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Heightening awareness of blistering disorders

Infectious endocarditis:
- Evolving distal signs
- Pioneers of endocarditis

A 72-year-old woman with new bullous lesions

Dual antiplatelet therapy: Personalizing the duration after percutaneous coronary intervention

Medical complications of bulimia nervosa

Point-of-care ultrasonography: A practical guide for the hospitalist

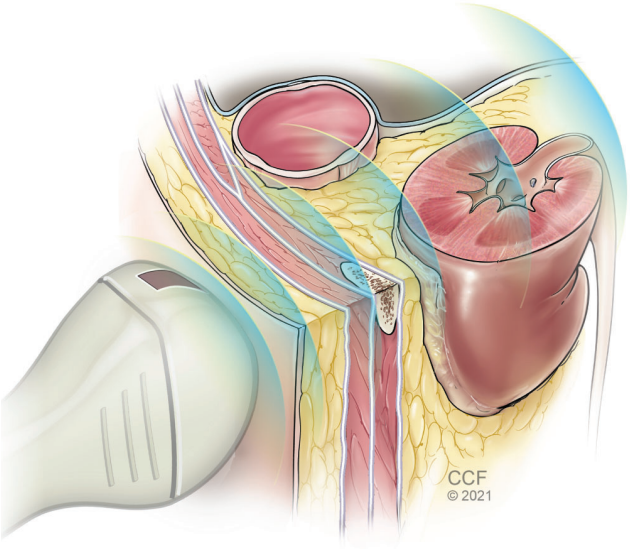

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Table of Contents

CONTINUED ON PAGE 307

Upcoming Features

- Asthma management: The GINA report
- Exercise in older women
- Tobacco cessation: Current management options

CONTINUED FROM PAGE 306

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Heightening awareness of blistering disorders

Among the different patterns of skin disease, blistering disorders link to one of the more diverse and potentially confusing sets of etiologies that confront nondermatologists. The spectrum of associated disorders ranges from annoying to life-threatening, and prompt suspicion and biopsy with direct immunofluorescence may be necessary for appropriate diagnosis and treatment.

The distribution of vesicular or bullous lesions, the clinical setting, medications, environmental exposures, and coexistent symptoms all come into play as the initial differential diagnosis is generated. Regional blistering lesions can occur with various triggers of contact dermatitis from adhesive tape and iodine, to plant-triggered "poison oak," and even bug bites under certain circumstances. (Consider underlying hematologic malignancy or HIV with particularly prolonged or disseminated reactions.)

We are all familiar with the localized, often recurrent vesicles of herpes simplex, as well as the crops of vesicular lesions with herpes zoster. Both can disseminate in patients lacking immunocompetence. The coincident odd occurrence of classic erythema multiforme on palms or soles with localized vesicular herpes infection elsewhere can sometimes cause initial diagnostic confusion, as all lip blisters are not herpetic.

Another viral infection causing vesicular lesions with "hand, foot, and mouth disease," particularly in children, is from a coxsackievirus that can also affect adults, causing some confusing systemic symptoms. Localized pruritic papulovesicular patches are the cardinal lesions in dermatitis herpetiformis, and they may occur without any other clinical features of the associated gluten sensitivity. And then there are the severe, life-threatening, diffuse, blistering, peeling allergic reactions to medications characterized as toxic epidermal necrolysis and Stevens-Johnson syndrome.

I highlight these few examples not as a comprehensive review, but because they have been the more common considerations I have had when seeing patients with vesicles and blisters. On reading the paper by Mendoza et al[1] in this issue of the *Journal* (page 319), I was reminded of some significant diagnoses that I may have not recognized as early as I might have.

Bullous pemphigoid is an autoimmune disease characteristically occurring in older individuals, and I think of it in that setting when I recognize the characteristic tense bullae. Its pathophysiology is understood as the generation of pathogenic autoantibodies against several defined skin basement membrane proteins, detected by routine immunofluorescence testing on biopsy of the blister and adjacent skin. The tense blisters—unlike the more superficial, often weeping, easily torn, and nonhealing lesions of (the more serious) pemphigus—are often surrounded by erythema. Many patients with bullous pemphigoid will describe a prodrome of significant patchy pruritus, sometimes with urticarial or eczematoid plaques, that may persist for weeks or even months prior to the appearance of the blisters and awareness of the likely diagnosis. Thus, pemphigoid should be included in the differential diagnosis for new-onset unexplained localized pruritus.

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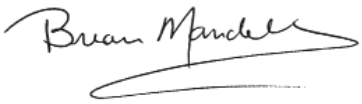
There are also subsets of pemphigoid localized to mucous membranes that warrant aggressive therapy to prevent scarring. They include involvement of the conjunctivae (cicatricial pemphigoid), which if untreated can lead to visual impairment or blindness, and involvement of the nasal and upper airways that can mimic limited granulomatosis with polyangiitis in its degree of local tissue damage. And there are several other forms characterized by specific locations and features.

While these autoimmune blistering diseases are uncommon, even in most dermatology practices, their potential severity and association with multiple systemic and often clinically disconnected features warrant our awareness.



Brian F. Mandell, MD, PhD
Editor in Chief

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Zackary D. Goff, MD
Thayer Firm, Osler Medical Service, Johns Hopkins Hospital; Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Sandra E. Zaeh, MD, MS
Thayer Firm, Osler Medical Service, Johns Hopkins Hospital; Postdoctoral Fellow, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD

Michael K. Poku, MD
Thayer Firm, Osler Medical Service, Johns Hopkins Hospital; Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

John N. Aucott, MD
Thayer Firm, Osler Medical Service, Johns Hopkins Hospital; Associate Professor of Medicine, Director of Lyme Disease Research Center, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Allan C. Gelber, MD
Thayer Firm, Osler Medical Service, Johns Hopkins Hospital; Professor of Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Evolving distal signs

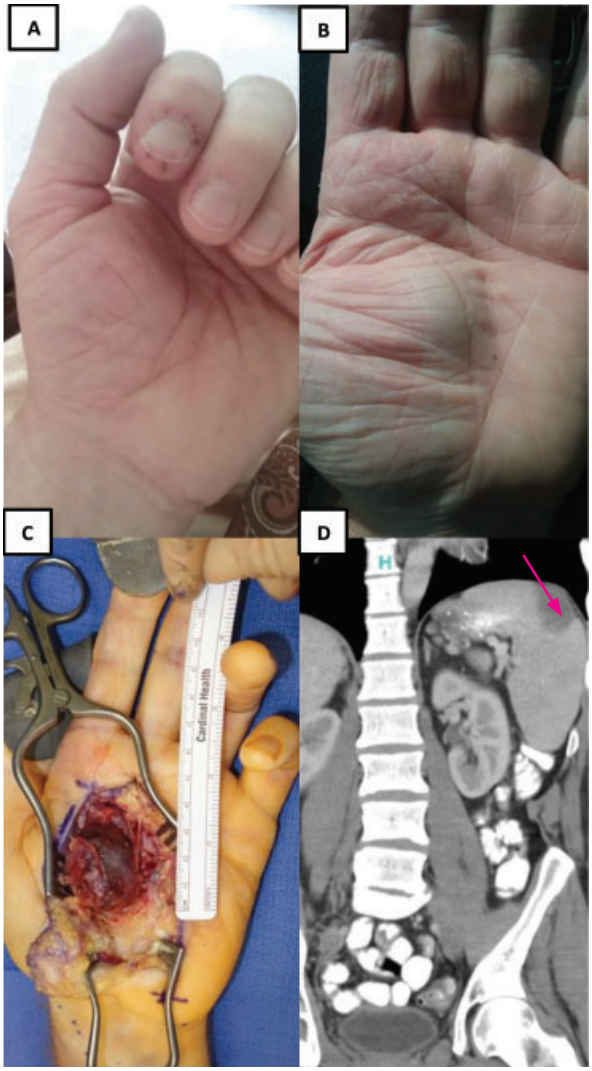

Figure 1. Findings before presentation: (A) painful periungual petechial rash on the left index finger; (B) pulsatile palmar mass; (C) intraoperative image of the aneurysm arising from the superficial palmar arch; and (D) abdominal computed tomography showing a wedge-shaped splenic infarct (arrow).

doi:10.3949/ccjm.88a.20126

A 40-YEAR-OLD MAN who hunted large and small game and had frequent exposure to ticks was admitted to the hospital with persistent fevers, peaking at 102.6 °F (39.2 °C), and a transient episode of monocular vision loss.

About 9 months earlier, he developed night sweats, fatigue, and arthralgias, and over the next several months he noted ongoing fatigue, intermittent night sweats, and a 10-lb weight loss. He also had an episode of transient loss of vision in his left eye. When he sought medical care about 4 months earlier, tests for *Borrelia burgdorferi* immunoglobulin M (IgM) and *Ehrlichia chaffeensis* IgG were positive; he was started on doxycycline and experienced modest improvement.

See related editorial, page 316

However, during the next month, he developed pain in his left index finger and right second toe, with periungual and digital petechiae (**Figure 1A**), and then developed a painful pulsatile palmar mass **(Figure 1B)**. Magnetic resonance angiography at another medical facility revealed a superficial palmar arch aneurysm that was subsequently excised (**Figure 1C**). He also developed new left scapular pain, and computed tomography showed evidence of a wedge-shaped splenic infarct (**Figure 1D**).

On admission to our hospital, he did not appear ill. Cardiac examination revealed a grade III/IV blowing diastolic murmur at the left lower sternal border. There were painful grouped petechiae and splinter hemorrhages affecting the left great toe (**Figure 2**). Results of laboratory testing were as follows:

- White blood cell count 6.48 × 10^9/L (reference range 4.5–11.0)
- Platelet count 280 × 10^9/L (150–350)

- Hemoglobin level 11.0 g/dL (13.9–16.3)
- Hematocrit 35% (41–53)
- Erythrocyte sedimentation rate 33 mm/h (1–15)
- C-reactive protein 5.6 mg/dL (< 0.5)
- Rheumatoid factor 649 IU/mL (0–35).

B burgdorferi antibody, *Babesia microti* IgG and IgM, and *E chaffeensis* polymerase chain reaction testing were negative.

Transthoracic echocardiography detected a vegetation on the left coronary cusp of the aortic valve. Blood cultures on the first and second hospital days were positive for *Streptococcus mutans*.

The patient's evolving distal signs, aortic regurgitation murmur, results of echocardiography, and microbiologic data were confirmatory of subacute bacterial endocarditis, and an extended course of antimicrobial therapy was implemented.

EMBOLIC MANIFESTATIONS OF ENDOCARDITIS

Early in this patient's course, the repeated exposure to ticks and the positive serology for Lyme disease and ehrlichiosis prompted treatment with doxycycline. However, the development of distal embolic phenomena, transient visual impairment, splenic infarct, and pulsatile palmar mass compelled reconsideration of the underlying infectious process.

Janeway lesions (painless hemorrhagic or erythematous lesions on the palms and soles developing as septic emboli) and Osler nodes (painful petechial eruptions on the finger pads and toes), understood to arise from immune complex deposition, are classic features of endocarditis.[1,2] They are helpful clues to uncover the diagnosis. This patient's sudden visual disturbances, albeit transient, and shoulder pain were instructive additive symptoms arising as immunologic and vascular occlusive insults to the retina and spleen, respectively.[1,3]

Elevated rheumatoid factor is present in one-third of patients with confirmed endocarditis, arising from sustained inflammation, thereby inducing polyclonal hypergammaglobulinemia.[3,4] The painful palmar swelling arose from a mycotic aneurysm of the superficial palmar artery. Surgical pathology identified a dilated arterial wall with granulation tissue, acute and chronic inflammation, and prominent luminal thrombus. Interestingly, mycotic aneurysms may occur in 10% to 20% of patients in large endocarditis series, and were described by Sir William Osler as "mycotic endarteritis" in 1885.[5] They may arise in the cerebral, splenic, coronary, pulmonary, and mesenteric arteries and in the abdominal aorta.[1,2]

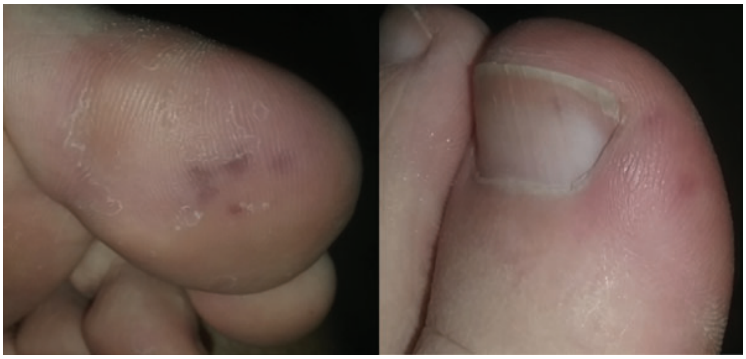

Figure 2. Painful petechial rash affecting the left great toe, compatible with Osler nodes, and splinter hemorrhage of the toenail.

THE PATIENT'S MANAGEMENT

In our patient, the evolving distal signs, along with the lack of specificity and potential for false-positive results of serologic bloodwork for Lyme disease and ehrlichiosis, necessitated a reformulation of the underlying disease process and the establishment of the diagnosis of bacterial endocarditis.[6]

On completion of a 4-week course of intravenous penicillin G, our patient achieved complete resolution of symptoms. ■

The patient's evolving signs and symptoms prompted a reconsideration of his diagnosis

DISCLOSURES

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

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***Address**: Allan C. Gelber, MD, Department of Medicine, Johns Hopkins University School of Medicine, Mason F. Lord Building, Center Tower, Suite 4100, 5200 Eastern Avenue, Baltimore, MD 21224; agelber@jhmi.edu*

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June 12
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June 15–19
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MELLEN CENTER UPDATE IN MULTIPLE SCLEROSIS
June 26
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JULY

MIDWEST MELANOMA AND HIGH-RISK SKIN CANCER SYMPOSIUM
July 16
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AUGUST

HOSPITAL MEDICINE 2021
August 5–6
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NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN
August 7–8
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August 14–15
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TRANSTHYRETIN CARDIAC AMYLOIDOSIS IN AFRICAN AMERICANS: WHAT PHYSICIANS NEED TO KNOW
August 24
Live stream

INTENSIVE REVIEW OF ENDOCRINOLOGY AND METABOLISM
August 27–29
Live stream

SEPTEMBER

STATE-OF-THE-ART DIAGNOSIS AND TREATMENT OF DEMENTIA
September 9
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THE PRACTICE OF ECHOCARDIOGRAPHY AT CLEVELAND CLINIC 2021
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COMPREHENSIVE LIFELONG EXPEDITIOUS (CLE) CARE OF AORTIC DISEASE
September 17–18
Cleveland, OH

INTENSIVE REVIEW OF GASTROENTEROLOGY AND HEPATOLOGY
September 17–20
Las Vegas, NV

PRIMARY CARE WOMEN'S HEALTH: ESSENTIALS AND BEYOND
September 18
Live stream

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

OCTOBER

VIRTUAL NEPHROLOGY UPDATE
October 1
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EDITORIAL

Adam J. Brown, MD
Department of Rheumatologic and Immunologic Disease, Cleveland Clinic, Cleveland, OH;
Author of *Rheumatology Made Ridiculously Simple*;
Host of the podcast *Rheuminations*

Famous and not-so-famous physical findings in infectious endocarditis: A look back

If you're looking for a disease that is the most quintessentially archetypal of internal medicine, it's difficult to surpass infectious endocarditis.

Gathering a thorough history, pushing and prodding a patient's spleen, pulling down the skin under the eyes to look for petechiae, hovering your face within inches of an open palm searching for a cutaneous clue to an infectious bomb dangling on the leaflet of the mitral valve—what is more emblematic of internal medicine?

See related article, page 310

Osler was the first to synthesize the known data and case reports on endocarditis in a lecture series in 1885

The physical examination findings of infectious endocarditis are storied and known by heart by every medical student who can rattle off Osler nodes, Janeway lesions, and splinter hemorrhages without a smart phone in sight, although they may mix up which one of those lesions is painful. These findings, though famous, are rare, and the more common findings like splenomegaly and subconjunctival petechiae are less readily listed.

The report by Goff et al in this issue is a great example of the many unusual ways infectious endocarditis can present.

To better appreciate the famous and not-so-famous physical examinaton findings of infectious endocarditis, it's important to look back at the evolution of the disease.

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OSLER'S CONTRIBUTIONS

The understanding of endocarditis evolved rapidly after the disease was put into the forefront of medicine by Dr. William Osler in 1885. Then came advances in microbiology like the introduction of blood cultures, allowing for more rapid and accurate diagnosis. Once the diagnosis of endocarditis became more established, clinicians began recognizing subtler clues that we apply at the bedside today.

Osler placed endocarditis on the medical map with his Gulstonian lecture series on the subject in 1885.[1] Before these lectures, infective endocarditis was a known entity, usually diagnosed at autopsy, but no comprehensive information existed on its presentation and natural course. Osler was the first to synthesize the known data and case reports at that time, presenting it in a cohesive way to better understand the condition. He recognized important aspects of the disease, noting the wide range of clinical presentations, the progression from an acute febrile illness leading to rapid deterioration and death. He also noted that the illness could present over months to years before death, what would later be called subacute bacterial endocarditis.

Osler also recognized that valvular abnormalities predisposed patients to endocarditis, and that a history of rheumatic fever was common.

Osler gave credit to Ontario physician Dr. J. A. Mullin for pointing out these lesions, but in 1913, Dr. F. Parkes Weber ascribed the findings to Osler.[2]

JANEWAY'S CONTRIBUTIONS

In 1899, Dr. Edward Janeway described painless lesions on the palms and soles in patients suffering from endocarditis. His objective in describing these lesions was a viable way for clinicians to differentiate endocarditis from another "malignant process" presenting with fever and weight loss. He described the lesions as "small hemorrhages with slight nodular character in the palms of the hand and soles of the feet."[2] He did not refer to them as Janeway lesions. That was done by Dr. Emanuel Libman, who also emphasized their painless nature.

In contrast to the painless palmar Janeway lesions, Osler nodes are painful and in the pulp of the fingers and toes, and the two lesions have forever confused medical students and clinicians alike. In a 1909 issue of the *Quarterly Journal of Medicine*, Osler described the ephemeral nature of the lesions: "I have known them to pass away in a few hours, but more commonly they last a day, or even longer,"[3] and he also noted that they are painful to touch.

