VOLUME 87 • NUMBER 3 • MARCH 2020 • www.ccjm.org

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Cleveland Clinic Journal of Medicine

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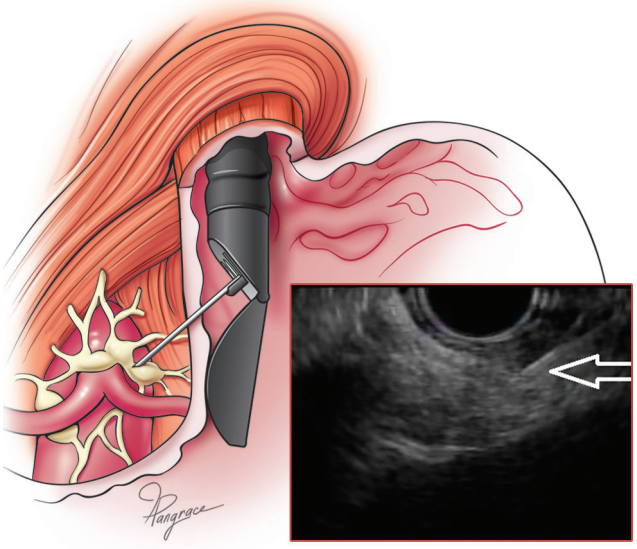

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Cleveland Clinic Journal of Medicine [ISSN 0891-1150 (print), ISSN 1939-2869 (online)] is published monthly by Cleveland Clinic at 1950 Richmond Rd., TR404, Lyndhurst, OH 44124.

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An unending ode to pneumonia

I must first note that due homage should be paid to the Internet and Google, clearly the editorialist's best friends.

In 1903, Dr. Arthur R. Reynolds, the Chicago Commissioner of Health, published an article in *JAMA*[1] entitled "Pneumonia: the new 'captain of the men of death.' Its increasing prevalence and the necessity of methods for its restriction." He wrote, "Figures are hard reading and harder hearing; but I must ask you to listen to a few in order that you may comprehend the magnitude of the pneumonia problem as I view it." He then noted that Professor William Osler, in the 1901 edition of his *Principles and Practice of Medicine*,[2] said of pneumonia: "The most widespread and fatal of all acute infectious diseases, pneumonia, is now the "Captain of the Men of Death."

Osler, who it seems attributed most acute bacterial pneumonia to the *Pneumococcus*, borrowed and amended this phrase from the 17th century Baptist preacher and philosopher John Bunyan.[3] That he knew of this verbiage, without access to the Internet, is testimony to Osler's keen literary as well as medical knowledge. Bunyan was referring to tuberculosis when he wrote in 1680 (in *The Life and Death of Mr. Badman*[3]), "He was dropsical, he was consumptive, he was surfeited, was gouty, and, as some say, he had a tang of the Pox in his Bowels. Yet the Captain of all these Men of Death that came against him to take him away, was the Consumption, for 'twas that that brought him down to the Grave."

The face of pneumonia has changed slowly over the centuries, although far more rapidly over the past few decades. But as Modi and Kovacs note in this issue,[4] community-acquired pneumonia remains a major health issue, and its management is still a component of bread-and-butter medicine, as tuberculosis (consumption) has faded in frequency but has clearly not disappeared.

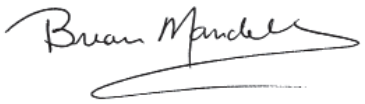
As our therapeutic and diagnostic armamentaria have grown, so has our understanding of the principles of pathophysiology and management of bacterial pneumonia, but there are still clear limitations to our knowledge and practice skills. Only some of those limitations stem from recognition of apparently new respiratory pathogens and syndromes (eg, *Legionella*, AIDS, Hantavirus, SARS, novel coronavirus). Frontline providers still face many of the same challenges and questions that Bass editorialized on in *Chest* in 1985[5] and that we struggled with as residents earlier that same decade: When should a patient with suspected pneumonia be admitted? How can we reliably recognize the patient with early pneumonia? How can we identify the likely bug and choose an appropriate antibiotic? And how long should antibiotics be administered? How should we factor into our decision the local antibiotic resistance pattern and the patient's comorbidities? (Regarding comorbidities, a forthcoming paper in the *Journal* will discuss the effect of heavy alcohol use on management of pneumonia.)

Reading through the different risk-stratification scores codified to help standardize clinical decision-making reminds me of emergency-room discussions between we residents (our fingers and white pants stained with Gram stain crystal violet) and our attending physician as to whether the patient was "sick enough" to need admission, or

doi:10.3949/ccjm.87b.03020

whether we should intravenously hydrate and then repeat the examination and chest x-ray to see if rales or infiltrate would appear before making that decision. The American Thoracic Society and Infectious Diseases Society of America[6] opine that use of clinical prediction rules enhances clinical judgment in making the appropriate decision to admit or provide outpatient therapy. I can see the rolling of eyes from several of my former ER attendings as to the need for this, but I can also recall scenarios where the availability of a validated tool to support the safety of outpatient treatment would have been most welcome.

At the end of the day, rules or not, in 2020 just as in 1980 (and 1903), the accurate examination, clinical history, and under certain circumstances the sputum Gram stain and culture results still factor into the gestalt of clinical judgment when dealing with the Captain.



BRIAN F. MANDELL, MD, PhD
Editor in Chief

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Acute lymphangitis

A HEALTHY 49-YEAR-OLD man presented to the emergency department with rapidly progressing right arm pain and malaise. He had noticed swelling in his right fourth finger 2 weeks earlier, and 5 hours before his presentation to the emergency department, the tender erythema began spreading rapidly to his right wrist, forearm, and upper arm.

On presentation, his temperature was 37.6°C (99.7°F), heart rate 77 beats per minute, and blood pressure 101/60 mm Hg. Physical examination revealed a small paronychia on the right fourth finger and linear erythematous streaks extending spirally toward the axilla with tender axillary lymphadenopathy (**Figure 1**). The patient had no history of cancer, immunodeficiency, recent insect bite, or animal contact.

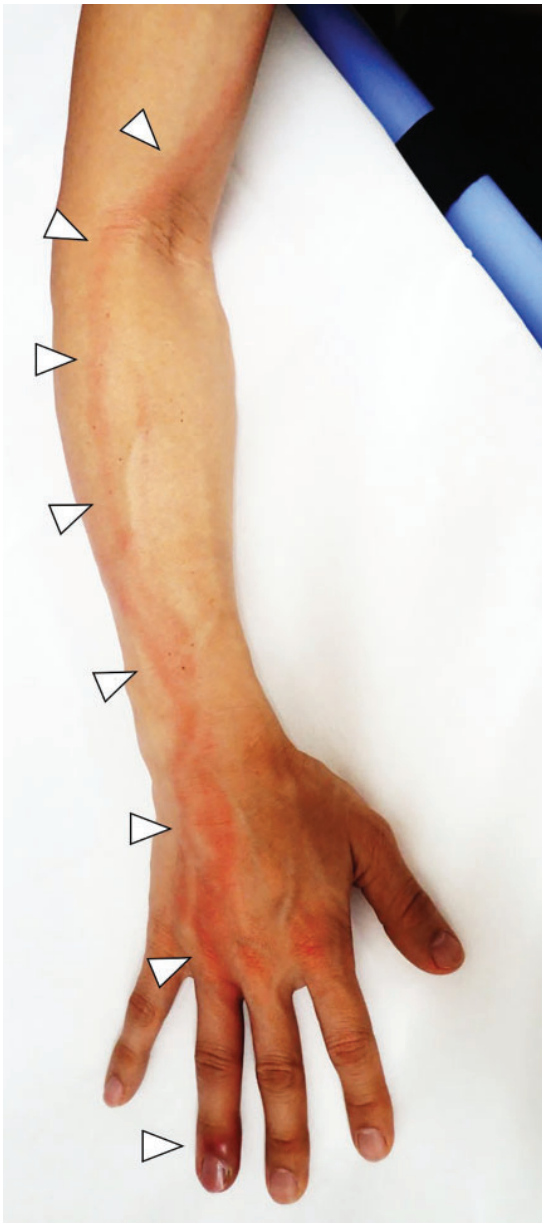
A clinical diagnosis of acute lymphangitis was made, and treatment was begun with amoxicillin. An 18-gauge needle was used to make an incision and drain the paronychia. His symptoms improved after several days.

LYMPHANGITIS

Lymphangitis is an inflammation of the lymphatic channels. Acute lymphangitis is commonly caused by a bacterial infection, but lymphangitis can also be caused by parasitic infection (filariasis), mycobacterial infection, and malignancy (neoplastic lymphangitis).

Linear erythematous streaks sometimes spread with remarkable speed—within a few hours. Acute lymphangitis is often accompanied by systemic symptoms including fever, chills, and malaise, which may appear as the initial symptoms but can develop into severe conditions such as bacteremia and sepsis.[1] The differential diagnosis includes superficial thrombophlebitis, cellulitis, erysipelas, and allergic reaction to insect bite.[2] However, the di-

doi:10.3949/ccjm.87a.19095



Linear erythematous streaks sometimes spread with remarkable speed—within a few hours

Figure 1. Linear erythematous streaks on the right arm extending from the paronychia on the fourth finger toward the axilla.

agnosis is not difficult due to the characteristic linear erythematous streaks.

The organisms that most commonly cause lymphangitis in individuals with normal immunity are gram-positive bacilli such as group A streptococci.[3] However, other organisms should be considered in specific cases: for example, *Pasteurella multocida* or *Spirillum minus* in cases with animal bites, *Erysipelothrix* in cases with fish exposure, and gram-negative organisms in immunocompromised patients.

Treatment of acute bacterial lymphangitis consists of antibiotics, but surgical intervention is sometimes required.

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Posterior reversible encephalopathy syndrome

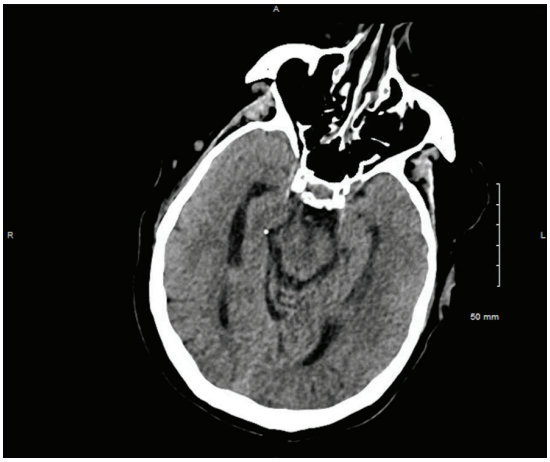

Figure 1. On presentation, noncontrast computed tomography (CT) was normal.

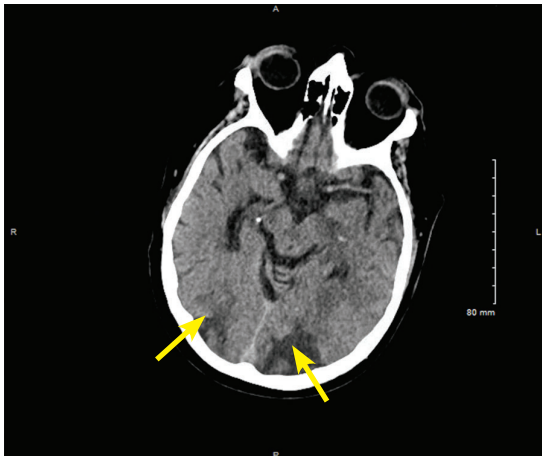

Figure 2. On hospital day 4, repeat CT imaging showed areas of hypodensity in both occipital lobes (arrows), indicating vasogenic edema.

A 70-year-old man with dyslipidemia and new-onset hypertension presented to the emergency room with nausea, fatigue, and confusion. His blood pressure was 148/87 mm Hg. Computed tomography (CT) without contrast was performed as part of the evaluation of his acute-onset altered mental status, and showed no acute intracranial abnormalities (**Figure 1**).

The patient was admitted to the hospital for observation. His blood pressure remained poorly controlled. On hospital day 4, he developed severe right occipital headache and blurred vision, and his blood pressure was noted to be 209/93 mm Hg. Repeat noncontrast CT showed hypodensities (vasogenic edema) in both occipital lobes (**Figure 2**), which, along with his symptoms, raised the suspicion of posterior reversible encephalopathy syndrome. The findings were confirmed on magnetic resonance imaging (MRI) (**Figure 3**).

doi:10.3949/ccjm.87a.18139

The patient's symptoms were better the next day, after his blood pressure had been brought under control with intravenous hydralazine. On day 10, repeat noncontrast CT showed the vasogenic edema had nearly resolved (**Figure 4**), and his visual complaints had completely resolved.

On day 4, his blood pressure was 209/93 mm Hg, with headache, blurred vision, and new vasogenic edema in the occipital lobes on CT

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Posterior reversible encephalopathy syndrome is a rare condition most often seen in hypertensive emergencies but also in sepsis, preeclampsia, eclampsia, and with the use of cytotoxic medications such as cyclosporine and tacrolimus.[1] It is thought to occur secondary to derangement in cerebral autoregulation with subsequent hyperperfusion, resulting in endothelial damage and vasogenic edema.[2] In a series of 70 patients admitted to the intensive care unit, 11 (16%) died within 90 days, but 33 (47%) had a good recovery.[3]

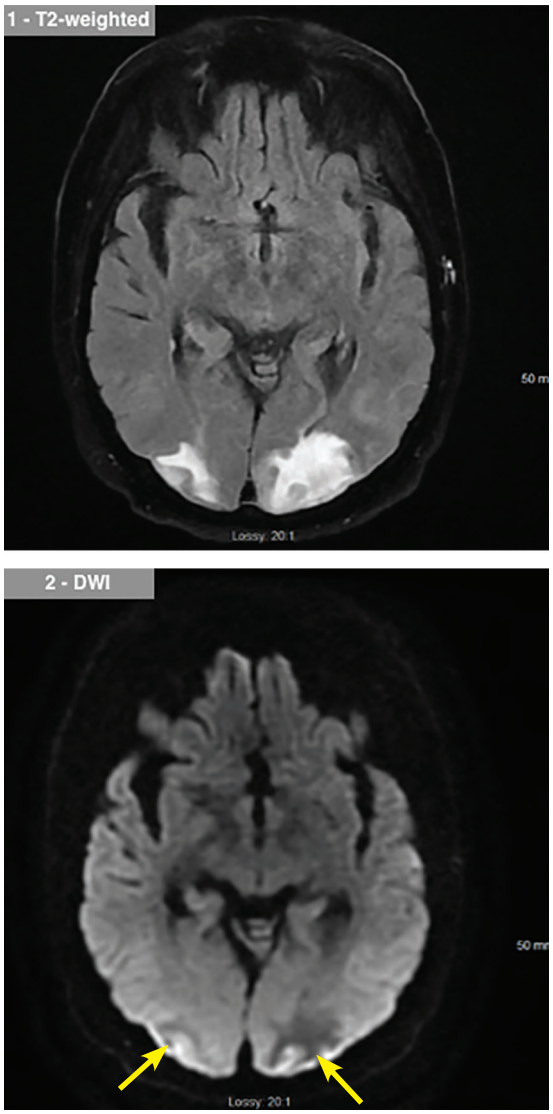

Figure 3. Magnetic resonance imaging on hospital day 4 noted hyperintensities on T2 (top) and diffusion-weighted images (bottom), confirming findings on tomography.

The clinical presentation typically consists of headaches, visual disturbances, seizures, and altered mental status

CLINICAL PRESENTATION AND TREATMENT

The diagnosis is often missed. The clinical presentation typically consists of headaches, visual disturbances, seizures, and altered mental status.[4] Features most commonly observed on CT or MRI are edema or swelling in the parieto-occipital white matter. On MRI, the syndrome usually manifests as a T2 hyperintensity with normal diffusion-weighted imaging.

Clinical symptoms and radiologic findings can improve rapidly with management of blood pressure. Late diagnosis or inadequate therapy may contribute to long-term sequelae such as permanent neurologic disability or death from progressive cerebral edema and intracranial hemorrhage.[5]

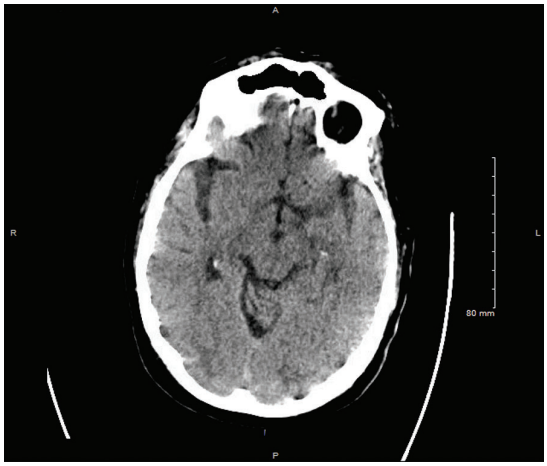

Figure 4. On hospital day 10, the vasogenic edema had nearly resolved.

TAKE-HOME POINTS

- Posterior reversible encephalopathy syndrome is usually reversible, and many patients recover fully.
- Clinical and radiologic manifestations resolve rapidly with blood pressure management.

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Leukoplakia of the tongue

A 75-year-old man presented to the dentistry and oral surgery department with an asymptomatic white spot on the right lateral border of the tongue that had been present for an unknown period of time. He had a history of hypertension. He drank alcohol almost every day, but he had never smoked.

Intraoral examination showed a homogeneous flat white plaque with slight corrugations measuring 45 mm by 20 mm (**Figure 1**), with no induration or tenderness on palpation. Extraoral examination showed no cervical lymphadenopathy. Blood testing and swab culture from the lesion revealed no significant abnormalities.

Incisional biopsy was performed, and histopathologic study showed squamous epithelial hyperplasia with parakeratosis consistent with leukoplakia. We suggested surgical excision to allow a complete histopathologic study of the lesion, but the patient requested observation only, because of the risks of paresthesia, dysgeusia, and motor dysfunction of the tongue. Three repeat biopsies over the next 14 months showed no significant change in the lesion.

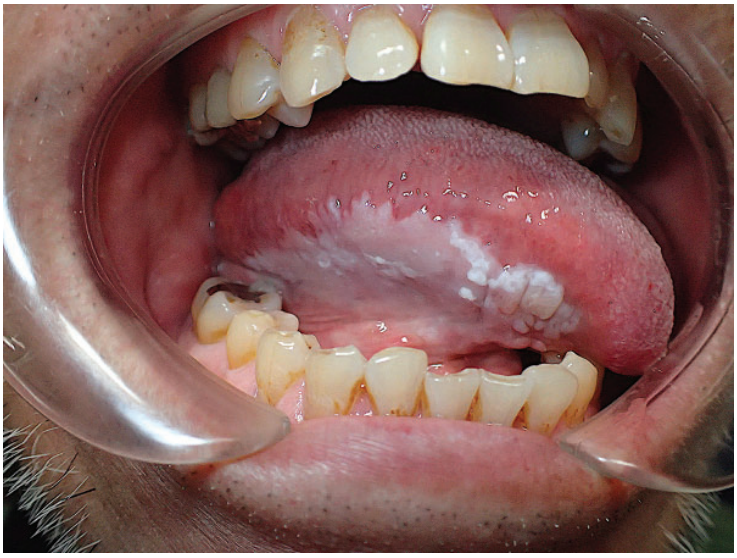

Figure 1. Homogeneous flat white plaque measuring 45 mm × 20 mm and with slight corrugations was seen on the right lateral border of the tongue.

