of gestation (2016 data)[3]
- 0.7% of births occurred before 28 weeks of gestation (2012 data).[4]

A 2013 meta-analysis found that Black women had twice the rate of premature births compared with White women after adjusting for potential confounders such as socioeconomic status, maternal age, and parity.[5]

Rates of prematurity in the United States have been increasing as more women become pregnant at older ages and as assisted reproductive technologies more often result in multiple gestations and higher-risk pregnancies.

WITH ADVANCES, IMPROVED SHORT-TERM SURVIVAL

Survival rates for premature infants dramatically improved in the 1980s and 1990s thanks to adoption of surfactant, antenatal corticosteroids, and noninvasive ventilation.[6] In general, better survival has been accompanied by better outcomes, ie, avoiding major impairments.[7]

Morbidity and mortality rates increase with shorter gestational age, with girls tending to fare better than boys.[8] In 2012, rates of survival to hospital discharge in the extremely premature ranged from 9% at 22 weeks to 94% at 28 weeks for those treated at an academic medical center that had expertise in high-risk obstetrics and specialized neonatal intensive care units.[4]

Prematurity is the main cause of neonatal death globally

HIDDEN LONG-TERM HEALTH EFFECTS

Despite improvements in short-term survival, early antenatal and postnatal exposures may have lifelong health consequences, a concept known as "developmental programming" or the Barker hypothesis.[9,10] As the third trimester of pregnancy (> 28 weeks) is a period of rapid organ growth and maturation, premature infants are born before major organ development is complete. Survivors of premature birth may have later adverse health effects related to organs failing to achieve optimal development or undergoing more rapid decline.[10]

In addition to specific organ vulnerabilities, oxidative stress of the altered environment at birth causes telomere length shortening and DNA methylation, leading to epigenetic modifications that may appear later in life.[11] The hypothalamic-pituitary-adrenal axis is overly stimulated as these babies face early adaptation to the outside world, possibly leading to more rapid "wear-and-tear."[12]

LATER SURVIVAL IMPACTED

As the first generation of survivors of extremely preterm birth are now entering middle age, primary care providers should be aware of the disease burden they may carry. Unfortunately, research into the long-term consequences of prematurity is limited; many of the population-based studies are based on Scandinavian birth and morbidity rates before the era of antenatal steroids and continuous positive airway therapy.

A 2011 Swedish national cohort study of people born between 1973 and 1979 who survived to 1 year found that preterm birth was associated with increased mortality in early childhood (ages 1–5 years) and young adulthood (ages 18–36), even in those born late preterm (34 to 36 weeks).[13] In a follow-up study extending the population to those born up to 1997, the prevalence of survival without any major comorbidities at ages 18 to 43 years was 55% of those born preterm (22% of those born extremely preterm, 49% of those born very preterm, and 58% of those born late preterm) vs 63% of those born full-term.[14]

Effects of prematurity on individual organ systems are summarized in **Table 1** and described in more detail below.

PULMONARY SYSTEM

Impaired vascular and alveolar development

Multiplication of lung capillaries and development of the air-blood barrier occur before the 26th week of gestation, but most alveolar development occurs in the last trimester.[15] Preterm birth is associated with alveolar simplification and impaired pulmonary vascular development and is a risk factor for neonatal and childhood pulmonary vascular disease. Strategies to reduce lung injury, including noninvasive ventilation, improve long-term outcomes.[4] However, aberrant lung vascularization as a consequence of premature birth adversely affects the lung's future vascular development. It may also stress the myocardium, with right ventricular dysfunction causing pulmonary artery hypertension later in life, especially with exposure to other factors that

TABLE 1

Effects of prematurity on organ systems, and management recommendations

Organ system	Increased risks	Management
Pulmonary	Obstructive disease, pulmonary hypertension	Evaluate previous asthma diagnosis
		Consider baseline pulmonary function testing
		Avoid smoking, maintain healthy weight, promote exercise
		Keep current on influenza and *Pneumococcus* vaccinations
Renal	Chronic kidney disease	Monitor blood pressure regularly
		Avoid nephrotoxins
		Control blood pressure (consider an angiotensin-converting enzyme inhibitor if a hypertension medication is needed)
		Limit salt intake
		Consider periodic urine microalbumin screening, renal ultrasonography
Cardiovascular	Hypertension, ischemic heart disease, congestive heart failure, peripheral vascular disease	Monitor blood pressure regularly
		Avoid smoking, maintain healthy weight, promote exercise
		Consider baseline echocardiogram with appropriate cardiovascular risk assessment
Endocrine	Diabetes, metabolic syndrome, obesity, osteoporosis	Monitor blood glucose, body mass composition, lipids
		Maintain healthy body weight and abdominal girth
		Ensure appropriate calcium and vitamin D supplementation
		Promote weight-bearing exercise
		Limit medications associated with causing metabolic abnormalities, dyslipidemia, worsening bone density
Central nervous system	Autism, mood disorders, intellectual disabilities	Be alert to need for early evaluation and support

further impair heart function.[16]