A debate still rages over the etiology driving both Janeway lesions and Osler nodes all these years later, ranging from septic embolic to immune complex deposition to possibly even the same etiology that just occurs at different locations (palms vs fingers).[4,5]

SPLINTER HEMORRHAGES

Splinter hemorrhages are another physical finding of infectious endocarditis on the fingers. These small, dark, straight lines often at the tips of the fingernails are a notoriously nonspecific finding, seen in clinical scenarios from trauma to sepsis but made famous because their initial description was in patients with endocarditis in the 1920s.

Dr. G. Blumer was the first to use the term splinter hemorrhages in 1926 after initially finding them on 2 patients with endocarditis. He later evaluated 48 patients with endocarditis and discovered the lesions only twice, so it was quickly recognized that they were not a very sensitive marker for endocarditis as they were found in a variety of other conditions.[6] Although famous, the findings on hand and foot examination in endocarditis are rare, found in fewer than 15% of cases.[7]

LIBMAN'S CONTRIBUTIONS

Libman was a key figure in elucidating the more common signs and symptoms of endocarditis, as well as introducing blood culture as a diagnostic tool in the United States.[8]

Libman was an American physician who studied microbiology in Graz, Austria, before returning to the United States to work at Mt. Sinai in New York City, where he focused on blood cultures and work with endocarditis. With blood cultures, physicians had a new tool to help recognize endocarditis earlier, and the opportunity to recognize more clinical symptoms associated with endocarditis at an earlier stage.

Libman wrote extensively on the signs and symptoms of endocarditis, recognizing the characteristic murmur, fever, splenomegaly, anemia, and transient petechiae (commonly subconjunctival).[9] He used these findings to diagnose the famous Viennese composer Gustav Mahler, who was conducting the New York Symphony in 1911 when he came down with a prolonged fever. Dr. Libman noted "a loud systolic-presystolic murmur over the precordium characteristic of chronic rheumatic mitral disease, a history of prolonged low-grade fever, a palpable spleen, characteristic petechiae on the conjunctivae, and slight clubbing of the fingers."[10] Blood cultures confirmed the diagnosis and Mahler decided to cross the Atlantic and die at home in Vienna at the age of 51.[11]

A debate still rages over the etiology driving Janeway lesions and Osler nodes

Perhaps Libman is best known for his description of noninfectious vegetations in patients with lupus erythematosus, alongside Dr. Benjamin Sacks.[8]

A cynic might question the importance of diagnosing endocarditis earlier in the era where antibiotics were still decades away. But it's important to note that even as progress was being made in microbiology and the recognition of endocarditis was becoming more widespread, it was still a universally fatal condition. The despair caused by the diagnosis and the seriousness that the physical examination findings had at the time are illustrated in a journal entry of a Harvard Medical student named Alfred Reinhart in 1931: "No sooner had I removed the left arm of my coat, than there was on the ventral aspect of my left wrist a sight which I shall never forget until I die.

There greeted my eyes about fifteen or twenty bright red, slightly raised, hemorrhagic spots about 1 millimeter in diameter…I took one glance at the pretty little collection of spots… and calmly said, 'I shall be dead within six months.'"[12]

Alfred Reinhart had a history of rheumatic fever as a child and, being a medical student, he was painfully aware that this put him at increased risk of endocarditis. He felt his fate was sealed by recognizing the rash and its relation to endocarditis, and he was correct to the month, as he died 6 months after noticing the rash on his arm.[12]

ENTERING THE MODERN ERA

While the early 20th century brought about increased recognition and understanding of infective endocarditis, it was not until the early 1940s with the implementation of penicillin that there was an effective treatment. The antibiotic sulfonamide preceded penicillin, but its use in endocarditis was disappointing: eg, a review in 1943 showed only 4% of patients having resolution of the endocarditis.[13] In 1944, the first published report of the use of penicillin demonstrated a near 75% resolution of disease.[14] For the first time, endocarditis was a potentially treatable disease. Clinicians could use their diagnostic acumen to diagnose a fatal condition, implement a therapeutic agent, and potentially save the patient.

OUR CURRENT UNDERSTANDING OF ENDOCARDITIS

Infectious endocarditis is a cornerstone of internal medicine. Its history is a fascinating story that coincides with the evolution of our understanding of microbiology, and illustrates the difficulty of making this diagnosis before advanced imaging. Numerous clinicians contributed to our understanding of the disease by recognizing a broad range of physical examination clues, and over time, clinicians became more adroit at the diagnosis of endocarditis.

Until the 1940s, endocarditis was a universally fatal diagnosis. The development of penicillin quickly changed how the disease was viewed, and the decades of work detailing the diagnostic clues paid off, as patients could be appropriately diagnosed and effectively treated.

DISCLOSURES

The author reports no relevant financial relationships which, in the context of his contributions, could be perceived as a potential conflict of interest.

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***Address**: Adam J. Brown, MD, Department of Rheumatologic and Immunologic Disease, A50, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; browna22@ccf.org*

GREGORY W. RUTECKI, MD, Section Editor

Hadrian Mendoza, MD
Department of Pediatrics,
Emory University School of Medicine,
Atlanta, GA

Justin Goodwin, MS
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New Haven, CT

Jeffrey Gehlhausen, MD
Department of Dermatology,
Yale School of Medicine,
New Haven, CT

Ian Odell, MD, PhD
Department of Dermatology,
Yale School of Medicine,
New Haven, CT

Jennifer McNiff, MD
Department of Dermatology and
Department of Pathology, Yale School of Medicine, New Haven, CT

Karthik Gnanapandithan, MD
Department of Internal Medicine,
Mayo Clinic, Jacksonville, FL

New bullous lesions in a 72-year-old woman

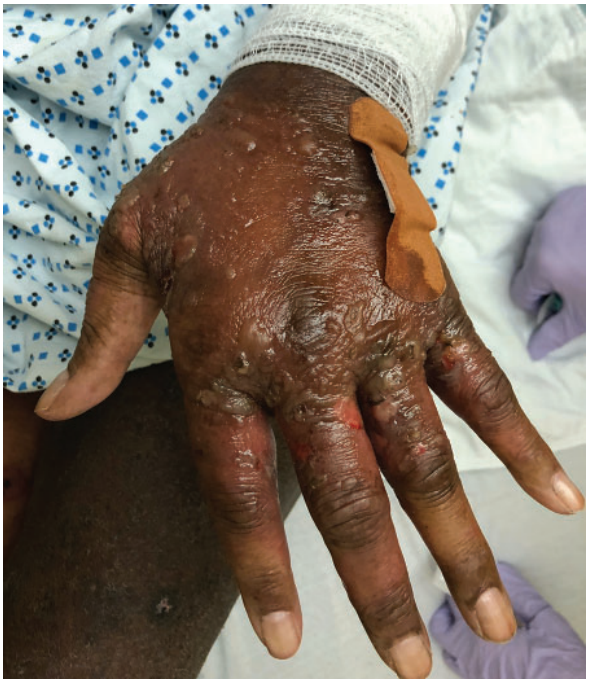

Figure 1. The dorsum of the left hand with tense bullae and erosions.

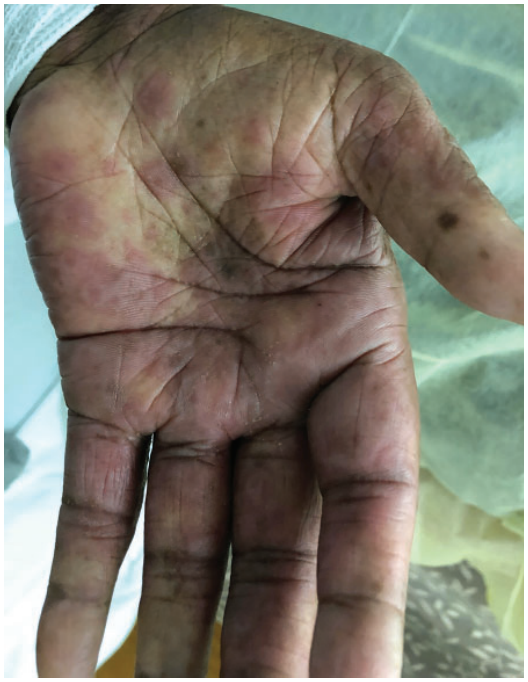

Figure 2. The left palm with red, atypical target lesions.

A woman with psoriasis, chronic edema, and hypertension presented with a progressive, painful blistering rash

A 72-YEAR-OLD WOMAN WITH A HISTORY of psoriasis, chronic lower-extremity edema, and hypertension presented to the emergency department with 2 days of a progressive painful blistering rash primarily involving her hands. She had previously experienced infrequent episodes of herpes labialis and symptoms of fatigue and myalgia. She denied any recent travel or contact with chemicals. She was taking losartan 50 mg/day and furosemide 20 mg/day, which had been prescribed 2 months before for hypertension and peripheral edema.

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INITIAL EVALUATION AND MANAGEMENT

Her temperature was 98.5 °F (36.9 °C), heart rate 107 beats per minute, blood pressure 180/83 mm Hg, respiratory rate 18 breaths per minute, oxygen saturation 100% on room air, weight 69 kg (152 lb), and body mass index 26 kg/m^2.

Skin lesions were present at several sites. The dorsum of her hands had dozens of clear vesicles 0.5 cm to 2 cm in diameter and bullae (**Figure 1**), and her palms had red target lesions 0.5 cm to 1 cm (**Figure 2**). Her thighs had red plaques that had central scale and were bordered by vesicles. Her left lower lip had 2

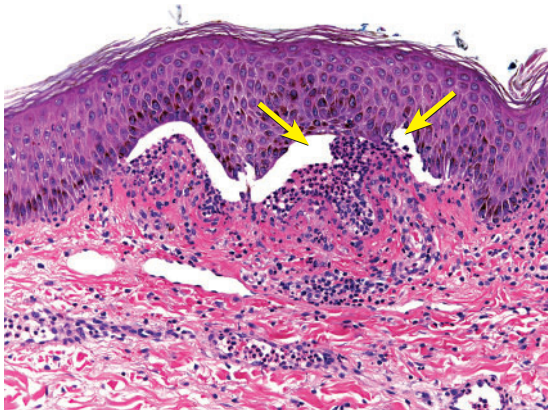

Figure 3. Biopsy from the left hand was significant for subepidermal bullae (arrows) with neutrophils.

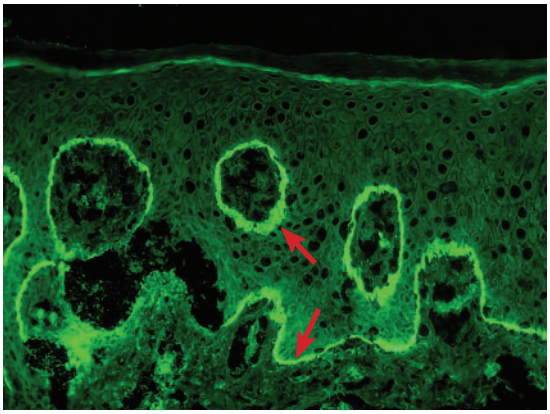

Figure 4. Immunofluorescence showed linear immunoglobulin G and C3 at the dermoepidermal junction (arrows).

flaccid vesicles 3 mm to 4 mm. No ocular or anogenital lesions were seen. The lesions were negative for the Nikolsky sign (separation of the epidermis from the dermis).

Her lungs were clear to auscultation. Although her heart rate was elevated, the rhythm was regular, and there were no murmurs, rubs, or gallops. Her abdomen was soft and nontender to palpation. She was alert and oriented, and her behavior was appropriate.

Drugs linked to bullous pemphigoid include etanercept, sulfasalazine, furosemide, and penicillin

Laboratory testing and histopathology

Laboratory tests taken while she was in the emergency department were notable for the following results:

- White blood cell count 12.1 × 10^9/L (reference range 4.0–10.0 × 10^9/L)
- Eosinophils 2.3% (0.0–7.0%)
- Absolute eosinophil count 0.3 × 10^9/L (0.0–1.0 × 10^9/L)
- Hemoglobin 10.4 g/dL (12.0–18.0 g/dL)
- Mean corpuscular volume 78.7 fL (78.0–94.0 fL)
- Platelet count 359 × 10^9/L (140–440 × 10^9/L)
- Erythrocyte sedimentation rate 86 mm/h (0–20 mm/h)
- C-reactive protein 80 mg/L (< 10 mg/L).

She was admitted to the hospital and treated empirically with famciclovir for a presumed herpes infection. Further evaluations returned negative results for antibodies to bullous pemphigoid 180 (BP180) and 230 (BP230) and collagen type VII in the serum. Polymerase chain reaction testing was negative for herpes simplex virus (HSV) 1 and 2, varicella, and enterovirus using viral skin swabs from her left hand. Viral swabs from the lip lesions were negative for HSV.

A skin biopsy of the left hand showed subepidermal bullae with numerous neutrophils in the superficial dermis (**Figure 3**). A second skin biopsy, on direct immunofluorescence testing, showed linear immunoglobulin G (IgG) and C3 at the dermoepidermal junction (**Figure 4**).

DIFFERENTIAL DIAGNOSIS

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

- ☐ Atypical coxsackievirus infection
- ☐ Recurrent herpes virus
- ☐ Bullous pemphigoid
- ☐ Epidermolysis bullosa acquisita

The skin biopsy results showing linear IgG and C3 on direct immunofluorescence confirmed a diagnosis of bullous pemphigoid.

Bullous pemphigoid is the most common autoimmune bullous dermatosis, affecting individuals with a median age of 70.[1] The pathogenesis involves formation of IgG autoantibodies against BP180 and BP230, which are components of hemidesmosomes that maintain dermoepidermal adhesion in stratified epithelia.[2]

Clinical features include tense bullae, often accompanied by erythematous or urticarial plaques on the abdomen, flexor surfaces of

the extremities, axillae, or inguinal folds that may persist for days before developing erosions and crusts. Blisters may be preceded by an intensely pruritic prodrome,[1] although this does not develop in at least 20% of cases.[3] Mucosal involvement, as seen in this patient, occurs in 10% to 20% of patients.[1]

The technical standard for diagnosis is direct immunofluorescence revealing linear IgG or C3 deposits, or both, at the dermoepidermal junction on skin biopsy, though indirect immunofluorescence testing and enzyme-linked immunosorbent assay detection of BP180 or BP230 antibodies may help with the diagnosis.[4]

The most likely causes of our patient's bullous pemphigoid are discussed in the following sections.

DRUG-INDUCED BULLOUS PEMPHIGOID

More than 50 medications have been associated with the development of bullous pemphigoid, including etanercept, sulfasalazine, furosemide, and penicillin.[5–7] Drug-induced bullous pemphigoid may present acutely and resolve quickly after the offending agent is removed, or it may follow a chronic course that resembles idiopathic bullous pemphigoid. In either case, symptoms may develop up to 3 months after the medication was started.[8]

Although losartan has been linked to bullous pemphigoid in a single case,[9] loop diuretics such as furosemide are among the most commonly reported culprits.[5] There seems to be no association with the dose of furosemide and development of bullous pemphigoid, with doses in case reports ranging from 40 to 120 mg daily.[10]

Because there are no known antibodies specific to drug-induced bullous pemphigoid,[11,12] it is possible that our patient coincidentally developed idiopathic bullous pemphigoid in the setting of furosemide therapy. However, her lesions improved after we stopped her furosemide while continuing losartan (see Management), supporting furosemide as the causative agent.

A 2020 systematic review found that in addition to loop diuretics, other agents with the greatest evidence supporting their role in drug-induced bullous pemphigoid are dipeptidyl peptidase 4-inhibitors (gliptins), inhibitors of programmed cell death protein 1 and programmed cell death ligand 1, and penicillin derivatives.[13]

Histopathology

Light microscopy of bullous pemphigoid lesions typically reveals subepidermal blisters with an eosinophil-rich superficial dermal infiltrate.[1] Neutrophilic infiltrates, as seen in this patient's biopsy, are rarely reported in bullous pemphigoid, and they are more typically associated with other bullous diseases such as linear IgA bullous dermatosis and dermatitis herpetiformis.[14] Nonetheless, in this patient, the absence of linear IgA deposits at the dermoepidermal junction on immunofluorescence ruled out linear IgA bullous dermatosis.[15]

Although BP180 and BP230 antibodies were not detected in her serum, about 8% of bullous pemphigoid cases do not have significant levels of circulating BP180 autoantibodies,[16] and 8% of people without bullous pemphigoid test positive for 1 or both autoantibodies.[17]

COXSACKIEVIRUS INFECTION

Coxsackievirus A16, a nonpolio enterovirus, causes hand, foot, and mouth disease (HFMD). This disease is most common in children under 5 years of age, but it may affect older children and adults.

Cases classically manifest as an oral enanthem or a nonpainful, nonpruritic exanthem of the hands, feet, buttocks, thighs, and arms. The enanthem is characterized by erythematous macules that progress to vesicles on erythematous bases before ultimately ulcerating. The exanthem may be macular, maculopapular, or vesicular, and most commonly arises on the dorsum of the hands and feet, occasionally affecting the palms and soles.

The diagnosis is clinical in children but may be confirmed by biopsy in adults, for whom the differential diagnosis is more extensive owing to consideration of autoimmune bullous diseases. Biopsy of HFMD lesions typically reveals loose strands of fibrin, lymphocytes, monocytes, and neutrophils with acantholysis of the epidermis.[18]

In the past decade, outbreaks of so-called

Topical steroids applied to the entire body except the face often suffice in mild, localized bullous pemphigoid regardless of the cause

atypical HFMD have been documented in adults with coxsackievirus A6. In contrast to typical HFMD, skin lesions in atypical HFMD are painful, are distributed more widely across the body, and may include bullae and eschar formation. Biopsy of atypical HFMD skin lesions reveals intense edema, necrotic keratinocytes, and neutrophilic exocytosis with T-cell infiltrate.[19] In our patient's case, biopsy results were not consistent with either typical or atypical coxsackievirus.

