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Discussing COVID-19 vaccines with patients: A perspective

Cellulitis and myositis from COVID-19 vaccine

Metronidazole and encephalopathy

Exanthem and enanthem with fever and dyspnea

A potential new paradigm for Peyronie disease

Immune thrombocytopenic purpura: Updated guidelines

Post-intensive care syndrome: Neuropsychiatric assessment

Changing US trends in contraception choices

Managing chronic venous outflow obstruction

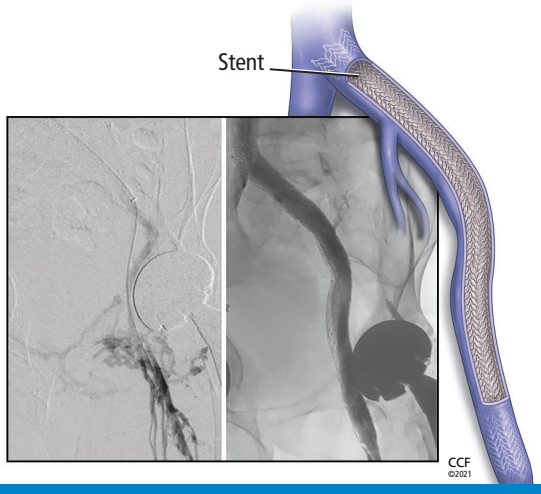

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Table of Contents

CONTINUED ON PAGE 643

Upcoming Features

- Discontinuing antidepressants
- Breast cancer risk evaluation
- Cardiac considerations in liver transplantation

CONTINUED FROM PAGE 642

A perspective on discussing COVID-19 vaccines: Efficacy and adverse effects

Not a day goes by in clinic without discussions with patients about COVID-19 vaccines. They are glad that they received their vaccinations but want to know if they can safely attend family gatherings over the upcoming holidays. And those who are taking immunosuppressive drugs may have heard that the medications may blunt their response to the vaccine. I emphasize with patients that the vaccines are effective overall in protecting them from becoming ill with COVID and requiring hospitalization. But because I can't guarantee or accurately measure the degree of protection my immunosuppressed patients achieve after vaccination, I emphasize the need to exercise common sense: to mask when in groups indoors, and to consider asking visitors and family members to get a rapid COVID test the day before any gathering.

Not all immunosuppressive medications equally blunt the response to the COVID vaccines. The B cell-directed therapies (eg, rituximab), mycophenolate, JAK inhibitors, and high-dose prednisone pose the greatest concerns, while the anti-TNF medications are not nearly as troublesome. But we cannot count on the available antibody tests to reliably predict the degree of protection. Thus, my recommendations for management of these medications before and after vaccination are for the moment based on immunologic principles and on what I hope is good clinical reasoning.

Completely different discussions take place with patients who are reluctant or completely resistant to receiving COVID vaccines. I try to understand their reasoning, but I point out that our overflowing hospitals are filled with COVID patients, most of whom have not been vaccinated, and that this situation cannot be attributed to chance alone (ie, the vaccines work). A few patients just "don't believe it" and believe that hospitals and "the government" are "making the numbers up." But in most cases, actual dialogue with patients is possible. Of course, the dialogue often lengthens the visit by 5 to 10 minutes, but I feel it has the chance to positively impact the health of the patient and those around them in a lasting way. Time well spent.

I've found particularly engaging the discussions with patients who say, "We don't know enough about the vaccines," or "The vaccines were developed too quickly." It is true that we do not know the 10-year post-vaccination outcomes, nor do we know 10-year post-COVID outcomes. But as I have thought about this in the clinic and in my role as editor, we actually know a surprising amount or, perhaps more accurately, we have a lot of data. Not all findings and conclusions will turn out to be true, as truth in science is often ephemeral.[1]

Hundreds of millions of COVID vaccines have been administered. Due to the virulence and infectivity of the virus, the efficacy of the vaccines has been relatively quickly demonstrated in both randomized and observational studies. The enormity of vaccine exposure, clinical importance, and the social and political implications have contributed to rapid awareness and study of many possible vaccine adverse events. With virtually all vaccines, side effects tend to occur early after administration. We

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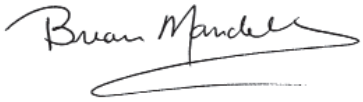
have no reason as yet to think the mRNA vaccines will be different. The literature is already replete with reports of side effects and studies of their pathobiology, even reports of attributed side effects that have occurred with an incidence of only 1 per thousands of vaccine recipients.

In this issue of the *Journal*, we present a Clinical Picture report of a presumed vaccine reaction[2] that has been colloquially coined "COVID arm." The authors describe a strikingly inflammatory soft-tissue reaction in the vaccine-injected arm. Although seemingly distinctive, as with all uncommon reactions, it is difficult to be certain whether this reaction is fairly unique to mRNA COVID vaccines, or if it has been highlighted here and elsewhere[3] because of a hyperacute level of vigilance and heightened desire to share information about these vaccines with the medical community.

As this reaction is infrequent (apparently 1 or 2 per thousand) and self-limited, it should not dissuade people from getting the vaccine. It is also worth noting that various non-vaccine-specific localized reactions can occur after upper-extremity injections. Actual bacterial cellulitis is likely exceedingly rare, particularly with the use of single-dose vaccine vials, and it generally manifests 3 to 5 days after the injection. Slightly earlier in timing, more common, and less likely to be spreading is a local firm swelling and ecchymotic reaction to needle trauma. I have seen several patients who suffered subdeltoid bursitis reactions from inadvertent injection of different vaccines into the bursal space rather than into the deltoid muscle. Localized reactions appearing and behaving as (nonbacterial) cellulitis within 1 to 2 days have been reported following zoster, tetanus, and pneumococcal vaccinations. So these subacute reactions cannot be uniquely attributed to the mRNA platform or even to the polyethylene glycol stabilizing component.

The passage of time with the collection and reporting of more data should inform us whether the seemingly rare delayed "hypersensitivity" and other reactions in patients receiving mRNA vaccines are uniquely more common with these vaccines. But for the moment, we should all be vigilant and open-minded about possible adverse reactions to these vaccines and take the time to discuss them with our patients, while emphasizing the demonstrated efficacy of the vaccines.



Brian F. Mandell, MD, PhD
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March 18–19
Fort Lauderdale, FL

APRIL

COMPREHENSIVE CARE FOR THE LIFETIME TREATMENT OF ADULT CONGENITAL HEART DISEASE
April 22–23
Chicago, IL

MAY

HEART, VASCULAR, AND THORACIC INSTITUTE ADVANCED PRACTICE PROVIDER SYMPOSIUM
May 20–21
Live stream

JUNE

MEDICAL DERMATOLOGY THERAPY UPDATE
June 1–3
Cleveland, OH

INTENSIVE REVIEW OF INTERNAL MEDICINE
June 13–17
Live stream

AUGUST

INTERPROFESSIONAL APPROACH TO MANAGEMENT OF CRITICALLY ILL LIVER PATIENTS
August 15–16
Cleveland, OH

SEPTEMBER

PRIMARY CARE WOMEN'S HEALTH: ESSENTIALS AND BEYOND
September 8–9
Cleveland, OH

DECEMBER

MASTERING THE MITRAL VALVE
December 2–3
New York, NY

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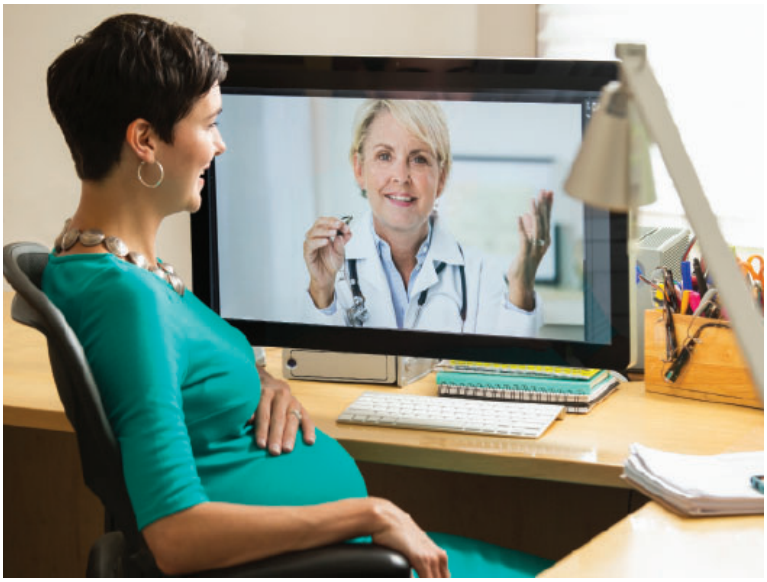

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COVID-19 vaccine-induced cellulitis and myositis

The patient had no history of allergies to medications or of adverse reactions to vaccinations previously

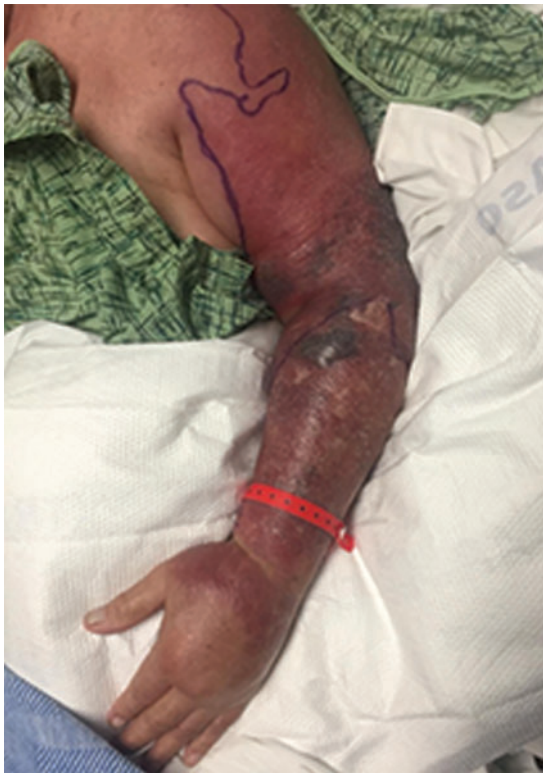

Figure 1. Erythema and swelling of the left upper extremity at presentation.

An 81-year-old man presented to the hospital with swelling, pain, and redness in the left arm that had started after he received his second dose of a messenger RNA (mRNA) vaccine. He had no history of allergies to medications and has had no adverse reactions to vaccinations in the past.

He had received the first dose of a messenger RNA (mRNA) COVID-19 vaccine in the right arm 4 weeks ago, and he noticed redness and pain at the injection site, which resolved within 2 days. But 4 weeks later, after receiving the second dose of the mRNA vaccine, this time on the left arm, he noticed redness and pain at the injection site the following day. The redness and swelling continued to increase, involving the whole left arm and shoulder.

His medical history included Parkinson disease, hypertension, paroxysmal atrial fibrillation, and giant cell arteritis, for which he was taking prednisone and tocilizumab. His blood pressure was 146/80 mm Hg, temperature 97.2°F (36.2°C), and heart rate 108 beats per minute. Physical examination revealed extensive erythema and tenderness involving the left upper extremity from the shoulder to the distal arm (**Figure 1**).

Laboratory testing revealed the following:

- White blood cell count 5 × 10^9/L (reference range 4–11 10^9/L)
- Creatine kinase 236 U/L (reference range 35–232 U/L)
- Lactic acid 3.1 mmol/L (reference range 0.4–2 mmol/L)
- Aldolase 20.9 U/L (reference range 1.5–8.1 U/L)
- C-reactive protein 6.3 mg/dL (reference range 0.0–0.9 mg/dL).

Computed tomography (CT) of the left upper extremity showed proximal cellulitis and myositis of the deltoid muscle, and fasciitis was not excluded due to multicompartment findings. Magnetic resonance imaging (MRI) revealed diffuse cellulitis and myositis of the deltoid and supraspinatus muscle concerning for myositis due to mRNA COVID-19 vaccine (**Figure 2**).