Premature infants who have pulmonary vascular disease in the first week of life are more likely to develop bronchopulmonary dysplasia and pulmonary hypertension in the postpartum period.[17] A Swedish population-based study found that survivors of preterm birth into childhood and young adulthood had a higher risk of pulmonary hypertension, even after adjusting for congenital heart defects and pulmonary diseases.[18]

Preterm birth, irrespective of whether babies require neonatal intensive care, is associated with more respiratory symptoms, partially reversible airflow obstruction, and abnormal thoracic imaging in childhood and young adulthood compared with those born at term. Premature infants have decreased alveolar volume and greater than normal age-related decline in lung function during life. Failing to reach optimal peak lung function in early adulthood results in crossing the threshold for respiratory symptoms early even if the rate of lung function decline is normal.[15,19]

Increased asthma risk, poorer lung function

Prematurely born individuals have a 4-fold higher incidence of asthma, but it is important to differentiate between true asthma (ie, with airway inflammation and responsiveness to bronchodilators) and milder forms of bronchopulmonary dysplasia found in extremely low-birth-weight infants born in this century.[15,20] Recently born premature babies have fewer but larger alveoli, with less surface area for gas exchange; they do not have ventilator-associated barotrauma as did the earlier generations of premature babies. Most infants born at 24 weeks of gestation suffer some degree of bronchopulmonary dysplasia, but this incidence significantly decreases to less than 40% in those born after 28 weeks.[6,18]

Children born preterm have a higher risk of wheezing disorders[21] including early and persistent wheezing[22] compared with children born at term. Kotecha et al[23] found a deficit of 7.2% in predicted forced expiratory volume in the first second of expiration (FEV_1) for preterm-born children without bronchopulmonary dysplasia compared with children born at term. Even late-preterm infants (33–36 weeks of gestation) exhibit respiratory abnormalities, including increased residual volume, lower respiratory compliance, and decreased expiratory flow ratio.[24] Preterm birth is associated with poorer lung function and airflow impairment in adult life, with the strongest association among those born the most immature, independent of underlying pregnancy disorders or risk factors (eg, maternal smoking in pregnancy or socioeconomic status).[25]

Early antenatal and postnatal exposures may have lifelong health implications

RENAL SYSTEM

Nephrogenesis interrupted

Nephrogenesis continues through 34 to 36 weeks of gestation, with more than half of nephrons formed in the third trimester.[10,26] Preterm babies have fewer nephrons and more abnormal glomeruli; as a result, the nephrons they do have must work harder to compensate.

Adults who were born prematurely are at higher risk of focal segmental glomerulosclerosis.[27,28] Their macrovasculature is anatomically different, with normal elastin replaced by less flexible collagen, resulting in blood vessel stiffening and a higher risk of hypertension.[13,29] In addition, premature infants tend to have endothelial damage, leading to higher vascular resistance, increased glomerular capillary pressure, sodium retention, and fewer glomeruli at baseline.[13,29] A potentially confounding factor is exposure to nephrotoxic medications while in neonatal intensive care.

Higher prevalence of kidney disease

In a Swedish study[13] with 40-year follow-up, adults born premature (< 37 weeks) had twice the risk of chronic kidney disease compared with term controls. Those born early term (37–38 weeks) had a 1.3-fold higher risk, and those born extremely premature (< 28 weeks) had a 3-fold risk, with risk being especially high in women. Despite subclinical kidney dysfunction and even 25% to 50% loss in glomerular filtration rate, tubular secretion of creatinine can maintain plasma creatinine in the normal range.[28,29]

A review of cardiorenal syndrome in preterm infants indicated that adults born preterm enter midlife with subclinical early chronic kidney disease (stage 2–3), and even patients with milder disease (stage 1–2) have a 25- to 100-fold higher risk of cardiovascular events.[29]

Monitoring may be useful

No medical society guidelines cover screening in adults who were born prematurely, although some experts suggest checking cystatin and urine microalbumin and performing renal ultrasonography.[28,29] Although cystatin is more sensitive than creatinine for diagnosing abnormalities in kidney function, these tests can be expensive, and no prospective studies exist to show their validity in detecting early disease. In addition, urine microalbumin can be seen in benign situations.

CARDIOVASCULAR SYSTEM

Cardiac and vascular insults

Premature infants are exposed to hostile intrauterine and extrauterine conditions that can adversely affect the heart and vascular tree. Evidence from animal models and small studies of preterm infants shows that preterm birth interferes with normal cardiac development with potential consequences into childhood and adulthood.[30–32]

Vascular abnormalities may be evident by adolescence or early adult life, including an elevated pulse-wave velocity, increased carotid intima-media thickness,[33] aortic narrowing and stiffness, and impaired microvascular function. Increased left ventricular mass with increased wall thickness and reduced luminal diameter has been reported in young adults who were born preterm.[34] The heart of a preterm infant develops under different conditions in the neonatal period than it would have encountered in utero and experiences higher pressure and volume loads.