HERPES VIRUS INFECTION

Given this patient's oral lesions and history of herpes labialis, erythema multiforme arising from HSV infection was included in the differential diagnosis. Herpes labialis typically presents as painful ulcerations at the vermilion border or the buccal mucosa that last up to 8 days and may be preceded by a painful or pruritic prodrome. It may be complicated by erythema multiforme, a self-limited cutaneous autoimmune disease characterized by targetoid lesions with 2 or 3 different concentric zones, with or without bullae formation in the center zone.

If bullae develop in a patient on furosemide, consider drug-induced bullous pemphigoid

Erythema multiforme most commonly arises from HSV infection, but it may also be caused by drug reaction or other infectious pathogens including *Mycoplasma pneumoniae*, hepatitis C virus, Epstein-Barr virus, or coxsackievirus. Histologic features of erythema multiforme vary depending on the cause of the disease, site of biopsy within the skin lesion, and time point of biopsy in the disease course, but they generally include spongiosis, keratinocyte necrosis, and inflammatory infiltrate at the dermoepidermal junction.[20] In patients with HSV-associated erythema multiforme, HSV DNA is detected in 43% of lesional skin biopsies.[21] It was not detected in our patient's skin lesions.

EPIDERMOLYSIS BULLOSA ACQUISITA

Epidermolysis bullosa acquisita (EBA) is a rare autoimmune blistering disorder characterized by the production of autoantibodies against type VII collagen, which anchors fibrils at the dermoepidermal junction and provides stability to structures in the extracellular matrixes. The clinical presentation varies but classically involves skin fragility and the formation of trauma-induced, noninflammatory, tense bullae in an acral distribution, with or without mucosal involvement.[22]

A subtype of EBA known as bullous pemphigoid-like EBA, which presents with tense bullae surrounded by inflamed or urticarial skin, was considered in this patient's differential diagnosis given the skin lesions on her hands.

Up to 50% of patients with EBA have a bullous pemphigoid-like presentation, and in a review of sera from 85 patients diagnosed with bullous pemphigoid, 10% of bullous pemphigoid patients had circulating EBA antibodies.[23] In our patient, the negative results for collagen type VII IgG antibodies excluded a diagnosis of EBA.

MANAGEMENT

2 What is the best next step in treating this patient's bullous lesions?

- ☐ Topical tacrolimus
- ☐ Oral corticosteroids
- ☐ Dapsone
- ☐ Tetracycline plus nicotinamide
- ☐ Discontinue furosemide

Furosemide was discontinued, and the patient was prescribed triamcinolone 0.1% cream to use on an outpatient basis. One month after discharge, she had only 2 urticarial plaques, and she was completely clear 2 months later.

Treatment with topical corticosteroids applied to affected areas and avoiding the face is often sufficient in mild, localized bullous pemphigoid regardless of the cause. Tapering the steroid dose may begin after 15 days of disease control, defined as the time point at which new bullous lesions and pruritus cease to form and existing lesions begin to heal, with a total treatment duration of 4 to 12 months. Supportive skin care such as baths containing antiseptics or wheat starch, or both, and application of nonadherent dressings to erosive lesions may improve the patient's comfort, reduce bacterial infection, and promote wound healing.[24] No large-scale clinical trial has evaluated the safety and efficacy of topical tacrolimus in bullous pemphigoid.

Severe or recurrent disease may warrant

use of oral steroids, tetracyclines plus nicotinamide, dapsone, or immunosuppressive agents, and should be supervised by a dermatologist.[24] In patients with drug-induced bullous pemphigoid, such as our patient, the suspected causative drug should be discontinued immediately.[5]

As a substitute for furosemide to treat her hypertension, the patient's losartan dose was increased to 100 mg daily, and she was also prescribed amlodipine 10 mg daily and hydralazine 50 mg every 8 hours, with plans for close follow-up with her primary care physician. At discharge, her blood pressure had improved but remained elevated at 150/75 mm Hg. There is not enough literature available to guide the choice of an alternative to loop diuretics in patients with a history of furosemide-induced bullous pemphigoid.

FOLLOW-UP

3 Patients with bullous pemphigoid are more likely than patients without the disease to develop which of the following morbidities?

- ☐ Kidney disease
- ☐ Neurologic disorders
- ☐ Malignancy
- ☐ Heart disease

Our patient was found to have Alzheimer dementia 4 months after developing bullous pemphigoid, consistent with the documented association between bullous pemphigoid and neurologic disorders including dementia, stroke, epilepsy, Parkinson disease, and multiple sclerosis.[25–27] While the mechanism of this association is unclear, immunologic cross-reactivity of antibodies targeting the BP230 isoforms in both the epidermis and brain may play a role.[28,29]

Retrospective studies have detected a higher rate of bullous pemphigoid in patients with laryngeal and renal cancers, as well as hematologic malignancies.[30,31] However, a recent systematic review and meta-analysis that included these studies did not identify an association between bullous pemphigoid and malignancy.[32]

Although patients with bullous pemphigoid have more frequent hospitalizations and comorbidities,[33,34] there is no documented association between bullous pemphigoid and heart or kidney disease in particular.

TAKE-HOME POINTS

- If bullae develop in a patient taking furosemide, consider drug-induced bullous pemphigoid.
- Bullous pemphigoid is diagnosed by a medical history, physical examination, and skin biopsy for evaluation by light microscopy and immunofluorescence.
- In treating drug-induced bullous pemphigoid, stop the causative drug immediately, and apply topical corticosteroids.
- Bullous pemphigoid is associated with neurologic disorders, including dementia. ■

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DISCLOSURES

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

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***Address**: Karthik Gnanapandithan, MD, Department of Internal Medicine, Mayo Clinic, 4500 San Pablo Rd S, Jacksonville, FL, 32224; gnanapandithan.karthik@mayo.edu*

REVIEW

Travis M. Howard, MD
Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, OH

Umesh N. Khot, MD
Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, OH; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Dual antiplatelet therapy after percutaneous coronary intervention: Personalize the duration

ABSTRACT

The recommended duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention with a drug-eluting stent has changed from 1 year for all to a more personalized approach based on the patient's risks of ischemia and bleeding. The trend is toward shorter treatment in view of lower rates of late and very late stent thrombosis with newer drug-eluting stents and the risk of bleeding with DAPT. But some patients at high risk of ischemic events and low risk of bleeding may benefit from longer treatment.

KEY POINTS

A shorter duration of DAPT (< 12 months) is favored for patients at high risk of bleeding or low risk of ischemia, or both.

DAPT for 12 months or more should be considered for patients at high risk of ischemic events (eg, due to prior myocardial infarction) and at low risk of bleeding.

For patients on DAPT who need noncardiac surgery, 3 factors should be considered: risk of bleeding if surgery is performed while the patient continues DAPT; risk of stent thrombosis if DAPT is interrupted; and consequences of delaying surgery. For some, a bridging protocol can be used.

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Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor after a percutaneous intervention (PCI) is one of the most commonly prescribed therapies in cardiovascular medicine. However, treatment strategies have evolved as our understanding of stent thrombosis has deepened and stents have improved, leading to uncertainty, even among cardiologists, about how to best manage DAPT.

This article reviews current guidelines on the duration of therapy and perioperative management of DAPT after PCI (**Table 1**).

BEYOND THE RIGID 1-YEAR RECOMMENDATION

Bare-metal stents, developed to keep an artery open after angioplasty, were associated with stent thrombosis and restenosis, requiring repeat revascularization in many patients.[1] The risk of stent thrombosis was found to be mitigated by aspirin and 1 month of ticlopidine, sparking the initial enthusiasm for DAPT as we know it today.[2]

Drug-eluting stents were subsequently developed to reduce the risk of stent restenosis.[1] However, concerns about late and very late stent thrombosis with first-generation drug-eluting stents precipitated the need for longer DAPT. Trials at the time assessed 1 year of therapy, and when it was found to be effective, it became the reference duration of DAPT after drug-eluting stent placement, regardless of the clinical presentation at the time of PCI.[3,4]

Second-generation drug-eluting stents have better polymers and smaller struts and

TABLE 1

Dual antiplatelet therapy (DAPT) after percutaneous coronary intervention with a drug-eluting stent

Initial DAPT duration

The rigid 1-year recommendation for initial DAPT duration has been revised, and the optimal duration is now defined by balancing risk of bleeding vs avoiding future ischemic events

In patients with high bleeding risk or low ischemic risk, or both, shorter durations of DAPT are favored; in those with low bleeding risk or high ischemic risk, or both, longer durations of DAPT are favored

Perioperative management of DAPT for noncardiac surgery

Consider: Risk of bleeding during surgery while on DAPT
Risk of stent thrombosis
Consequences of delaying surgery

Avoid surgery while patient is on DAPT unless emergent or bleeding risk is minimal

Risk of stent thrombosis is highest initially and decreases over time but is never zero. If possible, delay surgery for at least 3 months and ideally for 6 months

If DAPT is interrupted, continue aspirin, as it protect against stent thrombosis

Consider bridging with intravenous antiplatelet agents if the risk of stent thrombosis is particularly high and surgery cannot be delayed

Long-term DAPT (> 12 months)

Appraise the risks and benefits for the individual patient

Consider in patients at high risk of future ischemic events (eg, patients who have had prior myocardial infarction) and low bleeding risk

are associated with significantly lower rates of late and very late stent thrombosis.[1] These improvements propelled the use of drug-eluting stents rather than bare-metal stents, and they became the predominantly placed stent, even in patients for whom the duration of DAPT must be shorter.[5] However, increased bleeding with prolonged DAPT remained a major drawback, so an extensive evaluation of DAPT duration was undertaken. Knowing how long and under what conditions to continue DAPT after drug-eluting stent PCI is critical for best managing these patients.

Shorter DAPT for some patients

The 2016 American College of Cardiology and American Heart Association (ACC/AHA)[6] guidelines and the 2017 European Society of Cardiology (ESC)[7] guidelines provide the most recent updates on DAPT management. Despite subtle differences, their overall message is the same. The rigid recommendation for 1 year of DAPT after PCI with a drug-eluting stent irrespective of indication has been revised, and a new paradigm has been introduced. DAPT duration is now determined by balancing risk of future ischemic events against bleeding (**Figure 1**).

For patients with an acute coronary syndrome treated with a drug-eluting stent, at least 12 months of DAPT is recommended. However, just 6 months can be considered for those with high bleeding risk.

For patients with stable ischemic heart disease treated with a drug-eluting a stent, at least 6 months of DAPT with clopidogrel is recommended, but just 3 months can be considered for those at high bleeding risk, or even just 1 month if 3 months of DAPT poses safety concerns.

These guidelines were based on multiple randomized controlled trials over the previous decade that compared 6 months or less of DAPT with longer durations after PCI with a drug-eluting stent.[8–14] Meta-analyses of these trials demonstrated that in an all-comers population, regardless of PCI indication and underlying comorbidities, shorter durations of DAPT decrease bleeding at the expense of increased ischemic events, eg, stent thrombosis and myocardial infarction.[15–17] Further exploration of the data behind this conclusion illuminates the intricacies of DAPT management and provides the foundation for the current guidelines.

BALANCING RISKS

Bleeding risk from DAPT is directly proportional to the length of therapy, with longer periods leading to increased bleeding events and higher rates of noncardiovascular mortality.[15] On the other hand, the reduction of ischemic events from DAPT is greatest in the first few weeks due to protection from early stent thrombosis. Over time, the benefit from protection against stent thrombosis decreases, and the predominant advantage of DAPT shifts to protection from spontaneous myocardial infarction, ie, from plaque rupture at sites remote from the stented index lesion.[18]

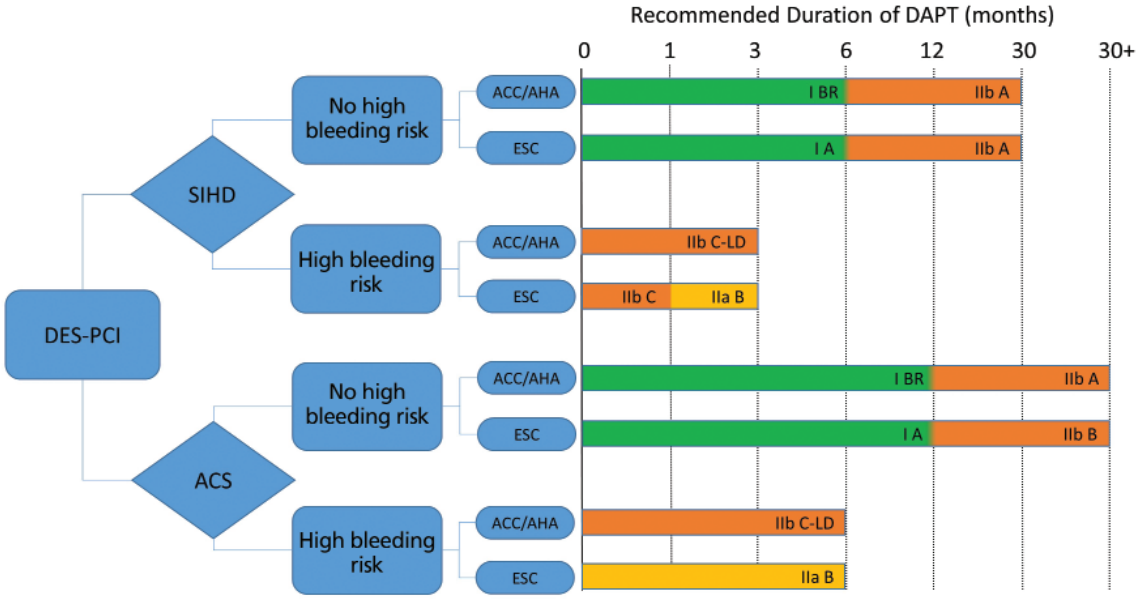

Figure 1. Recommended duration of dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting stents. Class of recommendation and level of evidence: class I, benefit much greater than risk; class II, benefit greater than risk, with conflicting evidence or opinion; class IIa, weight of evidence or opinion is in favor of usefulness; class IIb, usefulness is less well established. Level of evidence: A, from multiple randomized clinical trials; B or BR, from one or more randomized trials; C or C-LD, from nonrandomized observational studies.

ACC = American College of Cardiology; ACS = acute coronary syndrome; AHA = American Heart Association; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; ESC = European Society of Cardiology; PCI = percutaneous coronary intervention; SIHD = stable ischemic heart disease

Information from references 6 and 7.

Treatment has evolved, leading to uncertainty about how to best manage DAPT

Despite the reduction of stent thrombosis and myocardial infarction with persistent DAPT, cardiac mortality rates are the same with 6 months or less of therapy compared with longer durations.[15] This is likely due to the declining mortality risk of stent thrombosis over time and the inclusion of smaller myocardial infarctions with less prognostic relevance in trial end points.[19] Consequently, there is no effect on all-cause mortality comparing 6 months or less vs 1 year of DAPT.[15] Thus, it can be reasoned that patients at high risk of bleeding, low risk of ischemic events, or both, may benefit from a shorter duration of DAPT, and those at low risk of bleeding, high risk of ischemic events, or both, may benefit from a longer duration.

Although no study has exclusively focused on patients with stable ischemic heart disease who received drug-eluting stents, subgroup analyses demonstrate that they are at much lower risk of stent thrombosis and myocardial infarction,[20] hence the adequacy of DAPT for 6 months according to the most recent guidelines. The recommendations for patients with an acute coronary syndrome and high bleeding risk are based on the same logic. They were supported in the 2018 SMART-DATE trial (Safety of 6-month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndrome),[21] which demonstrated a higher risk of myocardial infarction in patients with acute coronary syndrome who received DAPT for 6 months compared with 12 or more months. But no difference was found in all-cause mortality with longer DAPT due to the higher incidence of bleeding.

INTERRUPT DAPT FOR NONCARDIAC SURGERY?

When patients on DAPT after drug-eluting stent PCI need noncardiac surgery, one must

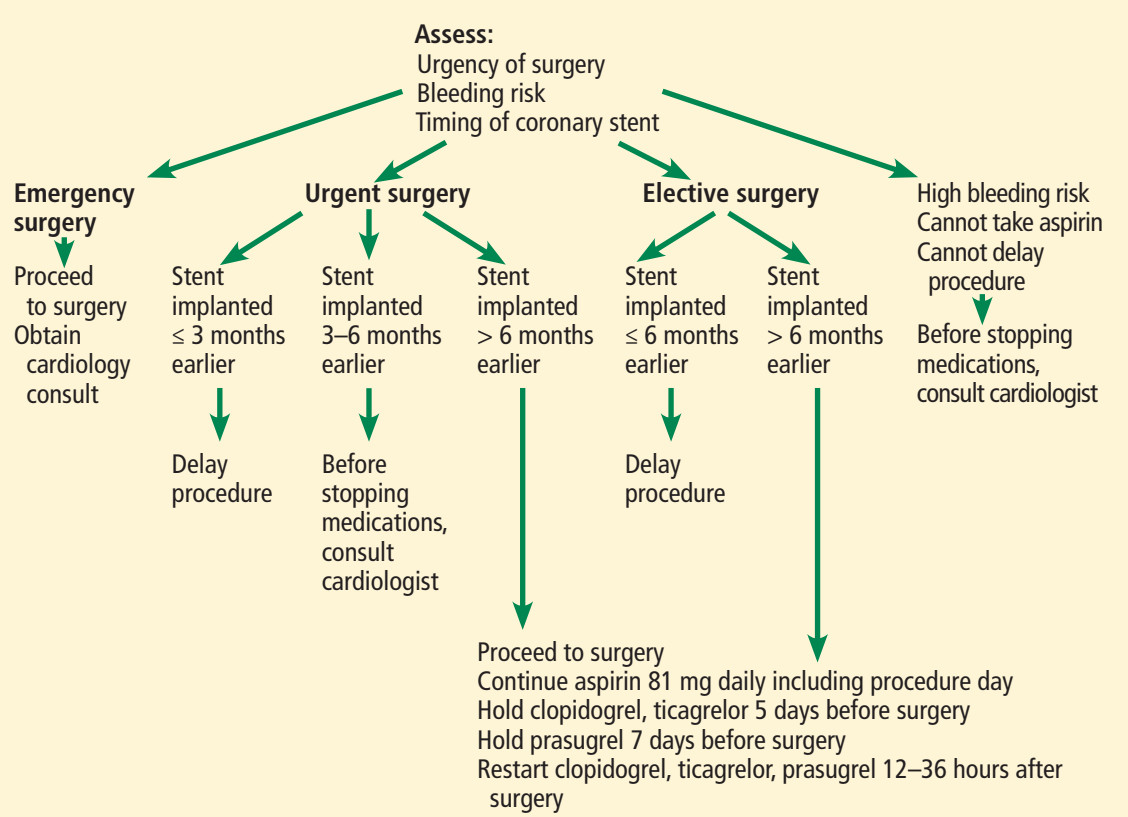

Figure 2. Guidelines for preoperative management of patients with coronary stents undergoing noncardiac surgery.