FEATURES OF ORAL LEUKOPLAKIA

Oral leukoplakia is the most common chronic keratotic lesion of the oral cavity and is potentially premalignant.[1,2] It is a clinical diagnosis and is characterized predominantly by adherent white plaques of the oral mucosa.[3]

Oral leukoplakia has an estimated prevalence of 0.1%[3] and is mostly found on the tongue of middle-aged and older men who smoke.[1]

Oral leukoplakia has various forms based on thickness, texture, color, and regularity, and each form has a different biologic behavior.[2] Tenderness and induration on palpation are indications of malignancy.[1]

Other conditions that can involve similar white plaques include oral lichen planus, candidiasis, lupus erythematosus, nicotinic stomatitis, graft-vs-host disease, white sponge nevus, frictional hyperkeratosis, and squamous cell carcinoma.[1]

MANAGEMENT

For the initial management of oral leukoplakia, incisional biopsy for histopathologic study is the gold standard. The histopathologic appearance of oral leukoplakia can range from hyperkeratosis to various degrees of epithelial dysplasia.[3] The clinical diagnosis of leukoplakia should change to a pathohistologic diagnosis in the presence of in situ carcinoma, squamous cell carcinoma, or verrucous carcinoma.[3]

doi:10.3949/ccjm.87a.19087

Malignant transformation occurs in 2% to 3% of cases. Features associated with a higher rate of malignant transformation are nonhomogeneous oral leukoplakia, presence of red lesions (erythroplakia), large lesion size (> 200 mm^2), location on the tongue or floor of the mouth, age over 50, female sex, no history of smoking, and the presence of severe dysplasia.[4] *Candida* and human papillomavirus are infectious risk factors.[1]

The approach to management—ie, surgical resection, laser treatment, or careful monitoring—should be selected based on the histopathologic degree of dysplasia and on clinical features.[2] Nonsurgical treatments have included administration of retinoids, vitamin C, beta carotene supplements, 5-fluorouracil, and bleomycin.[3]

These treatments may be effective for resolution of the lesions; however, there is no evidence that they prevent malignant transformation.[5]

But regardless of the treatment, long-term observation and periodic biopsy are important to monitor for recurrence and for evidence of malignant transformation.[3]

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COMMENTARY

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Mitral valve prolapse and sudden cardiac death: A perspective on risk-stratification

"[Mitral valve prolapse] is a completely benign and trivial condition…In my mind it rates in importance with freckles…occurrence of sudden death among young healthy women is so rare as to be almost unheard of."

—Bernard Lown, MD[1]

Mitral valve prolapse is common, but sudden cardiac death is rare; how can we stratify risk?

A 45-YEAR-OLD WOMAN with a history of mitral valve prolapse is admitted to the hospital after a cardiac arrest. She was found unresponsive at a local library, received early bystander cardiopulmonary resuscitation, and was found to be in ventricular fibrillation by emergency medical services. Return of spontaneous circulation was achieved, and she was taken to the hospital for further workup and evaluation.

Her electrocardiogram on admission showed normal PR, QRS, and QT intervals and biphasic T waves in leads II, III, and AVF. Coronary angiography revealed normal coronary anatomy. Echocardiography showed bileaflet mitral valve prolapse with mild to moderate mitral regurgitation. Frequent premature ventricular contractions were noted on telemetry throughout her hospitalization. She underwent placement of an implantable cardioverter-defibrillator (ICD) without complications and was discharged home after an 8-day hospitalization.

This case illustrates a patient who had a rare but significant complication of mitral valve prolapse: sudden cardiac death. Although mitral valve prolapse (previously known as Barlow disease) has been associated with sudden cardiac death for decades,[2] a causal relationship has been difficult to ascertain, given the significant prevalence of mitral valve prolapse in the general population (about 2%, more common in women) and the challenge of determining a specific etiology of sudden cardiac death postmortem.[3,4]

doi:10.3949/ccjm.87a.19096

A 'MALIGNANT' PHENOTYPE OF MITRAL VALVE PROLAPSE

Over time, observational data have accumulated regarding patients with mitral valve prolapse who survived a fatal ventricular arrhythmia in whom no other cause could be found, such as long or short QT syndrome, Brugada syndrome, or coronary or other arrhythmogenic structural heart disease. Together, these studies have demonstrated a "malignant" phenotype of mitral valve prolapse, with specific associated structural, extravalvular, and arrhythmogenic features.[5] These higher-risk characteristics include:

- Female sex
- Biphasic or inverted T waves in at least 1 inferior lead (II, III, aVF)
- Frequent premature ventricular contractions
- Bileaflet prolapse
- Evidence of papillary muscle fibrosis on cardiac magnetic resonance imaging.[3–7]

The mechanisms by which these characteristics increase the risk of sudden cardiac death are still not completely understood, but they are likely multifactorial and involve abnormal function or strain of the mitral valve apparatus, abnormalities in the conduction system, and cardiac responsiveness to nervous system and hormonal input.[5]

OUR EXPERIENCE

Even though sudden cardiac death in mitral valve prolapse is rare, our hospital system has some (albeit limited) experience with it. In recent years we have had 6 patients who had an episode of sudden cardiac death or ventricular tachycardia in the setting of mitral valve prolapse without another explanation for their fatal arrhythmia. Of these 6 patients:

- 5 were female
- 5 had inverted or biphasic T waves in at least 1 inferior lead
- 5 had premature ventricular contractions
- 3 had bileaflet prolapse
- 1 had papillary muscle fibrosis on cardiac magnetic resonance imaging (only 5 of the 6 underwent magnetic resonance imaging).

All of these high-risk patients were identified after developing a fatal ventricular arrhythmia or cardiac arrest, and all of them had an ICD placed for secondary prevention. Although this is a limited case series, it is congruent with what has been found in larger observational data sets and systematic reviews.[4]

OUR PERSPECTIVE

Based on the limited data available and on our clinical experience, we generally recommend further risk-stratification with exercise stress testing in patients who present with a diagnosis of mitral valve prolapse and other high-risk features, such as bileaflet prolapse and high-risk electrocardiographic findings. Exercise-related premature ventricular contractions or nonsustained ventricular tachycardia, especially with shorter coupling intervals, puts these patients at higher risk of developing a fatal ventricular arrhythmia.

Further risk-stratification may be considered in the form of electrophysiologic testing, during which induction of sustained ventricular tachycardia can be attempted in a controlled setting. This strategy helps determine which patients with mitral valve prolapse are most likely to benefit from ICD placement for primary prevention of sudden cardiac death, and thus may be lifesaving. The role of electrophysiologic testing, however, is undergoing further evaluation.

STUDY IS NEEDED

This proposed approach has several important limitations, however. The Heart Rhythm Society does not provide decisive guidelines for appropriate risk-stratification in patients with mitral valve prolapse, and there are no recommendations on prophylactic ICD placement for primary prevention in patients with mitral valve prolapse and high-risk characteristics. Given the lack of prospective data or randomized controlled trials in this area, the associated high-risk characteristics are based on retrospective analyses and reviews, which are prone to selection bias and publication bias.

Key questions remain:

- Which patients should be screened routinely for the high-risk mitral valve prolapse phenotype?
- Which methods of screening would be most cost-effective?
- What are the positive and negative predictive values of inducible ventricular tachycardia for sudden cardiac death? (No randomized prospective study has yet addressed this topic.)
- Does repairing or replacing the mitral valve decrease the risk of sudden cardiac death in patients with the high-risk phenotype?

Currently, a nonrandomized clinical trial is recruiting patients to undergo cardiac magnetic resonance imaging, exercise stress testing, and ambulatory external loop recording to assess if the level of mitral valve regurgitation increases the risk of ventricular arrhythmia.[8] Hopefully, the findings of this study will help practicing clinicians make more informed decisions as to which patients require further risk-stratification and possible intervention to reduce the risk of ventricular arrhythmias.

Mitral valve prolapse is common and, in general, should not cause significant alarm to patients or clinicians. However, we would argue that patients with mitral valve prolapse are not all the same, and that they should be screened for features associated with sudden cardiac death to help clarify their level of risk and possibly avoid a serious complication or tragic outcome.

We generally recommend exercise stress testing in patients with mitral valve prolapse and high-risk features

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CME CALENDAR

CME MOC

2020

MARCH

PAIN MANAGEMENT SYMPOSIUM
March 21–25
Orlando, FL

PREVENTION AND MANAGEMENT OF CV RISK: OLD PROBLEMS, NOVEL APPROACHES, NEW EVIDENCE
March 27
Chicago, IL

APRIL

UVEITIS UPDATE
April 4
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SOUTHWESTERN CONFERENCE ON MEDICINE
April 23–26
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MEDICAL DERMATOLOGY THERAPY UPDATE
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MAY

DR. VICTOR FAZIO IBD SYMPOSIUM: INNOVATIONS IN MEDICAL AND SURGICAL THERAPIES FOR INFLAMMATORY BOWEL DISEASE
May 4
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EMERGING CONCEPTS IN CARDIAC ELECTROPHYSIOLOGY: THE PRESENT AND THE FUTURE
May 5
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LEAD MANAGEMENT 2020: PREDICTING RISKS, STRENGTHS AND LIMITATIONS
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MULTIDISCIPLINARY MASTER CLASS IN ENDOCARDITIS AND OTHER CARDIOVASCULAR INFECTIONS
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ANNUAL DIABETES DAY
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JUNE

INTENSIVE REVIEW OF INTERNAL MEDICINE
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INNOVATIONS IN CEREBROVASCULAR CARE
June 4–5
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MELLEN CENTER UPDATE IN MULTIPLE SCLEROSIS
June 12
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INTERNAL MEDICINE BOARD REVIEW COURSE
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AUGUST

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NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN
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Washington, DC

INTENSIVE REVIEW OF CARDIOLOGY
August 15–19
Cleveland, OH

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CME MOC

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Gastroenteritis gone rogue

A 56-year-old woman presented to the emergency department with a 2-day history of vomiting. She reported vomiting almost immediately after eating and described her emesis as nonbilious and nonbloody. These symptoms were associated with mild, central, intermittent abdominal pain, generalized weakness, and nonbloody, nonmucoid diarrhea. She described 5 episodes of watery stools per day. She said she had no fever, recent travel, previous similar episodes, or sick contacts. Her symptoms were thought to be consistent with infectious gastroenteritis.

The patient had a history of hypertension and had undergone a partial hysterectomy for uterine fibroids. Her current medications included oral hydrochlorothiazide 25 mg daily and over-the-counter ibuprofen and acetaminophen occasionally for back pain. She worked as a medical assistant at a local hospital. She did not consume alcohol or use illicit drugs, and she smoked 5 cigarettes per day.

CHRONIC OR ACUTE?

1 What is the duration of symptoms consistent with the definition of "acute" diarrhea?

- ☐ Less than 2 days
- ☐ Less than 7 days
- ☐ Less than 14 days
- ☐ Less than 4 weeks

Diarrhea is defined as acute when it lasts less than 14 days.[1] This duration allows the resolution of most self-limited gastrointestinal illnesses. Conversely, diarrhea lasting more than 4 weeks is considered chronic and requires investigation.[1] Our patient presented with acute diarrhea, ie, with symptoms lasting 2 days.

doi:10.3949/ccjm.87a.19007

CASE CONTINUED: EVALUATION IN THE EMERGENCY DEPARTMENT

In the emergency department, the patient appeared comfortable. Her heart rate was 111 beats per minute, blood pressure 107/65 mm Hg, respiratory rate 20 breaths per minute, and oxygen saturation 97% on room air. Orthostatic vital signs were not checked, but she was ambulating without symptoms. She was afebrile, with a temperature of 37°C (98.6°F), and she was alert and oriented.

Her oral mucosa was dry. No heart murmurs were heard. Her abdomen was soft, nontender, and nondistended, with normal bowel sounds. Her chest was clear to auscultation. There was no palpable organomegaly. No rash was noted. Neurologic examination was normal. No lymphadenopathy was noted.

A woman presented with 2 days of vomiting and diarrhea

Initial laboratory blood results revealed the following values:

- Sodium 134 mmol/L (reference range 136–144)
- Blood urea nitrogen 58 mg/dL (7–21)
- Creatinine 2.70 mg/dL (0.58–0.96)
- Aspartate aminotransferase (AST) 20 U/L (13–35)
- Alanine aminotransferase (ALT) 24 U/L (7–38)
- Hemoglobin 12.2 g/dL (11.5–15.5)
- Platelet count 221 × 10^9/L (150–400)
- White blood cell count 9.4 × 10^9/L (3.7–11.0).

Urinalysis showed the following values:

- Protein 30 mg/dL
- Ketones 5 mg/dL
- Leukocyte esterase 25 mg/dL.

Urine microscopy showed the following:

- White blood cells 5–10 per high-power field
- Trace bacteria
- Few squamous epithelial cells
- More than 20 hyaline casts.

Noncontrast computed tomography of the abdomen and pelvis showed no abnormally dilated or distended loops of bowel or other pathology.

ARE STOOL STUDIES NEEDED?

2 Which of the following characteristics of this patient's history and presentation warrant further diagnostic workup with stool studies?

- ☐ Age > 50
- ☐ Employment as a healthcare worker
- ☐ Evidence of volume depletion
- ☐ Both healthcare employment and volume depletion

Diagnostic stool studies are indicated in acute diarrhea when there are public health concerns (eg, the patient works in a hospital, in daycare, or as a food-handler) and when the clinical presentation indicates significant volume depletion, both of which were present in this patient.[2]

Test results suggested volume depletion

Our patient's employment as a healthcare worker increases the potential of public health consequences of infectious diarrhea by exposing vulnerable populations. Additionally, the initial examination indicated volume depletion with tachycardia and normotension (rather than hypertension) in a patient who carries the diagnosis of hypertension. Laboratory testing also revealed acute kidney injury, with a blood urea nitrogen-to-creatinine ratio greater than 20:1, and hyaline casts in the urine, suggesting volume depletion.

Other features that warrant stool testing (but were absent in this case) include fever, bloody diarrhea, severe abdominal pain, sepsis, age over 70, immune-compromised status, known or suspected inflammatory bowel disease, community outbreaks, pregnancy, and significant comorbidities.[1–3]

CASE CONTINUED: SHE IS ADMITTED AND SPIKES A FEVER

The patient was admitted and started on intravenous normal saline at 100 mL/hour. Over the next 12 hours her symptoms resolved and her creatinine improved to 1.4 mg/dL. However, the next day she developed a fever, with a temperature reaching 39.2°C (102.6°F). Stool studies for gastrointestinal pathogens including *Salmonella sp.*, *Shigella sp.*, *Escherichia coli*, and *Clostridioides difficile* returned negative.

The patient continued to be febrile with sustained daily temperatures of 39°C. She reported a cough productive of thick white sputum. Intermittent tachycardia with a heart rate up to 120 beats per minute was noted.

Chest radiography showed increased interstitial markings. Auscultation of the lungs revealed bilateral crackles. Noncontrast computed tomography of the chest revealed bilateral ground-glass opacities. A ventilation-perfusion scan was negative for pulmonary embolism.

A nasopharyngeal swab was sent for viral pathogens and blood cultures.

ELEVATED PROCALCITONIN

Procalcitonin was measured and found to be elevated at 58.02 ng/mL. Reference levels for procalcitonin are as follows:

- ≤ 0.5—sepsis is not likely
- 0.5–2.0—sepsis is possible
- > 2.0—sepsis is likely, unless other causes are known
- ≥ 10.0—important systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock.

3 This procalcitonin level supports a diagnosis of lower respiratory tract infection with which of the following pathogens?

- ☐ Typical bacteria
- ☐ Atypical bacteria
- ☐ A virus
- ☐ Fungi

Typical bacteria are most likely. In adults hospitalized with community-acquired pneumonia, procalcitonin levels were noted by Self et al to be highest in those with typical bacterial infection.[4] Patients with viral or fungal pneumonia had lower procalcitonin elevations than those with atypical or typical bacterial infections; patients with a procalcitonin level of 10 ng/mL were 4 times more likely to have a bacterial pathogen than those with an undetectable procalcitonin (< 0.05 ng/mL).[4]

The marked procalcitonin elevation in

this patient exceeds the thresholds typically described (which range from 0.25 to 1 ng/mL) and may reflect bacterial illness or nonbacterial severe systemic inflammation.[5]

CASE CONTINUED: HER CONDITION WORSENS

Treatment was started with azithromycin, vancomycin, and piperacillin-tazobactam to cover atypical bacterial pathogens that may cause hospital-acquired pneumonia, but fevers continued.

On hospital day 5 the patient developed atrial fibrillation with rapid ventricular response requiring transfer to the progressive care unit. Intravenous diltiazem was administered, resulting in conversion to normal sinus rhythm.

Further laboratory testing indicated worsening leukocytosis, with white blood cell counts up to 18.9 × 10^9/L and worsening renal function after her initial recovery. New thrombocytopenia developed, with platelet counts falling to 109 × 10^9/L. She was now requiring supplementary oxygen by nasal cannula at 3 to 4 L per minute to maintain adequate saturation.

NEW ATRIAL FIBRILLATION IN SEPSIS

4 What is the incidence of new-onset atrial fibrillation in patients with severe sepsis?

- ☐ 2%
- ☐ 5%
- ☐ 10%
- ☐ 15%

The incidence of new-onset atrial fibrillation in patients with severe sepsis is 10%.

Cardiac arrhythmias are common in patients with sepsis, and atrial fibrillation is the most common. Physiologic stressors with resulting autonomic surges, volume shifts, and stress hormones are all contributing factors.[6] The incidence increases with illness severity, and the incidence of new-onset atrial fibrillation in patients with septic shock is estimated at 23%.[6] New-onset atrial fibrillation is associated with longer lengths of stay and increased risk of in-hospital death.[7]

CASE CONTINUED: TRANSFER TO INTENSIVE CARE

The patient's fevers continued, and her renal function, bilirubin, and thrombocytopenia continued to worsen. The creatinine level increased to 3.36 mg/dL. Evidence of new hepatic inflammation was noted, with the following blood values:

- Total bilirubin 22.3 mg/dL
- Direct bilirubin 18.4 mg/dL
- ALT 192 U/L
- AST 174 U/L
- Lactate dehydrogenase (LDH) 290 U/L
- Platelet count 49 × 10^9/L
- Hemoglobin 7.3 g/dL
- White blood cell count 32.9 × 10^9/L, with 2% myelocytes, 3% bands, 92% neutrophils, 2% lymphocytes, and 1% monocytes
- Free thyroxine 0.8 ng/dL
- Fibrinogen 740 mg/dL
- International normalized ratio 1.03
- Ferritin 2,455 ng/mL.

Peripheral smear results showed nucleated red blood cells, leukocytosis with left shift, and thrombocytopenia. Blood, urine, and sputum cultures showed no growth. A respiratory viral panel was also negative.

Her procalcitonin was elevated at 58.02 ng/mL

On hospital day 7, the patient was transferred to the intensive care unit due to worsening mentation, persistent fevers, deteriorating renal function, shock, and respiratory distress requiring continuous venovenous hemofiltration, pressors, and mechanical ventilation. No rash or lymphadenopathy developed in the interim.

Progressive thrombocytopenia led to the consideration of acute disseminated intravascular coagulation (DIC).

IS THIS ACUTE DISSEMINATED INTRAVASCULAR COAGULATION?

5 Which of the following laboratory profiles is expected in acute DIC?

- ☐ Elevated fibrinogen, prolonged prothrombin time, and reduced platelet count
- ☐ Reduced fibrinogen, prolonged prothrombin time, and reduced platelet count

☐ Elevated fibrinogen, prolonged prothrombin time, and elevated D-dimer

In DIC, the normal processes of coagulation and fibrinolysis become dysregulated and abnormally activated within the vasculature. Causes include sepsis, malignancy, trauma, and obstetric complications. It is a clinicopathologic diagnosis requiring both consideration of the clinical context and interpretation of laboratory data.