Studies have found indicators of cardiac and vascular impairments:

Cardiac dysfunction. Cardiac imaging studies in those born preterm show biventricular hypertrophy beginning in early postnatal development, and right ventricular dysfunction and reduced ejection fraction in early adulthood.[35]

Otherwise healthy adults born preterm demonstrate a blunted cardiac response to exercise, suggesting early cardiac dysfunction.[16] Huckstep et al[36] found impaired left ventricular response to physiologic stress in preterm-born young adults. The differences in cardiovascular response to exercise of normotensive young adults born preterm compared to term-born controls were striking; ejection fraction at 60% exercise capacity was 6.7% lower in the preterm group, which further declined to a 7.3% difference at 80% exercise capacity.

Hypertension. Prematurity confers a higher risk of developing hypertension. Toddlers born extremely preterm tend to have systolic blood pressure above the 90th percentile.[27] In young adults born preterm, the estimated difference in office-measured systolic pressure was 3.8 mm Hg higher than in term-born controls.[37] These differences appear small but are significant, given that at the population level, a 2 mm Hg reduction in diastolic pressure is estimated to result in a 6% reduction in the risk of coronary heart disease and a 15% reduction in risk of cerebrovascular events.[38]

Adolescents born preterm exhibit an imbalance in the circulatory renin-angiotensin system compared with term-born peers.[39] In a case series of 6 infants (born at 23–29 weeks of gestation) with hypertension associated with severe chronic lung injury, captopril, an angiotensin-converting enzyme inhibitor, improved respiratory and cardiac indices 5 to 7 weeks after birth.[40]

Ischemic heart disease. A population-based cohort study found that adults ages 30 to 43 who were born preterm (gestational age < 37 weeks) have a 53% increased relative risk of ischemic heart disease compared with a full-term birth cohort, and those born early term (37 to 38 weeks) have a 19% increased risk.[41]

Heart failure. Large epidemiologic studies in children and young adults have found that preterm birth is associated with an increased risk of heart failure. Individuals born extremely preterm (< 28 weeks) had a 17-fold increased risk of heart failure compared with those born at term (> 37 weeks), and very preterm infants (28–31 weeks) had a more than 3-fold risk increase.[42]

CENTRAL NERVOUS SYSTEM

The third trimester of pregnancy brings rapid brain development with axonal proliferation, myelination, and increased volume of gray and white matter.[6,43] Very preterm infants (< 32 weeks of gestation) have a smaller hippocampus and frontotemporal regions than term infants.[36,44]

The third trimester of pregnancy is a period of rapid organ growth and maturation

During infancy, babies born premature have a higher risk of cerebral palsy, cognitive disability, and seizure disorder. The subsequent hypoxia and periventricular leukomalacia alter the formation of the prefrontal cortex and its neural network, possibly leading to behavioral symptoms.

Several neurologic conditions have links to prematurity:

Autism. Children born premature have higher rates of autism spectrum disorder: the prevalence in the United States is 1.5% overall but is 7.1% in infants born at 23 to 27 weeks of gestation.[43] Differences in the disorder have also been detected. Chen et al[45] found that children with autism spectrum disorder born prematurely had better peer relationships but worse nonverbal behaviors than term children with the disorder.

Mood disorders. Premature-born children tend to develop anxiety, depression, attention deficit-hyperactivity disorder, and sleep disorders, which may be diagnosed at an early

age and may persist into adulthood.[10,43,46] Systematic reviews of mental health outcomes indicate that long-term risks of depression and anxiety in preterm and low-birth weight babies are 4 times higher than in those born full-term,[10] with even babies born between 36 and 38 weeks having a higher risk of developing inattention and hyperactivity.

Intellectual disability. Children born very preterm have cognitive IQ scores 12 points lower than term babies.[20] Lifelong neurodevelopmental complications are inversely correlated with gestational age at birth; in an Australian study, disability-free survival (disability defined as intellectual disability, autism, or cerebral palsy) was 42.4% for those born at 24 weeks, 78.3% for those born at 28 weeks, and 97.2% for those born full-term. Birth weight, Apgar score, socioeconomic background, and maternal ethnicity were prognostic indicators.[47]

ENDOCRINE SYSTEM

Disorders reflecting disruption of the endocrine system are also likelier to be found in adults who were born premature:

The first generation of survivors of extremely preterm birth are now entering middle age

Diabetes. Premature infants have a higher risk of eventually developing type 1 and type 2 diabetes and insulin resistance.[44,48,49] By age 18 to 43, the risk for having type 1 diabetes was 1.2 times higher, and for type 2 diabetes 1.5 times higher, than in adults born full-term.[50] Possible mechanisms include abnormal fat deposition, decreased beta cell formation (which typically occurs in the third trimester), and an altered T-cell response, leading to the autoimmune etiology of type 1 diabetes.[50]

Obesity. Fetal fat distribution, which typically begins in the second trimester of pregnancy with deposition in the head and neck area, followed by the trunk and upper and lower extremities, is radically altered. Babies born before the third trimester, a time when subcutaneous fat is rapidly deposited, tend to be leaner and have lower fat stores.[48] In the first months of life, premature infants are typically placed on high-calorie diets to try to "catch up," thus causing an adiposity rebound effect.