DAPT duration is now determined by balancing risk of ischemia vs risk of bleeding

consider:

- The risk of bleeding from surgery if DAPT is continued
- The risk of stent thrombosis if DAPT is interrupted
- The consequences of delaying surgery.

These are complicated questions but can be approached in a disciplined manner.

The risk of bleeding during surgery is higher for a patient on antiplatelet therapy.[22,23] Given the increased mortality and morbidity associated with bleeding,[24] antiplatelet therapy should be minimized before surgery unless it can be performed with minimal bleeding risk while on DAPT. However, because DAPT significantly reduces the risk of stent thrombosis, and interruption of DAPT after stent placement is one of the strongest risk factors for stent thrombosis,[6] the tension between the risks of bleeding and stent thrombosis must be balanced. When possible, this dilemma can be solved by delaying surgery. However, in many situations (eg, for malignant and vascular diseases), delaying surgery can be detrimental.[25,26]

Multiple observational studies have tried to determine a time frame after stenting when the risk of DAPT interruption is low enough for patients to undergo surgery.[27–29] Older observational studies based on bare-metal stents and mostly first-generation drug-eluting stents found that the risk of stent-related thrombotic complications is highest in the first 4 to 6 weeks but continues to be elevated for at least 1 year.[27] More recent observational studies suggest the time frame of increased risk is about 6 months,[28] and may even be as short as 30 days.[29]

Based on these data, Cleveland Clinic uses the approach shown in **Figure 2**. Developed by a multidisciplinary team of specialists, the algorithm balances the risks of bleeding, stent thrombosis, and delaying surgery and is similar to the one in the ACC/AHA guidelines.[6]

If DAPT is interrupted, aspirin should be continued if feasible, as it protects against ischemic events,[30] and P2Y12 therapy should

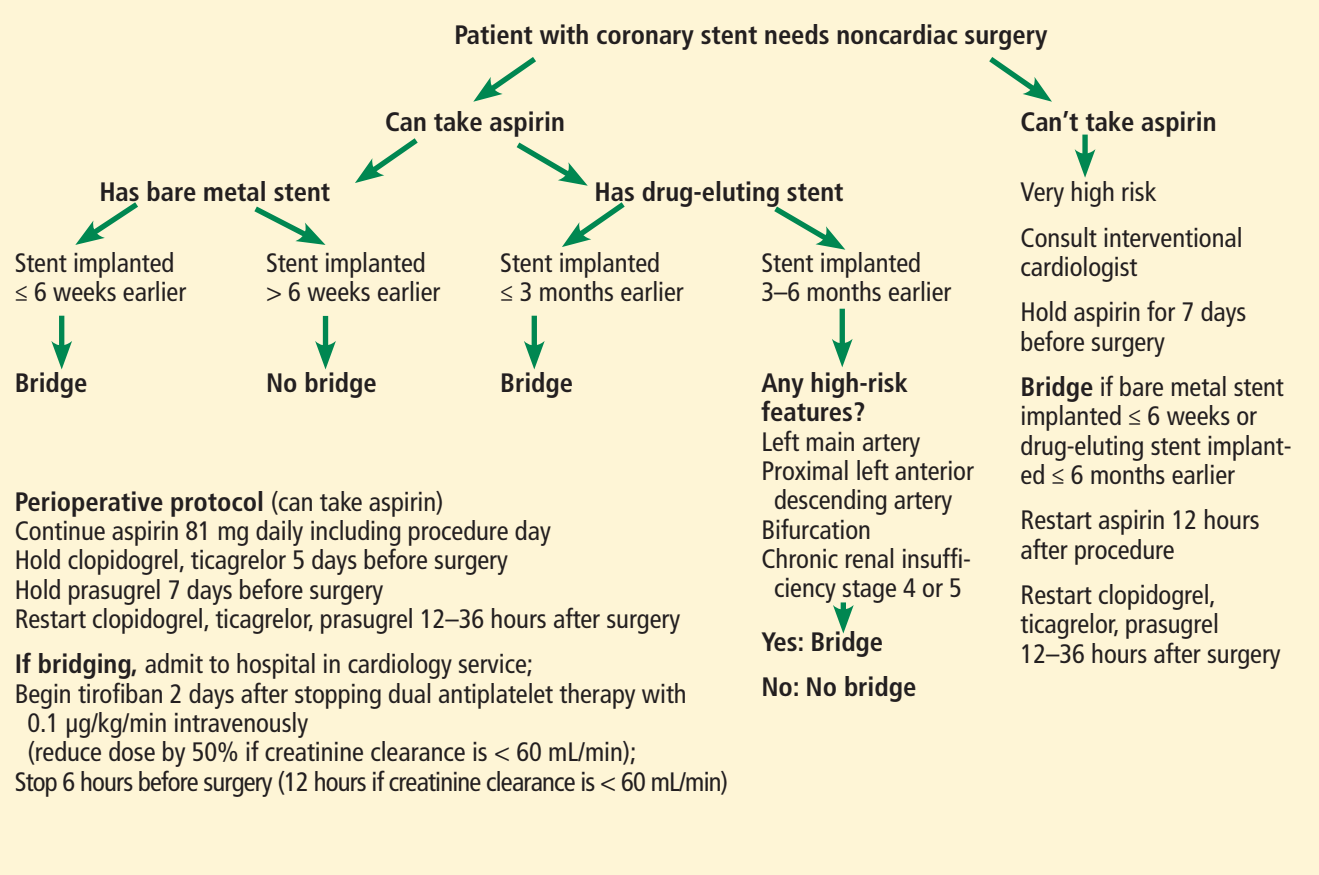

Figure 3. Guidelines for bridging before surgery in patients with prior coronary stent.

be restarted as soon as possible.[6,7] If the risk of stent thrombosis is particularly high and surgery cannot be delayed, it should be performed in hospitals where heart catheterization is readily available, and bridging with intravenous antiplatelet agents should be considered.[6,7] Our approach to intravenous antiplatelet bridging is shown in **Figure 3**.

WHO NEEDS LONGER DAPT?

Whether DAPT is beneficial for longer than 12 months has been debated for many years. After the first-generation drug-eluting stents were introduced and 12 months was subsequently identified as the standard DAPT duration, multiple trials have investigated whether extending DAPT further would be useful.[8,11,17,31–33] As for determining whether shorter DAPT duration could be indicated, risk of future ischemic events was balanced against bleeding.

The first and largest study to investigate this question[18] found that in patients who completed 12 months of DAPT after PCI without suffering an ischemic or bleeding event, continuing DAPT for 18 additional months reduced myocardial infarction and stent thrombosis rates but increased major bleeding and mortality compared with patients taking aspirin and placebo. The increase in mortality was driven by noncardiovascular causes. Subgroup analysis found that in patients with a prior myocardial infarction, the reduction in ischemic events was most pronounced and survival was greatest, although overall mortality was still neutral in this population. Subsequent meta-analyses of this and other randomized controlled trials comparing more than 12 months of DAPT and shorter durations demonstrated similar findings.[34,35] Notably, some of these trials enrolled patients with first- and second-generation drug-eluting stents, and a subgroup analysis of the DAPT

trial showed significant attenuation of benefit in those with second-generation drug-eluting stents.[36]

Attention subsequently turned to prolonged DAPT in patients with a prior myocardial infarction. The PEGASUS TIMI 54 trial (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared With Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54) tested prolonged DAPT in patients who had a myocardial infarction in the previous 1 to 3 years.[33] It found a reduction in most ischemic end points but no effect on the rate of all-cause mortality. These results were confirmed in a meta-analysis of the PEGASUS trial plus subgroups from 4 additional randomized controlled trials.[37]

Based on these findings, clinical decision-making surrounding more than 12 months of DAPT therapy requires an individualized appraisal of the risk and benefits. As discussed previously, with safer, newer-generation drug-eluting stents, the largest benefit of long-term DAPT is reduction of spontaneous myocardial infarction. This highlights the shift from local stent-related protection of early DAPT to systemic protection with longer therapy.

Bleeding risk from DAPT is directly proportional to the length of therapy

Bottom line. Long-term DAPT should only be considered in patients with a prior myocardial infarction who are at high risk of recurrence and low risk of bleeding (class of recommendation IIb).[6,7] The PRECISE-DAPT score and the DAPT score can be used to help determine if a patient may benefit from prolonged therapy.[7]

The PRECISE-DAPT score (**www.precisedaptscore.com**) is based on the patient's:

- Hemoglobin level
- White blood cell count
- Age
- Creatinine clearance rate
- History of bleeding.

The DAPT score (**http://tools.acc.org/daptriskapp/#!/content/calculator/**) is based on the following:

- Age
- Cigarette smoking
- Diabetes mellitus
- Myocardial infarction
- Prior PCI or prior myocardial infarction
- Paclitaxel-eluting stent
- Stent diameter less than 3 mm
- Congestive heart failure or left ventricular ejection fraction less than 30%
- Placement of a stent in a vein graft.

In patients who discontinue P2Y12 inhibitors, current recommendations are to continue aspirin indefinitely for cardiac protection. However, as noted below, this is an area of active research to identify the best option to ensure protection from cardiovascular risk while reducing the risk of bleeding.

FUTURE DIRECTIONS

In the future, DAPT management will likely continue to focus on defining the optimal level of platelet inhibition at various stages of post-PCI and tailoring therapy appropriately. Since much of the data underpinning current guidelines on DAPT management was accrued from observational studies with first- and second-generation drug-eluting stents, future guidelines will likely accept even shorter durations of DAPT for most patients, and provide considerations for P2Y12 monotherapy.

The recently published TWILIGHT (Ticagrelor With or Without Aspirin in High-Risk Patients After Coronary Intervention) trial emphasizes this model.[38] Patients at high risk of bleeding and ischemic events who completed 3 months of DAPT were randomized to continue DAPT or receive ticagrelor monotherapy for 12 months. Bleeding rates were significantly lower in the monotherapy group without a statistically significant increase in ischemic events. A 2020 meta-analysis of multiple similar trials confirmed these findings.[39]

DISCLOSURES

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

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***Address**: Umesh N. Khot, MD, Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, J2-4, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; khotu@ccf.org*

Allison Nitsch, MD
ACUTE Center for Eating Disorders at Denver Health, Denver, CO; Department of Medicine, University of Colorado School of Medicine, Aurora, CO

Heather Dlugosz, MD
Eating Recovery Center and Pathlight Mood & Anxiety Center, Cincinnati, OH

Dennis Gibson, MD
ACUTE Center for Eating Disorders at Denver Health, Denver, CO; Department of Medicine, University of Colorado School of Medicine, Aurora, CO

Philip S. Mehler, MD, FACP, FAED
ACUTE Center for Eating Disorders at Denver Health, Denver, CO; Department of Medicine, University of Colorado School of Medicine, Aurora, CO

Medical complications of bulimia nervosa

ABSTRACT

Bulimia nervosa, a mental illness 4 times more common than anorexia nervosa, is characterized by binge-eating followed by compensatory purging behaviors, which include self-induced vomiting, diuretic abuse, laxative abuse, and misuse of insulin. Patients with bulimia nervosa are at risk of developing medical complications that affect all body systems, especially the renal and electrolyte systems. Behavior cessation can reverse some, but not all, medical complications.

KEY POINTS

Most people with bulimia nervosa are young and of normal weight, or even overweight, making detection and diagnosis difficult.

As a consequence of purging behaviors, pseudo-Bartter syndrome can develop due to chronic dehydration, placing patients at risk for electrolyte abnormalities such as hypokalemia, as well as marked and rapid edema formation when purging is interrupted.

Electrolyte and metabolic disturbances are the most common causes of morbidity and mortality in patients with bulimia nervosa. Hypokalemia should be managed aggressively to prevent electrocardiographic changes and arrhythmias such as torsades de pointes.

Diabetic patients who purge calories through manipulation of their blood glucose are at high risk for hyperglycemia, ketoacidosis, and premature microvascular complications.

Gastrointestinal complaints are common and include gastroesophageal reflux disease.

doi:10.3949/ccjm.88a.20168

A 21-year-old woman with a history of depression and anxiety presents to your clinic for follow-up after an emergency room visit, where she had presented 2 days earlier for feeling like she was going "to pass out" during her college cross-country meet. At the emergency room, the patient was noted to have a serum potassium level of 2.9 mmol/L (reference range 3.7–5.1 mmol/L), bicarbonate 35 mmol/L (22–30 mmol/L), and orthostatic hypotension. She was given 2 L of intravenous normal saline and intravenous and oral potassium.

On follow-up, her vital signs are normal. Her body mass index is 24.5 kg/m^2. She reports feeling better but has noted marked swelling of both her lower extremities, which is causing her distress. The examination is notable for bilateral 2+ pitting edema and calluses on the dorsal aspect of her right hand.

A SERIOUS MENTAL ILLNESS WITH PHYSICAL CONSEQUENCES

Bulimia nervosa (BN) is a serious mental illness characterized by binge-eating followed by compensatory purging behaviors. It is frequently accompanied by medical sequelae that affect normal physiologic functioning and contribute to increased morbidity and mortality rates.[1] Most people with BN are of normal weight or even overweight,[2] and are otherwise often able to avoid detection of their eating disorder. Thus, it is important that clinicians familiarize themselves with these complications and how to identify patients with disordered eating patterns.

Recurrent binge-eating followed by purging

BN is characterized by overvaluation of body weight and shape and recurrent binge-eating

(consuming an excessive caloric amount in a short period of time, usually a 2-hour period, that the patient feels unable to control). This is soon accompanied by compensatory purging behaviors that can include abuse of laxatives and diuretics, withholding insulin (termed *diabulimia* or *eating disorder-diabetes mellitus type 1*), self-induced vomiting, fasting, and excessive exercise. Some patients also abuse caffeine or prescription stimulant medications commonly used to treat attention-deficit/hyperactivity disorder.

Self-induced vomiting and laxative misuse account for more than 90% of purging behaviors in BN.[3] The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) requires episodes of bingeing and compensatory behaviors in BN to occur at least once per week over the course of 3 months and not occur during an episode of anorexia nervosa.[3] The complications of purging behaviors found in BN are identical to those found in the binge-purge subtype of anorexia nervosa except that restriction of calories primarily and excessive weight loss are not present.

Self-induced vomiting and laxative abuse account for more than 90% of purging behaviors

The severity of BN is determined by the frequency of the mode of the purging behaviors (mild: an average of 1–3 episodes of inappropriate compensatory behaviors weekly; moderate: 4–7; severe: 8–13; extreme: 14 or more) or the degree of functional impairment.[2] Some patients may vomit multiple times per day while others may use significant amounts of laxatives. Some may engage in multiple different purging behaviors, which has been shown to be associated with a greater severity of illness.[4] Exercise is considered excessive if it interferes with other activities, persists despite injury or medical complications, or occurs at inappropriate times or situations.[2,5]

ONSET IN ADOLESCENCE, AND FAIRLY COMMON

BN typically develops in adolescence or young adulthood and affects both sexes, although it is much more common in girls and young women.[6] It affects people regardless of sexual orientation but has been shown to be more prevalent in nonheterosexual males.[7] Studies have found similar prevalence of BN among different racial and ethnic groups. Individuals with BN are generally within or above the normal weight range.[2]

According to pooled data from the World Health Organization, the lifetime prevalence of BN in adults is 1.0% using the older DSM-IV criteria,[7] which is greater than the reported prevalence of anorexia nervosa. Prevalence estimates are higher with the broadened DSM-5 criteria, ranging from 4% to 6.7%.[8]

There are multiple predisposing and perpetuating factors—genetic, environmental, psychosocial, neurobiological, and temperamental. These can include impulsivity, developmental transitions such as puberty, internalization of the thin ideal, and weight and shape concerns.[9] A history of childhood trauma, including sexual, physical or emotional trauma, has also been associated with BN.[10]

More than 70% of people with eating disorders report concomitant psychiatric comorbidity—affective disorders, anxiety, substance use, and personality disorders are most common in BN.[11] Psychiatric comorbidities as well as hopelessness, shame, and impulsivity associated with the illness may contribute to challenges with nonsuicidal self-harm, suicidal ideation, and death by suicide. Individuals with BN experience lifetime rates of nonsuicidal self-harm of 33% and are nearly 8 times more likely to die by suicide than the general population.[12,13] The reported standardized mortality rates in those with BN are less than in those with anorexia nervosa but are still significantly elevated at 1.5% to 2.5%.[1]

MEDICAL COMPLICATIONS

As noted earlier, BN is associated with a significantly increased mortality rate even though many of these patients are young. Much of this elevated mortality is attributable to the medical complications associated with BN, which are a direct result of the mode and frequency of purging behaviors. Thus, for example, if someone uses laxatives 3 times per day or vomits 1 time per day, there may be no medical complications, but many patients engage in their respective purging behaviors many times per day, leading to multiple complications.

Aside from the electrolyte aberrations from purging, some of the medical complications are unique to the mode of purging. Furthermore, BN has been found to increase the risk of any cardiovascular disease, including ischemic heart disease and death in females.[14] These same complications may also apply to patients with anorexia nervosa of the binge-purge subtype in contrast to those patients with anorexia nervosa who only restrict caloric intake but do not purge.

We will now discuss, in a systems-based approach, the medical complications that develop in people with BN as a direct result of their purging behaviors.

Skin

Russell sign (**Figure 1**), named after Dr. Gerald Russell, who first defined the disease BN in 1979, refers to the development of calluses on the dorsal aspect of the dominant hand.[15] It is pathognomonic for self-induced vomiting and is due to traumatic irritation of the hand by the teeth, from repeated insertion of the hand into the mouth to provoke vomiting.[15]

Russell sign is not commonly seen since many of these patients are able to spontaneously vomit or they utilize utensils to initiate self-induced vomiting.