In acute DIC, the fibrinogen level is typically low with prolongation of the prothrombin and activated partial thromboplastin times accompanying thrombocytopenia (the second answer choice above).[8] Thus, this patient's laboratory values are not consistent with acute DIC, as she had a normal international normalized ratio and elevated fibrinogen.

Nucleated red blood cells in the peripheral smear may indicate extreme stress, hemolysis, extramedullary hematopoiesis, hypoxia, or pathology that displaces normal bone marrow (myelophthisis),[8] and they predict a higher risk of death.[9]

She was diagnosed with hemophagocytic lymphohistiocytosis

CASE CONTINUED: THE DIAGNOSIS RECONSIDERED

The patient became critically ill, with multiorgan system failure. The negative cultures argued against active bacterial infection. Noninfectious causes were systematically considered. Acute DIC did not explain her thrombocytopenia, and with ongoing fevers and nucleated red blood cells in the periphery, the bone marrow was considered as a site of pathology. Disorders of the myeloid system that result in activation of the inflammatory cascade include leukemia. With multiple organs now affected, new hepatic injury, and elevated ferritin levels, hemophagocytic lymphohistiocytosis (HLH) was considered.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

6 Which additional laboratory values should be obtained to support the diagnosis of HLH?

☐ Fasting triglycerides
☐ Total cholesterol
☐ Repeat procalcitonin
☐ Serologic testing for Epstein-Barr virus

HLH is a syndrome characterized by excessive immune activation. According to the 2004 Histiocyte Society guidelines,[10] the diagnosis of HLH requires 5 of the following 8 criteria in the absence of evidence of malignancy:

- Fever
- Splenomegaly
- Cytopenias affecting at least 2 cell lines: hemoglobin < 90 g/L (< 100 g/L in infants < 4 weeks old), platelet count < 100×10^9/L, or neutrophil count < 1.0×10^9/L
- Fasting triglycerides ≥ 265 mg/dL or fibrinogen ≤ 1.5 g/L, or both
- Hemophagocytosis in the bone marrow, spleen, or lymph nodes
- Low or absent natural killer (NK) cell activity
- Ferritin ≥ 500 ng/mL
- CD25 (soluble interleukin 2 receptor) ≥ 2,400 U/mL.

Alternatively, the patient should have a molecular diagnosis of HLH based on the detection of genetic mutations related to the pathogenesis of HLH.

CASE CONTINUED: FURTHER TESTING

Further testing showed the following:

- Fasting triglycerides 316 mg/dL (reference range < 150)
- CD25 2,532 U/mL (45–1,105)
- Normal NK cell function
- No mutations linked to HLH detected on genetic testing: *AP3B1*, *BLOC156*, *LYST*, *RAB27A*, *SH2D1A*, *SLC7A7*, *STX11*, and *XIAP* were normal
- Hemophagocytosis on bone marrow biopsy study, consistent with HLH.

This patient met 6 of the 8 HLH diagnostic criteria, ie, fever, bicytopenia (anemia and thrombocytopenia), hypertriglyceridemia, hemophagocytosis in the bone marrow, elevated ferritin, and increased soluble CD25.

7 In clinically deteriorating patients, treatment for HLH should not be initiated until which of the following tests is completed?

☐ Demonstration of hemophagocytosis on bone marrow evaluation
☐ Molecular testing for genetic mutations
☐ Neither of the above

Neither of the above.

Delayed treatment portends a worse prognosis. In a single-center study of adult patients with HLH, 66% of patients had died after a median follow-up of 42 months. The median overall survival of the entire cohort was 2.1 months.[11]

The HLH 2004 diagnostic criteria[10] are largely based on pediatric data, and presentations in adults may differ.[12] Demonstration of hemophagocytosis is not required for diagnosis. In an unstable patient in whom the clinical index of suspicion is high, referral to a hematology service and treatment should not be delayed.

CASE CONTINUED: TREATMENT AND RECOVERY

The diagnosis of HLH was confirmed, and treatment was started with etoposide and dexamethasone, according to the HLH-94 treatment protocol.[13] After a prolonged hospitalization of 57 days, the patient was discharged home. Over the next 10 months, she had no recurrence.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IS LIFE-THREATENING

HLH is a life-threatening clinical syndrome resulting from an excessive, uncontrolled immune response. It is characterized as primary when it is caused by genetic mutations, or secondary when there are no associated genetic defects.[14]

The implicated genes code proteins responsible for cytotoxic processes. When this pathway is impaired, activated macrophages engulf normal tissues and trigger severe unregulated inflammation.[15] Primary HLH most commonly presents in children. Secondary HLH may be associated with predisposing conditions causing immune dysregulation, such as lymphoma, immunodeficiency, or autoimmune diseases.

Episodes in either primary or secondary HLH may be triggered by infection, most often with Epstein-Barr virus.[16]

Data on the incidence of HLH in adults are limited, but a nationwide survey in Japan estimated an annual incidence of 1 per 800,000.[16]

Cardinal symptoms include prolonged fever, hepatosplenomegaly, and cytopenias. As noted, the diagnostic guidelines for HLH include a list of 8 clinical and laboratory criteria, 5 of which must be met for the diagnosis of HLH, or the patient should have genetic testing consistent with HLH.[10]

However, HLH criteria are not fulfilled in all cases, and additional manifestations commonly seen in adults are not included in the criteria (eg, elevated AST and LDH).[12] Fever is noted in almost all presentations at diagnosis, while hepatosplenomegaly and cytopenias are noted in 80% of patients. Ferritin is elevated in 95% of cases of secondary HLH, while low fibrinogen is less common at 40%.[14] The incidence of skin manifestations ranges from 6% to 65%, and more than a third of patients have neurologic symptoms ranging from seizures to encephalopathy.

Each of the cardinal clinical and laboratory findings is linked to the underlying pathophysiology. High levels of inflammatory cytokines result in fever. Splenomegaly results from the infiltration by lymphocytes and macrophages. Cytopenias are related to high levels of tumor necrosis factor alpha and interferon gamma and to hemophagocytosis. Elevated triglycerides are caused by the decreased lipoprotein lipase activity initiated by increased tumor necrosis factor alpha levels. Ferritin is believed to accumulate as macrophages scavenge heme. High concentrations of soluble interleukin 2 receptor are produced by activated lymphocytes.[14] Liver function derangements are related to direct invasion of the liver and biliary tree by activated macrophages with resulting marked elevations of bilirubin and elevations in AST, ALT, and LDH.[13]

She was sent home after 57 days, and over the next 10 months had no recurrence

Hemophagocytosis is not required for the diagnosis of HLH and it neither confirms nor excludes the diagnosis. Fewer than half of patients may have hemophagocytosis evident on initial presentation.[17]

Differentiating between sepsis and HLH may be difficult due to the rarity of the disease in the adult population, but if suspicion is high, the pattern of clinical findings and disease progression can be used to aid the diagnosis.[18] Serial markers of inflammation, ferritin, and bone marrow evaluation may also aid the diagnosis.

The death rate in adult HLH has been re-

ported to range from 20% to 88%.[16] Every patient with suspected HLH should be referred urgently to a hematologist, as prompt initiation of treatment is important to improve survival. Treatment does not need to wait for definite diagnosis if suspicion is high. The initial goal of treatment is to suppress the excessive life-threatening inflammatory cascade; most regimens follow the HLH-94 protocol, which includes steroids and etoposide. After 8 weeks, patients are either weaned off therapy or transitioned to continuation therapy.[14]

KEY POINTS

- HLH is primarily a disease of children but can be seen in adults.
- Hemophagocytosis is not always evident and is not required for the diagnosis of HLH.
- Management requires input from specialists, and treatment should not be delayed for molecular diagnosis.
- HLH may be triggered by an illness, with Epstein-Barr virus being the most common infectious agent associated with it.

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REVIEW

CME MOC

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Community-acquired pneumonia: Strategies for triage and treatment

ABSTRACT

Community-acquired pneumonia significantly contributes to patient morbidity and healthcare costs. As our understanding of this common infection grows, collaborative efforts among researchers and clinical societies provide new literature and updated guidelines informing its management. This review discusses diagnostic methods, empiric treatment, and infection prevention strategies for patients with suspected community-acquired pneumonia.

KEY POINTS

Systematically stratifying patients with suspected community-acquired pneumonia based on mortality risk can aid in designating the safest level of care for each patient.

Empiric treatment should be informed by the local antibiogram (ie, local patterns of antibiotic resistance) with multidrug-resistant organism coverage added based on individual patient and institutional risk factors.

Prompt de-escalation to targeted antimicrobial therapy, guided by diagnostic testing, can reduce antibiotic resistance and antibiotic-related adverse drug reactions.

Appropriate clinical and radiographic follow-up after antibiotic course completion to assess for treatment failure is a subject of ongoing debate.

doi:10.3949/ccjm.87a.19067

While physicians have treated pneumonia for centuries, each stage of the clinical decision-making process still poses challenges, from determining the most appropriate setting of care for a patient with suspected pneumonia to planning follow-up after antibiotic completion. Over the years, physicians have witnessed the advent of new medical and respiratory therapies as well as the development of antibiotic resistance in the management of this common infection.

Inpatients with pneumonia fall into 2 categories: those with community-acquired pneumonia (CAP) who are admitted, and those who develop either hospital-acquired or ventilator-associated pneumonia while already hospitalized. Each patient population faces unique organism exposures, and thus, recommended diagnostic tests, empiric treatment regimens, and goals for infection prevention vary.

This article reviews guidelines by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS)[1] and interprets recent studies to address questions that arise specifically in the inpatient management of CAP.

COMMON AND COSTLY

CAP is a significant health concern, with one study reporting 915,500 episodes in adults at least 65 years of age in the United States every year, and medical costs associated with CAP exceeding $10 billion in 2011.[2,3]

The National Center for Health Statistics reported 1.7 million visits to emergency departments in the United States in 2017 in which pneumonia was the primary discharge diagnosis, and listed pneumonia as the cause of death for 49,157 people in 2017.[4]

TABLE 1

The CURB-65 calculator

	Criteria	Points
C	Confusion	1
U	Urea > 7 mmol/L	1
R	Respiratory rate > 30 breaths per minute	1
B	Systolic blood pressure < 90 mm Hg or diastolic blood pressure < 60 mm Hg	1
65	Age ≥ 65	1

Level of care required	Total score
Outpatient	0–1
Inpatient	2
Intensive care	3–5

Based on information in reference 1.

RISK-STRATIFICATION OF COMMUNITY-ACQUIRED PNEUMONIA

What level of care does the patient need: Outpatient? Inpatient? Intensive?

The IDSA/ATS 2019 guidelines[1] emphasize the importance of first determining what level of patient care is needed: Is outpatient treatment appropriate, or does the patient need to be admitted to the hospital, or even to the intensive care unit? Appropriate triage can prevent stresses on the patient and the healthcare system associated with under- or overestimating illness severity. Patients at high risk of death whose acuity is not fully appreciated face inadequate support, while those admitted despite low risk of death may be unnecessarily subjected to the risks of the hospital setting, such as infections from healthcare-associated multidrug-resistant organisms.

Risk calculators are routinely used to help physicians triage their patients in everyday practice, although they have not been specifically validated to predict the need for admission.

CURB-65 is a simple calculator based on 5 risk factors first identified in 1987 (**Table 1**).[1] Patients receive 1 point each for **c**onfusion, high blood **u**rea nitrogen, high **r**espiratory rate, low **b**lood pressure, and age **65** or older; the higher the total score, the higher the 30-day mortality risk. According to the IDSA/ATS, patients with scores of 0 or 1 can be managed as outpatients, those with scores of 2 should be admitted to the hospital, and those with scores of 3, 4, or 5 need care in the intensive care unit.

An abbreviated version of this calculator, CRB-65, allows risk-stratification of outpatients without laboratory work.[1]

The Pneumonia Severity Index incorporates 20 risk factors to place patients into 5 classes correlated with mortality risk (**Table 2**).[5] The authors suggest outpatient management for those in classes I or II and inpatient management for those in risk classes IV and V. Patients in class III may be safely treated in an outpatient setting with adequate support or in an inpatient observation unit.

While CURB-65 may be better in busy clinical settings, as it is a shorter risk stratification scale for CAP, the Pneumonia Severity Index is preferred by the IDSA/ATS 2019 guidelines as it has been more extensively studied and validated.[1]

The IDSA/ATS guidelines list a separate set of major and minor criteria to define "severe pneumonia" to determine which patients with suspected CAP merit intensive care.[1] At least 1 of the major criteria or at least 3 of the minor criteria are required for the diagnosis of severe pneumonia (**Table 3**).

The Pneumonia Patient Outcomes Research Team study, a multicenter, prospective controlled study of both ambulatory and hospitalized patients with CAP, also devised a list of risk factors associated with death within 30 days.[6] These risk factors include altered mental status, uremia, leukopenia, and hypoxemia. Chronic liver failure was a risk factor highlighted in this study but was not included in the IDSA/ATS criteria.

Yet none of these scoring systems can fully capture all medical or psychosocial comorbidities that may prevent successful recovery in the outpatient setting. A retrospective chart review of more than 1,800 patients found that 45% of patients who had "low-risk" CAP by the Pneumonia Severity Index were nevertheless admitted.[7] Patients with cognitive impairment, coronary artery disease, diabetes mellitus, pulmonary disease, multilobular radiographic opacities, home oxygen therapy, corticosteroid use, or use of antibiotics prior

to presentation had increased odds of hospitalization.

Clinical judgment should be applied to the results of any of these calculators to appropriately triage patients with pneumonia.

DIAGNOSIS OF COMMUNITY-ACQUIRED PNEUMONIA

Imaging

After triaging a patient with suspected CAP to the safest level of care, several radiographic and laboratory methods can be used to verify the diagnosis and identify the organism most likely responsible for the ongoing infection. Chest radiographs with demonstrable infiltrates are required to diagnose CAP and to distinguish it from upper respiratory tract infection.[1]

Different organisms can be associated with characteristic infiltrate patterns, which often manifest within 12 hours of symptom onset:

Focal nonsegmental or lobar pneumonia (Figure 1). Typical bacterial pneumonias caused by organisms such as *Streptococcus pneumoniae* tend to manifest with an airspace opacity in 1 segment or lobe, though antibiotic use can alter their pathophysiology to create a patchy, multilobular opacity pattern.

Multifocal bronchopneumonia or lobar pneumonia. Bronchopneumonias, similarly characterized by a patchy pattern, are most commonly caused by *Staphylococcus aureus*, *Haemophilus influenzae*, and fungi.[8]

Focal or diffuse "interstitial" pneumonia (Figure 2). Atypical bacterial organisms including *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* frequently involve the lung bases in a diffuse, bilateral, reticulonodular pattern, but can start as isolated lobar opacities on chest radiography.[9] Viral organisms are associated with diffuse, bilateral lung involvement as well.

Early radiographic identification of pulmonary complications, such as pleural effusions or cavitating lesions, can provide more clues to the causative organism and allow for timely intervention.[9]

How accurate is chest radiography?

The utility of chest radiographs in diagnosing CAP is ultimately subject to interobserver variability, with some studies citing 65% accuracy in diagnosing viral pneumonia, 67% in diagnosing bacterial pneumonia, and no statistical reliability for differentiating bacterial

TABLE 2

Pneumonia Severity Index calculator and associated risk classes

Risk factor	Points
Demographics	
Men	Age (years)
Women	Age (years) – 10
Nursing home resident	+10
Comorbidities	
Neoplasm	+30
Liver disease	+20
Heart failure	+10
Stroke	+10
Renal failure	+10
Physical examination findings	
Altered mental status	+20
Respiratory rate > 30 breaths per minute	+20
Systolic blood pressure < 90 mm Hg	+20
Temperature < 95°F or > 104°F	+15
Heart rate > 125 beats per minute	+10
Laboratory and radiographic findings	
Arterial pH < 7.35	+30
Blood urea nitrogen > 30 mg/dL	+20
Sodium < 130 mmol/L	+20
Glucose > 250 mg/dL	+10
Hematocrit < 30%	+10
Partial pressure of arterial oxygen < 60 mm Hg	+10
Pleural effusion	+10

Risk class	Total points
I	< 51
II	51–70
III	71–90
IV	91–130
V	> 130

From Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997; 336(4):243–250. Copyright 1997, Massachusetts Medical Society. Reprinted with permission from the Massachusetts Medical Society..

TABLE 3

Severe pneumonia: Infectious Diseases Society of America and American Thoracic Society criteria

Major criteria

Respiratory distress requiring mechanical ventilation

Septic shock

Minor criteria

Confusion

Respiratory rate > 30 breaths per minute

Blood urea nitrogen > 7 mmol/L

Leukopenia resulting from infection

Thrombocytopenia

Hypothermia

Hypotension requiring aggressive fluids

$Pao_2/Fio_2 < 250$

Multilobar infiltrates

Having at least 1 major criterion or at least 3 minor criteria suggests the need for intensive care.

From Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44(suppl 2):S27–S72, by permission of Oxford University Press.

TABLE 4

Indications for blood culture testing in suspected community-acquired pneumonia

Intensive care unit admission

Cavitary infiltrates

Leukopenia

Active alcohol abuse

Chronic liver failure

Asplenia (anatomic or functional)

Positive pneumococcal urine antigen test

Pleural effusion

Based on information in reference 1.

from nonbacterial pneumonias.[10] A Swedish retrospective chart review of 103 outpatients with suspected CAP noted that just 88% of patients with high clinical concern for CAP demonstrated radiographic evidence of infection.[11]

Microbiology

A thorough social history should be gathered for every patient with suspected CAP to screen for potential occupational, travel, or endemic exposures. This will guide microbiologic testing and empiric antibiotic treatment.[1] For example, patients presenting during flu season or with known exposures to poultry in areas of prior influenza outbreaks should be screened for influenza A and B with a nasopharyngeal swab.

Isolating a specific organism in outpatients with CAP may not be necessary but is recommended to guide de-escalation of empiric antibiotic regimens.[1] Pretreatment Gram stain and culture in patients able to adequately expectorate a good-quality specimen or endotracheal aspirate in intubated patients should be collected. Patients fulfilling criteria for severe pneumonia as defined by the IDSA/ATS guidelines merit blood and sputum cultures as well as urinary antigen tests for *L pneumophila* and *S pneumoniae* (**Table 4**).[1]

Overall, active surveillance of more than 2,200 patients with CAP requiring hospitalization noted that 38% of blood and sputum cultures, nasopharyngeal and oropharyngeal swabs, and urinary antigens yielded a causative organism.[12] Viral organisms accounted for 25% of these cases and bacterial organisms accounted for 14%; 5% of patients with viral pneumonias were coinfected with either another respiratory virus or a bacterial organism.

Procalcitonin testing

Procalcitonin testing can help differentiate viral from bacterial pathogens in patients admitted for CAP, preventing the use of unnecessary antibiotics and allowing prompt de-escalation of empiric therapy more effectively than clinical judgment alone.[13] While any infectious pneumonia can precipitate elevations of this serum biomarker, typical bacteria tend to result in higher procalcitonin levels than atypical bacteria or viruses.[14] Cytokines, associated with bacterial infections, enhance procalcitonin release, while interferons, associated with

viral infections, inhibit procalcitonin release. This biomarker is not perfect, however, and will not be elevated in up to 23% of typical bacterial infections.[14]

For this reason, procalcitonin should not replace clinical judgment in guiding the decision to initiate antimicrobial therapy for patients with suspected CAP but can be used in conjunction with clinical judgment to de-escalate therapy. In patients whose clinical histories suggest alternative causes of respiratory distress or improvement with concomitantly administered therapies such as diuresis, a negative procalcitonin can help guide cessation of antibiotics. On the other hand, in patients with polymerase chain reaction-proven influenza, an elevated procalcitonin can suggest continuation of antibiotics to treat bacterial superinfection.

MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA

Antibiotic therapy

The selection of antibiotics before a causative pathogen is identified should be informed by the patient's risk factors and degree of illness (**Table 5, Table 6**).[1]

Patients on a medical floor should be started on either a respiratory fluoroquinolone or a combination of a beta-lactam plus a macrolide; intensive care patients should receive a beta-lactam plus either a macrolide or a respiratory fluoroquinolone. Doxycycline can be used as an alternative to the macrolide or respiratory fluoroquinolone to cover atypical organisms such as *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae* in patients with prolonged QTc. In penicillin-allergic patients, aztreonam should be used in combination with an aminoglycoside and a respiratory fluoroquinolone.

Patients who may have been exposed to influenza or who have a history of injection drug use or structural lung disease or who have a lung abscess, cavitary infiltrates, or endobronchial obstruction also merit coverage against community-acquired methicillin-resistant *S aureus* (MRSA) with vancomycin or linezolid. Those with confirmed or suspected influenza A presenting within 48 hours of symptom

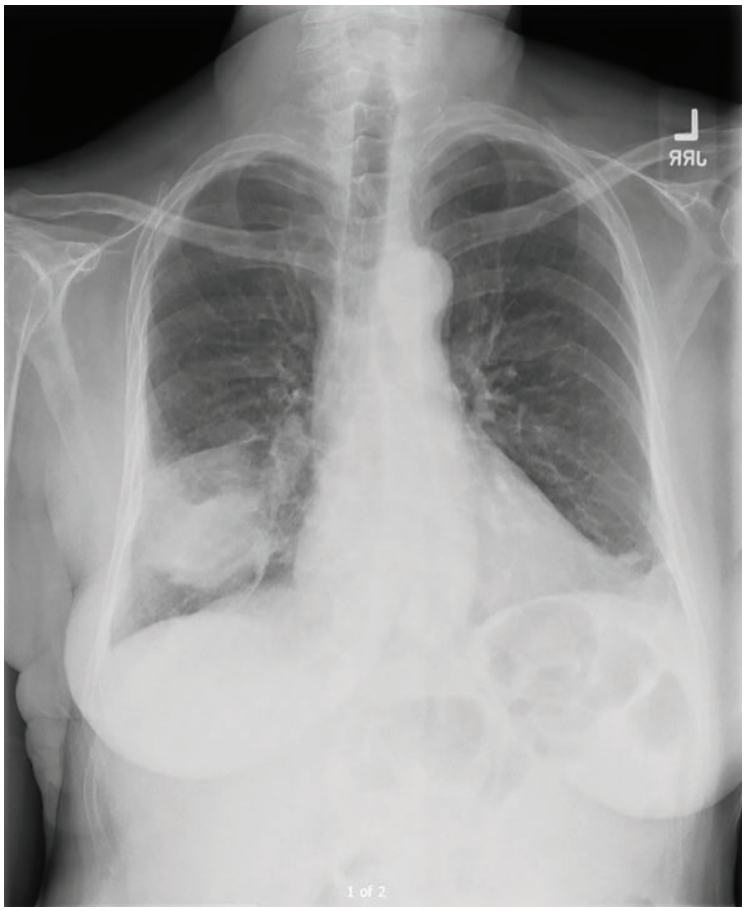

Figure 1. Focal lobar pneumonia.

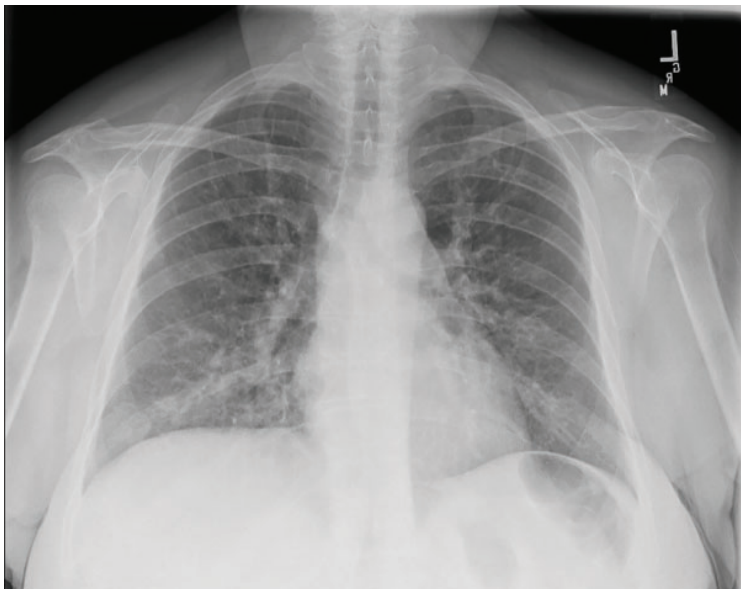

Figure 2. Diffuse interstitial pneumonia.

TABLE 5

Common organisms in community-acquired pneumonia

Outpatient care

Streptococcus pneumoniae

Mycoplasma pneumoniae

Haemophilus influenzae

Chlamydophila pneumoniae

Respiratory virus (influenza A and B, adenovirus, respiratory syncytial virus, parainfluenza)

Inpatient (non-intensive care)

S pneumoniae

M pneumoniae

C pneumoniae

H influenzae

Legionella species

Aspiration-related oral flora

Respiratory viruses

Inpatient (intensive care)

S pneumoniae

Staphylococcus aureus

Legionella species

Gram-negative bacilli

H influenzae

From Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44(suppl 2):S27–S72, by permission of Oxford University Press.

Use clinical judgment when triaging patients with community-acquired pneumonia

onset or with severe illness should be treated with oseltamivir.[1]

If an organism is identified by culture, polymerase chain reaction, or serology, the empiric antibiotic regimen should be tailored to this organism. MRSA nares screening can be reliably used to guide empiric and targeted antimicrobial regimens; patients started on vancomycin or linezolid based on the above-stated risk factors can be safely de-escalated on the basis of a negative nasal swab.[15] The pneumococcal urinary antigen has a similarly reliable negative predictive value and can also be used to de-escalate empiric antimicrobial therapy.[16]

Should microbiologic evaluation fail to identify a causative organism, the patient's individual risk factors as listed above must be considered in de-escalating therapy to a final regimen with coverage for MRSA, *Pseudomonas aeruginosa*, or atypical pathogens as indicated. Pseudomonal pneumonia has been associated with higher risk of mortality and relapse than pneumonia caused by other pathogens.

TABLE 6

Initial antibiotic therapy for community-acquired pneumonia

Outpatients without comorbidities[a]
Amoxicillin
Or doxycycline
Or a macrolide

Outpatients with comorbidities
Combination therapy:
Amoxicillin/clavulanate or a cephalosporin
Plus a macrolide or doxycycline
Or monotherapy with a fluoroquinolone

Patients on a medical floor
A fluoroquinolone
Or a combination of a beta-lactam plus a macrolide

Intensive care patients
A beta-lactam
Plus either a macrolide or a fluoroquinolone

Add coverage as needed for:
Methicillin-resistant *Staphylococcus aureus* (MRSA)
Pseudomonas aeruginosa
Influenza A

[a]Comorbidities include heart, lung, liver, or renal disease, diabetes mellitus, alcoholism, malignancy, and asplenia

Based on information from reference 1.

Corticosteroids as adjunctive therapy

The use of adjunctive corticosteroids for CAP management has been widely contested. The IDSA/ATS guidelines recommend against corticosteroid use for adjunctive treatment of CAP except in patients with refractory septic shock.[1]

Later management

Patients who are hemodynamically stable, can ingest medications safely, and have a normal gastrointestinal tract can be discharged

on oral therapy without waiting to observe the clinical response. Antibiotics should be given for at least 5 days, though longer durations may be needed in immunocompromised patients or in those with pulmonary or extrapulmonary complications.[1]

An infectious disease consultation may be beneficial if long-term intravenous antibiotic therapy is anticipated or if the patient progressively deteriorates on guideline-based antimicrobial therapy.

Pulmonary consultation may be needed for bronchoscopy to obtain deep respiratory samples, especially if the patient is clinically worsening and the causative pathogen remains unidentified. We acknowledge that the yield of bronchoscopy and bronchoalveolar lavage samples is reduced with longer durations of antibiotic therapy, yet believe that in the context of clinical worsening in spite of antibiotics, bronchoalveolar lavage may help successfully identify multidrug-resistant or atypical pathogens which may not be covered by the ongoing antibiotic regimen. Pulmonology consultation is also indicated for patients with complications of pneumonia such as empyema that require procedural intervention.

TAKE-HOME POINTS

- CAP continues to contribute to patient morbidity and mortality as well as healthcare costs.
- Professional societies have released collaborative guidelines to streamline practice patterns and provide evidence-based protocols for the diagnosis, treatment, and prevention of this common infection.
- Further research is needed to delineate appropriate strategies to de-escalate antibiotics in the absence of a causative organism, define the dose and duration of adjunctive steroid use, and clarify patient follow-up after discharge from the hospital.

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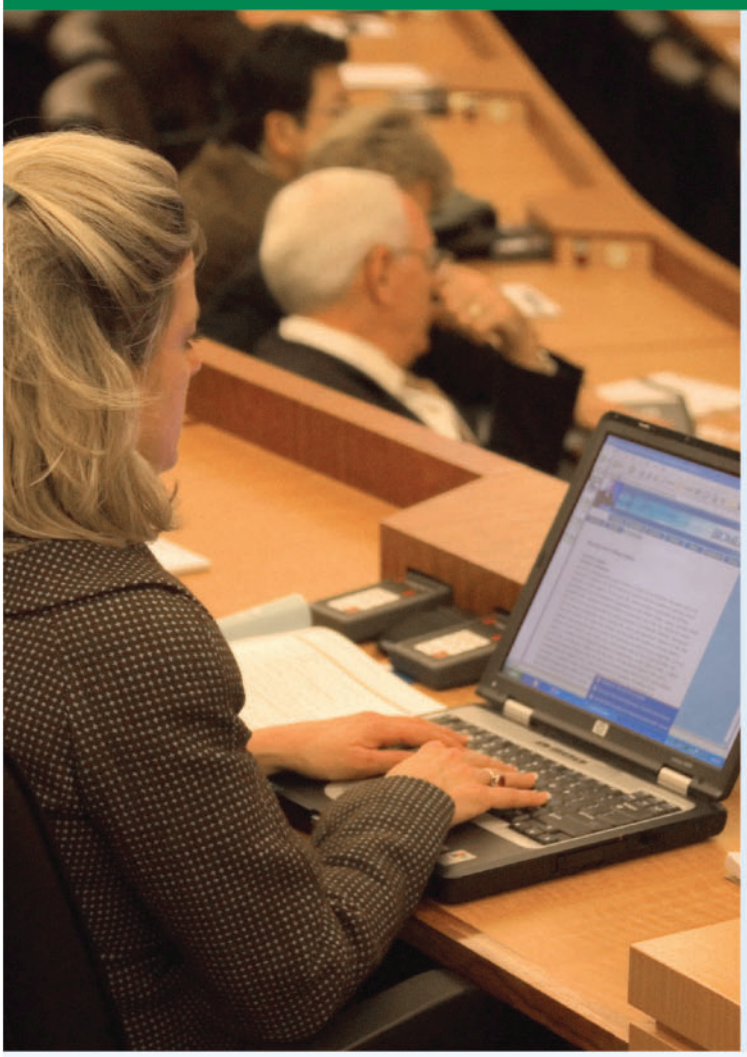

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Severe megaloblastic anemia: Vitamin deficiency and other causes

ABSTRACT

Megaloblastic anemia causes macrocytic anemia from ineffective red blood cell production and intramedullary hemolysis. The most common causes are folate (vitamin B_9) deficiency and cobalamin (vitamin B_{12}) deficiency. Megaloblastic anemia can be diagnosed based on characteristic morphologic and laboratory findings. However, other benign and neoplastic diseases need to be considered, particularly in severe cases. Therapy involves treating the underlying cause—eg, with vitamin supplementation in cases of deficiency, or with discontinuation of a suspected medication.

KEY POINTS

The hallmark of megaloblastic anemia is macrocytic anemia (mean corpuscular volume > 100 fL), often associated with other cytopenias.

Dysplastic features may be present and can be difficult to differentiate from myelodysplastic syndrome.

Megaloblastic anemia is most commonly caused by folate deficiency from dietary deficiency, alcoholism, or malabsorption syndromes or by vitamin B_{12} deficiency, usually due to pernicious anemia.

Both vitamin deficiencies cause hematologic signs and symptoms of anemia; vitamin B_{12} deficiency also causes neurologic symptoms.

Oral supplementation is available for both vitamin deficiencies; intramuscular vitamin B_{12} supplementation should be used in cases involving severe neurologic symptoms or gastric or bowel resection.

doi:10.3949/ccjm.87a.19072

Not all megaloblastic anemias result from vitamin deficiency, but most do. Determining the underlying cause and initiating prompt treatment are critical, as prognosis and management differ among the various conditions.

This article describes the pathobiology, presentation, evaluation, and treatment of severe megaloblastic anemia and its 2 most common causes: folate (vitamin B_9) and cobalamin (vitamin B_{12}) deficiency, with 2 representative case studies.

MEGALOBLASTIC ANEMIA OVERVIEW

Megaloblastic anemia is caused by defective DNA synthesis involving hematopoietic precursors, resulting in ineffective red blood cell production (erythropoiesis) and intramedullary hemolysis. Macrocytic anemia with increased mean corpuscular volume (MCV), defined as more than 100 fL, is the hallmark of megaloblastic anemia, but leukopenia and thrombocytopenia are also frequently present.

The incidence of macrocytosis is as high as 4% in the general population, but megaloblastic anemia accounts for only a small fraction.[1] Nonmegaloblastic causes of macrocytic anemia include ethanol abuse, myelodysplastic syndrome, aplastic anemia, hypothyroidism, liver disease, and drugs.[2,3] Although these causes are associated with increased MCV, they do not lead to the other features of megaloblastic anemia.

The most frequent causes of megaloblastic anemia are deficiencies of vitamin B_9 (folate) or vitamin B_{12} (cobalamin) (**Table 1**). Less-frequent causes include congenital disorders (inborn errors of metabolism), drugs (particu-

TABLE 1

Characteristics of vitamin B_{12} vs folate deficiency

	Vitamin B_{12} deficiency	Folate deficiency
Etiology	Lack of intrinsic factor: pernicious anemia Malabsorption: celiac disease, prior gastric or ileal surgery Dietary deficiency less common	Dietary deficiency: alcoholism, countries without food fortification Malabsorption: developed countries Increased demand: pregnancy, hemolytic anemia, eczema
Clinical presentation	Hematologic findings: cytopenias Neuropsychiatric symptoms: paresthesias, decreased proprioception and vibratory sense, dementia, confusion	Hematologic findings: cytopenias
Evaluation	Clinical history and physical examination: symptoms secondary to anemia and hemolysis, neurologic symptoms Laboratory testing: serum vitamin B_{12}, methylmalonic acid, homocysteine, antiparietal cell and anti-intrinsic factor antibodies, serum gastrin Gastric biopsy for suspected pernicious anemia	Clinical history and physical examination: similar to vitamin B_{12} deficiency, except no neurologic symptoms Laboratory testing: serum folate, red blood cell folate, methylmalonic acid, homocysteine
Differential diagnosis	Other macrocytic anemias without megaloblastic features: liver disease, thyroid dysfunction, alcohol abuse Myelodysplastic syndrome, acute myeloid leukemia Nitrous oxide exposure Medication effect	Other macrocytic anemias without megaloblastic features: liver disease, thyroid dysfunction, alcohol abuse Myelodysplastic syndrome, acute myeloid leukemia Medication effect
Treatment	Parenteral vitamin B_{12} 1–2 times per week until symptoms improve, then monthly High-dose oral vitamin B_{12} daily	Oral folate daily
Monitoring and follow-up	Clinical follow-up for improvement of neurologic symptoms Monitor hematologic response: complete blood cell count Pernicious anemia: consider monitoring methylmalonic acid	Monitor hematologic response: complete blood cell count

larly chemotherapeutics and folate antagonists), micronutrient deficiencies, and nitrous oxide exposure.[4,5]

FOLATE DEFICIENCY

Folate is found in green leafy vegetables, fruits, nuts, eggs, and meats. Normal body stores of folate are 5 to 30 mg. The recommended daily allowance depends on age, sex, and pregnancy status, but is generally 400 µg in adults and 600 µg during pregnancy.[6]

Folate deficiency has 3 main causes[4,5]:

- **Reduced intake** from diets lacking folate (rare in countries with vitamin fortification) and alcoholism (see **Case 1**)
- **Decreased absorption** from disorders affecting nutrient absorption in the small bowel, eg, celiac disease, inflammatory bowel disease, and tropical sprue
- **Increased demand** from pregnancy, hemolytic anemia, puberty, and eczematous conditions.

VITAMIN B_{12} DEFICIENCY

Vitamin B_{12} is produced by microorganisms and is found almost exclusively in foods of animal origin. Normal body stores of vitamin B_{12} are 3 to 5 mg, and the recommended adult daily intake is 2.4 µg.[7,8]

Causes of vitamin B_{12} deficiency are listed in **Table 2**. Dietary deficiency of vitamin B_{12} occurs less frequently than folate deficiency because body stores can last for years owing to efficient enterohepatic recycling mechanisms. Although uncommon, dietary B_{12} deficiency can occur even in industrialized countries in strict vegans and vegetarians, or in breastfed infants of mothers with vitamin B_{12} deficiency.

Complex absorption pathway

Dietary absorption of vitamin B_{12} is a complex process that begins with haptocorrin (also known as transcobalamin I or R-binder) production by the salivary glands.

When food is digested in the stomach by gastric acid and pepsin, free vitamin B_{12} is released and binds to haptocorrin.[4,9]

Simultaneously, gastric parietal cells secrete intrinsic factor, which cannot interact with the vitamin B_{12}-haptocorrin complex. Not until food moves into the duodenum, where trypsin and other pancreatic enzymes cleave haptocorrin, is vitamin B_{12} free to bind to intrinsic factor.[9] The resultant vitamin B_{12}-intrinsic factor complex binds to the cubam receptor on the mucosal surface of enterocytes in the ileum. From there, vitamin B_{12} is transported into the circulation by multidrug resistance protein 1, where it is readily bound by its transport protein transcobalamin II.[7,9]

The vitamin B_{12}-transcobalamin complex then binds to the transcobalamin receptors on hematopoietic stem cells (and other cell types), allowing uptake of the complex, with subsequent lysosomal degradation of transcobalamin. Free vitamin B_{12} is then available for cellular metabolism.

Nearly every step of this pathway can be disrupted in various pathologic states, but lack of intrinsic factor secondary to pernicious anemia is the cause of vitamin B_{12} deficiency in most cases.

TABLE 2

Causes of vitamin B_{12} deficiency

Common causes (related to malabsorption)
Autoimmune gastritis (pernicious anemia)
Celiac disease
Inflammatory bowel disease
Surgical gastrectomy, gastric bypass, ileal resection
Less common causes
Nutritional (strict vegans, breastfed infants of mothers with vitamin B_{12} deficiency)
Nitrous oxide abuse
Diphyllobothrium latum infection
Pancreatic insufficiency
Drug effect (metformin, proton pump inhibitors)
Inherited disorders affecting intrinsic factor or the cubam receptor
Rare inherited disorder (eg, methylmalonic acidemia, transcobalamin II deficiency)

Information from references 4, 5, and 7.

Pernicious anemia and autoimmune gastritis

Macrocytic anemia with a mean corpuscular volume > 100 fL is the hallmark of megaloblastic anemia

Chronic atrophic autoimmune gastritis is an autoimmune process directed specifically at either gastric parietal cells or intrinsic factor, or both.[10–12] Parietal cell damage leads to reduced production of gastric acid and intrinsic factor, accompanied by a compensatory increase in serum gastrin levels. Decreased intrinsic factor leads to significantly reduced absorption of dietary vitamin B_{12}, resulting in pernicious anemia.