Studies show that fat deposited too quickly the first year of life predicts future adult obesity.[22] Fat distribution is altered in preterm babies mostly with deposits in visceral fat rather than subcutaneous fat, as seen in healthy term neonates.[51] Breukhoven et al[52] found that fat mass, truncal fat, and limb fat mass were higher in young adults who were born premature. Visceral fat accumulation is highly inflammatory and excess fatty acid efflux damages healthy tissue, especially in the liver and pancreas of those born with extremely low birth weight.[48] Breastfeeding can help reduce the risk of obesity in low birth-weight babies.

Metabolic syndrome. Adults born preterm were 2.5 to 4 times more likely than those born full-term to meet criteria for metabolic syndrome. This held true not just for very premature infants but also for those born late preterm.[53,54] Evidence on effects of prematurity on lipid levels is mixed: some studies show lower levels of low-density lipoprotein levels in adults born preterm and others higher levels.[44,54]

Osteoporosis. Conflicting data surround the risk of osteoporosis in preterm-born adults. Placental transfer of calcium, magnesium, and phosphorus tends to occur in the last trimester.[55] Once born, premature neonates have restricted spontaneous movement and hence, less mechanical stimulation of bone.[56] Unfortified breast milk and parenteral nutrition do not include enough mineral content for appropriate bone formation. Bone mass is reduced in children born premature, especially those who had a low birth weight (< 1,500 g). This may correlate with higher fracture risk and osteoporosis in adulthood.[55]

BIRTH HISTORY SHOULD BE PART OF THE MEDICAL RECORD

Considering that prematurity is common and evidence for long-term health sequelae is strong, birth history should become a routine part of the patient medical record. It should include birth weight, gestational age, length of stay in neonatal intensive care, maternal smoking history, and perinatal complications (eg, the need for mechanical ventilation).[57] Unfortunately, such questions are only rarely asked in an adult primary or specialty care clinic. **Table 2** provides questions to ask adults about prematurity.

A British Thoracic Society survey[58] found that few adult respiratory physicians routinely consider early-life factors during patient assessment. Even when asked, acquiring such information can be a challenge; unless patients are accompanied by parents, they are unlikely to know some of these details. Studies have found that maternal recall of children's birth history provides accurate information.[59,60] Patients themselves usually know at least if they were born very premature, if from no other source than family discussion.

A more systematic method for recording neonatal data in adult patient records would be preferable; ICD-10 codes and linked electronic datasets in the medical record may be used to clarify and maintain this information through the continuum of pediatric to adult care. As pediatricians manage the early complications related to prematurity, they should play a role in keeping a patient's detailed medical history. Diagnoses acquired in childhood, such as asthma, should always be reconsidered in adulthood.

PROMOTE A HEALTHY LIFESTYLE

Birth history is nonmodifiable, but multiple other risk factors for future disease can be changed. Diet and exercise habits are especially important to review in patients who were born premature. Several studies have indicated that premature-born adults may not have well-rounded diets and may limit exercise, increasing risk of osteoporosis and cardiometabolic disease.[61] A Finnish study found that premature-born young women had a less nutritious diet than women born full-term or men born either premature or full-term.[62] Another study found that young adults who were born very low-birth weight had lower consumption of fruits, vegetables, and milk products.[63] A study evaluating physical fitness found that young adults born prematurely demonstrated lower muscular fitness than controls.[64]

Early focus on lifestyle modifications is key. Patients born prematurely should be educated about cardiovascular exercise, strength training, tobacco avoidance, good nutrition, and age-based immunizations. Primary care providers should encourage healthy habits at a young age to combat the future risk of high blood pressure, metabolic syndrome, impaired glucose regulation, reduced pulmonary function, and poorer bone health, and they should help patients understand the importance of normal blood pressure, body mass index, blood glucose levels, and cholesterol levels.

TABLE 2

Questions for acquiring a detailed history for premature-born adults

Were you born premature? If yes, do you know why?
What was your gestational age?
How much did you weigh at birth?
Were you on mechanical ventilation? If yes, for how long?
Did you have any surgeries during the neonatal period?
How long did you stay in the neonatal intensive care unit?
What was the nature and extent of any chronic disabilities after discharge from neonatal intensive care?
Did you have any other complications?
Do you have a history of long-term medication use?

WOULD SPECIAL SCREENING BE USEFUL?