The patient was treated with intravenous vancomycin and piperacillin-tazobactam, and

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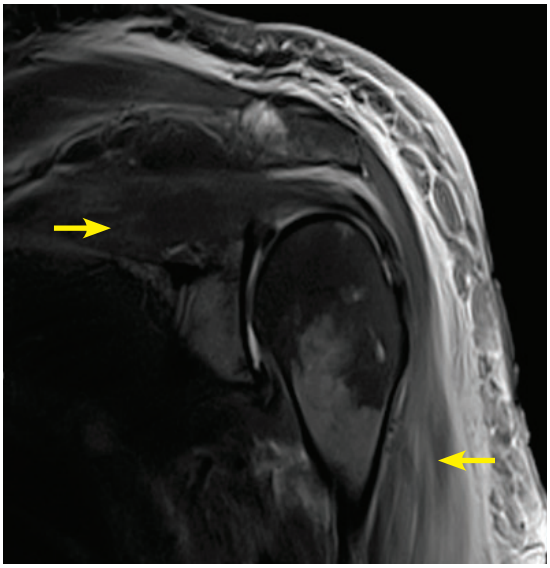

Figure 2. Magnetic resonance imaging without contrast showing diffuse soft-tissue edema (arrows) consistent with cellulitis and myositis of the deltoid and supraspinatus muscle.

methylprednisolone 40 mg once a day, but the erythema and swelling of the left arm worsened, and on day 3 of hospitalization, he underwent local incision and drainage, which showed extensive edema without necrosis. Gram staining was negative for bacteria, and blood and wound culture did not grow any bacteria.

On hospital day 4, repeat laboratory testing showed a creatine kinase level of 98 U/L and an aldolase level of 10.3 U/L. The swelling and redness of the left upper extremity improved (**Figure 3**), intravenous antibiotics were stopped, oral prednisolone 4 mg was started, and the patient was discharged on hospital day 7.

A RANGE OF REACTIONS TO mRNA COVID-19 VACCINE

The mRNA COVID-19 vaccine is a lipid nanoparticle-encapsulated, nucleoside-modified mRNA vaccine that encodes the prefusion spike glycoprotein of the SARS-CoV-2 virus responsible for COVID-19.[1] Local reactions include mild to moderate pain at the injection site, and systemic side effects like fatigue, headache, and fever have been common after the second dose.[2] Immediate reactions

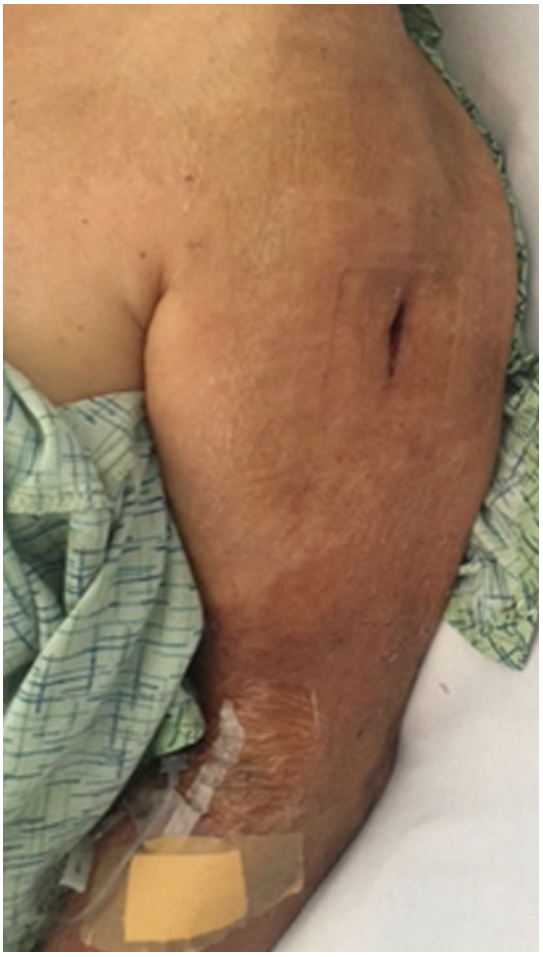

Figure 3. Improvement of the swelling and erythema on hospital day 7.

to mRNA COVID-19 vaccine like local pain, redness, and swelling occur within 2 to 3 days, and delayed injection reactions including erythema, induration, and tenderness occur after 5 days.[3] Infection at the injection site can happen due to contaminated needles.[4] Local reactions due to the vaccine can be treated with a cold compress, analgesics, and antihistamine.

The CT and MRI findings in this patient were consistent with cellulitis and myositis, and an elevated aldolase suggested damaged muscle cells in this setting,[5] although aldolase is not a specific muscle cell marker. Immediate hypersensitivity reactions including itching, flushing, urticaria, angioedema, and hypotension are immunoglobin E (IgE)-mediated allergic reactions that usually begin within minutes of administrating vaccines. Hypersensitivity reactions after the second dose of

The exact mechanism of cellulitis and myositis due to mRNA COVID-19 vaccines is unknown and requires further investigation

mRNA COVID-19 vaccine may be due to the immune response after the first dose.[3]

Delayed large local reactions to mRNA COVID-19 vaccine may be due to delayed-type or T-cell-mediated hypersensitivity, with perivascular and perifollicular lymphocytic infiltrates on skin biopsy.[6] The Arthus reaction, a type III immune complex-mediated hypersensitivity reaction, in which antibody-antigen complexes are deposited in the blood vessel causing acute inflammation and local skin necrosis, have been reported after tetanus, diphtheria, and acellular pertussis vaccine administration.[7] There have been reports of extensive vaccine-related limb-swelling involving the entire extremity and myositis.[8,9] Myositis has been reported after vaccination with live-attenuated measles, mumps, and rubella vaccine, diphtheria and tetanus vaccine, hepatitis B vaccine, and influenza and H1N1 vaccines.[10] The exact mechanism of cellulitis and myositis due to the mRNA COVID-19 vaccine is unknown and requires further investigation.

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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Metronidazole-induced encephalopathy: Symmetrical hyperintensity on imaging

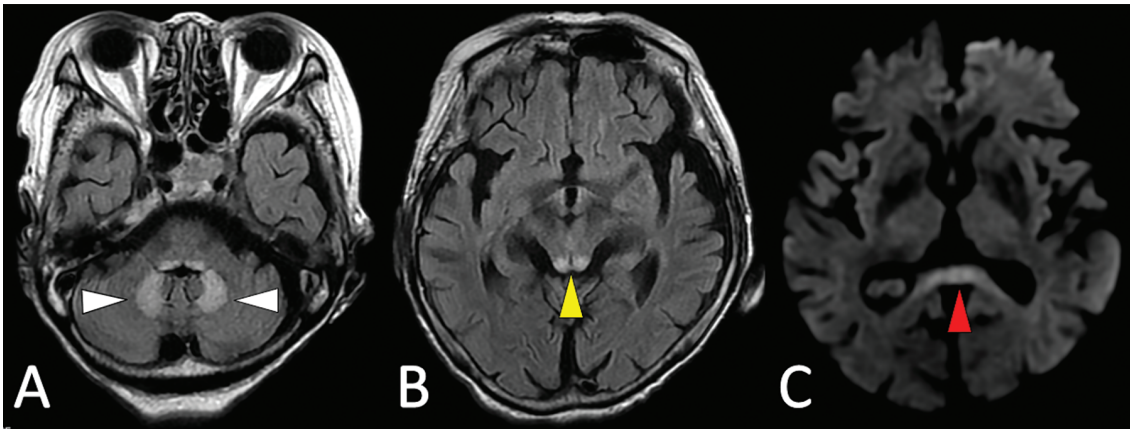

Figure 1. (A) T2 fluid-attenuated inversion recovery (T2-FLAIR) on MRI shows typical symmetrical hyperintensity in the dentate nuclei of the cerebellum, reflecting vasogenic edema (white arrowheads). (B) T2-FLAIR MRI shows hyperintensity in the tectum of the midbrain (yellow arrowhead). (C) Diffusion-weighted MRI shows hyperintensity in the splenium of the corpus callosum, indicating restricted diffusion or cytotoxic edema (red arrowhead).

An 83-year-old woman with mild hypertension and hypothyroidism was admitted to our hospital with acute pyelonephritis. She was treated with ampicillin plus sulbactam for 10 days with a good response while she was under rehabilitation receiving physical and speech therapy. However, she suddenly experienced fever, abdominal pain, and severe watery diarrhea. A stool sample was positive for *Clostridioides difficile* (*C difficile*) antigen and toxins, and she was prescribed metronidazole 1,500 mg/day for 4 weeks for gastrointestinal symptoms due to C *difficile* infection

Although the patient's gastrointestinal symptoms improved, she later presented with an acute onset of dysphagia, nausea, vomiting, dizziness, and progressively altered mental status. Her vital signs were stable. Physical findings revealed no nuchal rigidity or meningeal irritation. However, neurologic examination showed dysarthria, minimal horizontal nystagmus, and unsteady gait. Results of laboratory testing were unremarkable.

Computed tomography showed moderate atrophy without cerebral bleeding. Magnetic resonance imaging (MRI) showed symmetrical T2-hyperintensity in the tectum of the midbrain, pontine tegmentum, and dentate nuclei indicating parenchymal vasogenic edema (**Figure 1**). Based on the characteristic imaging finding and the clinical history, we made a diagnosis of metronidazole-induced encephalopathy and immediately stopped the metronidazole therapy. After metronidazole was stopped, her neurologic symptoms improved gradually without remission.

After metronidazole was stopped, her neurologic symptoms improved gradually, without remission

METRONIDAZOLE AND NEUROTOXICITY

Metronidazole-induced encephalopathy is a relatively rare central nervous system disorder,

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associated with prolonged duration and high cumulative doses of metronidazole.[1] Metronidazole is commonly used to treat a wide variety of infection-associated diseases, including pelvic inflammatory disease, bacterial vaginosis, intra-abdominal abscess, amebiasis, giardiasis, and C *difficile*. However, metronidazole has been reported to be inferior to vancomycin particularly for patients with severe cases of C *difficile* infection.[2]

The mechanism of neurotoxicity due to metronidazole is unknown. It is thought that metabolites of metronidazole may bind to ribonucleic acid and interfere with ribonucleic acid protein synthesis, which can lead to axonal degeneration.[3] Neurologic symptoms of metronidazole-induced encephalopathy vary widely among individual patients but can include cognitive deterioration, peripheral neuropathy, weakness, dizziness, vertigo, nausea, vomiting, headache, sensory loss, and seizures.[4]

A characteristic MRI finding in patients with metronidazole-induced encephalopathy is bilateral involvement of the cerebellar dentate nuclei.[5] However, this is also seen in other neurologic disorders such as Wernicke encephalopathy and isoniazid or methyl bromide toxicity. Thus, the definitive diagnosis should be based on a combination of the patient's clinical history, laboratory findings, and imaging results. In most cases, the encephalopathy is reversible and generally improves within a few weeks after metronidazole is stoppped.[6] However, a delayed diagnosis can have progressive, irreversible consequences, including death.[7] Clinicians should consider metronidazole-induced encephalopathy in a patient presenting with new psychiatric and neurologic symptoms and signs, especially in those with cerebellar symptoms who are taking metronidazole.

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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Exanthem and enanthem with fever and dyspnea

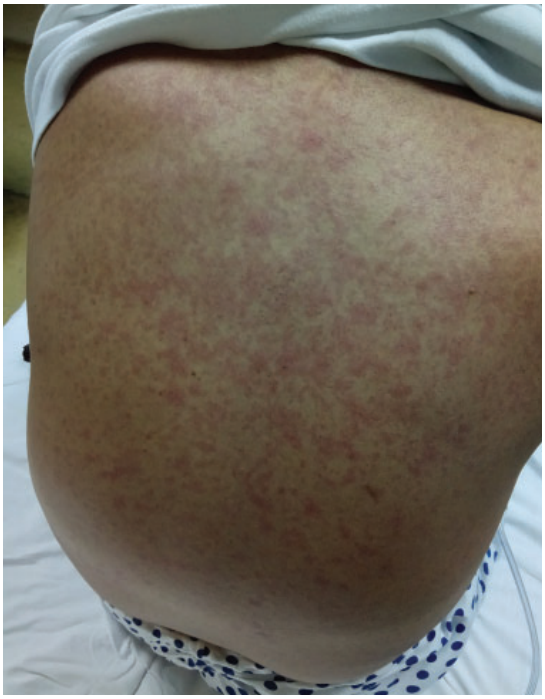

Figure 1. Erythematous, maculopapular, blanching rash on the trunk.