Teeth and mouth

Abnormalities of the teeth and mouth, specific for purging via vomiting, include dental erosions and trauma to the oral mucosa and pharynx.[16]

Dental erosion is the most common oral manifestation of chronic regurgitation. It is believed to be caused by the teeth coming into contact with acidic vomitus (pH 3.8), although just how changes in salivary composition and dietary intake contribute is unclear. It tends to affect the lingual surfaces of the maxillary teeth and is known as perimyolysis. Vomiting also potentially increases the risk of dental caries.

Trauma to the oral mucosa, especially the pharynx and soft palate, is also encountered and is presumed to occur either as a result of the patient inserting a foreign object into the mouth to induce vomiting or the caustic effect of the vomitus on the mucosal lining.

Dental erosions are irreversible once they have developed. Use of fluorinated mouthwash after purging and horizontal gentle brushing are recommended. Ongoing self-induced vomiting will also damage newly implanted teeth as well as dental prosthetics.

Figure 1. The Russell sign.

Head, ears, nose, and throat

Purging by vomiting increases the risk of subconjunctival hemorrhages from forceful retching, which can also cause recurrent epistaxis. Indeed, recurrent bouts of epistaxis that remain unexplained should prompt a search for covert BN.

Pharyngitis is often noted in those who vomit frequently, due to contact of the pharyngeal tissue with stomach acid. Hoarseness, cough, and dysphagia may also similarly develop. Pharyngeal and laryngeal complaints can be improved with cessation of vomiting and the use of medications to suppress acid production, such as proton pump inhibitors.

Dental erosion is the most common oral manifestation due to chronic regurgitation

Parotid glands

Parotid gland hypertrophy, or sialadenosis (**Figure 2**), may develop in more than 50% of people engaging in purging via self-induced vomiting.[17] Ironically, it usually develops 3 to 4 days after cessation of purging. Symptoms include bilateral painless enlargement of the parotid glands and, occasionally, other salivary glands. It is believed to develop due to ei-

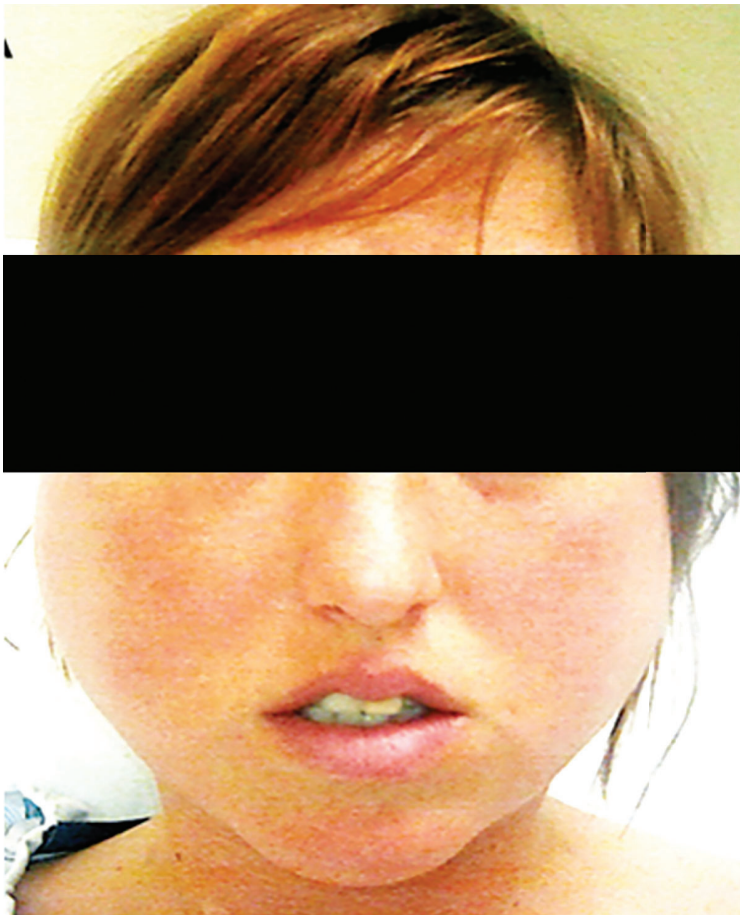

Figure 2. Sialadenosis.

ther cholinergic stimulation of the glands, hypertrophy of the glands to help meet demands of increased saliva production, or excessive backup of saliva that is no longer needed with cessation of vomiting.

Pathology study reveals hypertrophied acinar cells with otherwise preserved architecture without evidence of inflammation.

Swelling may subside with cessation of purging; failure of the parotid gland hypertrophy to resolve is highly suggestive of ongoing purging.[18] Sialadenosis also tends to resolve with the use of sialagogues such as tart candies. Heating pads and nonsteroidal anti-inflammatory drugs also have a therapeutic role and perhaps should be prophylactically initiated in those with a long history of excessive vomiting who engage in treatment to stop purging. In rare refractory cases, pilocarpine may be judiciously used to reduce the glands back to normal size.[19]

Cardiovascular

The cardiac complications that are specific for purging include electrolyte disturbances as a result of vomiting and diuretic or laxative abuse. Conduction disturbances, including serious arrhythmias and QT prolongation, are increasingly encountered in those participating in various modes of purging due to the electrolyte disturbances that ensue, especially hypokalemia and acid-base disorders. Also, excessive ingestion of ipecac, which contains the cardiotoxic alkaloid emetine, to induce vomiting can lead to various conduction disturbances and potentially irreversible cardiomyopathy.[20]

Abuse of caffeine or stimulant medications used to treat attention-deficit/hyperactivity disorder may cause palpitations, sinus tachycardia, or cardiac arrhythmias such as supraventricular tachycardia. Similarly, diet pill abuse, which is increased in this population, is associated with arrhythmias.[21]

Pulmonary

Retching during vomiting increases intrathoracic and intra-alveolar pressures, which can lead to pneumomediastinum.[22] Pneumomediastinum may also be encountered due to nontraumatic alveolar rupture in the setting of malnutrition and is therefore nonspecific in differentiating patients who purge from those who restrict.[23] Vomiting also increases the risk of aspiration pneumonia. Aspiration may be involved in the heretofore enigmatic pathogenesis of pulmonary infection with *Mycobacterium avium* complex organisms.

Gastrointestinal

The gastrointestinal complications of purging depend on the mode of purging used. Upper gastrointestinal complications develop in those who engage in vomiting, whereas lower gastrointestinal complications develop in those who abuse stimulant laxatives.

Esophageal complications. Excessive vomiting exposes the esophagus to gastric acid and damages the lower esophageal sphincter, increasing the propensity for gastroesophageal reflux disease and other esophageal complications, including Barrett esophagus and esophageal adenocarcinoma.[24] However, it is unclear if there truly is an association between purging by self-induced vomiting and reflux disease. Although

research indicates increased complaints of gastrointestinal reflux disease in those engaging in purging, and increased reflux may be present in those who purge when assessed by pH monitoring, endoscopic findings do not necessarily correlate with severity of reported symptoms.[24,25] This suggests a possible functional component to gastrointestinal reflux-related concerns.[26]

Cessation of purging is the recommended treatment, although proton pump inhibitors can be tried. Metoclopramide may also be beneficial, given its actions of accelerating gastric emptying and increasing lower esophageal sphincter tone. Endoscopy should be considered if symptoms continue or have been present for many years, to look for the precancerous esophageal mucosal abnormalities found in Barrett esophagus.

Rare complications are esophageal rupture, known as Boerhaave syndrome, and Mallory-Weiss tears, causing upper gastrointestinal bleeds due to the recurrent episodes of emesis. Mallory-Weiss tears commonly present as blood-streaked or tinged emesis or scant coffee ground emesis following recurrent vomiting episodes. Usually blood loss from such tears is minimal. Mallory-Weiss tears appear as longitudinal mucosal lacerations on endoscopy.

Colonic inertia. Individuals engaging in excessive and chronic stimulant laxative abuse may be at risk for "cathartic colon," a condition whereby the colon becomes an inert tube incapable of moving stool forward. This is believed due to direct damage to the gut myenteric nerve plexus.[27] However, it is currently speculative as to whether this condition truly develops in those with eating disorders and with use of currently available stimulant laxatives.[28] Regardless, in general, stimulant laxatives should be used only short-term, due to concerns regarding potential development of this condition, and should be stopped in those in whom it develops. Instead, osmotic laxatives, which do not directly stimulate peristalsis, are prescribed in a measured manner to manage constipation.

Melanosis coli, a black discoloration of the colon of no known clinical significance, is often reported during colonoscopy in those abusing stimulant laxatives. Rectal prolapse may also develop in those abusing stimulant laxatives, but again is nonspecific for this mode of purging as it can also develop solely as a consequence of malnutrition and the resultant weakness of the pelvic floor muscles.

Endocrine

A potential endocrine complication of BN is irregular menses,[29] as opposed to the amenorrhea frequently observed in both the restricting and binge-purge subtypes of anorexia nervosa.

Although patients with BN do not appear to be at a significantly increased risk for low bone mineral density—in contrast to those suffering from the restricting and binge-purge subtypes of anorexia nervosa—a bone density scan with dual-energy x-ray absorptiometry may still be warranted to evaluate for bone disease in those with a past history of anorexia nervosa.

Patients with type 1 diabetes mellitus may manipulate their blood glucose levels as a means to purge calories, a condition previously referred to as diabulimia and now termed eating disorder-diabetes mellitus type 1.[30] These patients are at risk of marked hyperglycemia, ketoacidosis, and premature microvascular complications such as retinopathy and neuropathy.

METABOLIC AND ELECTROLYTE DISTURBANCES

In addition to the above body system complications from purging, each of the common methods of purging used by patients with BN can be associated with specific electrolyte disturbances. These electrolyte abnormalities are likely the most proximate cause of death in patients with BN. When a patient simultaneously engages in multiple modes of purging behaviors, just as their level of psychiatric illness can be more profound, so too the electrolyte disturbance profiles can overlap and be more extreme.

Purging by emesis increases the risk of aspiration pneumonia

Patients with a history of a known purging behavior should be screened at increased frequency for serum electrolyte disturbances, up to even daily, depending on the frequency of their purging behaviors.[31] In a study of patients admitted to inpatient and residential eating disorder treatment without prior medical stabilization, 26.2% of the BN patients presented with hypokalemia (potassium < 3.6 mmol/L) on their admission laboratory test-

TABLE 1

Summary of electrolyte disturbances in bulimia nervosa

Behavior	Potassium	Sodium	Acid-base
Self-induced vomiting	Low	Low or normal	Metabolic alkalosis
Laxative abuse	Low	Low or normal	Metabolic alkalosis or non-anion gap acidosis
Diuretic abuse	Low	Low or normal	Metabolic alkalosis

ing, while 8.5% had hyponatremia (sodium < 135 mmol/L) and 23.4% had a metabolic alkalosis (bicarbonate > 28 mmol/L).[32]

Self-induced vomiting is the most common method of purging in BN.[33] Patients with self-induced vomiting or diuretic abuse, or both, have been shown to present with hypokalemia, hypochloremia, and a metabolic alkalosis.[34] The severity of the electrolyte abnormalities worsens with the frequency of vomiting.

Similarly, laxative abuse also results in hypokalemia and hypochloremia. However, either a non-anion gap metabolic acidosis or a metabolic alkalosis may be present, depending on the chronicity of the laxative abuse.[35] Generally, more chronic diarrhea results in a metabolic alkalosis. Hyponatremia can also be present with these 3 purging behaviors. The hyponatremia encountered is most often of the hypovolemic type due to chronic fluid depletion as a result of the purging behaviors.

Chronic hypokalemia is often asymptomatic and can slowly be corrected

Pathophysiology of hypokalemia and hypochloremia

The pathophysiologic reasons for hypokalemia and hypochloremia seen with all significant purging behaviors are 2-fold and interrelated. First, and most obvious, there is loss of potassium in the purged gastric contents, excessive stool from laxative abuse, or in the urine through diuretic abuse.

Second, chronic purging results in intravascular fluid depletion. This fluid depletion is sensed by the afferent arteriole of the kidney as decreased renal perfusion pressure, which in turn activates the renin-angiotensin-aldosterone system, resulting in increased production of aldosterone by the zona glomerulosa of the adrenal glands. Aldosterone acts renally at the distal convoluted tubules and cortical collecting ducts, causing them to resorb sodium and chloride in the body's attempt to prevent severe dehydration, hypotension, and fainting. Aldosterone also promotes renal secretion of potassium into the urine and thus hypokalemia. This mechanism of potassium loss is actually a larger contributor to the hypokalemia than the actual gastrointestinal or urinary loses from the behaviors themselves.

The mechanisms by which metabolic alkalosis occurs in self-induced vomiting and in laxative abuse are similar. Initially, hydrogen ions and sodium chloride are lost in the vomitus or through diarrhea. The loss of hydrogen ions produces an alkalemic state. Intravascular volume depletion resulting from the loss of sodium chloride increases the resorption of bicarbonate within the proximal renal tubule, preventing its loss in the urine, which would normally occur to correct the alkalemia. Hypokalemia, if concurrently present, also increases bicarbonate resorption in the proximal tubule, further propagating the metabolic alkalosis. Lastly, increased serum aldosterone levels, brought about from intravascular volume depletion, fuel resorption of sodium at the expense of hydrogen and potassium, resulting in increased loss of hydrogen and potassium in the urine and further maintenance of the alkalemic state.

In diuretic abuse, the diuretics themselves act directly on the kidney to promote loss of sodium chloride in the urine, resulting in intravascular depletion and aldosterone secretion. This results in loss of hydrogen and potassium into the urine, resulting in a metabolic alkalosis. Potassium-sparing diuretics, such as spironolactone, however, do not precipitate a metabolic alkalosis, as they inhibit the action of aldosterone in the kidney.

Table 1 summarizes the electrolyte derangements that occur with BN.

PSEUDO-BARTTER SYNDROME

The aforementioned process of renin-angiotensin-aldosterone system activation results in what has been termed pseudo-Bartter syndrome due to resulting serum and histochemical findings on renal biopsy that resemble Bartter syndrome.[36] However, the findings are not due to intrinsic renal pathology but rather are a result of the chronic state of dehydration from the purging behaviors. The resultant elevation in serum aldosterone, an integral part of pseudo-Bartter syndrome, can result in rapid edema formation when the purging behaviors are abruptly stopped. The reason is that the serum aldosterone levels remain high, causing salt and water retention even though the patient is no longer losing fluid, as the purging has ceased.

EVALUATION AND MANAGEMENT OF ELECTROLYTE DISTURBANCES AND PSEUDO-BARTTER SYNDROME

Covert purging should be strongly suspected in otherwise healthy young women presenting with hypokalemia without an alternative medical cause.[37] However, hypokalemia alone is not specific for underlying purging behaviors.[34]

If the patient is not forthcoming about their behavior when confronted, a spot urine potassium, creatinine, sodium, and chloride measurement can be obtained to further assess the source of potassium loss. A urine potassium-to-creatinine ratio less than 13 can identify hypokalemia resulting from gastrointestinal loss, diuretics, poor intake, or transcellular shifts. A urine sodium-to-chloride ratio can also be calculated. Vomiting is associated with a urine sodium-to-chloride ratio greater than 1.6 in the setting of hypokalemia, whereas laxative abuse is associated with a ratio less than 0.7.[36]

Chronic hypokalemia is often asymptomatic and can be corrected slowly. If the serum potassium level is no lower than 2.5 mmol/L and the patient has no physical symptoms or electrocardiographic changes of hypokalemia, the hypokalemia can be managed by stopping the purging behavior and giving oral potassium supplementation.[38,39] Adherence to oral potassium repletion can be improved by using potassium chloride tablets rather than liquid preparations.[38] Aggressive intravenous potassium supplementation places patients at risk of hyperkalemia and should be reserved for more critically low serum potassium levels.

Severe hypokalemia (serum potassium less than 2.5 mmol/L) requires both oral and intravenous repletion of potassium. This repletion process is aided by giving isotonic saline with potassium chloride intravenously at a low infusion rate (50–75 mL/hour). Correcting the patient's volume depletion is required to correct the metabolic alkalosis and interrupt renin-angiotensin-aldosterone system activation. Untreated severe hypokalemia can result in a prolonged corrected QT interval on electrocardiography, subsequent torsades de pointes, and other life-threatening cardiac arrhythmias. Simply attempting to replete potassium without attention to the concomitant metabolic alkalosis will be unsuccessful because of the ongoing kaliuresis due to aldosterone's ongoing effects on the kidneys. Rarely, chronic hypokalemia has been associated with acute renal failure, with renal biopsy demonstrating interstitial nephritis, termed hypokalemic nephropathy.[40]

Mild hyponatremia often will autocorrect with interruption of purging behaviors and oral rehydration. However, if the serum sodium is less than 125 mmol/L, hospitalization is warranted for close monitoring and for slow correction with isotonic saline—ie, at a rate that increases the serum sodium by no more than 4 to 6 mmol/L every 24 hours. This avoids the serious complication known as central pontine myelinolysis.[41] If hyponatremia is severe (serum sodium < 118 mmol/L), the patient will likely benefit from admission to an intensive care unit and renal consultation for consideration of administration of desmopressin to prevent overcorrection.

Mild hyponatremia will often correct itself with oral rehydration and interruption of purging behaviors

Metabolic alkalosis can develop in patients with BN as a result of decreased intravascular volume, elevated aldosterone, and hypokalemia; it is most often saline-responsive. A spot urine chloride can be used to inform care. If it is less than 10 mmol/L, the metabolic alkalosis is hypovolemic and will improve with slow intravenous saline administration. Clinicians may also rely on physical examination to help determine the patient's volume status.

Due to the underlying risk of pseudo-Bartter syndrome in patients with BN who abruptly stop purging, care should be taken to avoid aggressive fluid resuscitation. Interruption of purging behaviors in conjunction with rapid intravenous fluid resuscitation can result in marked and rapid edema formation and weight gain, which can be psychologically distressing. Thus, low infusion rates of saline (50 mL/hour) and low doses of spironolactone (50–100 mg initially with a maximum of 200–400 mg/day) should be initiated and titrated based on edema and weight trends to mitigate edema formation.[42] Spironolactone is generally continued for 2 to 4 weeks and then should be tapered by 50 mg every few days thereafter. Occasionally, in extreme laxative abusers, proclivity toward edema may persist and necessitate an even slower spironolactone taper.