There are currently no guidelines regarding care of adults who were born premature or low birth weight. Suggestions have been made to screen using echocardiography, computed tomography calcium score testing, incentive spirometry, renal ultrasonography, and specialized blood work to gauge disease risk. However, providers would be faced with making clinical decisions that may not be evidence-based. More population-based research is needed, especially in children and adults born this century, as their needs have changed compared with those born before the 1990s.

Prematurely born individuals have a 4-fold higher incidence of asthma

PREVENTING FUTURE PREMATURITY

As fertility treatments become ever more successful, multiple births, births to older mothers, and prematurity are an ongoing public health issue. Prematurity may even be considered a chronic and multigenerational condition: small studies have found that adult women who were born preterm have a higher risk of having pre-

mature births, independent of hypertension, diabetes, and abnormal fat distribution.[51,65] Preventing prematurity is important; newer practice guidelines have led to a decrease of elective labor inductions before the 39th week of gestation in uncomplicated pregnancies.[66]

REFERENCES

1. **Chawanpaiboon S, Vogel JP, Moller AB, et al**. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health 2019; 7(1):e37–e46. doi:10.1016/S2214-109X(18)30451-0
2. **Martin JA, Hamilton BE, Osterman MJK**. Births in the United States, 2018. NCHS Data Brief 2019; (346):1–8. https://www.cdc.gov/nchs/products/databriefs/db346.htm. Accessed November 16, 2020.
3. **Martin JA, Osterman MJK**. Describing the increase in preterm births in the United States, 2014–2016. NCHS Data Brief 2018; (312):1–8. https://www.cdc.gov/nchs/data/databriefs/db312.pdf. Accessed November 16, 2020.
4. **Stoll BJ, Hansen NI, Bell EF, et al**. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012. JAMA 2015; 314(10):1039–1051. doi:10.1001/jama.2015.10244
5. **Schaaf JM, Liem SM, Mol BW, Abu-Hanna A, Ravelli AC**. Ethnic and racial disparities in the risk of preterm birth: a systematic review and meta-analysis. Am J Perinatol 2013; 30(6):433–450. doi:10.1055/s-0032-1326988
6. **Glass HC, Costarino AT, Stayer SA, Brett CM, Cladis F, Davis PJ**. Outcomes for extremely premature infants. Anesth Analg 2015; 120(6):1337–1351. doi:10.1213/ANE.0000000000000705
7. **Serenius F, Ewald U, Farooqi A, et al**. Neurodevelopmental outcomes among extremely preterm infants 6.5 years after active perinatal care in Sweden. JAMA Pediatr 2016; 170(10):954–963. doi:10.1001/jamapediatrics.2016.1210
8. **Zisk JL, Genen LH, Kirkby S, Webb D, Greenspan J, Dysart K**. Do premature female infants really do better than their male counterparts? Am J Perinatol 2011; 28(3):241–246. doi:10.1055/s-0030-1268239
9. **Barker DJ**. The fetal and infant origins of adult disease. BMJ 1990; 301(6761):1111. doi:10.1136/bmj.301.6761.1111
10. **Raju TNK, Pemberton VL, Saigal S, et al**. Long-term healthcare outcomes of preterm birth: an executive summary of a conference sponsored by the National Institutes of Health. J Pediatr 2017; 181:309–318.e1. doi:10.1016/j.jpeds.2016.10.015
11. **Bayman E, Drake AJ, Piyasena C**. Prematurity and programming of cardiovascular disease risk: a future challenge for public health? Arch Dis Child Fetal Neonatal Ed 2014; 99(6):F510–F514. doi:10.1136/archdischild-2014-306742
12. **Sullivan MC, Winchester SB, Msall ME**. Prematurity and cardiovascular risk at early adulthood. Child Care Health Dev 2019; 45(1):71–78. doi:10.1111/cch.12616
13. **Crump C, Sundquist K, Sundquist J, Winkleby MA**. Gestational age at birth and mortality in young adulthood. JAMA 2011; 306(11):1233–1240. doi:10.1001/jama.2011.1331
14. **Crump C, Winkleby MA, Sundquist J, Sundquist K**. Prevalence of survival without major comorbidities among adults born prematurely. JAMA 2019; 322(16):1580–1588. doi:10.1001/jama.2019.15040
15. **Bolton CE, Bush A, Hurst JR, Kotecha S, McGarvey L**. Lung consequences in adults born prematurely. Thorax 2015; 70(6):574–580. doi:10.1136/thoraxjnl-2014-206590
16. **Goss KN, Beshish AG, Barton GP, et al**. Early pulmonary vascular disease in young adults born preterm. Am J Respir Crit Care Med 2018; 198(12):1549–1558. doi:10.1164/rccm.201710-2016OC