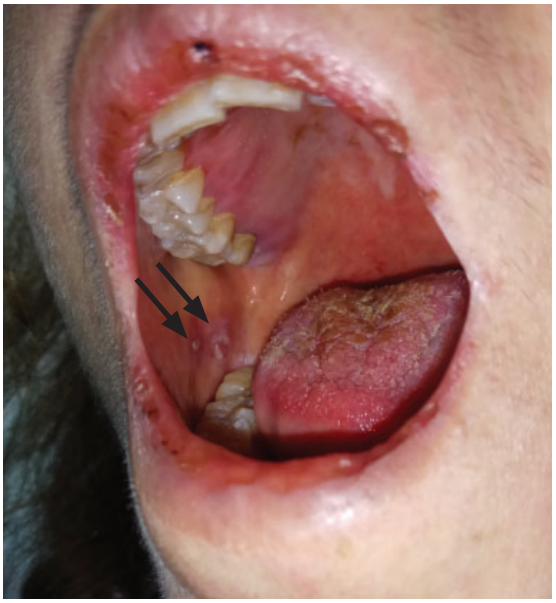

Figure 2. Koplik spots (black arrows), whitish, grayish, or bluish elevations of 1 to 3 mm with an erythematous base on the buccal mucosa opposite the molars.

Koplik spots are considered pathognomonic for measles

A 49-year-old woman presented with a 5-day history of high fever, productive cough, mild dyspnea, malaise, generalized myalgias, and conjunctivitis. Hours before admission she developed a maculopapular rash. She had been diagnosed 2 years earlier with decompensated liver cirrhosis due to autoimmune hepatitis–primary biliary cholangitis overlap syndrome and was currently being treated with prednisolone, azathioprine, and ursodeoxycholic acid.

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WORKUP AND HOSPITAL COURSE

On examination, her temperature was 38.3°C (100.9°F), heart rate 92 beats per minute, blood pressure 100/68 mm Hg, respiratory rate 24 breaths per minute, and oxygen saturation 92% on ambient air. An erythematous, maculopapular, blanching rash was noted on the face and trunk (**Figure 1**), as well as enanthem on the buccal mucosa opposite the molars (**Figure 2**). Auscultation detected basilar fine crackles in both lungs. A firm liver was palpable 2 to 3 fingers below the right costal margin without tenderness. The rest of the

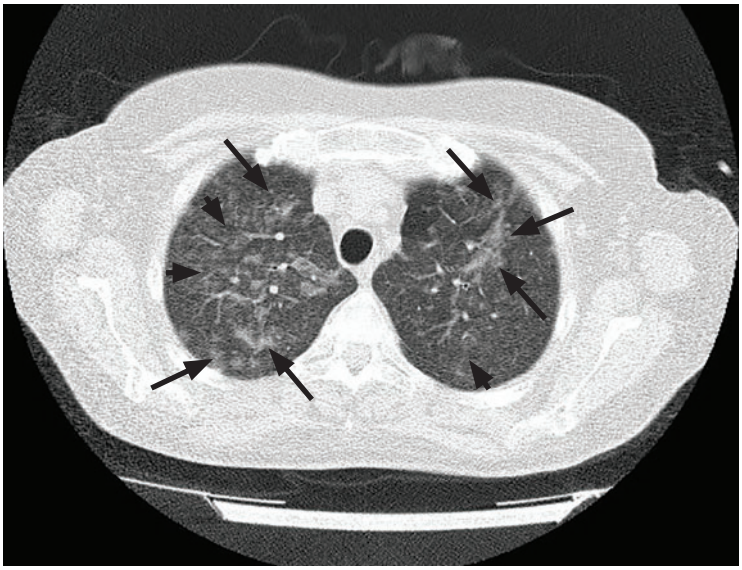

Figure 3. Computed tomography of the lungs revealed bilateral infiltrates (arrows) and ground-glass opacities (arrowheads) mainly in the upper lobes.

physical examination was unremarkable.

Laboratory testing revealed leukopenia, thrombocytopenia, and increased serum levels of aspartate aminotransferase, lactate dehydrogenase, creatine kinase, gamma-glutamyl transferase, and total bilirubin.

The patient's dyspnea deteriorated significantly over the next 2 days, accompanied by high fever, with temperatures of 39.6°C to 40.5°C (103.3°F to 104.9°F). The initial findings on auscultation worsened and included diffuse bilateral crackles. Arterial blood gas analysis revealed hypoxemia (Pao_2 59 mm Hg, Pco_2 27 mm Hg), while she was breathing 3 L of oxygen per minute by nasal cannula.

Computed tomography of the lungs revealed bilateral infiltrates and ground-glass opacities in the upper lobes (**Figure 3**). Serologic testing by enzyme-linked immunosorbent assay confirmed the presence of positive immunoglobulin M antibodies against measles virus. She was treated with 40% oxygen through a face mask, intravenous levofloxacin, and oral ribavirin. As the enanthem (Koplik spots) prevented the patient from consuming adequate fluids and food, supportive care was provided including D/W 5% daily by intravenous infusion. The patient was discharged 1 week later in good condition, and at a follow-up visit 1 month after discharge, she was asymptomatic.

The presence of Koplik spots along with symptoms typical for viral infection makes measles the most likely diagnosis, even before the development of exanthem

DISCUSSION

Measles is a highly contagious viral illness with a 90% transmission rate to susceptible individuals. The majority of deaths are from pneumonitis or encephalitis, while the most common complication is diarrhea. During the 2018 measles outbreak in Europe, tens of thousands of cases were reported, with two-thirds of patients requiring hospitalization.[1]

The incubation period for measles is 8 to 12 days[2] and begins after virus entry via respiratory mucosa or conjuctivae. The virus replicates locally, spreads to regional lymphatic tissues, and is then thought to be disseminated to other reticuloendothelial sites through the blood stream ("primary viremia").[3] The prodromal phase is defined by the appearance of symptoms that typically include fever, malaise, and anorexia, followed by conjunctivitis that may be accompanied by lacrimation or photophobia, coryza, and cough.[2,3] Respiratory symptoms result from mucosal inflammation from viral infection of epithelial cells.

Prodromal symptoms typically intensify a few days before exanthem appears. Around 48 hours before the onset of exanthem, patients may develop enanthem characterized by Koplik spots, whitish, grayish, or bluish elevations of 1 to 3 mm with an erythematous base, typically on the buccal mucosa opposite the molars. Koplik spots are considered pathognomonic for measles.[3] They may spread to cover the buccal and labial mucosa and the hard and soft palate.

Although a safe and effective measles vaccine was developed in 1963 and was eventually included in the trivalent measles-mumps-rubella vaccine in 1981 in the Greek National Vaccination Program, this patient had not been vaccinated against measles as a child or as an adult.

CLINICAL DIFFERENTIAL DIAGNOSIS

Once exanthem appears, the differential diagnosis for measles includes varicella, roseola (human herpesvirus 6 and 7), enteroviruses (coxsackievirus A9 and B5), erythema infectiosum (parvovirus B19), rubella, infectious mononucleosis, Epstein-Barr virus (especially during amoxicillin treatment), and group A streptococcal infection.

If dyspnea develops, the differential diagnosis may encompass Rocky Mountain spotted fever, meningococcemia, and Mycoplasma pneumoniae-induced rash and mucositis. In immunocompromised individuals like this patient, the differential diagnosis also includes *Candida albicans* mucositis with subsequent fungemia and pneumonia, and herpes simplex virus type 1 infection with viremia and end-organ disease.

The presence of Koplik spots along with the symptoms typical for viral infection makes measles the most likely diagnosis even before the development of exanthem.

SUPPORTIVE TREATMENT IS THE STANDARD

The mainstay of measles treatment is supportive. Treatment of bacterial superinfections such as bacterial pneumonia and otitis, as well as seizures and respiratory failure, may also be necessary. Administration of vitamin A to children with measles is associated with decreased morbidity and mortality.[4]

Early initiation of ribavirin treatment—within the first 5 days of disease onset—seems more effective than later in the disease course.[5] Given the high risk of measles-associated mortality in immunosuppressed individuals[6] and the absence of treatment guidelines, some authors have recommended ribavirin treatment in patients with measles complications (mostly pneumonitis and encephalitis).[5]

In a prospective study of 100 patients with measles, half were assigned to treatment with ribavirin and supportive therapy, and the other 50 patients received only supportive therapy. Those receiving ribavirin had earlier resolution of fever and constitutional symptoms and fewer complications than those receiving only supportive care.[7]

The optimal duration of ribavirin therapy is not known, but 5 to 7 days may be reasonable except for severely immunosuppressed patients, who may require 2 to 3 weeks of treatment.[8]

TEACHING POINT

In patients with short-term high fevers and symptoms of viral infection (eg, malaise, generalized myalgias, conjunctivitis) but no maculopapular rash, a thorough inspection of the buccal cavity for Koplik spots will allow for a timely diagnosis of measles and for prompt administration of ribavirin if dyspnea or other complications develop.[4]

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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Antiobesity drug therapy

To the Editor: The article by Mauer et al[1] in the August issue is an excellent and comprehensive review of antiobesity pharmacologic therapy. The authors twice mention the positive impact of antiobesity medications in reducing blood pressure. I wish to highlight that the pre-semaglutide trials of antiobesity medications have generally shown an underwhelming blood pressure effect given the amount of weight loss. It is important for physicians to consider these data when counseling patients about the magnitude of expected benefits in initiation of antiobesity therapies. For example, in the CONQUER[2] trial of phentermine-topiramate) and the SCALE[3] trial of liraglutide, placebo-adjusted reductions of systolic blood pressure were approximately 3 mm Hg, and of diastolic blood pressure approximately 1 mm Hg. In CONQUER, the effect was minimally better when examining only the subgroup of patients with preceding hypertension, ie, approximately 4 mm Hg for systolic and 2 mm Hg for diastolic. The clinical relevance of these mild improvements may be less certain.

Of note, recent trials demonstrating more robust weight loss, such as those of semaglutide[4] and tirzepatide,[5] demonstrate more significant blood pressure reduction. It remains to be seen whether the improved effectiveness is simply due to increased weight loss, or whether other factors in the complicated pathophysiology of hypertension are being impacted.

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doi:10.3949/ccjm.88c.12001

In Reply: I thank Dr. Modarressi for these comments and agree that the impact of many glucagon-like peptide 1 (GLP-1) receptor agonists on the lowering of blood pressure is modest but significant when compared with other glucose-lowering agents and thus have exerted cardioprotective benefits.

A meta-analysis[1] of 16 randomized controlled trials, including 2,417 control group participants and 3,443 patients enrolled in GLP-1 receptor agonist treatment, examined the blood pressure-lowering impact of exenatide and liraglutide.

Exenatide reduced systolic blood pressure (SBP) by a mean difference of −5.24 mm Hg compared with placebo (95% confidence interval [CI] −6.88 to −3.59, $P < .001$) and by −3.46 mm Hg compared with insulin glargine (95% CI −3.63 to −3.29, $P < .001$). In the exenatide-treated group, diastolic blood pressure (DBP) was reduced by −5.91 mm Hg compared with placebo (95% CI −7.53 to −4.28, $P < .001$) and by −0.99 mm Hg compared with sitagliptin (95% CI −1.12 to −0.87, $P < .001$).