MEDICAL COMPLICATIONS OF BINGE-EATING

The literature on complications of binge-eating specific to BN is limited, and thus, we must look to studies of binge-eating disorder. However, patients with binge-eating disorder tend to be overweight or obese, as they do not purge after binge episodes. Thus, many of the medical complications in binge-eating disorder, such as type 2 diabetes, hypertension, nonalcoholic fatty liver disease, and metabolic syndrome are obesity-related.[43]

Cognitive behavioral therapy is the recommended initial intervention in the treatment of bulimia nervosa

In contrast, many patients with BN have a normal body mass index. Therefore, it is difficult to infer that the medical complications that occur in binge-eating disorder are the same as those that occur from binge-eating in BN. However, the extrapolation does make sense in some instances. For instance, patients who binge are at higher risk of nutritional deficiencies because food taken in during a binge tends to be processed, high in fat and carbohydrates, and low in protein. A diet low in vitamins, including A and C, and minerals increases the risk of nutritional deficiencies. Additionally, patients with binge-eating disorder have more gastrointestinal complaints such as acid reflux, dysphagia, and bloating, which, as outlined above, are also seen in BN. Thus, bingeing may play a role in these symptoms.

Lastly, gastric perforation has been reported in patients with BN in the context of a bingeing episode marked by excessive stomach distention, resulting in gastric necrosis.[44] Furthermore, gastric outlet obstruction has also been reported in this patient population due to formation of a food bezoar.

IDENTIFICATION AND MENTAL HEALTH TREATMENT

The Eating Disorder Screen for Primary Care has been shown to effectively screen patients for disordered eating in a general medicine setting.[45] It consists of 5 questions:

- Are you satisfied with your eating pattern? ("No" is considered an abnormal response.)
- Do you ever eat in secret? ("Yes" is an abnormal response to this and the remaining questions.)
- Does your weight affect the way you feel about yourself?
- Have any members of your family suffered from an eating disorder?
- Do you currently suffer with or have you ever suffered in the past with an eating disorder?

Cotton et al[45] found that an abnormal response to 2 or more of these questions had a sensitivity of 100% and a specificity of 71% for eating disorders.

Standard mental health treatments for BN include nutritional stabilization and behavior interruption, monitoring for and appropriate management of associated medical complications, prescribing medications as clinically indicated, and psychotherapeutic interventions. Cognitive behavioral therapy is the recommended initial intervention for the treatment of BN. A recent network meta-analysis suggested that guided cognitive behavioral self-help and a specific form of cognitive behavioral therapy—individual cognitive behavioral therapy for eating disorders—may most likely lead to full remission.[46]

No drug has been developed specifically for the treatment of BN (**Table 2**). Fluoxetine, with a target dose of 60 mg daily independent of the presence of comorbidities, is the only medication approved by the US Food and Drug Administration for BN. This selective

serotonin reuptake inhibitor has been shown to reduce the frequency of binge-eating and purging episodes significantly, more so than fluoxetine 20 mg daily and placebo.[47] Fluoxetine is recommended for patients who do not respond adequately to psychotherapeutic interventions.[48]

Other selective serotonin reuptake inhibitor antidepressants along with the antiepileptic topiramate also have been shown to have modest efficacy.[49] Bupropion, which has a boxed warning and is contraindicated in the treatment of BN, should not be used due to an increased risk of seizure.

No clinical trials have evaluated the use of stimulant medications in the treatment of BN. Often, stimulant medications are discontinued in patients until there is a period of abstinence from purging behaviors. Following abstinence, reinitiation of the stimulant could be reconsidered off-label if bingeing behaviors persist or attention deficit hyperactivity disorder is a comorbidity, or both. There can be some utility to reinitiation with a clear treatment agreement outlining expectations for maintaining efforts at purging symptom interruption and continued stimulant prescribing.

In general, concomitant treatment for anxiety or depression should be pursued if these co-occur with BN. Selective serotonin reuptake inhibitors such as fluoxetine would also target these symptoms. If a trial of fluoxetine has failed, then sertraline or escitalopram would be reasonable second-line options. Typically, citalopram would not be used due to higher risk of prolonged QT interval than other selective serotonin reuptake inhibitors, especially given the possibility of electrolyte abnormalities in BN. Paroxetine would not be used due to the potential for weight gain as a side effect.

PROGNOSIS

Increased risk of relapse has been associated with greater psychosocial dysfunction and body image disturbance.[50] In patients requiring hospitalization, a number of factors have been shown to predict poor outcome, including fewer follow-up years, increased drive for thinness, older age at initial treatment, and more impairment in global functioning.[50]

TABLE 2

Psychopharmacology clinical pearls

Fluoxetine is the only US Food and Drug Administration-approved medication for the treatment of bulimia nervosa

Co-occurring anxiety and depression should be managed with therapy and pharmacologically

Stimulant medications have not been evaluated in the treatment of bulimia nervosa

Recovery is possible with variable remission rates, based on the type of study and definition of remission, from 38% and 42% at 11- and 21-year follow-up, respectively, and 65% of individuals at a 9-year and 22-year follow-up.[50,51] This reinforces the need to utilize accessible and effective treatments to achieve sustained recovery.

CONCLUSION

BN is a complex psychiatric disease with myriad medical complications, some of which may be life-threatening. Most of the morbidity and mortality in patients with BN is a direct result of the aforementioned purging behaviors and their resultant electrolyte and acid-base disorders. Thus, it is important that clinicians familiarize themselves with these complications as most patients with BN are of normal weight and are otherwise often able to avoid detection of their eating disorder.

Bupropion is contraindicated in the treatment of bulimia nervosa due to an increased risk of seizure

INITIAL CASE CONTINUED

You release the patient in the initial clinical scenario from her follow-up appointment without intervention or follow-up laboratory testing. You fail to recognize the Russell sign, and you advise her that the edema is due to fluids administered in the emergency department and will self-resolve. She returns to her purging behaviors with increased vigor due to perceived weight gain from the edema.

One month later, she experiences a syncopal episode during cross-country practice, again necessitating oral potassium and intravenous saline administration. On follow-up, her edema is worse, and you recognize the Russell sign, having just read this review article. On follow-up laboratory testing, you note ongoing mild hypo-

kalemia and screen her for an eating disorder. The screening is positive, and she discloses to you not only about her daily self-induced vomiting, but also her abuse of stimulant laxatives and bingeing episodes.

You initiate a referral to a residential treatment facility for eating disorders, start her on daily potassium chloride 40 mmol, and plan for weekly follow-up laboratory testing until she enters residential treatment.

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***Address**: Philip S. Mehler, MD, FACP, FAED, Denver Health Medical Center, 723 Delaware Street, Pav M, Denver, CO 80204; pmehler@dhha.org*

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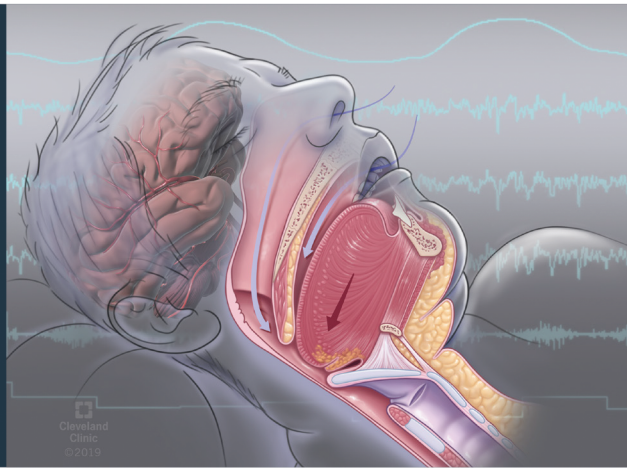

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REVIEW

Guramrinder Singh Thind, MD
Department of Critical Care Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, OH

Steven Fox, MD
Department of Critical Care Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, OH

Mohit Gupta, MD
Department of Hospital Medicine, Cleveland Clinic, Cleveland, OH; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Praveen Chahar, MD
Anesthesiology Institute, Cleveland Clinic, Cleveland, OH; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Robert Jones, DO, FACEP
Department of Emergency Medicine, MetroHealth Medical Center, Cleveland, OH; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Siddharth Dugar, MD
Department of Critical Care Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, OH; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Point-of-care ultrasonography for the hospitalist

ABSTRACT

Point-of-care ultrasonography (POCUS) has emerged as a vital tool in medicine. Initially used for procedural guidance, POCUS is now used for diagnostics and monitoring of the lung, heart, abdomen, and deep vein thrombosis. This wide applicability makes it an essential tool for hospitalists in daily clinical practice. This article provides an overview of the clinical integration of POCUS and basic image interpretation.

KEY POINTS

Lung POCUS can help in evaluating pneumothorax, alveolar-interstitial syndrome, lung consolidation, and pleural effusions as the cause for respiratory distress.

Focused cardiac ultrasonography can help in evaluating left and right ventricular function, right atrial pressure, pericardial effusion, and tamponade.

Abdominal ultrasonography can aid evaluation of ascites, hemoperitoneum, hydronephrosis, acute pyelonephritis, and gallstones, and can confirm Foley catheter placement.

Point-of-care compression ultrasonography can rapidly detect deep vein thrombosis with high accuracy.

POCUS can guide numerous procedures, including central venous catheter insertion, peripheral intravenous catheter insertion, abdominal paracentesis, and thoracentesis.

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Hospitalists are increasingly using point-of-care ultrasonography (POCUS), and have access to ultrasound machines that are more portable, more available, and less expensive. The numerous uses of POCUS for procedural guidance, diagnosis, and monitoring can add considerable value to patient care.

All hospitalists should have an understanding of POCUS nomenclature, applications, and findings. This review highlights various uses of POCUS in hospitalized patients.

DIRECT CLINICIAN INVOLVEMENT

Ultrasonography is low-cost, radiation-free, and noninvasive, allowing it to be repeated multiple times with little risk to patients. What sets it apart from traditional diagnostic ultrasonography is that it is wholly performed by a bedside clinician directly involved in patient care, without requiring a sonographer and radiologist for image acquisition and interpretation (**Table 1**). A hospitalist can quickly perform a physical examination combined with goal-directed ultrasonography of various organs based on presenting signs and symptoms. Serial scans can be performed to assess progression or response to therapy.

POCUS enhances patient experience and patient-clinician rapport by increasing interactions between the clinician and patient.[1] POCUS has become notably important in the COVID-19 pandemic, allowing protocolized ultrasonographic assessment of multiple organs by a bedside physician, thereby minimizing exposure and the need for formal studies.[2]

Recognizing the importance of POCUS, numerous medical schools have integrated training in ultrasonography in their curricula.

TABLE 1

Point-of-care ultrasonography workflow compared with traditional consultative ultrasonography

	Consultative ultrasonography	POCUS
Decision to perform ultrasonography	Primary clinician	Primary clinician
Image acquisition	Sonographer	
Image interpretation	Sonographer Radiologist	
Clinical integration	Radiologist Primary clinician	

The Society of Hospital Medicine, the American College of Physicians, and the Alliance for Academic Internal Medicine, have also endorsed its use.[3–5]

Billing for ultrasound-assisted procedures may provide a means to offset the costs of equipment, training, and administration.

IMPROPER USE AND INTERPRETATION CAN CAUSE HARM

POCUS can improve patient care but may also cause harm through improper use and interpretation.[6] It needs to be applied in a deliberate and thoughtful manner: multiple views should be obtained for appropriate interpretation, and images must be evaluated in the clinical context. A comprehensive imaging study should be considered if POCUS was of limited utility and the probability of a particular disorder remains high despite negative findings with POCUS.

The absence of lung sliding should prompt the search for 'lung point,' which is virtually pathognomonic for pneumothorax

The accuracy of POCUS depends on the skills and judgment of the operator. Even if basic findings are understood, many nuances and potential pitfalls exist. Clinicians may be falsely reassured by seemingly normal POCUS findings while the patient actually has a serious disease that a radiologic study could detect. Conversely, incidental findings may lead to unnecessary treatments and testing.

But because POCUS may be used improperly does not mean it should not be used. In fact, the major medicolegal issue surrounding POCUS is failure to perform it in a timely fashion.[7]

LUNG AND PLEURAL ULTRASONOGRAPHY

Lung and pleural ultrasonography can narrow the broad differential diagnosis of respiratory distress (**Table 2**)[8–11] and facilitate prompt management.[12] In many hospitals, no radiologist is available to perform lung ultrasonography, making lung and pleural POCUS a critical skill for hospitalists. Training in lung and pleural POCUS is feasible with a simple curriculum consisting of didactics and limited supervised examinations.[13,14]

Initial lung assessment

Lung assessment starts with identifying the pleural line, a shimmering hyperechoic structure between the ribs (**Figure 1**). Respirophasic sliding of the pleura gives a shimmering appearance, referred to as "lung sliding."

The tissue-air interface in the subpleural region of aerated lung is a strong reflector. Ultrasound is repeatedly reflected between the pleura and the probe, leading to a reverberation artifact appearing as equidistant parallel echoic lines, known as A lines (**Figure 1**). An A-line pattern indicates normal lung, but it can also be seen with pneumothorax and in conditions with normally aerated pulmonary parenchyma, such as pulmonary embolism, chronic obstructive pulmonary disease, and asthma.[15]

Evaluation of pneumothorax

In pneumothorax, the air between the parietal and visceral pleurae prevents pleural contact, giving an A-line pattern without lung sliding. Absence of lung sliding has good sensitivity (> 95%) for pneumothorax but poor specificity (60%–99%).[8,16] This pattern also occurs

TABLE 2

Meta-analyses evaluating pleural and lung ultrasonography

Diagnosis	Meta-analysis	No. of studies	No. of patients	Pooled sensitivity	95% confidence interval	Pooled specificity	95% confidence interval	Positive likelihood ratio	Negative likelihood ratio
Pleural effusion	Yousefifard et al,[11] 2016	12	1,554	94%	88%–97%	98%	92%–100%	53.96	0.06
Acute cardiogenic pulmonary edema	Maw et al,[9] 2019	7	1,075	94.1%	81.3%–98.3%	92.4%	84.2%–96.4%	12.38	0.06
Pneumonia	Alzahrani et al,[10] 2017	20	2,513	85%	84%–87%	93%	92%–95%	12.14	0.16
Pneumothorax	Alrajab et al,[8] 2013[a]	13	1,514	78.6%	68.1%–98.1%	98.4%	97.3%–99.5%	49.13	0.22

[a] Included 1 study that used lung sliding sign alone, 12 studies that used lung sliding and comet tail signs, and 6 studies that included lung point in addition to the other 2 signs.

with pleural adhesions, apnea, pneumonia, and right mainstem bronchus intubation.[16,17] The absence of lung sliding should prompt the search for "lung point," ie, the transition point at the edge of the pneumothorax where lung sliding is seen in one part and no lung sliding is seen in the rest. Lung point is virtually pathognomonic for pneumothorax (**Video 1**).[17]

Unlike lung point, absent lung sliding is not specific for pneumothorax and should not by itself prompt tube thoracostomy in the absence of extenuating circumstances (eg, severe cardiorespiratory instability, high clinical suspicion).

Evaluation of alveolar-interstitial syndrome

The pathologies of alveolar-interstitial space are characterized by B lines, a sonographic pattern of vertically oriented, laser-like hyperechoic artefacts originating at the pleural interface, extending downwards, and moving synchronously with the pleura (**Figure 2**). One or 2 B lines are routinely seen; 3 or more in a single field of view is considered abnormal.[18–20] Any condition that leads to thickening of subpleural interlobular septa generates B lines, the most common being pulmonary edema (cardiogenic or noncardiogenic in origin).

The sensitivity of B lines in identifying pulmonary edema is at least 90%,[9,21,22] making POCUS an excellent tool to differentiate car-

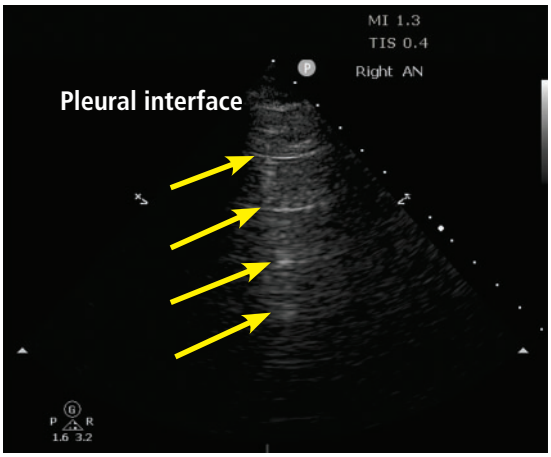
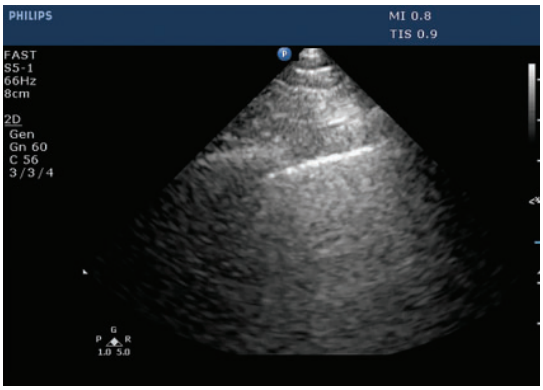


Figure 1. A lines. The A-line pattern occurs in normal lung and in pneumothorax. Ultrasound waves (arrows) reflect off the pleural interface repeatedly, producing repeated horizontal lines throughout the field.



Video 1. Lung point.