Chronic atrophic autoimmune gastritis affects the body and fundus of the stomach, replacing normal oxyntic mucosa with atrophic-appearing mucosa, often with associated intestinal metaplasia.[11]

The associated inflammatory infiltrate consists predominantly of lymphocytes and plasma cells. Enterochromaffin-like cell hyperplasia is also seen in biopsies of the fundus or stomach body (highlighted by staining for chromogranin A and synaptophysin) and is thought to be a precursor to neuroendocrine (carcinoid) tumors. In addition to having vitamin B_{12} defi-

CASE 1: An older man with suspected myelodysplastic syndrome

A 68-year-old man with no significant past medical history presented from prison to the emergency department with fatigue, occasional shortness of breath, weight loss, and numbness and tingling of both hands.

Initial complete blood cell count findings showed pancytopenia with macrocytic anemia, with the following values:

- White blood cell count 1.81 × 10^9/L (reference range 4.5–10)
- Hemoglobin 6.2 g/dL (14–18)
- Mean corpuscular volume 121.5 fL (80–95)
- Platelet count 41 × 10^9/L (150–450).

Because of his clinical symptoms and severe pancytopenia with macrocytosis, bone marrow biopsy was performed to evaluate for myelodysplastic syndrome and acute leukemia.

Bone marrow biopsy results

Findings from bone marrow aspirate smear and core biopsy included the following (**Figure 1**):

- Hypercellularity (70%–80%; reference range 30%–70%)
- Erythroid hyperplasia, indicated by a reduced ratio of myeloid to erythroid precursor cells (0.7; reference range 2–4:1) and 2% blasts
- Severe megaloblastic changes in the erythroid and granulocytic lineages; erythroid precursors showed significant nuclear-cytoplasmic dyssynchrony, multinucleation, nuclear budding, nuclear irregularities, and basophilic stippling; granulocytic precursors showed hypersegmentation of mature neutrophils and occasional giant metamyelocytes and band forms
- Mildly increased ring sideroblasts (10%) seen with iron stain
- Megakaryocyte dysplasia in the form of small hypolobated forms.

Bone marrow findings of multilineage dysplasia, in addition to megaloblastic changes, were strongly suggestive of myelodysplastic syndrome.

Further evaluation

Additional testing yielded the following results:

- Serum folate level 18.1 ng/mL (> 4.7)
- Serum vitamin B_{12} level < 150 pg/mL (232–1,245)
- Parietal cell antibody positive (1:40)
- Conventional cytogenetics: normal male karyotype
- Hematologic neoplasm next-generation-sequencing panel (62 genes): negative for disease-associated mutations.

In conjunction with normal cytogenetic and next-generation-sequencing panel results, undetectable vitamin B_{12} levels helped confirm severe vitamin B_{12} deficiency. This may be the underlying cause of the cytopenias and dysplasia. It was speculated that a restricted diet during incarceration was the source of the problem.

Treatment

Intramuscular cyanocobalamin (1,000 µg) was started, followed by high-dose oral cyanocobalamin (1,000 µg/day). Abnormal complete blood cell count findings improved, as did neurologic symptoms.

ciency, patients with chronic atrophic autoimmune gastritis are at increased risk of gastric adenocarcinomas and neuroendocrine tumors.

Hyperplasia of gastrin cells can be identified using gastrin immunohistochemistry on gastric antral biopsies. Serologic testing for antiparietal and anti-intrinsic factor antibodies, as well as increased serum levels of gastrin, help confirm the diagnosis.[10–12]

FOLATE AND VITAMIN B_{12} METABOLISM ARE INTERTWINED

Folate and vitamin B_{12} metabolism are intimately interconnected, so deficiency in either vitamin leads to many similar manifestations. Both vitamins are involved in single carbon transfer (methylation), which is necessary for the conversion of deoxyuridylate to deoxythymidylate.[7] Insufficient folate or vitamin B_{12} leads to decreased thymidine available for DNA synthesis, hampering cell division and replication.

In pyrimidine synthesis, 5,10-methylenetetrahydrofolate serves as the methyl donor,[7] after which it is converted to dihydrofolate, which must be reduced and then methylated to be used again. The reduction of dihydrofolate to tetrahydrofolate by dihydrofolate re-

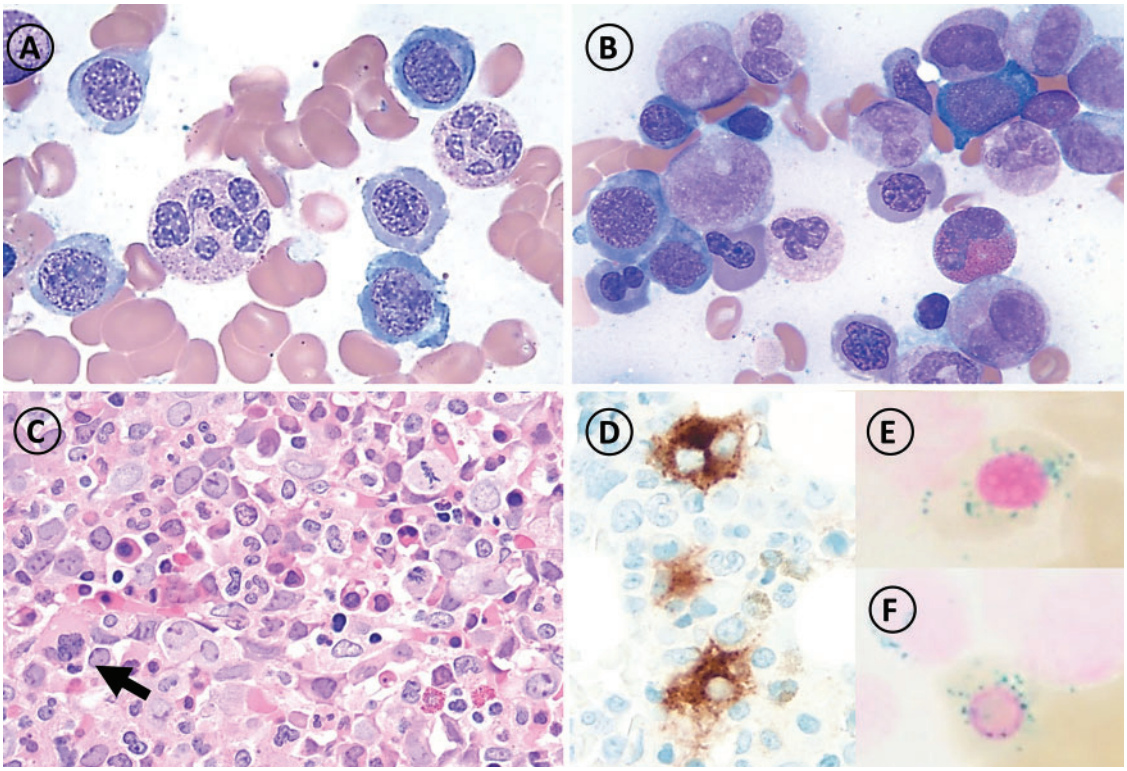

Figure 1. A,B: Bone marrow aspirate smears showing severe megaloblastic changes: nuclear-cytoplasmic dyssynchrony, binucleation, nuclear irregularity, and basophilic stippling in erythroid lineage cells, and also hypersegmentation, nuclear-cytoplasmic dyssynchrony, and giant metamyelocytes or band forms in granulocytes (Wright-Giemsa, × 1,000). **C:** Bone marrow core biopsy showing hypercellularity, erythroid hyperplasia, left shift in maturation, and small dysplastic megakaryocytes (arrow) (hematoxylin and eosin, × 400). **D:** Small dysplastic megakaryocytes highlighted by CD61 immunohistochemistry on the core biopsy. **E,F:** Increased ring sideroblasts in iron stain on the aspirate smears.

ductase is targeted by multiple drugs,[5,13] which have the effect of decreasing available deoxythymidylate for DNA synthesis, resulting in megaloblastic anemia.

DRUG EFFECTS

Owing to vitamin fortification of common foods in developed countries, megaloblastic anemia related to vitamin deficiency is increasingly uncommon.[2,14] However, this reduced incidence is offset by a growing list of drugs that can cause megaloblastic anemia by interfering with DNA synthesis in various ways.[2,4,13]

Drugs that affect purine synthesis include[2,13]:

- Immunosuppressants, eg, azathioprine and mycophenolate mofetil
- Chemotherapeutics, eg, purine analogues (fludarabine, cladribine, and thioguanine)
- Allopurinol, a xanthine oxidase inhibitor used to treat gout.

Drugs that affect pyrimidine synthesis include[13]:

- Immunomodulatory drugs, eg, leflunomide and teriflunomide
- Chemotherapeutics, eg, cytarabine, gemcitabine, and fluorouracil
- Methotrexate, an immunosuppressant and chemotherapeutic
- Sulfa drugs and trimethoprim.

Numerous drugs from multiple classes can reduce folate or vitamin B_{12} absorption, although this rarely leads to clinically significant deficiency.

CASE 2: A young woman with worsening anemia and family history of autoimmune disease

A young woman, age 17, presented to the emergency department with headache and abdominal pain that had worsened over the previous month. She had sought medical care several times over the past 6 months with similar symptoms, when moderate anemia was attributed to iron deficiency from heavy menses (the most common cause of anemia in women of reproductive age). Family history was notable for her sister having autoimmune thyroid disease and type 1 diabetes mellitus. On additional questioning, she reported paresthesias in the hands. Physical examination revealed decreased proprioception and vibratory sense and a wide-based gait.

Results of initial testing were as follows:

- Hemoglobin 6.8 g/dL (down from 8.5 g/dL at her last visit)
- Mean corpuscular volume 104.2 fL (elevated)
- White blood cell count 6.91 × 10^9/L (normal)
- Platelet count 300 × 10^9/L (normal)
- Peripheral blood smear: several hypersegmented neutrophils with no left-shift in maturation (**Figure 2**).

Further tests were performed:

- Direct antiglobulin test negative
- Serum iron, ferritin, and total iron-binding capacity normal
- Haptoglobin < 10 mg/dL (reference range 31–238)
- Lactate dehydrogenase 4,131 U/L (135–214)
- Relative reticulocytosis—reticulocyte count 48 × 10^9/L (18–100); 2.6% (0.4%–2.0%).
- Serum vitamin B_{12} < 150 pg/mL (232–1,245)
- Serum folate normal
- Serum methylmalonic acid 8,361 nmol/L (79–376)
- Antiparietal cell antibody negative
- Anti-intrinsic factor antibody positive.

The laboratory and clinical findings were consistent with vitamin B_{12} deficiency, and the presence of anti-intrinsic factor antibody confirmed the diagnosis of pernicious anemia. Although it tends to occur in older women, it is occasionally seen in young adults. A strong family history of autoimmune disease is common in patients with pernicious anemia.

She was also tested for the following:

- Serum thyroid-stimulating hormone level 6.72 µU/mL (0.40–2.80)
- Free thyroxine 1.3 ng/dL (0.8–1.5)
- Thyroid peroxidase antibody 1,224 IU/mL (< 5.6).

These findings indicate she is at risk for developing symptomatic thyroid disease.

Treatment

Treatment was started with parenteral cyanocobalamin, at first with daily intramuscular 1,000-µg cyanocobalamin injections. Treatments were then weekly, then monthly, with rapid improvement of hematologic symptoms and slower but complete resolution of her neurologic symptoms.

Future considerations

Given the personal and family history of autoimmune disease, a diagnosis of polyglandular autoimmune syndrome should be considered. Extensive clinical and laboratory evaluation for other signs of autoimmune disease is warranted. Antiadrenal and GAD65 antibody testing should be performed to assess risk for developing adrenal insufficiency.

CLINICAL FEATURES

Vitamin B_{12} deficiency causes hematologic and neuropsychiatric manifestations that may occur together or independently.[15,16] Megaloblastic anemia due to folate deficiency and other causes shares the same hematologic manifestations as vitamin B_{12} deficiency but lacks the neurologic features (see **Case 2**).[4,7]

Hematologic features

The most common hematologic manifestation is megaloblastic anemia, which includes macrocytic erythrocytes in the peripheral blood and megaloblastic precursor cells in the bone marrow that exhibit nuclear-to-cytoplasmic dyssynchrony.[7] Ineffective erythropoiesis leads to intramedullary hemolysis, classically with high lactate dehydrogenase and undetectable haptoglobin, but without schistocytes in the peripheral blood.

Symptoms secondary to anemia include fatigue, shortness of breath, and poor exercise tolerance.

Neuropsychiatric features

Vitamin B_{12} deficiency can cause subacute combined degeneration of the dorsal and lateral columns of the spinal cord. Patients may experience bilateral and symmetrical pares-

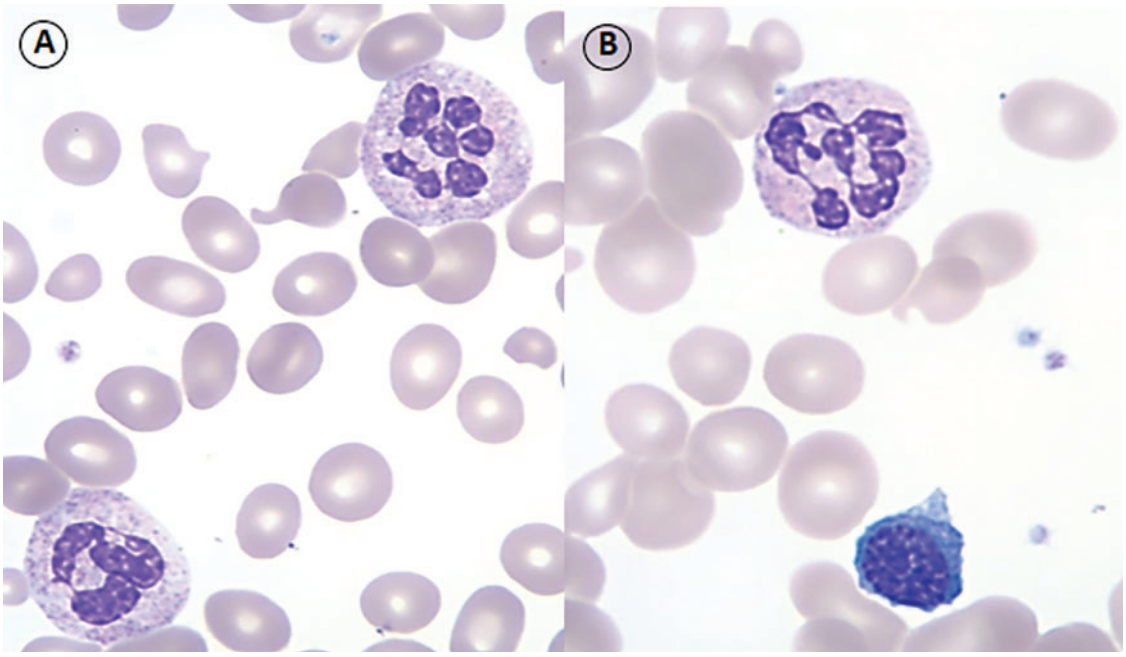

Figure 2. A,B: Two hypersegmented neutrophils (> 6 nuclear lobes) in a peripheral blood smear (Wright-Giemsa, × 1,000).

thesia and decreased vibratory and positional sense. Psychiatric manifestations include memory loss, delirium, dementia, depression, mania, and hallucinations.[15,17,18]

Atypical presentations

Although neuropsychiatric symptoms often develop after hematologic abnormalities, more than 25% of patients with neurologic manifestations of vitamin B_{12} deficiency have either a normal hematocrit or a normal MCV.[17]

Why certain patients are prone to hematologic complications of vitamin deficiency and other patients have neurologic sequelae remains unclear, but those with underlying abnormalities such as pre-existing neurologic comorbidities or bone marrow failure conditions may be more likely to develop side effects related to those conditions.

Other findings

An increased risk of thrombosis is seen in vitamin B_{12} and folate deficiency, possibly as a consequence of hyperhomocysteinemia.[19] Atrophic glossitis (swollen, erythematous, smooth tongue) is a common, albeit nonspecific, finding in vitamin B_{12} deficiency.

INITIAL EVALUATION

While there is no gold standard for diagnosing megaloblastic anemia, appropriate clinical and laboratory evaluation can usually establish the correct diagnosis.

Diets lacking folate are rare in countries with vitamin fortification

History and physical examination

A complete history and physical examination are imperative. Targeted questions should cover the following areas[20]:

- Diet—vegan or vegetarian?
- Surgical history—gastric or ileal resection?
- Gastrointestinal symptoms—celiac disease or gastritis?
- Neurologic symptoms such as paresthesias, numbness, ataxia, or gait disturbances?
- Medications—folate antagonists, chemotherapeutics?

Initial blood work

The complete blood cell count reveals anemia that is generally macrocytic (MCV > 100 fL). Anemia can be seen in isolation or with leukopenia or thrombocytopenia. Note that concurrent iron deficiency anemia can result in a normal MCV but increased red cell distribution width.

The peripheral blood smear shows morphologic changes in red blood cells (RBCs),

including marked size variation (anisocytosis) and abnormal morphology (poikilocytosis), including macro-ovalocytes, teardrop cells, microcytes, and in severe cases, schistocytes, basophilic stippling, Howell-Jolly bodies, and nucleated RBCs.

Polychromasia is not typically present. In the setting of cytopenias and neurologic symptoms, absence of schistocytes excludes thrombotic thrombocytopenic purpura.

Hypersegmented neutrophils (ie, ≥ 1% of neutrophils having 6 or more nuclear lobes, or ≥ 5% of neutrophils with 5 nuclear lobes) in the setting of macrocytic anemia are considered specific for megaloblastic anemia and are rarely seen in other diseases.[2,7]

Folate laboratory evaluation

Laboratory testing for suspected folate deficiency starts with evaluating serum or plasma folate. Fasting serum folate generally reflects tissue levels of folate; however, postprandial increases in folate occur and can cause falsely normal results in nonfasting samples.[6] After a meal, increased serum folate occurs within 2 hours, then quickly returns to baseline. Falsely elevated folate levels can also be seen with sample hemolysis and vitamin B_{12} deficiency. In the latter situation, inadequate vitamin B_{12} causes folate to be trapped in the 5-methyltetrahydrofolate state.[5]

An alternative method of evaluating folate stores is RBC folate, which reflects the folate status of the prior 3 months and has the advantage of not being affected by recent dietary intake. Disadvantages include slower turn-around time and higher cost. Also, recent transfusion of RBCs can lead to inaccurate results, as it will reflect the folate level of the donor.

Lack of intrinsic factor secondary to pernicious anemia is the cause of vitamin B_{12} deficiency in most cases

Vitamin B_{12} laboratory evaluation

Specific laboratory evaluation for vitamin B_{12} deficiency begins with total serum cobalamin levels.[21,22] Vitamin B_{12} levels lower than 200 pg/mL are highly suggestive of deficiency, although false-positive and false-negative results can happen. A normal cobalamin level makes deficiency unlikely, although it may occur in nitrous oxide exposure or abuse, which involves metabolically inactive vitamin B_{12}.[7] In addition, in pernicious anemia, anti-intrinsic factor antibodies can interfere with vitamin B_{12} assays, leading to falsely normal results.[5] On the other hand, pregnancy, drugs such as oral contraceptives and anticonvulsants, human immunodeficiency virus infection, and folate deficiency can falsely reduce vitamin B_{12} levels.