For liraglutide, SBP changes in this meta-analysis were assessed in the groups treated with 1.2 mg/day or 1.8 mg/day of liraglutide. In the 1.2-mg/day group, liraglutide reduced SBP by a mean difference of −5.60 mm Hg compared with placebo (95% CI −5.84 to −5.36, $P < .001$) and by −2.38 mm Hg compared with glimepiride (95% CI −4.75 to −0.01, $P = .05$). In the 1.8-mg/day group, liraglutide also reduced SBP by −4.49 mm Hg compared with placebo (95% CI −4.73 to −4.26, $P < .001$) and by −2.62 mm Hg compared with glimepiride (95% CI −2.91 to −2.33, $P < .001$).

In summary, treatment with the GLP-1 receptor agonists exenatide and liraglutide reduced SBP and DBP by 1 to 5 mm Hg compared with antidiabetic drugs including insulin and glimepiride and with placebo for patients with type 2 diabetes mellitus. GLP-1 receptor agonists may offer an alternative therapy for these patients and will help provide additional cardiovascular benefits.

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Physician resistance to obesity pharmacotherapy

To the Editor: Obesity, excessive body fat that impairs health, is defined by a body mass index (BMI) greater than 30 kg/m^2.[1] Although the prevalence of obesity has dramatically increased in the United States, treatment of obese Americans remains suboptimal. Stigma, costs, and physician lack of confidence in medical management of obesity may all contribute to this state of affairs.[1]

In a survey of 13,158 obese patients,[2] only 40.4% received weight-loss counseling. In another study of 45 physicians,[3] most reported calculating patient BMI, but only 13.5% consistently discussed the results with their patients.[3] Weight bias, including concerns about insulting patients, may contribute to physicians' reluctance to discuss obesity as a legitimate health concern.[1]

Further, providers who broach the subject often recommend lifestyle interventions. One survey showed that physicians were more comfortable counseling about lifestyle modification and least comfortable discussing pharmacotherapy.[3] Physical activities, while essential, may not be sufficient to maintain weight loss over time. This is due to compensatory physiology that promotes weight maintenance.

In theory, patients with a BMI greater than 30 kg/m^2 or a BMI greater than 27 kg/m^2 with obesity-related complications who do not respond to a healthy low-calorie regimen and physical activity are eligible for medications. In practice, only 2% of appropriate patients receive pharmacotherapy.[4]

In a review by Mauer et al,[5] the authors conclude that pharmacotherapy aids in weight loss and prevents regain. However, analysis of a survey of 94 primary care physicians found 76% did not recommend pharmacotherapy for long-term weight loss, and 58% had negative views towards pharmacotherapy.[4] These data suggest that the prevailing philosophy is to avoid medications at all costs except in severe cases.[4] Delaying pharmacotherapy until patients are severely obese may be too little, too late.

Recent guidelines suggest essential components of obesity care.[1] Clinicians should ask the patient for permission to discuss obesity. Core tenets consist of individualized nutritional, physical, and psychological interventions along with surgery and medications.[1] These guidelines also offer a new conceptualization of treatment that shifts the focus from BMI to improving overall health and well-being.

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doi:10.3949/ccjm.88c.12003

In Reply: We thank Dr. Modesto-Lowe and colleagues for their comments. We agree that primary care providers need to increase their efforts to diagnose patients with obesity and adiposity-related comorbidities and to discuss with patients the therapeutic options including behavioral, pharmacotherapy,

and possibly bariatric surgery. Pharmacotherapy should not be considered a last resort as antiobesity agents are safe and effective and should be offered for patients with a body mass index of 30 kg/m^2 or greater and with a body mass index over 27 kg/m^2 in the presence of obesity-related comorbidity. Though we also recognize that the cost of antiobesity medications and the lack of insurance coverage for them continue to be major barriers to the regular use of these agents.

In general, primary care doctors need to become more comfortable discussing obesity as a medical problem that requires treatment like all other medical problems.

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CORRECTION

DXA and fracture risk assessment

In the November 2021 issue, an error appeared in *Williams S, Khan L, Licata AA. DXA and clinical challenges of fracture risk assessment in primary care. Cleve Clin J Med 2021; 88(11):615–622. doi:10.3949/ccjm.88a.20199*. On page 621, the second paragraph in the section titled "Pharmaceutical management recommended" should have read as follows: "Further, advising only the use of calcium and vitamin D is inadequate management. Her provider should recommend that she use an antiresorption agent as first-line therapy and consider anabolic drugs if there are problems with the initial drug choice. She should not reinstate hormone therapy at her age for bone health alone as there may be increased risk for cardiovascular disease.[44] However, this caveat is not absolute and requires a balance of risk and reward if hormone therapy is also needed for vasomotor, genitourinary, or other problems." Reference 44 has been changed to the following: *Flores VA, Pal L, Manson JE. Recommended hormone therapy in menopause: concepts, controversies and approach to treatment [published online ahead of print, 2021 Apr 15]. Endocr Rev 2021; bnab011. doi:10.1210/endrev/bnab011.*

Article is correct on ccjm.org.

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COMMENTARY

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Peyronie disease and erectile dysfunction: A potential new paradigm

Peyronie disease (PD), first reported in 1743 as a disease,[1] is now recognized in most cases to be the result of coital trauma to the penis. In 1997, Devine et al suggested that poor rigidity during penetrative sex causes delamination of the elastic covering (tunica albuginea) of the penile corpora cavernosa.[2] The scar that forms as healing takes place is usually palpable, and this "plaque" and the erectile deformity are manifestations of PD.[2]

According to the National Institutes of Health consensus panel on impotence, erectile dysfunction (ED) is defined as the consistent inability to attain or maintain an erection of the penis sufficient to permit satisfactory sexual intercourse on more than 50% of attempts.[3] Secondary ED that presents after a period of normal sexual function is preceded by declining penile rigidity with erection until a threshold is reached at which ED can be considered to exist.

Although PD and ED are linked, it is not clear which comes first owing to the lack of literature and studies regarding the timing of PD and ED onset.[4,5] Men who have erections with decreased rigidity, even if still capable of penetrative sex and not yet diagnosed with ED, are at risk for penile fractures and PD.[5]

REPORTED PREVALENCE OF PEYRONIE DISEASE

According to the Peyronie's Disease Guidelines panel of the American Urological Association, PD prevalence ranges from 0.5% to 20.3%, noting that rates are historically underestimated and may be higher among male patients who present with comorbidities.[6] Further, the panel stated that the most common presentation is in the male patient in his mid-50s with recent onset of penile curvature accompanied by mild to moderate pain.[6]

The reported prevalence of PD varies, but a compelling study of 534 patients ages 40 to 75 who presented for prostate cancer screening[4] noted the presence of a penile nodule in 48 patients (8.9%) that significantly correlated with age, diabetes, hypertension, and ED. PD has been associated with other factors such as family history,[7] autoimmune disease,[8] and Dupuytren contracture;[7] although these factors do not typically account for high prevalence of PD.

Peyronie disease is recognized in most cases to be the result of coital trauma to the penis associated with erectile insufficiency or erectile dysfunction

MANAGEMENT AND PREVENTION

The Peyronie's Disease Guidelines panel of the American Urological Association characterized PD symptoms as having a variable course, noting that some symptoms may improve or resolve without treatment in some patients.[6] For most, pain will resolve over time without intervention although curvature is less likely to resolve. It is important to distinguish between active disease that is characterized by penile pain or discomfort with or without erection and stable disease with symptoms clinically unchanged for at least 3 months.[6]

When treating patients with ED or PD, it is important to gather information by asking the patient to compare current erectile rigidity on a scale of 10, with the normal range at age 20 being 10/10. Current erections with ri-

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gidity scores of 6/10 or greater are sufficient for intromission; but with coital thrusting, damage to the tunica albuginea is more likely than with a normal erection (10/10). In PD injuries, the forces are not great, many are silent, and they may recur although this is unknown because they are silent. Recurrent injuries may account for the variation of duration of the active phase of PD.

Thus, ED is not a yes-or-no diagnosis but occurs on a spectrum. Patients with decreased erectile rigidity that has not reached the threshold for ED defined by the National Institutes of Health are able to have penetrative sex but with increased risk of injury. I have suggested the term *erectile insufficiency* to describe this prodromal period while considering erectile insufficiency and ED, and I have posited that PD is the consequence and not the cause,[5,9] thus allowing for the possibility to prevent PD in patients with erectile insufficiency.

Oral medications for ED, ie, phosphodiesterase type 5 (PDE5) inhibitors, are generally not prescribed without the formal diagnosis of ED. However, if prescribed earlier, when only erectile insufficiency is present, the increased rigidity that would likely result would lessen the chance of injury, thus making coitus safer.

Men who have erections with decreased rigidity are at risk for penile fractures and Peyronie disease

Long-term use of these agents has demonstrated safety,[10] and measures to improve erections such as smoking cessation, weight loss, exercise, and decreased alcohol use should be advised.[11] Additionally, the following recommendations should be offered to the patient and his partner:

- During coitus, manually guide the penis in or back in if it comes out
- Ensure adequate lubrication
- Avoid the partner-on-top position
- Thrust straight in-and-out to avoid torque on the penis
- Avoid coitus if the man is tired or has consumed too much alcohol.[5,9]

Ideally, men would be aware of these recommendations before they develop PD. These practices should be discussed with all at-risk patients, including those with newly diagnosed PD.

SURGICAL MANAGEMENT

Men with PD who are not sexually active or who have sexual activity not involving penetration can be reassured that PD does not affect their health, and treatment is not necessary. If the patient with PD wants to have penetrative sex, straight and reliably firm erections are required.

If the PD patient has good rigidity after a trial of a PDE5 inhibitor, penile straightening can be accomplished surgically by tunica albuginea plication.[12] Penile straightening can also be attempted by plaque collagenase injections[13] with or without the use of a traction device.[14] Plaque excision or incision with placement of a graft is another way to straighten the erection. However, this more extensive surgery often increases erectile insufficiency and ED and, consequently, is usually avoided.[12] Treatment for ED involving intracavernosal injection of vasoactive medications is best avoided in patients with PD, as this mode of therapy may lead to increased deformity.[15]

If PD does not respond to a PDE5 inhibitor trial with increased erectile rigidity, then implantation of a penile prosthesis should be considered.[16,17] Inflatable penile prostheses straighten erections, and the reliability of these erections assure that repetitive injuries will not occur.[16,17]

CLINICIAN EXPERIENCE

Evidence from the literature has been insufficient to constitute evidence-based diagnosis and treatment for PD.[6] As a result, the American Urological Association uses a variety of sources for their recommendations, including expert opinion. Their 2015 PD guidelines are based primarily on clinical principle or expert opinion.[6] According to Sackett, evidenced-based medicine integrates individual clinical expertise with the best available evidence from systematic research.[18]

It has been through my years of experience with patients with PD, as well as the adoption of the paradigm noted above, that I have been able to provide effective relief for these patients. However, prospective studies to test this hypothesis are very difficult to execute.

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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Updated guidelines for immune thrombocytopenic purpura: Expanded management options

ABSTRACT

The current American Society of Hematology (ASH) guidelines for the management of patients with immune thrombocytopenic purpura (ITP) are an update to the 2011 guidelines. The updates focus on treating patients with ITP without bleeding in both outpatient and inpatient settings, including those with newly diagnosed, persistent, and chronic ITP refractory to first-line therapy. Recommendations for therapy include corticosteroids, intravenous immunoglobulins, anti-D immunoglobulin, rituximab, splenectomy, and thrombopoietin-receptor agonists, as well as observation.

KEY POINTS

- Inpatient management is suggested for patients with newly diagnosed ITP who have a platelet count below 20 × 10^9/L and are asymptomatic or have minor symptoms.
- Outpatient management can be considered in patients with a platelet count of at least 20 × 10^9/L who are asymptomatic or have minor mucocutaneous bleeding.
- Observation can be considered for newly diagnosed patients with a platelet count of at least 30 × 10^9/L who are asymptomatic or have minor mucocutaneous bleeding.
- Corticosteroid therapy should be considered for newly diagnosed patients with a platelet count less than 30 × 10^9/L who are asymptomatic, or for patients with minor or more significant bleeding.