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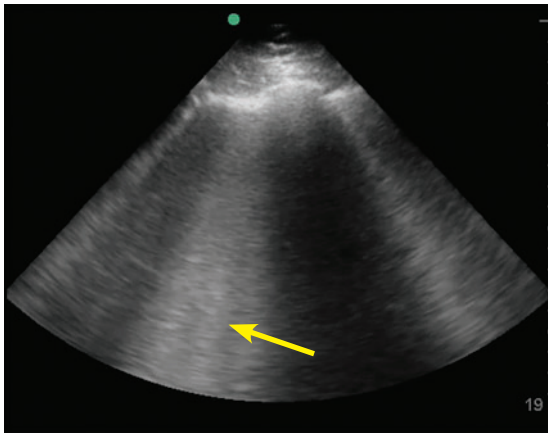


Figure 2. B lines. The B-line pattern occurs in the setting of interstitial thickening by any cause, including cardiogenic pulmonary edema, noncardiogenic pulmonary edema, interstitial fibrosis, and interstitial pneumonia/pneumonitis. It is analogous to ground-glass opacity on computed tomography. It is demonstrated by vertical lines resembling the tail of a comet and extending to the bottom of the screen. In this image, confluent B lines (arrow) indicate significant interstitial involvement.

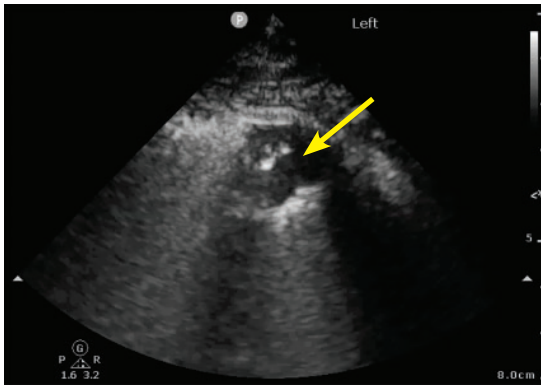


Figure 3. Small peripheral (subpleural) consolidation. This is demonstrated by a small area of lung parenchyma visualized directly beneath the pleura (arrow). This pattern is common in bacterial or viral pneumonia, including COVID-19 pneumonia.

Focused cardiac ultrasonography provides critical insight into hemodynamic status

diogenic pulmonary edema from exacerbation of chronic obstructive pulmonary disease. In addition, B lines may help guide diuresis and assess fluid tolerance.

B lines also occur in pneumonia, pulmonary fibrosis, acute respiratory distress syndrome, and pneumonitis of any etiology. Careful evaluation of the pattern of B-line distribution and the pleural line, along with clinical correlation, can help distinguish these different causes (**Table 3**).[23–25]

The presence of B lines effectively rules out pneumothorax, as they are produced from subpleural lung units.[17]

Evaluation of consolidation

Ultrasound waves can traverse subpleural lung consolidation, resulting in the absence of A lines and a true 2-dimensional image of the consolidated lung (**Figure 3**). Almost all acute alveolar consolidations (98.5%) are found adjoining the visceral pleura, providing the necessary window for detection.[26]

The finding of subpleural consolidation or focal B lines, or both, is suggestive of pneumonia. The sensitivity and specificity of lung ultrasonography for diagnosing pneumonia is just 85% or more.[10] Nonetheless, supportive clinical and laboratory data with the characteristic ultrasound patterns can substantiate a diagnosis of pneumonia.

Evaluation of pleural effusion

Portable chest radiography has a sensitivity of 60% for detecting pleural effusion[27]; in contrast, lung ultrasonography is 94% sensitive and 98% specific.[11] Lung ultrasonography can also better characterize basal opacities by distinguishing consolidation from pleural effusion (**Figure 4**). It can also detail the features of pleural effusion, with simple effusion appearing anechoic, and complex effusions characterized by septations, loculations, and debris. The size of a pleural effusion can also be quantified using lung ultrasonography.[28]

FOCUSED CARDIAC ULTRASONOGRAPHY

Focused cardiac ultrasonography (this term is preferred to "echocardiography" to highlight its focused nature) provides critical insight into hemodynamic status. It can be performed with excellent diagnostic accuracy for important cardiac abnormalities (**Table 4**).[29]

Focused questions, including global assessment of left ventricular function, presence or absence of a pericardial effusion, assessment of right ventricular size and function, and estimation of right atrial pressure, can help nar-

TABLE 3

Characteristics of B lines based on etiology [a]

	Cardiogenic pulmonary edema	Noncardiogenic diffuse pulmonary interstitial edema	Interstitial pneumonia or pneumonitis (bacterial, viral, or inflammatory)	Interstitial fibrosis
Distribution	Diffuse Usually bilateral and symmetric Predominant in dependent regions	Diffuse or patchy Often asymmetric	Focal or patchy Usually asymmetric	Diffuse or patchy Variable symmetry
Spared areas	Absent	Often present	Present	Often present
Number of B lines	Variable	Variable	Variable	Variable
Pleura	Smooth	Irregular	Irregular	Irregular
Subpleural consolidations	Absent	Present	Present	Typically absent
Reduced lung sliding	Absent	May be present	May be present	May be present
Pleural effusion	Often present	Typically absent	May be present	Typically absent

[a] Defining the terminology: diffuse = present throughout; patchy = present in many areas throughout, absent in other areas throughout; focal = present in one region but not in others; spared areas = regions of lung with A-line pattern (amid a background of B-line pattern).

row a differential diagnosis and guide management in patients with cardiorespiratory distress.

Evaluating left ventricular function

Evaluation of left ventricular systolic function is one of the primary objectives of focused cardiac ultrasonography. As a general rule, multiple views should be obtained for appropriate interpretation. Although objective methods of left ventricular systolic evaluation are available and recommended, qualitative "eyeball estimation" is appropriate and feasible, with studies demonstrating high accuracy of visual estimation compared with recommended objective measures.[30,31] Left ventricular systolic function can be qualitatively graded as severely reduced, moderately reduced, mildly reduced, normal, or hyperdynamic. Cardiology-performed echocardiography can be requested for further quantitative evaluation (**Video 2, Video 3**).

Evaluating right ventricular function

Better understanding of the importance of right ventricular function has led to including its evaluation in various protocols assessing shock and respiratory failure.[32] Although objectively estimating right ventricular size and function is challenging, qualitative assessment can be made at the bedside by directly comparing the left and right ventricle.

Size. The right ventricle is normally less than two-thirds the size of the left. A right ventricle-to-left ventricle ratio of 1 or higher is associated with poor outcomes in pulmo-

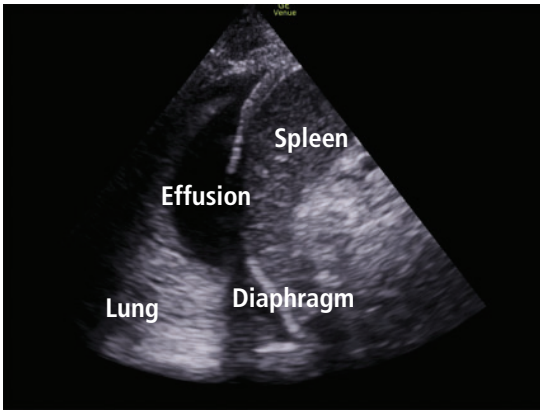
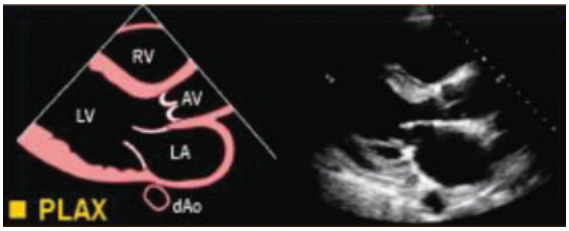
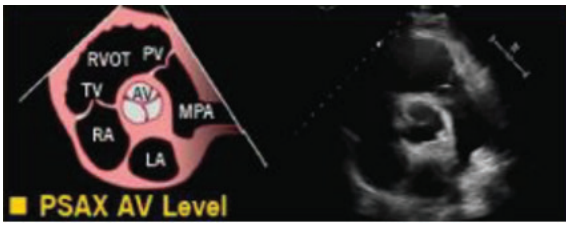
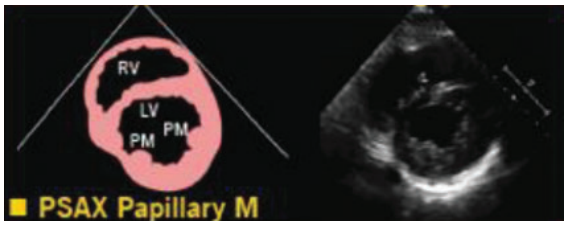
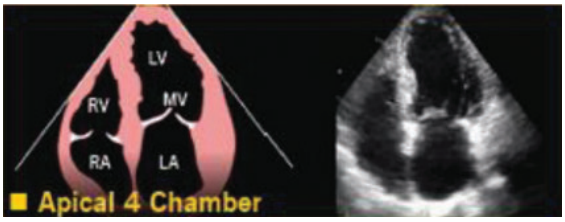
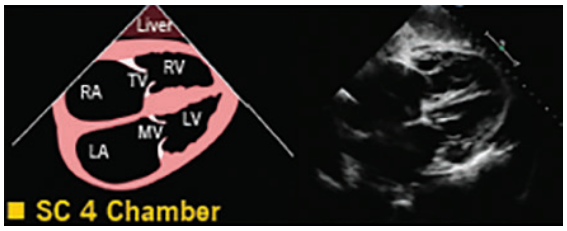
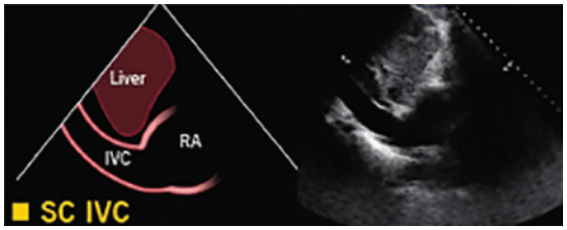


Figure 4. Pleural effusion and consolidation.

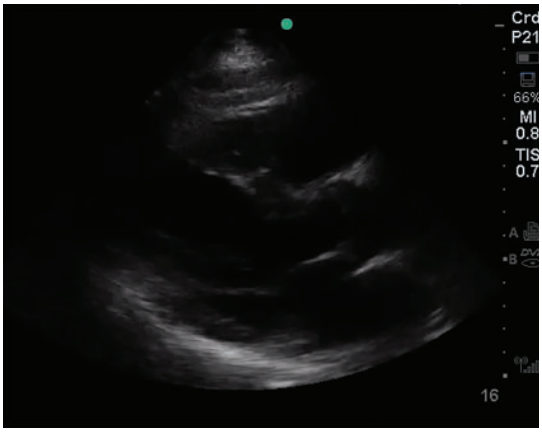
Evaluating left ventricular systolic function is one of the primary objectives of focused cardiac ultrasonography

TABLE 4

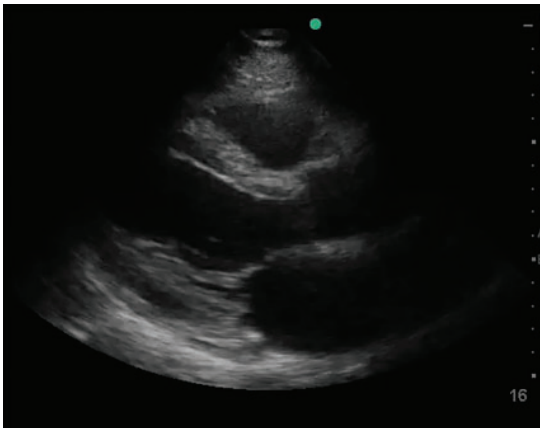
Focused cardiac ultrasonography: Basic views and key findings

Views	Probe position	Possible findings
	Left 3rd to 5th intercostal space adjacent to the sternum, with probe marker pointing toward the right shoulder	Pericardial effusion Signs of tamponade Left ventricular size and systolic function Mitral and aortic valvular pathology Aortic root dissection
	From the PLAX view, the probe is rotated 90° clockwise. PSAX views are obtained by tilting the transducer from the base to the apex of the left ventricle.	Left ventricular systolic function Tricuspid, aortic, and mitral valvular pathology Interventricular septal deviation Wall-motion abnormalities
		
	With the probe marker pointing toward the left, the probe is placed at the apex of the left ventricle. The apical impulse can be used as a guide.	Left ventricular size and function Right ventricular size and function Pericardial effusion and signs of tamponade Valvular pathology Interventricular septal deviation Wall-motion abnormalities
	The probe is placed below the xiphoid process, with the marker pointing toward the left. From the subcostal long-axis view, the probe is rotated 90° counterclockwise and angulated slightly toward the left.	Pericardial effusion and signs of tamponade Inferior vena cava size and collapsibility
		

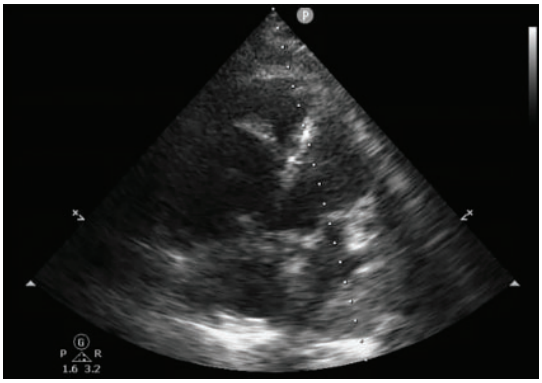
AV = aortic valve; IVC = inferior vena cava; LV = left ventricle; MV = mitral valve; PLAX = parasternal long axis; PSAX = parasternal short axis; RV = right ventricle; TV = tricuspid valve



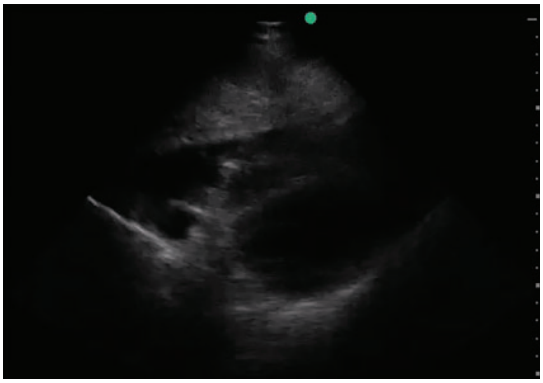
Video 2. Normal parasternal long axis view.



Video 3. Reduced ejection fraction.



Video 4. Dilated right ventricle.



Video 5. Pericardial effusion and tamponade.

nary hypertension, pulmonary embolism, and other critical conditions.

Septal kinetics. Assessing septal kinetics can also provide vital insights and help identify the cause of right ventricular dysfunction: septal deviation occurs toward the left ventricle in diastole with right ventricular volume overload, and during systole with right ventricular pressure overload.

Chronicity. It is important to distinguish acute from chronic right ventricular dysfunction, as their causes differ. Distinguishing them is challenging with focused cardiac ultrasonography, yet certain subtle findings can point to the cause.

Chronic dysfunction is seen in long-standing cases of pulmonary hypertension. It is associated with right ventricular hypertrophy with right ventricular free-wall thickness of more than 5 mm (**Video 4**).

Acute dysfunction raises concern for massive pulmonary embolism, acute respiratory distress syndrome, and acute right ventricular infarction. In acute right ventricular dysfunction, particularly pulmonary embolism, the McConnell sign (ie, right ventricular free-wall akinesis with sparing of the apex) is just 70% sensitive and 33% specific for diagnosing acute pulmonary embolism (positive likelihood ratio [PLR] 1.04, negative likelihood ratio [NLR] 0.91).[33] Hence, pulmonary embolism cannot be definitively diagnosed with focused cardiac ultrasonography, with the notable exception of detecting a visible thrombus in the right heart (ie, a clot in transit).

B lines may help guide diuresis and assess fluid tolerance

Evaluating valvular abnormalities

Limited evaluation of the mitral, tricuspid, and aortic valves can be performed using standard views. With some experience, gross abnormalities that may significantly alter management (eg, flail leaflet, prolapse, large vegetation, chordae rupture) can be detected on visual examination and color Doppler. Dynamic left ventricular outflow tract obstruc-

TABLE 5

Estimates of central venous pressure based on inferior vena cava size and collapsibility

Inferior vena cava size	Percent collapse	Estimated central venous pressure
≤ 2.1 cm	> 50%	3 mm Hg
≤ 2.1 cm	< 50%	8 mm Hg
> 2.1 cm	> 50%	8 mm Hg
> 2.1 cm	< 50%	15 mm Hg

Based on reference 35.

tion due to systolic anterior motion of the mitral valve can be detected visually and by using motion mode (M mode). Although systolic anterior motion is classically seen with hypertrophic cardiomyopathy, it may also occur in other situations that lead to worsening hemodynamics (eg, sepsis, acute hemorrhage, dehydration). Systolic anterior motion may be associated with severe mitral regurgitation, which resolves with resolution of systolic anterior motion.

However, bedside echocardiography is limited for assessing valvular pathologies. A detailed assessment of valvular lesions (especially stenotic lesions) involves use of spectral Doppler in multiple views, which is not part of basic cardiac ultrasonography. Hence, a comprehensive echocardiographic examination should be considered for evaluating valvular abnormalities and pathology.[34]

Lung ultrasonography is 94% sensitive and 98% specific for detecting pleural effusion

Estimating right atrial pressure

In spontaneously breathing patients, right atrial pressure can be estimated by measuring inferior vena cava size and collapsibility with deep inspiration or "sniff" (**Table 5**).[35] The influence of respiratory effort, intra-abdominal pressure, and positive-pressure ventilation may limit the accuracy of the measurement and should be considered. Additionally, the long-axis view of the inferior vena cava is prone to error due to off-plane assessment and respirophasic movement. This can be overcome by acquiring a short-axis (transverse) view.[36]

Evaluating pericardial effusion and tamponade

Focused cardiac ultrasonography has excellent sensitivity (96%) and specificity (98%) for detecting pericardial effusion (PLR 48, NLR 0.04)[37] and can trigger further consultation for evaluation of tamponade, if clinically suspected (**Video 5, Table 4**). Hemodynamic instability from cardiac tamponade results from increased pericardial pressure, impairing venous return. The rate of fluid accumulation plays a more prominent role than size in tamponade physiology. Thus, a large volume of pericardial effusion can accumulate over time without impairing hemodynamics, while a smaller pericardial effusion or hemorrhage in the setting of trauma or postprocedure can lead to the need to diligently inspect echocardiographic signs of tamponade.