17. **Mourani PM, Sontag MK, Younoszai A, et al**. Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. Am J Respir Crit Care Med 2015; 191(1):87–95. doi:10.1164/rccm.201409-1594OC
18. **Naumburg E, Söderström L**. Increased risk of pulmonary hypertension following premature birth. BMC Pediatr 2019; 19(1):288. doi:10.1186/s12887-019-1665-6
19. **Bertagnolli M, Luu TM, Lewandowski AJ, Leeson P, Nuyt AM**. Preterm birth and hypertension: is there a link? Curr Hypertens Rep 2016; 18(4):28. doi:10.1007/s11906-016-0637-6
20. **Luu TM, Rehman Mian MO, Nuyt AM**. Long-term impact of preterm birth: neurodevelopmental and physical health outcomes. Clin Perinatol 2017; 44(2):305–314. doi:10.1016/j.clp.2017.01.003
21. **Been JV, Lugtenberg MJ, Smets E, et al**. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. PLoS Med 2014; 11(1):e1001596. doi:10.1371/journal.pmed.1001596
22. **Kotecha SJ, Watkins WJ, Lowe J, Granell R, Henderson AJ, Kotecha S**. Comparison of the associations of early-life factors on wheezing phenotypes in preterm-born children and term-born children. Am J Epidemiol 2019; 188(3):527–536. doi:10.1093/aje/kwy268
23. **Kotecha SJ, Edwards MO, Watkins WJ, et al**. Effect of preterm birth on later FEV1; a systematic review and meta-analysis. Thorax 2013; 68(8):760-766. doi:10.1136/thoraxjnl-2012-203079
24. **Kotecha SJ, Dunstan FD, Kotecha S**. Long term respiratory outcomes of late preterm-born infants. Semin Fetal Neonatal Med 2012; 17(2):77-81. doi:10.1016/j.siny.2012.01.004
25. **Näsänen-Gilmore P, Sipola-Leppänen M, Tikanmäki M, et al**. Lung function in adults born preterm. PLoS One 2018; 13(10):e0205979. doi:10.1371/journal.pone.0205979
26. **Stritzke A, Thomas S, Amin H, Fusch C, Lodha A**. Renal consequences of preterm birth. Mol Cell Pediatr 2017; 4(1):2. doi:10.1186/s40348-016-0068-0
27. **Eriksson JG, Salonen MK, Kajantie E, Osmond C**. Prenatal growth and CKD in older adults: longitudinal findings from the Helsinki birth cohort study, 1924–1944. Am J Kidney Dis 2018; 71(1):20–26. doi:10.1053/j.ajkd.2017.06.030
28. **Carmody JB, Charlton JR**. Short-term gestation, long-term risk: prematurity and chronic kidney disease. Pediatrics 2013; 131(6):1168–1179. doi:10.1542/peds.2013-0009
29. **DeFreitas MJ, Katsoufis CP, Abitbol CL**. Cardio-renal consequences of low birth weight and preterm birth. Progress in Pediatric Cardiology 2016; 41:83–88. doi:10.1016/j.ppedcard.2016.01.012
30. **Lewandowski AJ, Augustine D, Lamata P, et al**. Preterm heart in adult life: cardiovascular magnetic resonance reveals distinct differences in left ventricular mass, geometry, and function. Circulation 2013; 127(2):197–206. doi:10.1161/CIRCULATIONAHA.112.126920
31. **Chehade H, Simeoni U, Guignard JP, Boubred F**. Preterm birth: long term cardiovascular and renal consequences. Curr Pediatr Rev 2018; 14(4):219–226. doi:10.2174/1573396314666180813121652
32. **Benny M, Hernandez DR, Sharma M, et al**. Neonatal hyperoxia exposure induces aortic biomechanical alterations and cardiac dysfunction in juvenile rats. Physiol Rep 2020; 8(1):e14334. doi:10.14814/phy2.14334
33. **Hovi P, Turanlahti M, Strang-Karlsson S, et al**. Intima-media thickness and flow-mediated dilatation in the Helsinki study of very low birth weight adults. Pediatrics 2011; 127(2):e304–e311. doi:10.1542/peds.2010-2199
34. **Kowalski RR, Beare R, Doyle LW, Smolich JJ, Cheung MM; Victorian Infant Collaborative Study Group**. Elevated blood pressure with reduced left ventricular and aortic dimensions in adolescents born extremely preterm. J Pediatr 2016; 172:75–80.e2. doi:10.1016/j.jpeds.2016.01.020
35. **Aye CYL, Lewandowski AJ, Lamata P, et al**. Disproportionate cardiac hypertrophy during early postnatal development in infants born preterm. Pediatr Res 2017; 82(1):36–46. doi:10.1038/pr.2017.96
36. **Huckstep OJ, Williamson W, Telles F, et al**. Physiological stress elicits impaired left ventricular function in preterm-born adults. J Am Coll Cardiol 2018; 71(12):1347–1356. doi:10.1016/j.jacc.2018.01.046
37. **de Jong F, Monuteaux MC, van Elburg RM, Gillman MW, Belfort MB**. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. Hypertension 2012; 59(2):226–234. doi:10.1161/HYPERTENSIONAHA.111.181784