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IMMUNE THROMBOCYTOPENIC PURPURA (ITP) is an acquired autoimmune disorder characterized by thrombocytopenia caused by autoantibodies against platelet antigens. ITP is a diagnosis of exclusion, with an estimated incidence of 2 to 5 per 100,000 people in the general population.[1]

The updated American Society of Hematology (ASH) guidelines for the management of patients with ITP, published in 2019,[1] are based on systematic reviews that included hundreds of studies by a multidisciplinary panel under the direction of the University of Oklahoma Health Sciences Center. Recommendations cover management strategies for ITP in patients with newly diagnosed, persistent, and refractory disease and include therapy with corticosteroids, intravenous (IV) immunoglobulins, anti-D immunoglobulins, rituximab, splenectomy, and thrombopoietin receptor agonists, as well as observation.

WHAT'S NEW IN THE GUIDELINES?

The main focus of the guidelines is on patients with ITP without bleeding in both outpatient and inpatient settings. The purpose is to help practitioners decide on inpatient vs outpatient management, thresholds for when to initiate treatment, and options for second-line treatment in adults. Pediatric patients are discussed in the guidelines, but that population is beyond the scope of this review. **Table 1** lists the key differences between the 2019 update and the previous guidelines for the management of patients with ITP.[1,2]

TABLE 1

Current vs previous guidelines on immune thrombocytopenic purpura in adults

	2019	2011
Nomenclature	Corticosteroid dependence recognized as an entity needing intervention	
Diagnosis	Diagnosis of ITP not discussed	Workup including HIV, hepatitis C testing, and bone marrow biopsy discussed
Criteria for admission	**Inpatient vs outpatient** Inpatient: Platelet count < 20×10^9/L asymptomatic or minor symptoms and new diagnosis Outpatient: Platelet count ≥ 20×10^9/L asymptomatic or minor symptoms or established ITP	Inpatient vs outpatient not discussed
First-line therapy	**Choice of agent** Either prednisone (0.5–2.0 mg/kg/day) or dexamethasone (40 mg/day for 4 days); dexamethasone preferred if rapidity of response is valued **Corticosteroids alone vs in combination.** Prefer corticosteroids alone rather than in combination with rituximab for initial treatment **Duration of therapy** Recommends in favor of short course (≤ 6 weeks) and against longer course of prednisone (> 6 weeks including taper)	**Choice of agent** Anti-D immunoglobulins added as a treatment option for Rh-positive, nonsplenectomized patients **Duration of therapy** Longer course of steroid (prednisone 1 mg/kg × 21 days followed by taper) recommended over shorter course
Second-line therapy	Introduces concept of shared decision-making with patients, particularly with regard to the choice of second-line therapy Provides guidance on considerations while choosing second-line therapy	**Choice of therapy** Splenectomy if steroids fail TPO-RA for relapse after splenectomy or if splenectomy is contraindicated Rituximab after failure of steroids, IVIG, or splenectomy
Special populations and other considerations	**Elderly** Raises concern regarding potential complications of steroid use in elderly and those with diabetes **Cost** Considers eltrombopag more cost-effective than romiplostim Rituximab and splenectomy are considered cost-equivalent, but TPO-RAs are more expensive and may not be covered by all insurance payers	Discusses management of ITP in pregnancy and treatment of secondary ITP

HIV = human immunodeficiency virus; ITP = immune thrombocytopenic purpura; IVIG = intravenous immune globulin; TPO-RA = thrombopoietin-receptor agonist

Inpatient vs outpatient management

Inpatient management is suggested for those with newly diagnosed ITP who have a platelet count below 20 × 10^9/L and are asymptomatic or have minor symptoms such as wet purpura, gum bleeding, continuous epistaxis needing intervention, menorrhagia, or multiple large bruises larger than 3 cm.

Outpatient management can be considered for patients with a platelet count of at least 20 × 10^9/L who are asymptomatic or have minor mucocutaneous bleeding such as few petechiae, small bruises of less than 3 cm, or epistaxis on nose-blowing. It can also be considered for patients with established ITP who have a platelet count below 20 × 10^9/L and are asymptomatic or have minor symptoms. Asymptomatic patients or those with a documented good response to rescue agents can be followed as outpatients.

Observation vs corticosteroid therapy

Observation can be considered for newly diagnosed patients with a platelet count of at least 30 × 10^9/L who are asymptomatic or have minor mucocutaneous bleeding. The updated guidelines note the need for clinical judgment for patients who have additional comorbidities, who are scheduled for procedures, or who have more than minor bleeding. It is important to consider concomitant medications such as anticoagulant and antiplatelet drugs, as higher platelet thresholds are more desirable in this setting. Patients with a history of bleeding also warrant consideration for a higher platelet goal and may warrant treatment rather than observation.

The guidelines focus on inpatient and outpatient treatment for patients with ITP without bleeding

Corticosteroid therapy should be considered for newly diagnosed patients with a platelet count less than 30 × 10^9/L who are asymptomatic or patients with minor or more significant bleeding. The presence of severe thrombocytopenia also warrants consideration for a more aggressive approach, such as a combination of high-dose steroids and other rescue agents (eg, IV immunoglobulins or anti-D immune globulins).

Steroid therapy warrants extra consideration in patients with poorly controlled diabetes and those who are immunocompromised.

First-line therapy recommendations

Regarding the type and duration of steroids, the guidelines recommend against a long course of prednisone (> 6 weeks including taper) in favor of a shorter course (≤ 6 weeks). When considering dexamethasone vs prednisone, either is acceptable (prednisone 0.5–2.0 mg/kg/day or dexamethasone 40 mg/day for 4 days). However, if a rapid response is desired, dexamethasone is preferred. Of note, there appears to be no benefit with regard to response at 1 month, durability of response, or major bleeding between these treatment options. Furthermore, practitioners should ensure that the patient is adequately monitored for potential corticosteroid side effects regardless of the duration or type of corticosteroid selected.

In addition, the guidelines suggest using corticosteroids alone for initial treatment rather than in combination with rituximab as first-line therapy.

Second-line therapy recommendations

The guidelines provide recommendations on managing adults with ITP who are corticosteroid-dependent or unresponsive to corticosteroids. Of note, corticosteroid dependence has been defined as an ongoing need for continuous prednisone at more than 5 mg/day (or corticosteroid equivalent) or as requiring frequent courses of corticosteroids to maintain a platelet count of at least 30 × 10^9/L or to avoid bleeding.

The updated guidelines are based on retrospective and indirect comparisons given the lack of prospective clinical trial data from head-to-head comparisons of second-line treatment options. Although the guidelines read as direct suggestions, in practice the recommendations for second-line therapy are based on shared decision-making after a review of risks and benefits and patient preferences.

When choosing a second-line therapy in adults with ITP lasting 3 months or longer, the guidelines suggest the following:

- Either splenectomy or a thrombopoietin-receptor agonist (TPO-RA), such as romiplostim or eltrombopag
- Rituximab rather than splenectomy
- A TPO-RA rather than rituximab.

When choosing between a TPO-RA, splenectomy, or rituximab for a second-line therapy, practitioners should use shared decision-making with the patient, taking into account

patient preferences with regard to potential complications, side effects, and treatment duration, along with the following:

- If possible, splenectomy should be avoided within the first year of ITP diagnosis, given the potential for spontaneous remission
- If durability of response is valued, TPO-RAs or splenectomy can be considered over rituximab
- If avoidance of long-term medications is valued, rituximab or splenectomy may be considered over a TPO-RA agent
- If avoidance of surgery is the goal, rituximab or a TPO-RA may be preferred, recognizing that the latter option often requires a prolonged treatment course
- Patients should have appropriate immunizations before and after splenectomy
- Practitioners should educate the patient on prompt recognition and management of fever and refer to current recommendations on pre- and post-splenectomy care
- Infections can occur after treatment with rituximab, and hepatitis testing should be done before initiating rituximab.

For the TPO-RAs eltrombopag and romiplostim, it should be noted that no clinical trials have been completed that directly compared these agents. Guidelines suggest either eltrombopag or romiplostim, noting that individual patients may place a higher value on a daily oral medication vs weekly subcutaneous injection.

Of note, these guidelines did not mention avatrombopag as an option for a second-line agent. Avatrombopag is a TPO-RA approved by the US Food and Drug Administration (FDA) in 2019 for treating thrombocytopenia in patients with chronic ITP who have had an insufficient response to previous therapy. Avatrombopag is now considered an option for second-line therapy based on its FDA approval as well as safety and efficacy data showing that it is an effective option for patients with ITP who have had insufficient response to the initial treatment regimen.

Eltrombopag is considered more cost-effective than romiplostim. Oral administration (eltrombopag and avatrombopag) vs subcutaneous injection (romiplostim) along with food interactions (with eltrombopag) should be discussed with the patient.

DO OTHER SOCIETIES AGREE OR DISAGREE?

A Joint Working Group representing several European hematological societies published guidelines in 2018.[3] Their guidelines discuss treatment of patients with platelet counts below 20×10^9/L and observation for patients with higher platelet counts. There was agreement on generally shorter duration of steroids, but no preferred steroid was recommended. The use of rituximab and TPO-RAs is suggested as rescue therapy to raise platelet counts in the setting of severe hemorrhage in patients without adequate response to steroid or IV immune globulin therapy. However, for second-line therapy, TPO-RAs are favored over rituximab or splenectomy, and rituximab is recommended as third-line therapy after failure of TPO-RAs.

A dose-tapering regimen for eltrombopag or romiplostim is suggested for patients maintaining platelet counts above 50×10^9/L for several months. The use of a recombinant thrombopoietin molecule approved in China was discussed, noting particularly that it appears to be safe for use during pregnancy. Splenectomy is reserved as a last- resort therapy for patients failing all other lines of therapy, with a recommendation to reserve it until after the first 12 months of ITP treatment. The differences in guidelines are likely in part due to cost and economics and healthcare litigation concerns in the United States.

Guidelines recommend against a long course of prednisone (> 6 weeks including taper) in favor of a shorter course

WHAT IS THE CLINICAL IMPACT?

For patients with a predictable response to rescue therapy, the updated ASH guidelines will help reduce hospital admissions for patients with asymptomatic ITP with severe thrombocytopenia. The advantages and disadvantages of available second-line therapies are briefly discussed to inform shared decision-making with patients. The guidelines stress the importance of monitoring for side effects of glucocorticoid therapy and highlight pre- and post-splenectomy vaccination care. Thus, the side effects of ITP treatment may be managed better by these guidelines. With multiple drugs approved for ITP management since the 2011 guidelines, the updated guidelines help to stratify the sequence of use of the newer drugs

to minimize cost, side effects, and long-term complications.

WHEN DO THE GUIDELINES NOT APPLY?

Although these guidelines address decision-making for patients with symptomatic ITP with severe thrombocytopenia, there is limited guidance about treating asymptomatic patients whose platelet counts are below 100×10^9/L but over 30×10^9/L. The guidelines are broadly applicable to ITP management and to most patient populations. However, the guidelines do not specifically comment on pregnant patients, management of secondary ITP, or treatment options beyond the use of TPO-RA, rituximab, or splenectomy as second-line agents. Fostamatinib, a splenic tyrosine-kinase inhibitor, is an approved ITP therapy but is not specifically discussed in these guidelines, as it has primarily been studied in the third-line setting.

CONCLUSION

The updated ASH guidelines are meant to help with clinical judgment and patient care, especially if multiple treatment options are available. Despite the guidelines, which include some direct recommendations, clinical judgment should prevail. Also, the guidelines may not always apply. For example, there is no concrete evidence that an asymptomatic patient with a normal bleeding risk and a platelet count just under 30×10^9/L will have a different meaningful outcome if treated with close observation vs corticosteroid treatment.

It is important to note that these guidelines are not exhaustive and do not serve as a substitute for discussions between providers and patients. These recommendations support shared decision-making as a method to individualize care based on the available options and patient preferences. When appropriate, clinical trial enrollment should be considered to help improve our knowledge and care of this patient population.