A plethoric inferior vena cava from impaired filling is highly sensitive (92%) but not specific for cardiac tamponade. Right atrial collapse for more than one-third of the cardiac cycle is highly sensitive and specific for diagnosing tamponade, followed by right ventricular collapse during diastole.[38] Absence of chamber collapse has a negative predictive value of 90%. Assessing for tamponade can be difficult, and M mode may help identify chamber collapse. Concerning or indeterminate findings for tamponade should prompt urgent expert consultation or a confirmatory echocardiogram, or both.

POCUS has been shown to reduce time to pericardiocentesis and is recommended to guide drainage of effusion.[39]

Common pitfalls of focused cardiac ultrasonography

Focused cardiac ultrasonography is prone to the following common issues:

Not obtaining a complete echocardiogram when needed. A focused study serves a

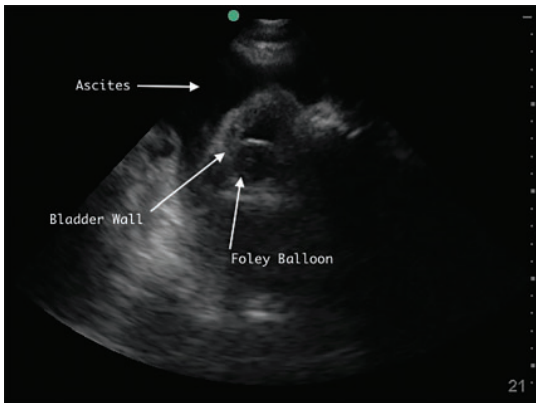


Figure 5. Right lower quadrant with large ascites fluid pocket; Foley catheter in bladder.

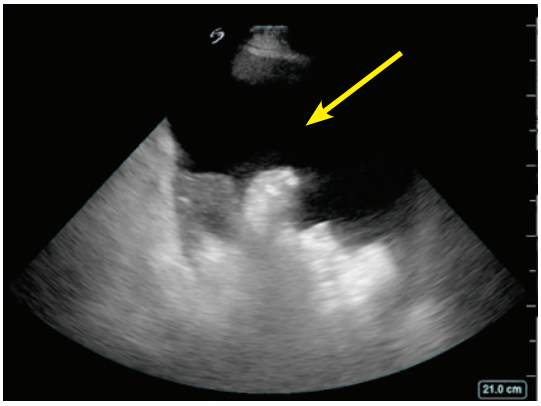


Figure 6. Ascites pocket.

different purpose from a complete study and should not replace one. Hence, a "normal" focused cardiac ultrasonographic evaluation does not obviate the need to order a complete transthoracic echocardiogram that is clinically indicated.

Over-relying on POCUS to manage volume. POCUS findings are useful as part of volume status assessment, but a single POCUS finding in isolation should not be used to determine volume management (eg, giving fluids for an apparently "collapsed" inferior vena cava). Findings are prone to variability and must be integrated into overall assessment, not used in isolation.

Delaying POCUS during shock. Focused cardiac ultrasonography should be performed promptly in a patient with shock. Not doing so may lead to an important missed diagnosis, such as pericardial tamponade, ventricular dysfunction, or valvular abnormality.

ABDOMINAL ULTRASONOGRAPHY

Evaluation of ascites and hemoperitoneum

Evaluating thoracoabdominal trauma is often a diagnostic challenge, prompting clinicians to depend on ancillary tests to detect potentially life-threatening internal injuries. Ultrasonographic evaluation of free fluid in the abdomen has been extensively studied in trauma literature for detecting hemoperitoneum. Today, ultrasonography has virtually replaced diagnostic peritoneal lavage as a primary, bedside imaging method for trauma patients.[40] Numerous studies have found that examinations performed and interpreted by treating physicians are reliably accurate compared with those read by radiologists.[41]

POCUS can also help hospitalists detect ascites. It is more sensitive and specific than physical examination and can guide the decision to perform paracentesis (**Figure 5, Figure 6**).[42]

Evaluation of kidney and bladder

Hydronephrosis, a commonly encountered and often reversible cause of acute kidney injury, can be detected with high sensitivity and specificity by a bedside clinician using POCUS (**Figure 7**).[43] Hydronephrosis results from urinary flow obstruction, which can be internal (eg, from ureteral calculus or a mass) or external (eg, from ureteral compression from structures such as an enlarged abdominal aortic aneurysm, an advanced pregnancy, or a pelvic mass). Evaluation for hydronephrosis can be useful in cases in which urinary obstruction is considered. This may be particularly important in patients with acute pyelonephritis. However, mimics of hydronephrosis include prominent renal pyramids, prominent renal vasculature, and parapelvic cysts.

Hydronephrosis can be detected with high sensitivity and specificity with POCUS

Distal obstruction (eg, prostatic hypertrophy) usually results in bilateral hydronephrosis, so it is important to scan both kidneys.

A study found more than 90% sensitivity and specificity for detecting hydronephrosis by POCUS performed by internal medicine residents given 5 hours of training compared with comprehensive radiologic ultrasonography.[44]

POCUS is also helpful in acute pyelonephritis to evaluate for obstruction. Detecting large obstructive calculi would prompt urgent

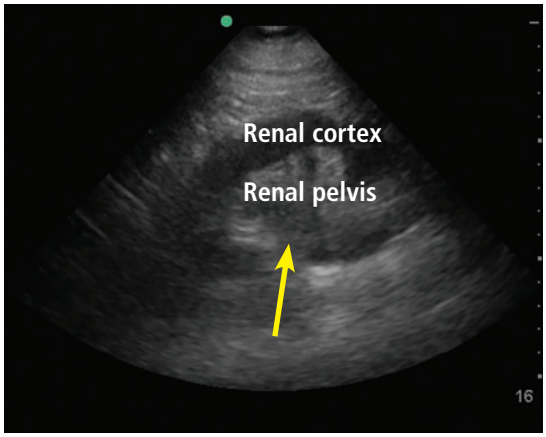


Figure 7. Hydronephrosis. Hypoechoic (dark) fluid (arrow) is shown extending into the renal pelvis.

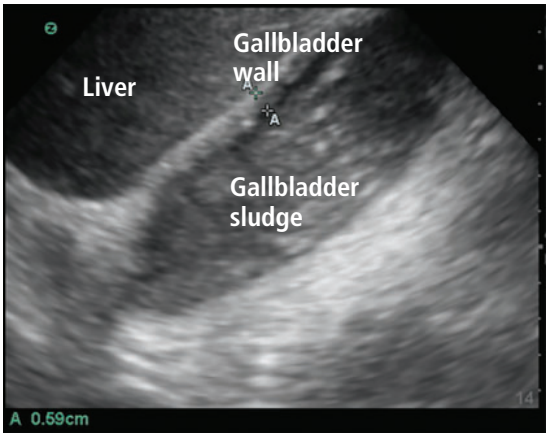


Figure 8. Gallbladder containing sludge, with a thickened anterior wall, in a patient with acute cholecystitis.

urologic consultation.

A distended bladder, being a large fluid-filled structure, is easily visualized by ultrasonography and can be distinguished from ascitic fluid. POCUS can be used to estimate bladder volume and confirm proper placement of a urinary catheter by visualizing a Foley balloon inside the bladder (**Figure 5**). This application may be particularly useful in a patient with obesity or ascites, which can make physical examination or bladder scanner determinations inaccurate. In patients without a urinary catheter, bladder volume estimation should be performed post-void.

Findings that suggest acute cholecystitis can be assessed with POCUS with good specificity

Ultrasound evaluation of the biliary system

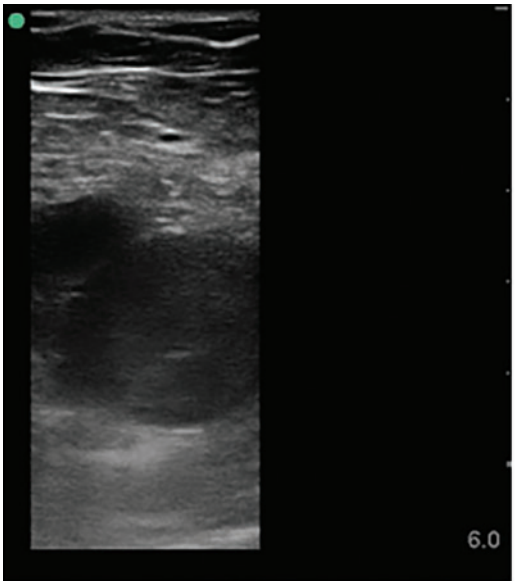
Gallstones appear by ultrasonography as round hyperechoic structures in the gallbladder or bile ducts, with posterior acoustic shadowing. POCUS has demonstrated excellent sensitivity (89.8%) and specificity (88.0%) for detecting cholelithiasis (PLR 7.48, NLR 0.12).[45] Findings suggestive of acute cholecystitis include gallstones, pericholecystic fluid, gallbladder wall thickening, and sonographic Murphy sign (ie, abdominal pain elicited by probe pressure), all of which can be assessed at the bedside with good specificity (**Figure 8**).[46]

The common bile duct can also be measured by POCUS, although it is technically challenging, especially for a novice user.[47] Requesting a formal ultrasonographic study is prudent to obtain this information.

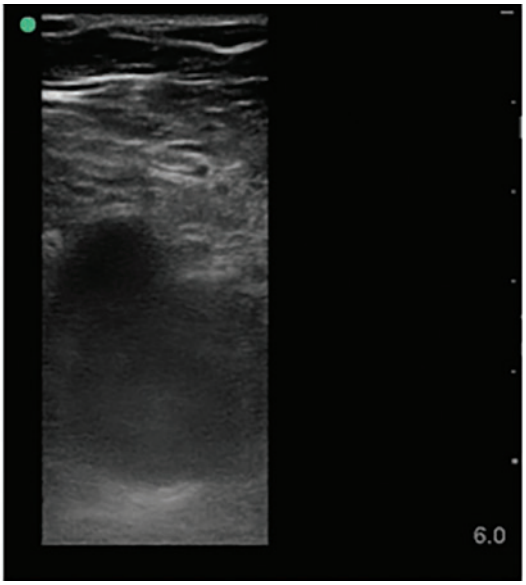
EVALUATION OF LOWER-EXTREMITY DEEP VEIN THROMBOSIS

Although complete duplex ultrasonography is the standard radiological study traditionally performed to evaluate for deep vein thrombosis (DVT), point-of-care compression ultrasonography can be performed rapidly with high diagnostic accuracy after limited training (**Figure 9**).[48] A multicenter study of hospitalist-performed compression ultrasonography found a sensitivity of 100% and specificity of 96% for identifying lower extremity DVT, reducing the time to diagnosis by nearly 5 hours compared with corresponding vascular studies interpreted by radiologists.[49] Meta-analyses have also reported sensitivity and specificity higher than 90% (**Table 6**).[50–52] However, inadequate compression, lymph nodes, Baker cysts, and superficial venous thrombosis may be mistaken for a DVT.

A focused DVT study is performed using a high-frequency (5–12 MHz) linear probe with compression of the vein at multiple sites, traditionally using a 2-point (common femoral vein and popliteal vein) or 3-point (same, plus superficial femoral vein) method. The 3-point examination demonstrated higher sensitivity (91% vs 83%) and similar specificity (96%) to the 2-point examination, but it still can miss 5% of isolated femoral vein DVTs.[53] An extended compression examination employing compressing the femoral vein every 2 to 3 cm until it dives into the adductor canal and popliteal vein along its course is more com-



With applied compression of probe



Without applied compression of probe

Figure 9. Right common femoral vein deep vein thrombosis. The left image shows lack of compression of the vein with applied compression of the probe. The right image shows vein without compression.

prehensive and is currently the recommended method.[3]

Duplication of the venous system in the lower extremity is common, and the presence of a DVT in duplicated systems could easily be missed.[54] A positive POCUS examination may prompt early initiation of anticoagulation and ordering of confirmatory imaging; a negative POCUS test in a patient with high pretest probability needs a comprehensive vascular study. The negative predictive value for a POCUS DVT study is not sufficient to effectively rule out DVT in such patients.

EVALUATING SKIN AND SOFT-TISSUE INFECTIONS

The major role of POCUS in evaluating skin and soft-tissue infection is to detect abscess formation in the soft tissue. It has been found to change management in more than half of patients presenting with a skin or soft-tissue infection.[55]

The cobblestone appearance of cellulitis (**Figure 10**) is nonspecific and can be seen in any cause of subcutaneous edema, while ultrasonography is 98% sensitive and 88% specific for abscess detection (PLR 8.17, NLR 0.02).[56] The appearance of abscesses ranges from anechoic to hyperechoic and may demonstrate posterior acoustic enhancement.

Color Doppler is highly informative, as abscess cavities do not have internal Doppler flow. The presence of flow within the cavity may suggest a vascular structure such as a pseudoaneurysm. Air within the cavity, suggestive of high-grade infection, can be easily detected with ultrasonography.

Ultrasonography may also help diagnose necrotizing fasciitis by detecting fascial and subcutaneous thickening, abnormal fluid accumulation in the deep fascia layer, and subcutaneous air. However, ultrasonography should not be used to rule out the diagnosis of necrotizing fasciitis.

The major role of POCUS in evaluating skin and soft-tissue infection is to detect abscess formation in soft tissue

ULTRASONOGRAPHY FOR PROCEDURAL GUIDANCE

Numerous procedures common to hospital medicine practice may be performed more safely and effectively with ultrasonography. The Society of Hospital Medicine has published recommendations for the use of ultrasonography in common hospital medicine procedures, including abdominal paracentesis,[42] thoracentesis,[57] lumbar puncture,[58] and

TABLE 6

Meta-analyses evaluating point-of-care ultrasonography for diagnosing deep vein thrombosis

Meta-analysis	No. of studies	No. of patients	Pooled sensitivity	95% confidence interval	Pooled specificity	95% confidence interval	Positive likelihood ratio	Negative likelihood ratio
Burnside et al,[50] 2008	6	936	95%	87%–99%	96%	87%– 99%	23.75	0.05
Pomero et al,[51] 2013	16	2,379	96.1%	90.6%–98.5%	96.8%	94.6%–98.1%	30.03	0.04
West et al,[52] 2015	13	1,806	96.5%	90.1%–98.8%	96.8%	94.7% –98.0%	30.16	0.04

venous access,[59] as well as for procedural credentialing.[60]

Procedures may be "ultrasound-assisted" or "static" (ie, ultrasonography is used for site selection, then the procedure is performed without ultrasonography) vs "ultrasound-guided" or "dynamic" (ie, the procedure is performed with live ultrasonographic guidance, with the ultrasound probe in one hand and a needle in the other).

Many predict that POCUS will be the standard of care in the near future

Central venous catheter insertion

For central venous catheter insertion, ultrasonography reduces time to completion and decrease failed attempts, with fewer complications like pneumothorax and arterial punctures. It also aids in preprocedural detection of stenosis and thrombosis of the target vein, and it is currently the standard of care for upper-extremity central venous catheter insertion.[61] Nonetheless, this procedure remains highly user-dependent, and adequate training is critical.[62]

Peripheral intravenous catheter insertion

Ultrasonography is increasingly used to guide peripheral intravenous catheter insertion. In addition to increasing patient satisfaction, it has demonstrated a higher success rate, particularly in patients with difficult access, reducing the need for a central venous catheter. Ultrasonography can also be used to confirm the correct placement by visualizing the catheter in the vein or detecting bubbles with saline flush.[63]

Abdominal paracentesis

Ultrasonographic guidance of paracentesis has been found to have a 95% success rate compared with 61% using the traditional landmark-based method.[64] Unsurprisingly, paracentesis was successfully completed with ultrasonography in 87% of the patients for whom the landmark method failed. In a large observational database study of 70,000 patients undergoing paracentesis, ultrasonographic guidance significantly reduced bleeding complications.[65,66]

In addition, a linear probe can help identify underlying vasculature, including the inferior epigastric artery, further minimizing major bleeding risk.

Thoracentesis

Ultrasonography has also demonstrated a higher rate of success and fewer complications for thoracentesis. In a meta-analysis of 24 studies with 6,605 thoracentesis procedures, ultrasonography significantly reduced pneumothorax compared with the landmark technique, even with inexperienced operators.[67] The procedure can be performed using static or dynamic ultrasonographic guidance. If static technique is used, the patient position needs to be maintained after marking the spot.

Evaluation of normal lung sliding preprocedure and postprocedure obviates the need for chest radiographs to rule out pneumothorax.[57]

Common pitfalls

Ultrasound gel can prevent effective preprocedural aseptic skin preparation and postprocedural dressing adherence. Gel should dry before cleaning the skin or applying a dressing.

In addition, use of ultrasonography may sometimes lead to failure to look at anatomical landmarks, leading to performing a procedure at a nonideal site. Users should be mindful of anatomic landmarks in addition to sonographic features.

CONCLUSION

The role of bedside ultrasonography has undergone a paradigm shift, with a variety of applications being explored. This shift has been driven by the realization that performance of POCUS is a readily achievable skill and is rewarding in daily practice. It is no surprise that many predict that it will be the standard of care in the near future. Hospitalists are at the forefront of patient care and should be cognizant of the many benefits of POCUS. We hope that wider utilization of ultrasonography at the bedside can improve medical decision-making, translating to better patient care. ■

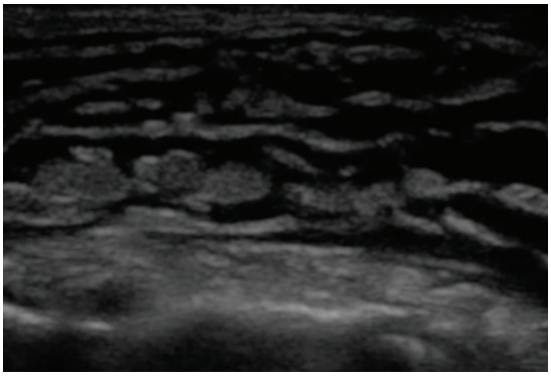


Figure 10. On ultrasonography, subcutaneous fluid is demonstrated as hypoechoic or anechoic (dark) layering within islands of subcutaneous tissue (gray). This occurs in any process leading to fluid within the subcutaneous tissue, including cellulitis and hydrostatic edema.

DISCLOSURES

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

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***Address**: Guramrinder Singh Thind, MD, Department of Critical Care Medicine, A90, Respiratory Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; thindg@ccf.org*

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