38. **Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH**. Implications of small reductions in diastolic blood pressure for primary prevention. Arch Intern Med 1995; 155(7):701–709. pmid:7695458
39. **South AM, Nixon PA, Chappell MC, et al**. Association between preterm birth and the renin-angiotensin system in adolescence: influence of sex and obesity. J Hypertens 2018; 36(10):2092–2101. doi:10.1097/HJH.0000000000001801
40. **Sehgal A, Krishnamurthy MB, Clark M, Menahem S**. ACE inhibition for severe bronchopulmonary dysplasia—an approach based on physiology. Physiol Rep 2018; 6(17):e13821. doi:10.14814/phy2.13821
41. **Crump C, Howell EA, Stroustrup A, McLaughlin MA, Sundquist J, Sundquist K**. Association of preterm birth with risk of ischemic heart disease in adulthood. JAMA Pediatr 2019; 173(8):736–743. doi:10.1001/jamapediatrics.2019.1327
42. **Carr H, Cnattingius S, Granath F, Ludvigsson JF, Edstedt Bonamy AK**. Preterm birth and risk of heart failure up to early adulthood. J Am Coll Cardiol 2017; 69(21):2634–2642. doi:10.1016/j.jacc.2017.03.572
43. **Ream MA, Lehwald L**. Neurologic consequences of preterm birth. Curr Neurol Neurosci Rep 2018; 18(8):48. doi:10.1007/s11910-018-0862-2
44. **Raju TNK, Buist AS, Blaisdell CJ, Moxey-Mims M, Saigal S**. Adults born preterm: a review of general health and system-specific outcomes. Acta Paediatr 2017; 106(9):1409–1437. doi:10.1111/apa.13880
45. **Chen LW, Wang ST, Wang LW, et al**. Behavioral characteristics of autism spectrum disorder in very preterm birth children. Mol Autism 2019; 10:32. doi:10.1186/s13229-019-0282-4
46. **Roggero P, Giannì ML, Garbarino F, Mosca F**. Consequences of prematurity on adult morbidities. Eur J Intern Med 2013; 24(7):624–626. doi:10.1016/j.ejim.2013.01.011
47. **Bourke J, Wong K, Srinivasjois R, et al**. Predicting long-term survival without major disability for infants born preterm. J Pediatr 2019; 215:90–97.e1. doi:10.1016/j.jpeds.2019.07.056
48. **Crane JD, Yellin SA, Ong FJ, et al**. ELBW survivors in early adulthood have higher hepatic, pancreatic and subcutaneous fat. Sci Rep 2016; 6:31560. doi:10.1038/srep31560
49. **Crump C, Winkleby MA, Sundquist K, Sundquist J**. Risk of diabetes among young adults born preterm in Sweden. Diabetes Care 2011; 34(5):1109–1113. doi:10.2337/dc10-2108
50. **Crump C, Sundquist J, Sundquist K**. Preterm birth and risk of type 1 and type 2 diabetes: a national cohort study. Diabetologia 2020; 63(3):508–518. doi:10.1007/s00125-019-05044-z
51. **Mathai S, Derraik JG, Cutfield WS, et al**. Increased adiposity in adults born preterm and their children. PLoS One 2013; 8(11):e81840. doi:10.1371/journal.pone.0081840
52. **Breukhoven PE, Kerkhof GF, Willemsen RH, Hokken-Koelega AC**. Fat mass and lipid profile in young adults born preterm. J Clin Endocrinol Metab 2012; 97(4):1294–1302. doi:10.1210/jc.2011-2621
53. **Sipola-Leppänen M, Vääräsmäki M, Tikanmäki M, et al**. Cardiometabolic risk factors in young adults who were born preterm. Am J Epidemiol 2015; 181(11):861–873. doi:10.1093/aje/kwu443
54. **Sipola-Leppänen M, Kajantie E**. Should we assess cardiovascular risk in young adults born preterm? Curr Opin Lipidol 2015; 26(4):282–287. doi:10.1097/MOL.0000000000000190
55. **Wood CL, Wood AM, Harker C, Embleton ND**. Bone mineral density and osteoporosis after preterm birth: the role of early life factors and nutrition. Int J Endocrinol 2013; 2013:902513. doi:10.1155/2013/902513
56. **Xie LF, Alos N, Cloutier A, et al**. The long-term impact of very preterm birth on adult bone mineral density. Bone Rep 2018; 10:100189. doi:10.1016/j.bonr.2018.100189
57. **Crump C, Sundquist J, Winkleby MA, Sundquist K**. Gestational age at birth and mortality from infancy into mid-adulthood: a national cohort study. Lancet Child Adolesc Health 2019; 3(6):408–417. doi:10.1016/S2352-4642(19)30108-7
58. **Bolton CE, Bush A, Hurst JR, et al**. Are early life factors considered when managing respiratory disease? A British Thoracic Society survey of current practice. Thorax 2012; 67(12):1110. doi:10.1136/thoraxjnl-2012-202637
59. **Crump C**. Birth history is forever: implications for family medicine. J Am Board Fam Med 2015; 28(1):121–123. doi:10.3122/jabfm.2015.01.130317
60. **Bonner R, Bountziouka V, Stocks J, et al**. Birth data accessibility via primary care health records to classify health status in a multi-ethnic population of children: an observational study. NPJ Prim Care Respir Med 2015; 25:14112. doi:10.1038/npjpcrm.2014.112
61. **Kajantie E, Hovi P**. Is very preterm birth a risk factor for adult cardiometabolic disease? Semin Fetal Neonatal Med 2014; 19(2):112–117. doi:10.1016/j.siny.2013.11.006
62. **Matinolli HM, Männistö S, Sipola-Leppänen M, et al**. Food and nutrient intakes in young adults born preterm. Pediatr Res 2018; 83(3):589–596. doi:10.1038/pr.2017.301
63. **Kaseva N, Wehkalampi K, Hemiö K, et al**. Diet and nutrient intake in young adults born preterm at very low birth weight. J Pediatr 2013; 163(1):43–48. doi:10.1016/j.jpeds.2012.12.076
64. **Tikanmäki M, Tammelin T, Sipola-Leppänen M, et al**. Physical fitness in young adults born preterm. Pediatrics 2016; 137(1). doi:10.1542/peds.2015-1289
65. **Boivin A, Luo ZC, Audibert F, et al**. Risk for preterm and very preterm delivery in women who were born preterm. Obstet Gynecol 2015; 125(5):1177–1184. doi:10.1097/AOG.0000000000000813
66. **Grobman WA, Rice MM, Reddy UM, et al**. Labor induction versus expectant management in low-risk nulliparous women. N Engl J Med 2018; 379(6):513–523. doi:10.1056/NEJMoa1800566