DISCLOSURES

Dr. DeSouza reports being an advisor or review panel participant for Sanofi. Dr. Angelini reports no relevant financial relationships which, in the context of her contributions, could be perceived as a potential conflict of interest.

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REVIEW

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Neuropsychiatric assessment and management of the ICU survivor

ABSTRACT

Any survivor among the millions of patients admitted to the intensive care unit (ICU) for critical illness each year is susceptible to persistent health problems that continue after discharge and may lead to post-intensive care syndrome (PICS), defined as new or worsening dysfunction from physical impairment, cognitive impairment, or emotional impairment, or a combination. Considering the increased rates of ICU survival and the growing elderly population more likely to utilize ICU resources, critical care practitioners have broadened their focus on outcomes and care of ICU survivors to include the acute post-ICU survival period as well as months and even years after ICU discharge. This review focuses on the neuropsychiatric aspects of PICS in ICU survivors including diagnostic, screening, and treatment recommendations. It also highlights the value of post-ICU clinics and the unique role of the consultation psychiatrist in the care of this patient population.

KEY POINTS

From 50% to 70% of the millions of patients admitted to the ICU each year will experience PICS, defined as new or worsening dysfunction in one or more of the following domains: physical impairment, cognitive impairment, and emotional impairment.

Critical care practitioners have broadened their focus of post-ICU care to include more than just the typical acute post-ICU care of 30 days after discharge.

To help navigate post-ICU care for survivors, post-ICU clinics have been developed where ICU survivors can receive outpatient follow-up care from a multidisciplinary team of providers to address their targeted needs.

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Millions of patients are admitted to the intensive care unit (ICU) annually in the United States.[1] The most frequent diagnoses associated with ICU admissions include the following:

- Respiratory failure including acute respiratory distress syndrome (ARDS)
- Acute myocardial infarction
- Cerebral infarction
- Percutaneous cardiovascular procedures
- Severe sepsis or septic shock.[1]

Considering the increased rates of ICU survival (currently 71% to 90%)[1] and the growing elderly population (20% of the global population will be over age 65 by 2050),[2] more people are likely to utilize ICU resources.

Any survivor of a critical illness and ICU stay is susceptible to health problems that continue to persist after discharge and may lead to post-intensive care syndrome (PICS). PICS was designated as a syndrome by the Society of Critical Care Medicine in 2010,[3] occurs in 50% to 70% of ICU survivors,[4] and is defined as new or worsening dysfunction in one or more of the following domains: physical impairment, cognitive impairment, and emotional impairment. We will explore each of these domains through a psychiatric lens.

As a result, critical care practitioners have broadened their focus on outcomes and care of ICU survivors to include the acute post-ICU survival period (30 days after ICU discharge) as well as the months and even years after ICU discharge. Post-ICU recovery care is even more necessary during the COVID-19 pandemic as early studies noted ICU admission rates of 32% of all COVID-19 patients,[5,6] increasing the number of ICU survivors in need of care.

This review focuses on neuropsychiatric

aspects of care of ICU survivors, particularly regarding symptoms associated with PICS including neuropsychiatric diagnostic, screening, and treatment recommendations, as well as the value of post-ICU recovery clinics.

POST-INTENSIVE CARE SYNDROME

Physical impairment

ICU-acquired weakness can be categorized as critical illness polyneuropathy, critical illness myopathy, and critical illness neuropathy and myopathy. It may affect up to half of ICU survivors admitted for 1 week or more.[1] Specifically, about two-thirds of mechanically ventilated patients, 60% of patients with adult respiratory distress syndrome, and half of patients with sepsis will experience some degree of ICU-acquired weakness.[7,8]

Several aspects of critical illness contribute to ICU-acquired weakness, from the cellular level (mitochondrial dysfunction, release of inflammatory cytokines) to systemic concerns such as inactivity and malnutrition.[2] Patients with ICU-acquired weakness who also have comorbid cognitive or emotional dysfunction may be less able to participate in physical rehabilitation and other therapies to improve weakness, thus placing them at further risk of prolonged physical weakness and highlighting the importance of targeted prevention and intervention for overall mental and physical recovery.

Post-intensive care syndrome occurs in 50% to 70% of ICU survivors and can include physical, cognitive, and emotional impairments

Other important aspects of physical morbidity are exercise limitation, fatigue, joint immobility, impairment of activities of daily living, shortness of breath, hair loss, voice changes, dysphagia, and sexual dysfunction.[9–11] All of these impairments may affect quality of life and can subsequently interfere with the mental health of ICU survivors.

Cognitive impairment

ICU survivors are at risk of acute and chronic cognitive dysfunction.[12–18] From 20% to 40% of ICU survivors experience persistent cognitive impairment, an undeniable major complication of critical illness that most commonly affects cognitive areas of executive function, attention, and memory.[12] Cognitive dysfunction in ICU survivors has been associated with decreased quality of life, even in patients who recover physically.[19] Some patients with persistent cognitive impairment are no longer able to work. Studies have shown that 30% to 38% of patients were able to return to work 3 months after ICU discharge.[13–15] At 12 months post-ICU, 42% to 58% of patients were able to return to work.[13,16–18] Depending on the severity of the cognitive impairment, patients' family members are sometimes obligated to forfeit their social and occupational roles and adopt a new role of caregiver; this can be a significant financial burden for patients and families and also has societal impact considering substantial productivity loss.[4]

Delirium. Delirium is a well-known cognitive complication of ICU admission, affecting up to 75% of ICU patients with an increased incidence in mechanically ventilated patients.[20] Pandharipande et al[20] noted a longer duration of delirium to be associated with worse global cognition and executive function at 3 and 12 months and with worsening depressive symptoms and quality of life 1 year after ICU discharge. Pathophysiologic causes of delirium include acute inflammatory responses, metabolic derangements—particularly hyperglycemia and hormonal disturbances, and toxic or medication-induced delirium from exposure to benzodiazepines, opiates, sedatives, hypnotics, steroids, and anticholinergic medications.[12]

Delirium is not always associated with persistent cognitive impairment as many patients recover cognitive function with treatment of their underlying medical conditions. However, Gunther et al linked delirium duration to brain changes in patients admitted to the ICU with respiratory failure or shock.[21] Longer delirium duration was independently associated with smaller overall brain volumes on magnetic resonance imaging (MRI) as well as smaller superior frontal lobe volumes at hospital discharge and 3-month follow-up. Significantly smaller hippocampal volumes were noted at time of discharge in patients with increased delirium duration; these differences were statistically significant, but there was not a statistically significant difference at 3-month follow-up. Serial MRI studies have shown decreased thalamic and cerebellar volumes at 3-month follow-up in patients with longer periods of hospital delirium that were associated with worse executive functioning

and visual attention impairment at 12 months post-ICU.[21]

Delirium in COVID-19 patients. Delirium has been identified in 10% to 30% of COVID-19 hospitalized patients.[22,23] The incidence of delirium that can present even in the absence of respiratory symptoms in COVID-19 ICU patients is not precisely known, but estimates range from 50% to 80%.[24,25] Furthermore, management of delirium associated with COVID-19 involves a step-based pharmacologic intervention protocol established by Massachusetts General Hospital with a graduated progression from melatonin, to alpha-2 agonists, to low-potency antipsychotics, to valproic acid and dopamine agonists.[26]

Delirium risk factors. There are several nonmodifiable pre-ICU risk factors for delirium including older age, lower level of education, pre-existing cognitive impairment, acute severity of illness, and presence of the apolipoprotein E epsilon 4 allele or major genetic risk factor for Alzheimer disease (even in the absence of major neurocognitive disorder).[12] Thus, practitioners need to identify and implement prevention strategies for potentially modifiable risk factors for delirium including sleep hygiene, frequent reorientation, assurance that sensory augmentation devices are provided (eyeglasses, hearing aids), avoidance of deliriogenic medications (narcotics, hypnotics, anticholinergics), metabolic and hemodynamic stability, and appropriate sedation weaning. Delirium prevention is reviewed later in this article including the use of the Society of Critical Care Medicine ICU Liberation Bundle (A–F).[27,28]

Emotional impairment

Up to one-third of ICU survivors may experience a range of psychiatric dysfunctions after discharge.[29] Patients with emotional impairment related to PICS are more likely to experience decreased quality of life.[29] For the purpose of this article, emotional impairment encompasses psychiatric, psychological, and mental health symptoms.

Depression. Post-ICU depression affects about 30% of ICU survivors and is associated with increased medical admissions and emergency department visits.[30] Of note, patients with post-ICU depression more often report somatic symptoms (fatigue, decreased physical energy, psychomotor slowing) rather than cognitive-affective symptoms. These symptoms can be difficult to differentiate from physical symptoms of critical illness. Somatic symptoms of depression are less likely to respond to antidepressant medications and may require more comprehensive treatment strategies.[30] The BRAIN-ICU study reported that severe depressive symptoms in the early post-ICU period (first 3 months) were likely to persist as 33% of the study population experienced at least mild depressive symptoms at 3-month follow-up that continued at 12-month follow-up.[31]

Anxiety. The prevalence of anxiety in ICU survivors is estimated to be about 70%.[4] Patients with post-ICU anxiety often have comorbid post-ICU depression or post-traumatic stress disorder (PTSD).[29] As previously noted, patients who report anxiety after ICU admission also report decreased quality of life. Many patients with post-ICU anxiety had anxiety symptoms that persisted 12 months after discharge.[29]

Post-traumatic stress disorder. PTSD prevalence after ICU care ranges from 10% to 50%.[32,33] Davydow et al[33] reported that 40% of ICU survivors developed clinically significant symptoms of avoidance and hyperarousal, occurring twice as frequently as intrusion symptoms (nightmares and flashbacks); this is crucial for accurate assessment of post-ICU trauma symptoms.[34] It is important to ask patients if they are avoiding medical appointments, taking alternate routes to avoid driving by hospitals or their doctor's office, or feeling constantly "on guard" since hospitalization. These post-ICU PTSD symptoms also lower health-related quality of life.[35]

Predictors of post-ICU PTSD include psychopathology (particularly PTSD or depression) prior to hospitalization and greater ICU benzodiazepine use.[32,33] Interestingly, there is a greater risk of PTSD symptoms with higher total benzodiazepine dose rather than prolonged benzodiazepine duration.[35] Finally, post-ICU memories of frightening or psychotic ICU experiences are risk factors.[32,33] In examining post-ICU PTSD, mechanical ventilation use or duration of use, ICU length of stay, and ICU admission diagnosis have not been

Care of ICU survivors now includes the acute post-ICU period, as well as months and even years after ICU discharge

TABLE 1

Screening instruments for post-intensive care unit cognitive impairment

Screening tool	Number of questions	Interpretation of results	Further information
Montreal Cognitive Assessment (MoCA)	30	26–30 Normal cognitive function < 26 Ninety percent sensitive for mild cognitive impairment and 100% sensitive for dementia of Alzheimer (although scores for Alzheimer disease are typically much lower) ≤ 18 Cutoff typically used for dementia of Alzheimer Note: If patient has ≤ 12 years of education, add 1 point to score	Promising, larger studies needed for validation in critical illness patients Excellent reliability independent of intensive care unit setting
MoCA-blind (MoCA without visual elements)	22	≥ 18 No cognitive impairment ≤ 17 Suggestive of cognitive impairment	Scoring is only suggestive and has not been validated
Mini-Mental State Examination	30	24–30 No cognitive impairment 18–23 Mild cognitive impairment 0–17 Severe cognitive impairment Note: Ranges may vary based on education level	Poor sensitivity in survivors of acute respiratory illness

Based on information in references 40–44.

shown to be significant risk factors. There is mixed evidence on whether delirium is a risk factor for post-ICU PTSD.[32,33]