For borderline cobalamin levels (200–400 pg/mL), additional laboratory testing, including serum methylmalonic acid and serum homocysteine levels, should be performed.[5] Methylmalonic acid and homocysteine are intermediaries in vitamin B_{12} metabolism and are increased in vitamin B_{12} deficiency. Homocysteine is also elevated in folate deficiency and renal disease but methylmalonic acid is not, making it a more specific marker of vitamin B_{12} deficiency.[4]

Vitamin B_{12} deficiency secondary to increased intramedullary destruction of RBC precursors can cause undetectable haptoglobin levels and elevated lactate dehydrogenase and indirect bilirubin.

For suspected pernicious anemia, serologic testing for antiparietal cell and anti-intrinsic factor antibodies, as well as gastrin, are useful.[10] Antiparietal cell antibodies in patients with autoimmune pernicious anemia demonstrate high sensitivity (81%) and specificity (90%), while anti-intrinsic factor antibodies have high specificity (100%) but low sensitivity (27%–50%). The combination of these 2 tests significantly increases their diagnostic performance, with 73% sensitivity and 100% specificity in pernicious anemia.[23,24] Elevated gastrin is highly sensitive (85%) for pernicious anemia; however, it can also be elevated in Zollinger-Ellison syndrome, therapy with proton pump inhibitors or histamine 2 receptor blockers, *Helicobacter pylori* infection, or renal failure.[4,24]

SPECIAL TESTING

Neuroimaging for atypical cases

Neuroimaging is unnecessary for patients with a classic clinical presentation of vitamin B_{12} deficiency. However, in suspected cases without hematologic manifestations, magnetic resonance imaging is indicated. The most consistent finding in vitamin B_{12} deficiency is a symmetric, abnormally increased T2 signal intensity, involving the posterior or lateral columns (or both) in the cervical and thoracic spinal cord.[14]

Bone marrow aspiration and biopsy

If vitamin deficiency or drug effects cannot be determined clinically and by laboratory testing as the cause of anemia, bone marrow biopsy may provide useful information. In megaloblastic anemia, the bone marrow shows the following:

- Hypercellularity for age
- Erythroid predominance, with a decreased myeloid-to-erythroid ratio
- A left-shift in hematopoietic maturation.

Megaloblastic changes are best appreciated with bone marrow aspirate smears using Wright-Giemsa stain. The typical findings in the erythroid lineage include increased overall size and nuclear-cytoplasmic dyssynchrony (ie, a large, immature-appearing nucleus with an open chromatin pattern accompanied by a mature-appearing cytoplasm).[7] Findings are also apparent in the granulocytic lineage, as seen by giant metamyelocytes and bands.[7] Hypersegmented neutrophils can be seen in either peripheral blood or bone marrow smears. Occasionally, megakaryocytes are also affected, with large forms having hyperlobation and decreased cytoplasmic granularity.

In severe vitamin deficiency, dysplastic features can be observed, most often involving the erythroid lineage in the form of nuclear irregularities, eg, binucleation, multinucleation, nuclear fragmentation, and nuclear budding, which resemble features seen in myelodysplastic syndrome (see "Differential diagnosis" below).

Severe ineffective hematopoiesis can markedly increase iron stores (detectable with iron stain), although ring sideroblasts are rarely seen in megaloblastic anemia.

Gastric biopsy

Gastric biopsy can confirm chronic atrophic autoimmune gastritis.

DIFFERENTIAL DIAGNOSIS

Establishing the correct diagnosis of megaloblastic anemia is paramount, as the treatment and prognosis for different conditions can be vastly different. The differential diagnosis includes conditions that cause nonmegaloblastic macrocytic anemia, such as medication effects, ethanol abuse, hypothyroidism, liver disease, and post-splenectomy status. A detailed clinical and medication history and laboratory findings, including vitamin B_{12} and folate levels, can help determine the correct diagnosis.

Megaloblastic anemia can also mimic malignant conditions. Cytopenias, combined with severe megaloblastic findings in the bone marrow, overlap with the neoplastic processes of low-grade myelodysplastic syndrome or acute myeloid leukemia.[3,25,26] Diagnostic considerations include myelodysplastic syndrome with excess blasts and erythroid predominance, as well as pure erythroid leukemia (ie, a neoplastic proliferation of immature erythroid cells with > 80% erythroids and > 30% proerythroblasts) without increased myeloid blasts.[27]

Although myelodysplastic syndrome and severe megaloblastic anemia have overlapping features, careful morphologic evaluation of the bone marrow aspirate and biopsy can identify differentiating characteristics. Dysplastic features characteristic of myelodysplastic syndrome that are not typical of megaloblastic anemia include the following:

- Hyposegmentation or hypogranulation of granulocytes
- Hypolobation or small forms of megakaryocytes
- Hypogranular platelets
- Increased blasts.

Laboratory findings, including vitamin B_{12} and folate levels, conventional cytogenetics, and next-generation sequencing, can also help distinguish the 2 entities.[26] Identifying an acquired clonal abnormality, such as a myelodysplastic syndrome-associated cytogenetic abnormality or mutation, would strongly support a neoplastic process.

Vitamin B_{12} deficiency causes hematologic and neuropsychiatric manifestations

TREAT UNDERLYING PROBLEM

After establishing the diagnosis, treatment should be initiated promptly. Treatment is specific to the underlying condition and usually involves supplementing the deficient vitamin. With either vitamin B_{12} or folate supplementation, the rapid bone marrow response can push borderline iron stores into deficiency, so patients should be monitored for iron and provided with supplementation as needed. Megaloblastic anemia secondary

TABLE 3

Estimated cost of treatment per month for vitamin B_{12} and folate deficiency[a]

Formulation		Dose	Cost per month
Vitamin B_{12}	Intramuscular injection	1,000 µg/mL, single vial of 1 mL	$5–$15
	Oral	1,000 µg/pill, 30 pills per month	$2–$5
	Nasal spray	500 µg/spray, single spray per day, carton of 4	$500–$640
	Sublingual lozenges	3,000 µg/lozenge, single lozenge per day, ~ 30 lozenges per month	$5
Folic acid		1 mg/pill, 30 pills per month	$3–$5

[a]The dose and cost are adapted from GoodRx.com.

to drug effect is best treated by stopping the causative agent if feasible.

Generally, response to therapy is rapid, with hemoglobin levels improving within a week. Neurologic symptoms of vitamin B_{12} deficiency generally resolve more slowly than hematologic symptoms and may not resolve completely.

Hypersegmented neutrophils in the setting of macrocytic anemia are considered specific for megaloblastic anemia

FOLATE SUPPLEMENTATION

Megaloblastic anemia secondary to folate deficiency is generally treated with oral folate, as it is most often caused by dietary deficiency rather than malabsorption. For supplementation and treatment, it is available as either of the following:

- The synthetic form, known as folic acid or pteroylglutamic acid
- The naturally occurring form, folinic acid.

Folate deficiency is typically treated with oral folic acid 1 to 5 mg per day.[28] This dosage is more than the recommended dietary allowance of 400 µg per day, thereby allowing for adequate repletion even in the setting of malabsorption. Treatment is continued for the duration of hematologic recovery or until the cause of deficiency is addressed. In patients with malabsorption, treatment is continued indefinitely.

VITAMIN B_{12} SUPPLEMENTATION

Prompt treatment is particularly important for patients with vitamin B_{12} deficiency in order to prevent neurologic symptoms from becoming permanent.

Multiple supplementation options are available, with the choice depending on clinical and nonclinical factors. All forms are generally well tolerated, but adverse reactions such as hypersensitivity have been reported.[28,29]

Formulations vary

Vitamin B_{12} can be supplemented in different forms; noted preferences vary worldwide: cyanocobalamin in the United States, hydroxycobalamin in Europe, and methylcobalamin in Asia.[30] Although all forms are well absorbed, hydroxycobalamin may be best for those with inherited errors of cobalamin metabolism. Cyanocobalamin is more expensive but appears to be more stable for oral supplementation.

Vitamin B_{12} is available as a pill, sublingual lozenge, intranasal spray, and intramuscular injection. Oral and intramuscular administration are the most widely studied and used.

Oral vs intramuscular vitamin B_{12}

About 1.2% of oral cobalamin is passively absorbed unbound, while the remainder requires intrinsic factor to be absorbed in the ileum.[31] Eussen et al[32] found that high-dose oral vitamin B_{12} (> 200 × the recommended dietary allowance of 2.4 µg/day) produces adequate reductions in methylmalonic acid. However, despite multiple studies demonstrating the effectiveness of oral vitamin B_{12} even in pernicious anemia, a 2018 Cochrane review[33] found a lack of data demonstrating equivalence to intramuscular administration, mainly due to a limited number of quality randomized studies.

The most common oral dosage is 1,000 to 2,000 µg daily, compared with 1,000 µg intramuscularly daily for 7 days, then weekly for a month, then monthly thereafter.[34]

Advantages of intramuscular administration include improved adherence and less-frequent dosing during the monthly maintenance stage of treatment. As intramuscular administration avoids reliance on gastrointestinal tract absorption, it is particularly useful in patients who have undergone bowel surgeries or in patients with severe neurologic impairments who need optimal and quick repletion of vitamin B_{12}. Unless the patient self-administers it, the main disadvantages are the inconvenience and increased costs associated with receiving it at a medical facility. Actual monthly costs of oral and intramuscular formulations are otherwise similar (**Table 3**).[35]

In general, mild vitamin B_{12} deficiency should be treated with oral dosing, reserving intramuscular dosing for patients with significant neurologic symptoms, adherence issues, or extensive gastric or bowel resections. Patients with neurologic symptoms should have frequent injections until neurologic symptoms have disappeared and undergo more extended treatment if symptoms are severe.

Intranasal

Given the variable absorption of intranasal supplementation, closer clinical and serum methylmalonic acid monitoring is indicated to ensure therapeutic response. If the response is inadequate, switching to the intramuscular route should be considered.

Monitoring

There is no standard approach to monitoring response. Symptoms of anemia usually improve fairly quickly, but neurologic symptoms tend to resolve slowly or incompletely. The severity of neurologic symptoms at diagnosis may be predictive of outcome.[3,36]

Serum vitamin B_{12} levels fluctuate significantly with the timing of oral or intramuscular dosing, making testing of little value except in diagnosis. Serum methylmalonic acid levels do not necessarily correlate well with clinical improvement, as patients sometimes continue to report symptoms after levels have normalized. Therefore, a combination of clinical and laboratory testing is used to monitor therapy response.

Laboratory testing should include complete blood cell and reticulocyte counts. The reticulocyte count should increase after approximately 2 to 3 days, peaking at 5 to 7 days.[37] We recommend checking a complete blood cell count and reticulocyte count 4 weeks after the initiation of vitamin B_{12} therapy. The time point will also give an opportunity to reassess the symptoms and plan a transition to less-frequent dosing, if the response is adequate.

Hemoglobin typically starts increasing in a week, with expected complete normalization in 4 to 8 weeks.[37] Delayed or incomplete response should prompt further evaluation for other causes of anemia, including iron deficiency. In their dose-finding study, Eussen et al[32] reported absolute reductions of serum methylmalonic acid concentrations of at least 0.22 µmol/L at initial testing at 8 weeks and also at 16 weeks. Although the expected reduction of methylmalonic acid level is not standardized to vitamin B_{12} dosage, evidence nevertheless supports monitoring methylmalonic acid levels to assess response to B_{12} supplementation, especially in patients with pernicious anemia.[32,37] We recommend doing this at 4 weeks after initiation and on follow-up every 6 months to a year, as long as the complete blood cell count remains normal and there are no new symptoms. ■

Testing for suspected folate deficiency starts with serum or plasma folate

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REVIEW

CME MOC

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Restrictive eating disorders in previously overweight adolescents and young adults

ABSTRACT

Eating disorders are common in adolescents and young adults, including those with a history of overweight or obesity, and are associated with numerous systemic sequelae. Understanding the differences in presentation between these patients and those who have a more classic anorexia nervosa phenotype is critical to ensuring timely recognition and treatment.

KEY POINTS

Patients who are overweight or obese are as likely to experience disordered eating as their normal-weight peers.

Patients with a history of premorbid overweight or obesity present differently than their previously healthy weight peers in clinic.

Malnutrition resulting from restrictive eating disorders affects many systems in the body and can occur even in the face of obesity or overweight status.

Few studies have assessed treatment goals and recovery course in previously overweight patients presenting with eating disorders, making it difficult to use evidence-based medicine to manage these cases and assess response to treatment.

doi:10.3949/ccjm.87a.19034

Jeannette is a 22-year-old woman who presents with a chief complaint of fatigue. A history reveals that she has lost weight in the past 6 months—she used to weigh 220 lb but now weighs 180; her height is 5'4". She lost weight by reducing her portion sizes, eliminating junk food and anything else "unhealthy," attending a spinning class 4 days a week, and walking at least 10,000 steps every day, as recommended at her well visit a year ago when her body mass index (BMI) was 37.8 kg/m^2. Her BMI is now 30.9 kg/m^2. On examination, her heart rate is 50 beats per minute, and she has mild orthostatic changes in pulse but not in blood pressure. What do you think is going on?

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Some patients with restrictive eating disorders are hiding in plain sight. Although a patient who starts at 120 lb and loses 40 will look anorectic, someone who starts at 220 lb and comes in weighing 180 may not, despite losing the same amount of weight through the same disordered eating behaviors and putting herself or himself at the same risk of physical harm through starvation.

Patients who are overweight or obese are in a tough position. We *want* them to lose weight, but we want them to do so safely. Restrictive eating disorders tend to be underrecognized in this group, even though research suggests that these patients may have a greater likelihood of disordered eating habits than those with no history of overweight or obesity. It is therefore important for primary care physicians to consider eating disorders in young patients at a variety of weights.

This paper discusses the distinguishing features of eating disorders in patients with a history of overweight or obesity, the systemic effects of malnutrition in the body, and general guidelines for medical management.

RISING OBESITY RATES MEET UNREALISTIC NORMS

In today's body-conscious world, marketers aggressively advertise weight-loss strategies to the public, especially adolescents and young adults. Given that many young people are overweight or obese and that the campaigns tend to focus on the negative effects of excess body fat, disordered eating has been normalized and, in some settings, encouraged. Successful weight loss is praised, even though the methods may be pathologic and involve eating disorder attitudes or behaviors.

It is therefore not surprising that eating disorders are common among children, adolescents, and adults, including those who are overweight or obese.

COMMON AND UNDERRECOGNIZED

Heavier patients are as likely to have disordered eating as are their peers with normal weight

A systematic review of 94 studies published between 2000 and 2018 reported that the prevalence of eating disorders in the United States was 4.6%, with lower rates in Europe (2.2%) and Asia (3.5%), and higher rates in women (5.7%) than in men (2.2%).[1] The onset of these disorders peaks in adolescence and young adulthood and is associated with poor physical and psychological outcomes.[2]

Although one study reported that a higher percentage of men with eating disorders had a history of premorbid overweight than women, another found no difference by sex.[3,4]

Traditionally, restrictive eating disorders were characterized by low weight or failure to grow appropriately within expected growth curves, maladaptive weight loss strategies, and fear of weight gain. However, these criteria were modified in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), demonstrating the evolving clinical understanding of restrictive eating disorders. Of note, the numeric definition of low weight as less than 85% of median body weight for age has been modified to include patients with less than minimally normal weight. These changes reflect the growing recognition that disordered eating behaviors and associated sequelae can occur at a variety of weights.

In adolescents and young adults with restrictive eating disorders, the prevalence of a history of overweight or obesity ranges from 19.3% to 36.7%.[3–5] These numbers mirror the national prevalence of overweight or obesity, suggesting that patients with higher weight status are as likely to experience disordered eating as their normal-weight peers.[4]

Indeed, overweight adolescents report greater concern about their weight and more body dissatisfaction than their normal-weight peers.[6] These concerns could lead them to engage in disordered eating behaviors, including bingeing, purging, and diet pill use.[6–9] There is now a greater recognition of eating disorder diagnoses in young adults who may not meet low-weight criteria but otherwise have classic symptoms.

GREATER WEIGHT SUPPRESSION IN PREVIOUSLY OVERWEIGHT PATIENTS

Although they present with a higher BMI compared with patients with anorexia nervosa or bulimia nervosa who started out in the normal-weight category, those who started out overweight or obese lose more weight (have greater "weight suppression"), whether the change is measured in kilograms, BMI, or percent body weight.[3,4] The higher weight at presentation results in a more common diagnosis of atypical anorexia nervosa in these patients.[3]

The amount of weight suppression is a valuable indication of disease severity as well as a prognostic tool.[3,4] A greater percent weight loss has been associated with worse psychological and physical symptoms in patients with anorexia nervosa.[10,11] A position paper from the Society for Adolescent Health and Medicine has advocated for greater recognition of the clinical utility of percent weight loss and emphasizes the dual roles of weight status as well as rate and relative amount of weight loss.[12]

When the degree of weight suppression based on percent body weight loss is considered, then there is no difference in the likelihood of inpatient treatment, suggesting that weight suppression is a more appropriate met-

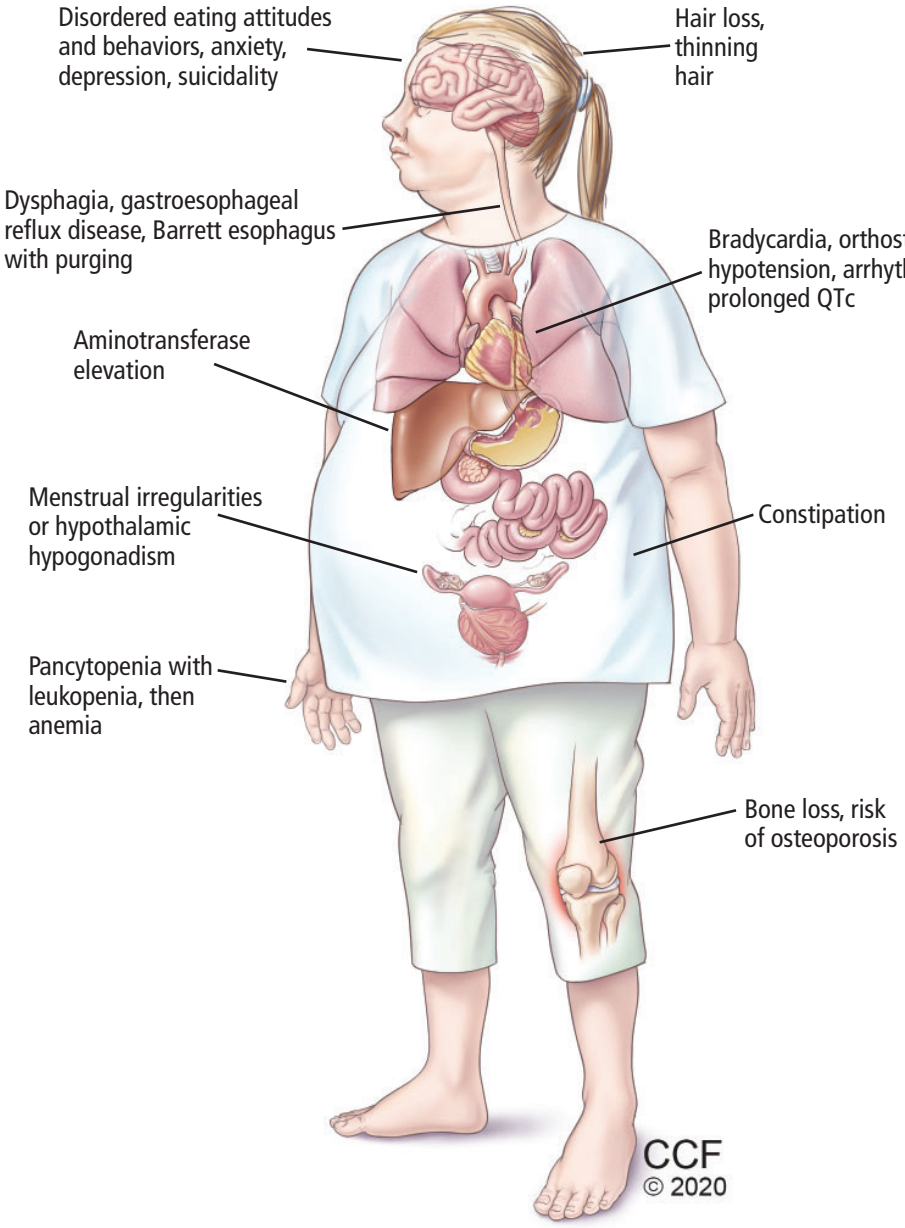

Figure 1. Sequelae and correlates of unhealthy weight loss.