***Address**: Cristina I. Pravia, MD, Department of Internal Medicine, University of Miami, 1150 NW 14th Street, Suite 150, Miami, FL 33136; cpravia@med.miami.edu*

CME MOC

How to earn *AMA PRA Category 1 Credit*™ and ABA, ABIM, ABP, ABPath, ABS 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.

Maintenance of Certification (MOC) Points

All *Cleveland Clinic Journal of Medicine* CME activities are now eligible for 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.

December 2020 CME/MOC activity

Estimated time to complete the activity: up to 1 hour

Optimal surveillance and treatment of renal and splenic artery aneurysms

Release date: December 1, 2020
Expiration date: November 30, 2021

FINANCIAL DISCLOSURES: In accordance with the Standards for Commercial Support issued by the Accreditation Council for Continuing Medical Education (ACCME), the Cleveland Clinic Foundation Center for Continuing Education requires resolution of all faculty conflicts of interest to ensure CME 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 consulting, teaching, and speaking for Genentech; consulting for Horizon Pharma; and consulting and membership on advisory committee or review panels for Takeda Pharmaceuticals. Dr. Christian Nasr (Associate Editor) reports service on advisory committees and review panels for Exelixis and Nevro. Dr. Bernard Silver (Associate Editor) reports board membership for Takeda Pharmaceuticals.

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.

ACCREDITATION: The Cleveland Clinic Foundation Center for Continuing Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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

Each activity may be submitted for American Osteopathic Association Continuing Medical Education credit in Category 2.

ABA MOC: This activity contributes to the CME component of the American Board of Anesthesiology's redesigned Maintenance of Certification in Anesthesiology™ (MOCA®) program, known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements.

Successful completion of this activity enables the participant to earn up to 1.0 MOCA 2.0 points; points earned will be equivalent to the amount of CME credit claimed for the activity. Please note: It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOCA 2.0™ points.

Maintenance of Certification in Anesthesiology™ program and MOCA® are registered trademarks of The American Board of Anesthesiology®. MOCA 2.0® is a trademark of The American Board of Anesthesiology®.

Your credit will be reported to the ABA within 60 days of claiming credit after the course.

ABIM MOC: 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. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Your credit will be reported to the ABIM within 60 days of claiming credit after the course.

ABPath CC: Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 Lifelong Learning (Part II) credits in the American Board of Pathology's Continuing Certification (CC) program (formerly known as MOC). Participants will earn CC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABPath CC credit.

Your credit will be reported to the ABPath within 60 days of claiming credit after the course.

ABP MOC: Successful completion of this CME activity, which includes participation in the activity and individual assessment of and feedback to the learner, enables the learner to earn up to 1.0 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABP MOC credit.

Your credit will be reported to the ABP within 60 days of claiming credit after the course.

ABS MOC: This activity qualifies for 1.0 self-assessment credit toward Part 2 of the American Board of Surgery (ABS) Maintenance of Certification (MOC) Program.

Please note: It is the participant's responsibility to self-report their participation to the American Board of Surgery, per board policy.