Substance abuse. Post-ICU substance abuse has not been well studied. It is known that alcohol use disorders are independent risk factors for the development of critical illness[36] and are associated with an increased risk of mortality in critically ill patients.[37] However, there are minimal data outlining alcohol use disorders before and after ICU admission. In examining alcohol use in patients at the time of critical illness and up to 12 months after ICU discharge,[38] Davydow et al found a significant decrease in alcohol use from the period just before critical illness to 3 months after ICU discharge. This is not atypical as patients tend to make healthier lifestyle choices and avoid harmful behaviors after critical illness. However, alcohol use significantly increased from 3.8% of the study population at 3 months to 7.5% at 12 months after ICU discharge.[38] Many patients with post-ICU alcohol abuse also had unhealthy alcohol use in the year before ICU admission: 80% and 67% of patients with unhealthy alcohol use at 3-month and 12-month follow-up, respectively, exhibited unhealthy alcohol use in the year prior to ICU admission.[38]

ASSESSMENT AND SCREENING

Several screening tools are used to identify the different aspects of PICS, thereby complicating result comparisons.[39–44] Turnbull et al[39] examined 425 studies and found 250 instruments used for different measures of ICU survivorship, including physical limitations, cognitive limitations, mental health limitations, participation restrictions, and quality of life. Needham et al[40] aimed to minimize heterogeneity through the Core Outcome Measurement Set with the objective of developing a core set of measurement tools for use in all clinical research of acute respiratory failure survivors after hospital discharge (including acute respiratory distress syndrome). Although identification of these measurement tools is a significant advance in consistency

TABLE 2

Screening instruments for post-intensive care unit emotional impairment

Screening tool	Number of questions	Interpretation of results	Further information
Depression			
Hospital Anxiety and Depression Scale (HADS)	14 total, 7 focusing on depression symptoms	0–7 Normal 8–10 Borderline abnormal (borderline case) 11–21 Abnormal	Validated in ICU population
Hamilton Depression Rating Scale (HAM-D)	21 items, scoring based on first 17 items	10–13 Mild 14–17 Mild to moderate > 17 Moderate to severe	
Beck Depression Inventory-II	21 items (13-item short-form available)	0–14 Minimal 14–19 Mild 20–28 Moderate ≥ 29 Severe	
Patient Health Questionnaire–9 (PHQ-9)	9	1–4 Minimal 5–9 Mild 10–14 Moderate 15–19 Moderately severe 20–27 Severe	
Anxiety			
Hospital Anxiety and Depression Scale (HADS)	14 total, 7 focusing on depression symptoms	0–7 Normal 8–10 Borderline abnormal 11–21 Abnormal	Validated in ICU population
Hamilton Anxiety Rating Scale (HAM-A)	14	0–13 Minimal 14–17 Mild 18–24 Moderate 25–30 Severe	
Generalized Anxiety Disorder 7-item (GAD-7)	7	0–4 Minimal 5–9 Mild 10–14 Moderate 15–21 Severe	
PTSD			
Impact Event Scale-Revised (IES-R)	22	24–32 Clinical concern for PTSD 33–38 Clinical cutoff for probable PTSD diagnosis ≥ 39 Significant enough symptoms to suppress immune system (even 10 years after impact event)	Validated in ICU population
Impact Event Scale-6 (IES-6) (abbreviated IES-R)	6	Calculated as mean of 6 questions with higher scores representing more-severe PTSD symptoms	Validated in ARDS survivors[47]
Posttraumatic Symptom Scale, 10 items (PTSS-10)	10	Cutoff score ≥ 35 predicts PTSD (PTSS-High)	Validated in ICU population Good reliability Detects PTSD symptoms but does not diagnose PTSD
PTSD Checklist for DSM-5 (PCL-5)	20	Total score of 31–33 or higher suggests patient may benefit from PTSD treatment	
Abbreviated Posttraumatic Checklist (PCL-C)	6	≥ 14 suggestive of difficulties with posttraumatic stress	

ARDS = acute respiratory distress syndrome; DSM = Diagnostic and Statistical Manual of Mental Disorders; ICU = intensive care unit; PTSD = posttraumatic stress disorder

Based on information in references 5, 40, and 45–47.

TABLE 3

The ICU Liberation Bundle (A–F)

A: Assessment, prevention, and management of pain

B: Both spontaneous breathing trials and spontaneous awakening trials

C: Choice of analgesia and sedation

D: Delirium: assessment, prevention, and management

E: Early mobilization and exercise

F: Family engagement and empowerment

Adapted from information in references 27, 28, and 48.

in clinical research of symptoms of critically ill patients who have been discharged, caution should be used when implementing these tools in the general ICU survivor population as the study focused only on patients with acute respiratory failure.

Screening tools

Table 1[40–44] presents screening tools most commonly used for cognitive impairment in PICS patients. Needham et al[40] noted that for the "cognitive" outcome group in acute respiratory failure survivors, no instrument reached a priori for consensus; however, the highest rated tool was the Montreal Cognitive Assessment (MoCA-Blind), used to screen patients for neurocognitive symptoms in the post-ICU period. It has been shown to be a reliable screening tool independent of being used for patients who were hospitalized or in the ICU.[41] MoCA-Blind uses a cutoff score of 26 to differentiate between normal cognitive function and cognitive impairment; these cutoffs have been found to differ based on patient race and ethnicity.[42] It has been recommended to use the traditional MoCA-Blind, excluding the areas with visual elements (visuospatial, executive functioning, and naming portions) to facilitate administering the instrument by phone if needed. The Mini-Mental State Examination (MMSE) has been shown to be a poor measure of cognitive deficits in survivors of acute respiratory failure[43] and may underestimate the degree of cognitive impairment compared with other assessment tools that focus on specific cognitive domains.[44]

PTSD prevalence after ICU care ranges from 10% to 50%

Table 2[5,40,45–47] lists commonly used tools for measuring post-ICU emotional dysfunction, including the Hospital Anxiety and Depression Scale (HADS) for detection of anxiety and depression symptoms[45] and the Impact Event Scale-Revised (IES-R)[46] for assessment of PTSD symptoms. Both the HADS and IES-R have been recommended as core outcome measurement sets by Needham et al.[40] From a psychiatric perspective, the Patient Health Questionnaire-9 (PHQ-9) is used to screen for depression while the Generalized Anxiety Disorder-7 (GAD-7) is used to screen for anxiety, and the Impact Event Scale-Revised (IES-R) is used to screen for PTSD.

INTERVENTIONS

There are several intervention strategies for management of cognitive and emotional disturbances. While some treatments are for specific post-ICU impairments, many are useful in managing symptoms spanning multiple domains of PICS. Many critical care units have adopted the ICU Liberation Bundle (**Table 3**) to prevent delirium, prolonged cognitive impairment, and significant post-ICU psychiatric symptoms.[27,28,48] For example, dexmedetomidine has been associated with a lower incidence of delirium compared with other analgesia and sedative agents.[49]

COGNITIVE REHABILITATION

Prolonged post-ICU cognitive impairment may warrant further investigation. Physical, cognitive, and vocational rehabilitation have been studied in patients with ongoing cognitive dysfunction.[31,49,50] In the Returning to Everyday Tasks Utilizing Rehabilitation Networks study,[50] cognitive rehabilitation was delivered in the patient's home once every 2 weeks over a 12-week study period. ICU survivors suffering from post-ICU cognitive impairment who received post-discharge cognitive rehabilitation in addition to "usual" post-discharge care (physical rehabilitation, occupational rehabilitation, nursing care) showed improvement in cognitive function at 3-month follow-up compared with patients who did not undergo cognitive rehabilitation.[50] Given variability of cognitive interventions and studied populations, evidence-based

recommendations for clinical practice are difficult to determine. There are promising data for the role of aerobic exercise in improving post-ICU cognitive function,[12] and neurocognitive testing has been employed for patients with prolonged cognitive impairment.[51] However, barriers to assessing cognitive function and thereby providing care to this population include social stigmatization and financial strain, loss of patients to follow-up, and patient frustration over testing performance.[51] Of note, there are limited data on the role of these strategies in preventing prolonged cognitive impairment in critical care patients.

MEDICATIONS

Few studies have investigated pharmacologic treatments for cognitive impairment in ICU survivors specifically. Current strategies are from studies of cognitive impairment treatment in patients with traumatic brain injury. Methylphenidate and donepezil have been studied in the traumatic brain injury population and were associated with improvement in memory and attention.[52–54] Although these strategies may be considered for ICU survivors with cognitive impairment, they should be implemented cautiously as further investigation is warranted for the critical care population specifically.[49] Rosuvastatin was studied in the prevention of delirium and cognitive impairment in ICU patients but was not found to have significant benefit in prevention.[55]

PSYCHOTHERAPY

Psychotherapy may be beneficial for psychiatric symptom management in ICU survivors. The patient's presenting psychiatric symptoms may guide the type of therapy recommended. For example, some patients with mild depression, anxiety, or PTSD symptoms may benefit from supportive therapy. Moderate to severe mood and anxiety symptoms may respond more appropriately to cognitive behavioral therapy, while patients with more advanced trauma symptoms may benefit from trauma-based therapy, including but not limited to eye-movement desensitization and reprocessing, a form of psychotherapy that allows patients to access and process traumatic memories through simultaneous focus on external stimuli such as eye movement. Haerizadeh et al reviewed psychological treatment modalities for PTSD in medically ill patients.[56] Although limited data were available, 2 of the included trials showed exposure-based cognitive behavioral therapy resulted in a lower incidence of PTSD symptoms compared with control groups. And 3 trials included found eye-movement desensitization and reprocessing to be more effective in reducing PTSD symptoms than relaxation therapy, imaginal exposure, and conventional cognitive behavioral therapy.[56]

Patients with more severe psychiatric symptoms may warrant pharmacologic management. There is a lack of literature analyzing pharmacologic treatment for depression, anxiety, and PTSD in ICU survivors. It is important to note that ICU survivors warrant ongoing monitoring by a primary care provider or mental health clinician as they may be more sensitive to medication side effects given their underlying medical comorbidities and potential risk of drug interactions with other medications.

ICU DIARIES

Post-ICU recovery clinics provide targeted outpatient follow-up care

ICU diaries are used to fill memory gaps for ICU survivors and provide an understanding of ICU events in a chronologic or narrative account.[57] The diaries are often completed by ICU staff including physicians, advanced practice providers, nurses, consultants, and other providers involved in ICU patient care (eg, physical therapists, occupational therapists, music therapists, art therapists). Families may also participate in construction and completion of the ICU diaries.

ICU diaries have been increasingly used as a management strategy for emotional disturbances of PICS in ICU survivors. Data analyzing effects of ICU diaries on psychiatric symptoms in ICU survivors have been mixed. Barreto et al[57] found that the use of ICU diaries was associated with decreased rates of depressive symptoms and depression diagnoses, mostly beneficial in ameliorating anxiety symptoms, but did not significantly improve PTSD symptoms. Garrouste-Orgeas et al [58] found no statistically significant benefit in reduction of PTSD symptoms from use of

Figure 1. The multidisciplinary team approach used in the Cleveland Clinic Post-ICU Recovery Clinic (PIRC).

Neuropsychiatric symptoms are prevalent and at times disabling in ICU survivors

ICU diaries in mechanically-ventilated ICU patients at 3-month follow-up.[58]

Of note, there is no universal template for ICU diaries. This unstructured document is used by the patient and, after discharge, also by the family if the patient so chooses.

THE ROLE OF POST-ICU RECOVERY CLINICS

PICS symptoms after ICU stays led to a re-evaluation of methods of care. Traditionally, within 1 month of hospital discharge, ICU survivors would have a brief follow-up visit with their primary care provider to address the complexities of a potentially extended critical care hospitalization. However, the time constraints of a brief office visit increased the risk that the patient's complex post-discharge needs would be suboptimally addressed.

Recognizing these issues, critical care providers have developed post-ICU recovery clinics where ICU survivors can receive outpatient follow-up care targeted to their needs. These clinics are composed of multidisciplinary teams usually including but not limited to critical care specialists, physical therapists, case managers, social workers, respiratory therapists, pharmacists, and mental healthcare professionals such as psychiatrists and psychologists.