Patients with a history of overweight or obesity present with greater absolute weight loss, but higher BMI

ric of starvation state than absolute weight status.[3]

Previously overweight adolescents are less likely to receive inpatient treatment despite similar symptoms compared with their previously normal weight peers.[3] This discrepancy has been attributed to the higher weight at presentation.[3] This relationship was found to be mediated by weight suppression, supporting the trend toward assessing degree of weight loss rather than focusing primarily on presentation weight when evaluating for eating disorder symptoms.[3]

Comparisons of eating disorder symptom burden based on the Eating Disorder Examination-Questionnaire reveal that previously overweight patients have similar symptoms such as degree of restraint around food and concern about shape or weight.[4] However, overweight and obese children are more at

risk than their normal-weight peers of engaging in disordered eating behaviors and exhibiting unhealthy weight loss strategies.[13]

Finally, the duration of illness before presentation may be more variable. Two studies[3,4] found that the duration of illness is significantly longer in patients with higher premorbid BMIs, whereas another reported that the duration of illness was comparable to that among healthy-weight peers who developed restrictive eating disorders.[14] These discrepancies may be explained by differences in definitions or small sample sizes.

SYSTEMIC EFFECTS OF MALNUTRITION

The malnutrition resulting from restrictive eating disorders affects every system in the body and can occur even in the face of obese or overweight status, as seen in the case of Jeannette. Consequences (**Figure 1**) can be lifelong and include the following:

Cardiovascular manifestations such as bradycardia and hypotension, possibly secondary to increased vagal tone.[15,16] Consistent hypotension may cause decreased left ventricular mass, resulting in decreased cardiac output.[15] Additionally, abnormal electrolyte levels and vagal tone can contribute to arrhythmias such as prolonged QTc interval.[15,16]

Recognize eating disorders as readily in a patient who shifts from 220 to 180 lb as in a patient who went from 120 to 80 lb

Gastrointestinal effects include gastroparesis and constipation from slow colonic transit.[15,16] In an extremely underweight patient, loss of fat that normally cushions the superior mesenteric artery (SMA) can result in SMA syndrome, in which the duodenum is pinched between the SMA and the aorta and consequently dilates. Dysphagia from weakening of pharyngeal muscles can hinder refeeding and result in aspiration. Patients can also have aminotransferase elevations due to liver cell apoptosis.[15,16]

Hematologic effects include pancytopenias due to a hypoplastic marrow with fat deposition within the marrow space.[15-18] Despite the neutropenia, patients with eating disorders are not at higher risk of infections. However, impaired inflammatory responses may result in slower recognition of an infection.[15,16]

Musculoskeletal effects. Patients with eating disorders are at risk of losing both muscle and bone mass. Bones have both altered structure and decreased strength.[15,16,18] Contributors to weakened bone include derangements in the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis, as well as thyroid dysfunction. Adolescent girls with anorexia were found to have increased fracture risk even in the absence of decreased bone mineral density as measured by dual energy x-ray absorptiometry, suggesting that loss of mass incompletely explains the bone sequelae of eating disorders.[18]

Hormone disturbances include low insulin-like growth factor 1 and estrogen levels, leading to decreased bone deposition, increased resorption, osteopenia, and osteoporosis.[15] In addition, there may be impaired thyroid response to low thyroid hormone levels, and high cortisol levels with slower clearance may result in longer cortisol half-lives.[15,16]

Menstrual disturbances such as oligomenorrhea and amenorrhea can occur due to dysregulation of the hypothalamic-pituitary-gonadal axis, resulting in low estrogen status.[19] There are similar reductions in testosterone levels for boys.[15]

The consequences for adolescents are tremendous, as 40% to 60% of bone density is deposited during early adolescence in girls and late adolescence in boys. Further, hypoestrogenism in adolescence may also be associated with earlier risk of cardiovascular disease.[20–22] Thus, addressing amenorrhea and hypothalamic hypogonadism is a well-established goal of eating disorder treatment.[23,24]

Death. People with anorexia nervosa have a mortality rate up to 6 times higher than their peers, which is among the highest in psychiatric illnesses.[25–27] Although the mortality rate associated with bulimia nervosa is lower, these patients have a high rate of suicide.[28–31]

MANAGING EATING DISORDERS IN PREVIOUSLY OVERWEIGHT PATIENTS

Although many overweight and obese people have eating disorders, most research is limited to underweight patients only.[23,24,32] Thus, there are few data to guide management of weight loss-related sequelae in previously overweight patients presenting with eating disorders.

In general, body fat mass, amount of relative weight loss, and appropriate hormonal

levels and interactions contribute to normal menstrual function.[33,34] Disruption of the hypothalamic-pituitary-ovarian axis by weight loss may be mediated by changes in gonadotropin-releasing hormone (GnRH) release. Typical GnRH function is pulsatile and relies on leptin and insulin-like growth factor 1 (IGF-1) signaling.[35–37] Fat mass contributes to normal production of both leptin and IGF-1, and therefore loss of fat mass can disrupt the hormonal signaling underlying normal menstruation.[22,38,39]

Previously overweight patients follow a different course than their previously healthy-weight peers in menses recovery. In one study, amenorrheic patients with a history of overweight or obesity resumed menses at a higher weight but with similar amounts of absolute gain in weight.[5] Additionally, the likelihood of menses resumption decreases with greater weight suppression and increases with greater weight gain during treatment in both groups.[5] This finding suggests that weight goals associated with resumption of menses may need to be higher for patients with a history of overweight.

Weight restoration may therefore have different effects on adolescents who had different baseline hormonal production, given different fat mass before the onset of illness. The difference in patterns of menses resumption highlights the need to identify physiologic alterations that may differ between previously overweight and previously normal-weight teens at the onset of eating disorders.

That only one study has compared outcomes between adolescents and young adults with eating disorders by premorbid weight status shows the understudied nature of this comparably high-risk population. While there is greater recognition of the differences in the population, there remains a paucity of studies on treatment goals and recovery course, making it difficult to use evidence-based medicine to assess response to treatment.

Until definitive guidelines are published, the primary care physician can use the following general treatment advice:

Encourage healthy forms of weight loss while establishing minimum requirements for nutrition, including protein, fat, carbohydrates, calcium, and vitamin D. Overweight or obese individuals who wish to pursue a ketogenic or "clean eating" diet should consult with both their primary care clinician and a registered dietician who is experienced in treating patients with eating disorders and obesity to avoid electrolyte imbalances and other medical complications of starvation. If patients are younger than 26 years, recommend adequate fat intake—50 to 90 g a day—because myelination is still occurring in the brain. The primary care clinician, in concert with the dietitian, can help tailor a meal plan to an individual's needs, preventing "hard-wiring" of eating disorder behaviors while ensuring adequate intake of essential nutrients.

Monitor for sequelae of caloric energy restriction, including bradycardia, orthostatic hypotension, amenorrhea and oligomenorrhea.

Be vigilant for pathologic weight loss strategies in overweight as well as underweight patients: recognize eating disorders as readily in the patient who shifts from 220 to 180 lb as one would recognize if the patient went from 120 to 80.

CASE FOLLOW-UP

Jeannette returns after 1 month, having seen the dietitian and increased her intake to 1,800 kcal per day from her previous 400 to 600 kcal per day. Her weight is now 185 lb. Her heart rate has increased to the 60s, but she has ongoing amenorrhea. Her luteinizing hormone level is 2.0 mU/mL and her follicle-stimulating hormone level is 2.6 mU/mL. These values are on the low-normal side, consistent with functional hypothalamic amenorrhea, in which there is suppression of gonadotropins that is centrally mediated through the release of GnRH from the hypothalamus. Her thyroid-stimulating hormone level is normal, and her white blood cell count has normalized (she was previously mildly leukopenic).

TAKE-HOME POINTS

Restrictive eating disorders are common among adolescents, including those with a history of overweight or obesity.

These patients present with greater weight loss from a higher starting weight but have comparable eating disorder symptoms that may go unrecognized for a longer time and result in suboptimal access to care.

Differences in presentation and recovery highlight the need for earlier detection of pathologic behaviors as well as more personalized intervention strategies.

The paucity of evidence on treatment goals makes it challenging to treat previously overweight patients. Early recognition and prevention of significant morbidity is key as further investigations on differences in recovery course are conducted.

Markers of recovery such as resumption of menses suggest that previously overweight patients resume physiologic function at a higher weight and with comparable amount of weight gain as their previously normal weight peers. The differences in weight status at menses resumption reflect the complex neurohormonal mechanisms that underlie functional hypothalamic amenorrhea.

The differences in presentation characteristics underscore the need to emphasize percent weight loss alone rather than extreme low body weight as a metric for eating disorder pathology. How a patient loses weight, as well as the accompanying disordered eating attitudes and behaviors, can illuminate pathology in the obese patient as well as in the severely underweight individual. If the emphasis remains on extreme low body weight as the marker of illness, other findings of starvation—including low heart rate and lower blood pressure in the obese, overweight, and even normal-weight patient who is in the same state of starvation—will continue to be unrecognized.[3]

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EDITORIAL

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Atypical anorexia nervosa can be just as bad

THE CASE REPORT and literature review by Rastogi and Rome in this issue[1] reminds us that eating disorders can occur in patients with a wide variety of weights and that those who were previously overweight present differently from those with classic anorexia nervosa. The case presented meets the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for atypical anorexia nervosa, which describes patients who have lost a significant amount of weight but whose weight remains in the normal or above-normal range.[2]

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Eating disorders can occur in patients with a wide variety of weights

Before the DSM-5 was published, most children, adolescents, and young adults seeking treatment at specialized eating disorder programs who did not meet the criteria for either anorexia nervosa or bulimia nervosa were assigned the diagnosis of "eating disorder not otherwise specified" (EDNOS).[3] Revisions have since been made to the diagnostic criteria in DSM-5 to improve the clinical utility of the diagnostic categories. The EDNOS diagnosis has been eliminated and new diagnostic categories have been introduced, including atypical anorexia nervosa.

The proportion of patients with atypical anorexia nervosa in specialized eating disorder programs has increased dramatically, often accounting for 25% to 40% of patients admitted to inpatient units. The number of these patients presenting to one tertiary care inpatient service increased 5-fold over a period of 5 years.[4]

doi:10.3949/ccjm.87a.19146

PROBLEMS WITH CUTOFFS

"Low body weight" has always been a key clinical feature of anorexia nervosa, but what constitutes low body weight in adolescents remains problematic. In the DSM-IV, the suggested weight cutoff of less than 85% of expected body weight meant that a patient with all the features of anorexia nervosa but with a higher body weight would not meet the diagnostic criteria.

Although body mass index (BMI) cutoffs are useful in determining low weight in adults, determining low weight is challenging in children and adolescents who are undergoing rapid changes in height, weight, body composition, and fat distribution associated with normal growth and development. Absolute BMI cannot be used. A BMI of 17 kg/m^2 would be low for an adult woman but would be normal for a 13-year-old female adolescent.

In addition, the methods used to determine expected body weight during adolescence vary widely.[5] In DSM-5, the diagnosis of anorexia nervosa requires restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health.[2] While no specific weight cutoff is included, a BMI lower than the 5th percentile suggests underweight. It is understood, though, that children and adolescents with a BMI above this percentile could still be underweight if they fail to maintain their expected growth trajectory.[2]

ATYPICAL ANOREXIA NERVOSA HAS CONSEQUENCES

Compared with those who have anorexia nervosa, patients with atypical anorexia nervosa

usually present for treatment after a longer duration of illness[6] and are less likely to receive inpatient care,[7] suggesting that the seriousness of their illness is not recognized because of their normal weight. Yet patients with atypical anorexia nervosa can be just as medically ill as their peers with anorexia nervosa and can have even greater eating disorder psychopathology.[8,9]

While it is well recognized that no body system is immune from the medical complications of restricting eating disorders, what is now emerging is an understanding that some of these same complications occur in patients with weight suppression (ie, who lose a lot of weight, regardless of whether they end up underweight). Specifically, from a cardiac standpoint, marked bradycardia, hypotension, and pulse nadir have been described. Although these cardiac findings resolve with nutritional rehabilitation and their long-term significance is not yet known, it is noteworthy that they can occur even when the absolute current weight is not low by traditional standards.

Moreover, with emerging evidence suggesting that bradyarrhythmias may be causal in the increased risk of sudden death in patients with anorexia nervosa, the finding of marked bradycardia in patients with atypical anorexia nervosa is noteworthy.[10]

In addition, and frankly surprising, the highly prevalent and perhaps permanent loss of bone mineral density present in anorexia nervosa also seems to adversely affect patients with the atypical form. The etiologic reasons for this are unclear because the many purported factors that cause loss of bone mineral density in anorexia nervosa would not be expected to be present in patients with atypical anorexia nervosa, including elevated cortisol levels, abnormalities of growth hormone and insulin-like growth factor 1, and sarcopenia. But clearly, neurohormonal aberrations are involved in the amenorrhea of patients with atypical anorexia nervosa as enumerated by Rastogi and Rome,[1] and these may indeed start the process toward osteopenia and osteoporosis.

REFEEDING HYPOPHOSPHATEMIA

An additional area of potential concern arises during the initial phases of refeeding of those with marked weight suppression. The need for assiduous follow-up of serum phosphorus during the early stages of refeeding to screen for refeeding hypophosphatemia has long been part of weight restoration in anorexia nervosa. The anabolic processes that are activated and the need for phosphorus to drive the production of high-energy compounds such as adenosine triphosphate are operative and well-accepted to avoid the dangerous refeeding syndrome.

What is unexpected is this problem in the early phases of nutritional rehabilitation of those who have atypical anorexia nervosa. Refeeding hypophosphatemia has been noted anecdotally in patients with atypical anorexia nervosa. This common complication of refeeding is relevant not only to those with low absolute body weight; it can also occur in those with marked weight suppression who are being judiciously refed early in their recovery.

NOT JUST WEIGHT, BUT ALSO WEIGHT LOSS DETERMINES SEVERITY

The timely review by Rastogi and Rome[1] reminds readers that not only absolute weight but also weight suppression (the difference between highest weight and presentation weight) and the rapidity of weight loss determine disease severity, medical complications, and the treatment outcome in this emerging area along the spectrum of eating disorders.[9–12]

What constitutes low body weight in adolescents remains problematic

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REVIEW

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Endoscopic ultrasonography: An inside view

ABSTRACT

Endoscopic ultrasonography (EUS) has been used since the mid-1980s. Initially a diagnostic tool, it has since evolved into a therapeutic, minimally invasive surgical tool with significant impact on the diagnosis and management of a range of benign and malignant conditions. The authors review current indications, safety, and efficacy of EUS for diseases of the upper and lower gastrointestinal tract, posterior mediastinum, pancreas, bile duct, gallbladder, retroperitoneum, liver, adrenal glands, and kidneys.

KEY POINTS

EUS is commonly used in the diagnosis and management of biliary and pancreatic diseases, including guidance of biliary drainage in bile duct or pancreatic duct obstruction.

EUS-guided fine-needle aspiration aids staging of malignancies of the upper and lower digestive tract.

EUS is now increasingly used to drain abdominal fluid collections of nonpancreatic etiology.

doi:10.3949/ccjm.87a.19003

Endoscopic ultrasonography (EUS) has evolved from a diagnostic tool to a therapeutic procedure for a wide range of conditions of the upper and lower gastrointestinal tract, hepatobiliary system, pancreas, adrenal glands, kidneys, retroperitoneum, and lymph nodes around the gastrointestinal tract. It can help differentiate benign from malignant disease and in many cases is an alternative to surgery.

This review of current and evolving diagnostic and therapeutic indications for EUS will help physicians identify patients who may benefit from this procedure.

EUS VS OTHER IMAGING TESTS

EUS offers advantages over other imaging tests. It does not involve radiation as in computed tomography (CT) or positron emission tomography, and it is not subject to the contraindications of magnetic resonance imaging (MRI) such as metal implants or claustrophobia. EUS offers high-resolution real-time imaging and can be combined with Doppler to evaluate vasculature and perform diagnostic procedures, angiotherapy, fine-needle aspiration biopsy, and core biopsy for tissue diagnosis. In addition, EUS allows therapeutic interventions.[1]

PROCEDURAL REQUIREMENTS FOR THE PATIENT

EUS is an outpatient procedure that usually takes 30 to 60 minutes and can be done under moderate sedation or general anesthesia.

Periprocedural considerations

According to guidelines of the American Society for Gastrointestinal Endoscopy (ASGE),[2] patients fast for 8 hours before the procedure.

For patients taking antithrombotics, guidelines recommend a platelet level greater than 50 × 10^9/L and an international normalized ratio below 1.5.

The endoscope

EUS is performed with a flexible wide endoscope with a small ultrasound probe and camera at the tip; other equipment in the scope depend on the indication and can include a fine-aspiration needle, a core biopsy needle, a celiac plexus blockade and neurolysis needle, and a metal or plastic stent. EUS can be performed using either a radial (360°) or a linear (approximately 120°) view. A narrow angle of view is required to allow endoscopic fine-needle aspiration.

Expanding indications

The indications for EUS are rapidly expanding. Uses identified by the American Cancer Society and the ASGE now include evaluation and staging of upper gastrointestinal malignancies, mediastinal adenopathy, pancreatic lesions and cancers, submucosal tumors, rectal cancer, and lung cancer staging.[3] In particular, EUS has changed the approach to diagnosis and management of biliary and pancreatic diseases.

EUS with fine-needle aspiration improves diagnostic accuracy for pancreatic masses

PANCREATIC DISORDERS

Pancreatic cancer

Pancreatic cancer has a poor prognosis since it is usually diagnosed at an advanced stage. According to the American Cancer Society, the 1-year relative survival rate is 20%, and the 5-year rate is 8% for all stages of pancreatic cancer. Current studies show that EUS has a sensitivity of 90% to 95% for detecting malignant pancreatic tumors measuring 2 cm to 3 cm, which is far superior to other imaging modalities.[4] EUS is considered complementary to CT or MRI for diagnosis and staging of pancreatic adenocarcinoma. EUS is also used to rule out pancreatic cancer if results of CT or MRI are ambiguous.

EUS in combination with fine-needle aspiration biopsy improves diagnostic accuracy for pancreatic masses and helps in histologic confirmation.[5] Immediate cytologic evaluation or rapid on-site cytologic evaluation helps improve the yield.

The sensitivity of EUS declines in the setting of severe underlying chronic pancreatitis or severe acute pancreatitis. The challenges of detecting pancreatic malignancy in the setting of chronic pancreatitis are being addressed with the advent of EUS elastography, which evaluates tissue stiffness and helps with characterization of the lesion.[6]

Acute pancreatitis

Gallstones are the most common cause of acute pancreatitis. EUS has higher sensitivity than ultrasonography, CT, and magnetic resonance cholangiopancreatography in detecting common bile duct stones and sludge in patients with acute pancreatitis or recurrent pancreatitis.[7]

The ASGE recommends EUS for the assessment of choledocholithiasis in patients at intermediate risk. If EUS confirms bile duct stones, therapeutic endoscopic retrograde cholangiopancreatography (ERCP) can be performed with the patient under the same sedation; and if a stone is not present, an additional diagnostic procedure can be avoided.[2]

EUS also helps determine other causes of acute pancreatitis such as pancreas divisum, small pancreatic tumors undetected on CT or MRI, autoimmune pancreatitis, and chronic pancreatitis, and it can be an important investigative test in patients with idiopathic pancreatitis.[8]

Pancreatic fluid collections

The revised Atlanta classification categorizes pancreatic fluid collections according to 4 types[9]:

- Acute peripancreatic fluid collection, occurring in interstitial edematous pancreatitis
- Pancreatic pseudocyst, occurring as a delayed complication (> 4 weeks) of interstitial edematous pancreatitis
- Acute necrotic collection, occurring in necrotizing pancreatitis
- Walled-off necrosis, which has a radiologically identifiable capsule (> 4 weeks).

Surgical and percutaneous approaches have traditionally been used to drain symptomatic pancreatic and peripancreatic fluid collections.[10] However, disadvantages of these procedures include higher cost, longer hospital stay, possibly higher morbidity risk, and

discomfort of external catheters requiring multiple exchanges.

In the past few years, EUS-guided transgastric or transduodenal drainage has been used more frequently with comparable success and lower morbidity and costs than surgical and percutaneous drainage. The procedure is feasible in more than 90% of patients, is minimally invasive, and results in shorter hospital stays than surgical drainage, and compared with CT or MRI, it more accurately differentiates pseudocyst from cystic neoplasms.[11]

Complications of endoscopic drainage of pancreatic fluid collections are minimal and include bleeding, perforation, and infection, all with rates of less than 5%.[12]

Chronic pancreatitis

Chronic pancreatitis is a complex disease with an ill-defined epidemiology but significant rates of morbidity and mortality. Smoking and alcohol consumption are main risk factors. Chronic abdominal pain is the most common presentation.

Diagnosis can be challenging in early, mild, or moderate disease. Studies[13–16] have shown that the diagnostic accuracy of EUS is comparable to that of ERCP and pancreatic function testing. In addition, technologic advances in EUS such as contrast-enhanced harmonics and elastography offer improved diagnostic accuracy in patients with chronic pancreatitis.[17,18] As a result, EUS is being increasingly used as a frontline test for this indication.

Pancreatic cystic neoplasms

The challenge in management of pancreatic cystic neoplasms lies in the timely and accurate diagnosis of premalignant mucinous cysts.

Differentiation of premalignant mucinous cysts from benign nonmucinous cysts by EUS with fine-needle fluid aspiration has become a valuable tool, providing high-quality imaging of the cyst and samples for fluid analysis, leading to increased diagnostic accuracy.

Periprocedural antibiotics are administered to minimize the risk of infection from fine-needle aspiration. Cyst fluid samples are sent to the laboratory for cytologic study and for analysis for carcinoembryonic antigen, glucose, amylase, and mucin.[19,20] Premalignant mucinous cysts are managed according to the international consensus guidelines.[21,22]

GALLBLADDER AND BILIARY DISORDERS

Choledocholithiasis

Common bile duct stones can be present in 20% of patients with cholelithiasis. Noninvasive imaging with abdominal ultrasonography or CT has a diagnostic accuracy of only 50% for these stones. Magnetic resonance cholangiopancreatography is the most accurate noninvasive imaging test (diagnostic accuracy from 81% to 99%).[23–26]

ERCP and intraoperative cholangiography are accurate but invasive and can cause complications. Same-session EUS and ERCP (if stones are confirmed on EUS) for common bile duct stones are usually performed in patients with intermediate probability of stones according to the ASGE criteria or in patients with contraindications to magnetic resonance cholangiopancreatography.

Obstructive jaundice

Obstructive jaundice can result from benign and malignant diseases. Common benign causes are choledocholithiasis, postcholecystectomy bile duct injury, liver transplant, portal cavernoma cholangiopathy, primary sclerosing cholangitis, acquired immunodeficiency syndrome cholangiopathy, chronic pancreatitis, and immunoglobulin G4 cholangiopathy. Malignant causes include cholangiocarcinoma, gallbladder carcinoma, pancreatic malignancies, ampullary carcinoma, metastasis, metastatic lymph nodal compression on bile duct, and hepatocellular carcinoma. The proximity of the stomach and duodenum to the extrahepatic biliary system makes EUS useful for imaging the biliary anatomy. EUS-guided fine-needle aspiration from the bile duct wall and surrounding lymph nodes enables histologic diagnosis.

EUS is routinely used for diagnosis and staging of malignant esophageal tumors

ERCP is the standard procedure for biliary drainage in benign or malignant biliary obstruction. However, it is not feasible in surgically altered anatomy as in Roux-en-Y anastomosis and duodenal bulb infiltration by tumor. In these cases, EUS-guided biliary drainage is being used with high success rates.[27,28] EUS-guided cholangiopancreatography has been done in patients in whom ERCP could not be performed. This procedure requires a high level of technical expertise and can cause complications such as perforation and bile leak.

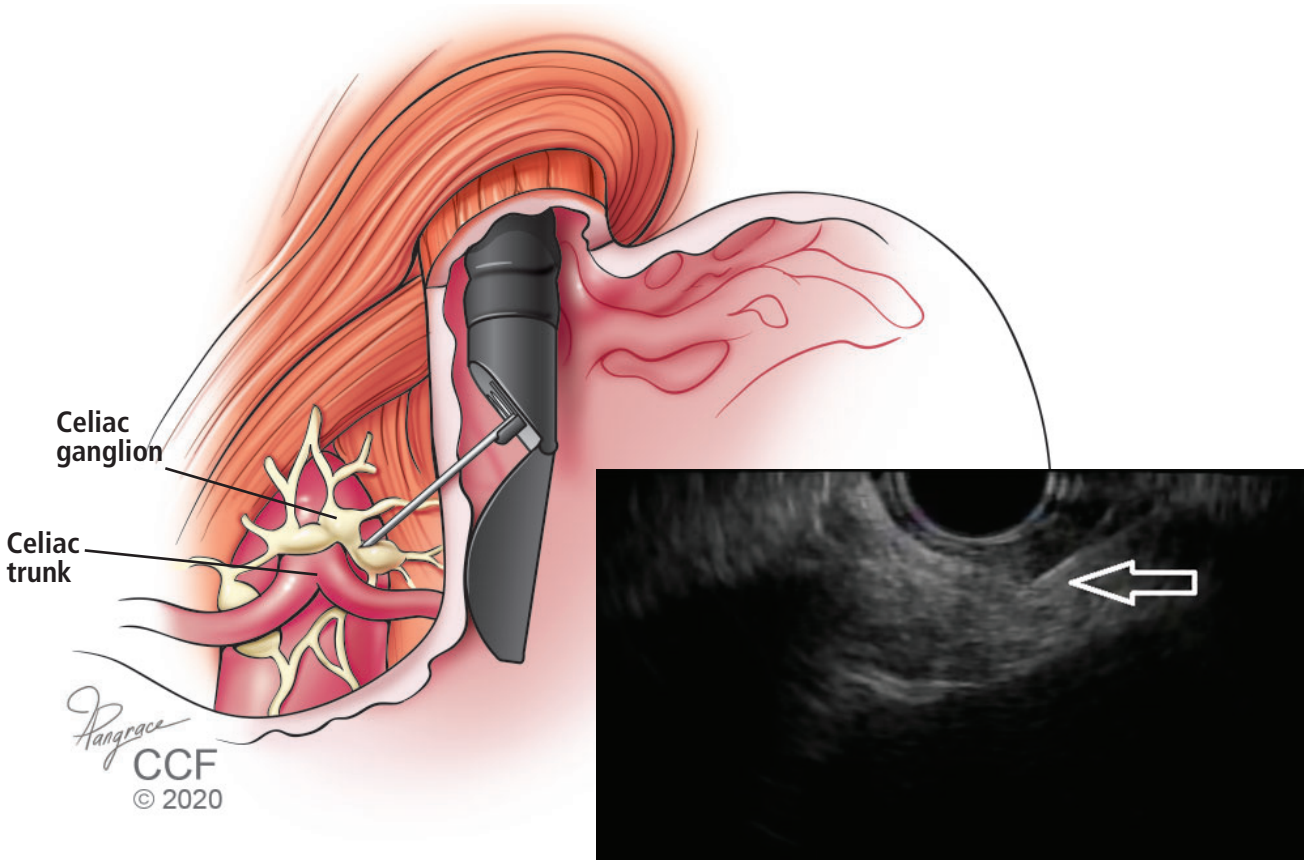

Figure 1. Control of chronic abdominal pain with first-line medications in patients with chronic pancreatitis or intra-abdominal malignancy may be inadequate or fraught with adverse effects. One alternative is endoscopic ultrasonography-guided fine-needle (EUS) celiac plexus block, performed under echoendoscopic guidance with passage of an injection needle. This procedure has been shown to be safe, is technically easy to perform, and is a safe alternative to percutaneous block guided by computed tomography. The arrow shows the EUS-guided placement of the needle.

Cholecystitis

Cholecystectomy is the optimal treatment for acute calculous or acalculous cholecystitis. Patients deemed high-risk surgical candidates cannot undergo the procedure and traditionally undergo percutaneous placement of a cholecystostomy tube by interventional radiology for decompression of the gallbladder. EUS can be used to perform transgastric or transduodenal gallbladder drainage with a covered metal stent. Case series have shown outcomes comparable to those of percutaneous tube placement.[29,30]

GASTROINTESTINAL TRACT DISEASE

Upper tract conditions

EUS can be used to identify benign tumors of the upper gastrointestinal tract, including submucosal esophagogastric tumors.[31] EUS-guided fine-needle aspiration and biopsy can aid the cytohistologic diagnosis of esophagogastric solid subepithelial lesions.[32]

EUS is routinely used for diagnosis and staging of malignant esophageal tumors. The procedure may not be technically feasible if high-grade malignant esophageal stricture precludes passage of echoendoscope.

EUS-guided evaluation and biopsy are particularly useful to diagnose linitis plastica, a gastric cancer characterized by marked thickening of deeper layers of gastric wall. It is difficult to diagnose with superficial mucosal biopsies rendered with esophagogastroduodenoscopy.

Mediastinal adenopathy and non-small-cell lung cancer

Nearly 26% of lung cancer patients present with mediastinal lymph node involvement.[33] CT, MRI, and positron emission tomography are the common modalities for diagnosing mediastinal lymph node enlargement. However, lack of tissue sampling results only in a presumptive diagnosis. Posterior and inferior mediastinal lesions are especially suitable for EUS-guided fine-needle aspiration and biopsy for histologic diagnosis, thus avoiding an invasive surgical intervention like mediastinoscopy. However, EUS is unable to visualize anterior upper mediastinal nodes.

Mediastinal staging in lung cancer is an area in which EUS has made most significant impact.[34] It also allows for evaluation of distant metastases involving adrenal glands.

Submucosal lesions

EUS provides a detailed image of gastrointestinal wall layers and therefore has become the principal tool for assessment of submucosal masses in this area.

Gastrointestinal stromal tumors are the most common mesenchymal tumors, and the stomach is the most common site. EUS-guided fine-needle aspiration is considered the procedure of choice for preoperative diagnosis of these tumors, although it may provide inadequate material in one-third of cases. However, with the advent of newer biopsy needles, the histologic yield has improved significantly.

In addition to the diagnosis of gastrointestinal stromal tumors, EUS can distinguish between other benign lesions (leiomyoma, pancreatic rest, indolent neuroendocrine tumor, granular cell tumor, schwannoma, duplication cyst) and malignant lesions (primary or metastatic). EUS elastography is a promising technique that may also improve the distinction of benign from malignant lesions.

Retroperitoneal masses

For evaluation of idiopathic abdominal masses, EUS-guided fine-needle aspiration and biopsy provide a minimally invasive technique to obtain tissue samples for safe and accurate diagnosis, thus avoiding the need for exploratory laparotomy; it also helps guide subsequent therapy.[35] These procedures are useful for evaluation of peri-intestinal and peri-esophageal lymph nodes and are more accurate than CT.[36]

Apart from providing adequate diagnostic tissue in lymphoproliferative tumors, EUS is highly useful in nonpancreatic retroperitoneal masses such as adrenal metastasis, leiomyosarcoma, paraganglioma, and lymphangioma. EUS-associated seeding of the needle tract has been reported but is rare.

Lower tract disease

Accurate preoperative staging of rectal cancer leads to targeted treatment strategies, increased cure rates, and reduction in short-term and long-term treatment failure. EUS and MRI have comparable accuracy in TNM staging of colorectal cancer, but MRI is perhaps more advantageous than EUS for nodal staging since it images the entire mesorectum.

CELIAC PLEXUS BLOCK AND NEUROLYSIS

Chronic abdominal pain is common and often disabling in patients with intra-abdominal malignancies and chronic pancreatitis. Pain relief from first-line medications including opiates may be inadequate or fraught with intolerances and adverse effects.[37]

Celiac plexus block with CT-guided percutaneous and EUS-guided neurolysis has been shown to be safe and technically easy to perform (**Figure 1**). In a Cochrane review of 6 randomized controlled trials with a total of 358 pancreatic cancer patients,[38] the authors found that celiac plexus block with either approach caused fewer adverse effects than opioid analgesia. More study is needed to confirm a statistically significant improvement in pain scores.

EUS-guided gastrojejunostomy offers shorter recovery time than surgical gastrojejunostomy and is more cost-effective

RECENT DEVELOPMENTS, NEWER INDICATIONS

EUS-guided fine-needle injection

EUS-guided fine-needle injection is being evaluated for intratumoral chemotherapy in pancreatic and esophageal cancers. It has been used for tissue ablation by injection of ethanol in nonmalignant pancreatic cystic tumors and in radiofrequency ablation and brachytherapy in unresectable pancreatic cancers. Portal injection of chemotherapy has been shown to be safe and feasible. It may prove useful in the

management of primary liver malignancies.

EUS-guided botulinum toxin injection for achalasia and for management of obesity has been done in few cases. Botox administration in the stomach promotes early satiety and weight loss through inhibition of acetylcholine-mediated peristalsis, ultimately delaying gastric emptying.[39]

EUS-guided gastrojejunostomy

Gastric outlet obstruction can result from malignancies involving stomach, duodenum, gallbladder, or pancreas. EUS-guided gastrojejunostomy has been reported to be a safe, durable, and successful treatment option.[40–42] Compared with enteral (duodenal) stenting, which can be complicated by tumor ingrowth resulting in stent occlusion, EUS-guided gastrojejunostomy has been shown to provide longer-lasting symptom relief since it is performed remotely from the tumor location. It also offers shorter recovery time and is more cost-effective than surgical gastrojejunostomy.[43,44]

Contrast-enhanced harmonic EUS

Contrast-enhanced harmonic EUS has been developed to detect a microvascular pattern of lesions, which can help differentiate benign from malignant disease. An intravascular contrast agent is injected that contains microbubbles. On exposure to ultrasound, these microbubbles oscillate, and the transducer can make out the appearance of the peripheral microvasculature.[45]

DNA analysis of specimens obtained by EUS-guided fine-needle aspiration can aid diagnosis

Molecular marker analysis

DNA analysis of specimens obtained by EUS-guided fine-needle aspiration can aid diagnosis. Microdissection-based genotyping is now available at some centers. This has specific value in distinction of pancreatic cysts seen on CT. DNA quantification can help distinguish benign cysts from malignant ones.

EUS-directed transgastric ERCP in patients with gastric bypass

Duodenal and ampullary access with ERCP is difficult in patients who have undergone Roux-en-Y gastric bypass. Classically, enteroscopy-assisted ERCP is associated with a low success rate. Surgically assisted ERCP (laparoscopy or laparotomy) has a good success rate but is more invasive, has higher complication rates and longer length of stay in the hospital, with associated costs.

EUS-directed transgastric ERCP involves accessing the excluded stomach from the gastric pouch or Roux limb by creation of a fistula with placement of a removable lumen-apposing metal stent. Conventional ERCP can then be performed through the stent. A multicenter study comparing the EUS-directed procedure and laparoscopic ERCP found that the 2 procedures had similar success rates and adverse events.[46] The EUS-directed procedure has the benefit of being an outpatient minimally invasive procedure with significantly shorter procedure time and cost.[46,47]

Drainage of other nonpancreatic abdominopelvic fluid collections

EUS is safe and effective in accessing and draining nonpancreatic abdominopelvic fluid collections from the stomach, duodenum, and colon. Multiple case series have reported safe and successful drainage of subphrenic abscesses, hepatic abscesses, bilomas, and pelvic and retroperitoneal abscesses. In addition, EUS has been increasingly utilized to drain postsurgical fluid collections, which can form anywhere in the abdominal cavity and can become symptomatic or infected. There is mounting recent evidence of successful EUS-guided drainage of such collections after common surgical procedures including Whipple surgery and Roux-en-Y gastric bypass.[48]

EUS-guided angiotherapy

EUS-guided angiotherapy is a relatively novel application that allows control of variceal bleeding by injecting coils and cyanoacrylate glue directly into the varices and confirming the thrombosis in real time with Doppler. It is purported that the combination of coil and glue might decrease the risk of glue embolization. However, further study is needed to establish the safety and superiority of this technique.[34,49,50]

DRAWBACKS AND COMPLICATIONS

Adverse events associated with sedation and standard endoscopic procedures are also applicable to EUS. However, since the echoendoscope has a larger diameter with a stiffer tip

than the standard endoscope, it can be difficult to maneuver around the cricopharyngeus and duodenal bulb. It is also more time-consuming than standard routine endoscopy if fine-needle aspiration or intervention is planned. Despite this, complications, as reviewed below, are infrequent.

Perforation

Perforation is reported in the cervical esophagus and less often in the duodenum. The risk is usually similar to that with routine endoscopy (0.03%). A prospective study of 4,894 patients undergoing upper EUS found a cervical esophageal perforation rate of 0.06% (3 patients, with a curved linear array endoscope).[51] A recent systematic review reported a perforation rate of 0.02% with EUS.[52] The risks may be higher in patients with strictures, malignancy, older age, or history of difficult intubation, and with a less experienced operator.

Infection

The risk of bacteremia after EUS-guided fine-needle aspiration is lower than with diagnostic endoscopy, and prophylactic antibiotics are not recommended for aspiration of solid masses and lymph nodes.[53,54] Some experts recommend prophylactic antibiotics as well as 48 hours of antibiotics after fine-needle aspiration of the perirectal space.[55]

EUS-guided aspiration of cystic lesions may carry an increased risk of febrile episodes and possibly sepsis. Therefore, prophylactic antibiotics followed by a short postprocedure course has been recommended.[56]

There have been isolated reports of streptococcal sepsis, mediastinitis, retroperitoneal abscess, perirectal abscess, and cholangitis.[57]

Pancreatitis

EUS-guided fine-needle aspiration of pancreatic lesions involves direct passage of the needle through pancreatic tissue. Reported rates of pancreatitis associated with this procedure range from 0% to 2%.[58] A recent meta-analysis of 51 studies found a rate of of 0.44%.[59]

Hemorrhage

A recent meta-analysis of related adverse events reported a bleeding rate of 0.13%.[59]

Avoiding complications

Careful patient selection, familiarity with the equipment, and planning of the procedure are keys to avoiding complications. Early recognition of complications and prompt intervention can reduce morbidity and mortality risk. ■

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We thank those who reviewed manuscripts submitted to the *Cleveland Clinic Journal of Medicine* in 2019. Reviewing papers for the *Journal*—both for specialty content and for relevance to our readership—is an arduous task that involves considerable time and effort. Our publication decisions depend in no small part on the timely efforts of reviewers, and we are indebted to them for contributing their expertise this past year.

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