Reported outcomes of post-ICU clinics have been positive overall in improving depression, anxiety, and PTSD symptoms.[59,60] Also, qualitative outcomes have revealed positive results for patients and families, who reported higher levels of satisfaction from involvement in these clinics.[60]

The Post-ICU Recovery Clinic (PIRC) at Cleveland Clinic (**Figure 1**) involves an ICU physician, ICU advanced practice provider, pharmacist, physical therapist, respiratory therapist, and mental health providers. Patients are triaged as they are discharged from the ICU based on inclusion and exclusion criteria found in **Table 4.** The patients that meet inclusion criteria are tracked while on the regular nursing floor to capture discharge disposition; patients discharged to skilled nursing facilities are not eligible for the clinic. The PIRC project manager consults with the patient to discuss PICS and the PIRC. If the patient voices interest, a post-discharge PIRC visit is scheduled. The goal is to see patients in the clinic within 4 weeks after hospital discharge.

During the post-discharge PIRC visit, several screening tools (**Tables 1 and 2**) are used to determine the patient's level of physical, cognitive, and emotional impairment. Based on the patient's symptom severity on screening tools and during personal interviews, a referral may be made to a clinical psychologist for psychotherapy or to a consultation psychiatrist for medication management. If patients show cognitive impairment based on screening or are reporting significant cognitive dysfunction compared with their pre-ICU baseline, a referral is made to neuropsychiatry for further symptom management.

IMPORTANT CHANGES TO MEET A PRESSING NEED

Neuropsychiatric symptoms are prevalent and at times disabling in ICU survivors. Previously, survivors have been at increased risk of psychiatric symptoms going undetected owing to limitations in post-discharge follow-up, mental health stigma, and limitations in financial

TABLE 4

Cleveland Clinic Post-ICU Recovery Clinic: Inclusion and exclusion criteria

Inclusion criteria	Shock (requiring vasopressor support)
	Acute respiratory distress syndrome
	Mechanical ventilation ≥ 3 days
	Prolonged intensive care unit (ICU) stay (≥ 7 days)
	Delirium present during intensive care unit stay
	Cardiac arrest
	COVID-19 with intensive care unit stay > 48 hours
Exclusion criteria	Hospice care
	Discharged to skilled nursing facility
	Significant cognitive impairment
	Long-term mechanical ventilation before intensive care unit admission (eg, for chronic respiratory failure)

and social circumstances due in part to acute and chronic medical conditions. ICU survivor neuropsychiatry is an emerging field that continues to be evaluated and is even more pressing in the COVID-19 era.

Clinicians seeing patients in the ICU and in the outpatient setting should be knowledgeable about the potential for PICS and appropriate screening tools for patient monitoring. Even with advances made in identifying screening tools in ICU respiratory survivors, further studies are warranted to evaluate these and other assessments for neuropsychiatric symptoms of PICS across various diagnoses and conditions in ICU survivors.

Another area of continuing research is that of the post-ICU clinic in investigation of long-term outcomes of PICS, including long-term prevalence of neuropsychiatric symptoms, treatment strategies, mortality rates, readmission rates, financial impact for the healthcare system, and patient and caregiver satisfaction. These clinics allow for collaborative care not only in the areas covered in the Cleveland Clinic PIRC but also with geriatric medicine, otorhinolaryngology, endocrinology, nutrition, psychology, neuropsychiatry, and neuropsychology. Establishment of the post-ICU clinics allows clinicians and researchers to further investigate treatment modalities and prevention strategies and to improve care for ICU survivors.

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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Chronic venous outflow obstruction: An important cause of chronic venous disease

ABSTRACT

Chronic venous outflow obstruction is a significant cause of chronic venous disease and therefore chronic morbidity. When conservative measures fail, intervention through deep venous reconstructive techniques should be considered. Referral should be considered in all patients with features of chronic venous disease that are life-affecting. Imaging relies primarily on duplex ultrasonography, supplemented by computed tomographic and magnetic resonance venography, and intraoperatively by intravascular ultrasonography. Intervention is primary endovenous, using angioplasty and stenting. Open surgical procedures are used in very select patients.

KEY POINTS

Chronic venous disease is common and costly in terms of physical discomfort and quality of life.

Chronic venous outflow obstruction is an important cause of chronic venous disease.

Although invasive and costly, intravascular ultrasonography is the gold standard for detection.

Early treatment including anticoagulation and other preventive measures reduces the likelihood of recurrent deep vein thrombosis.

Referral to a vascular specialist center with experience of deep venous reconstruction is recommended.

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Recent advances in imaging and stent technology are changing the management of chronic venous outflow obstruction (CVOO), an important cause of chronic venous disease (CVD). Evidence increasingly supports endovascular intervention as a potentially effective and safe treatment option.

This article reviews the key factors to consider in management of CVOO and advises on how best to get patients the care they need.

CHALLENGES: QUALITY OF LIFE, TREATMENT OPTIONS

CVOO negatively affects quality of life and mental health. The presentation of CVOO can be similar to that of superficial venous incompetence, but proximal edema tends to be more significant in CVOO. Common manifestations include leg-swelling and pain, limited mobility, chronic ulceration, and venous claudication. Neglen[1] and Raju[2] estimated that such lesions occurred in up to 55% of patients with significant CVD, especially in those with postthrombotic syndrome (PTS). Recent reports suggest that CVOO may also contribute to chronic pelvic pain, including pelvic congestion syndrome,[3] although this observation remains controversial and requires further study.

Consequently, patients are subjected to long-term pain and discomfort, the need for chronic leg ulcer management, and reduced physical activity.[4] Healthcare systems therefore allocate significant resources for the treatment of CVOO and related CVD.[5]

Although endovenous and open surgical

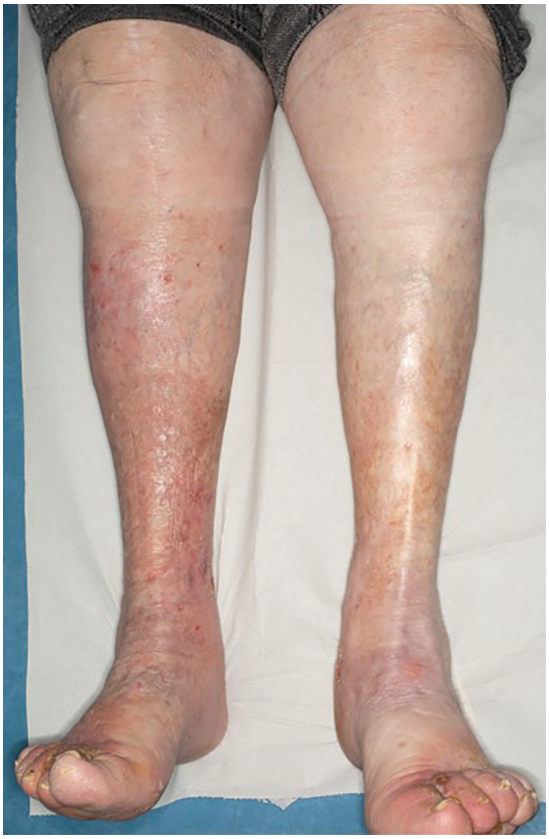

Figure 1. Venous eczema associated with chronic venous insufficiency of the lower limbs. The condition is worse on the right leg.

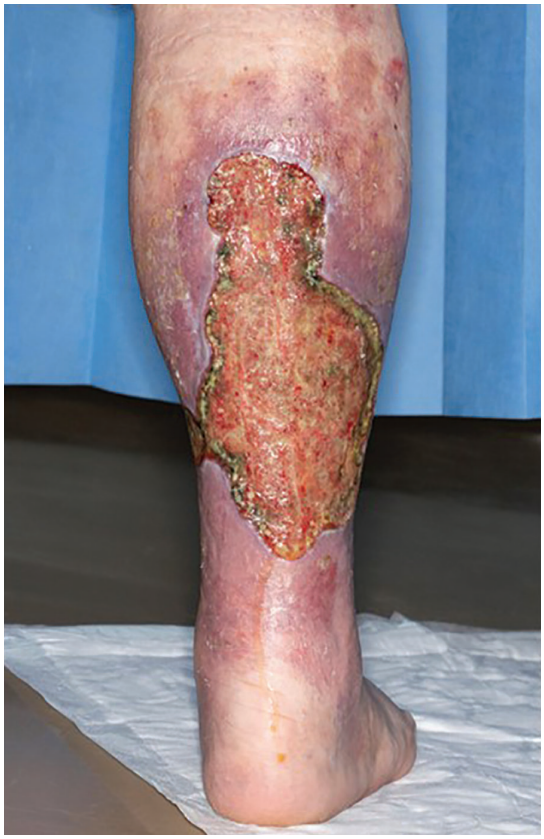

Figure 2. Severe venous ulceration associated with chronic venous insufficiency. Venous ulceration typically occurs in the ankle (gaiter) with surrounding skin changes such as venous eczema (purplish discoloration around the ulcer) and lipodermatosclerosis as well as edema. No clinical feature of the ulcer indicates that chronic venous outflow obstruction (CVOO) is the cause, but the severity of the disease is often worse with CVOO than with superficial venous incompetence, although not exclusive.

interventions are effective and safe treatments for superficial venous incompetence, mainstay management for CVOO until recently has been limited to compression therapy and supportive measures such as lifestyle changes. These nonsurgical measures are often unsatisfactory to patients as well as clinicians. Open deep venous reconstructive surgery also has limitations: it is invasive, evidence is insufficient to support the benefits, and its use is limited to a very select group of patients and surgeons.[6] Endovascular intervention is a promising option.

Terminology

The definition of CVD is wide-ranging and patient-specific, often characterized by manifestations of chronic venous hypertension. Symptoms and signs include varicose veins, telangiectasias, pain and discomfort, cramps, restless legs, itching, heaviness, and edema. Skin changes can include venous eczema, lipodermatosclerosis, and ulceration (**Figures 1 and 2**), and explain why patients may consult or be referred to dermatologists instead of vascular specialists. CVOO often refers to long-standing stenotic and occlusive disease of the central veins, ie, iliofemoral veins or inferior vena cava (IVC) for the lower limbs, or both.

Patients may experience long-term pain and discomfort

WHAT CAUSES CVOO?

CVOO can be thrombotic or nonthrombotic in origin.

Thrombotic CVOO is a long-term com-

TABLE 1

Evaluating the severity of postthrombotic syndrome (PTS): The Villalta-Prandoni scale

	No PTS	Mild	Moderate	Severe
Symptoms				
Pain	0	1	2	3
Cramps	0	1	2	3
Heaviness	0	1	2	3
Paresthesia	0	1	2	3
Pruritus	0	1	2	3
Clinical signs				
Pretibial edema	0	1	2	3
Skin induration	0	1	2	3
Hyperpigmentation	0	1	2	3
Redness	0	1	2	3
Venous ectasia	0	1	2	3
Pain on calf compression	0	1	2	3
Venous ulcer	Absent			Present
Severity score				
None < 5				
Mild 5–9				
Moderate 10–14				
Severe > 14, with or without venous ulcer				

Based on information in reference 8.

plication of deep vein thrombosis (DVT) involving the central veins, causing chronic occlusion or incomplete recanalization (stenosis), or both. There are varying degrees of collateral vein formation. The DVT can be associated with an underlying extrinsic compression, which can be malignant or benign.

Nonthrombotic obstruction also can occur, either benign or malignant. Benign lesions include nonthrombotic iliac vein lesions (NIVLs), uterine fibroids, and retroperitoneal fibrosis.

Recruitment of collateral veins to bypass an obstruction is often inadequate, partly due to their much smaller cross-sectional areas compared with the central veins. According to Poiseuille's law, volumetric flow rate is related to the fourth power of the vessel radius. Therefore, CVOO causes reduced venous return from the lower limbs, which leads to repeated and long-standing venous stasis and pooling. As a result, chronic venous hypertension develops in the affected lower limb. This is thought to trigger inflammatory processes that affect the microcirculation, ultimately manifesting as CVD.

At the microvascular level, chronically elevated venous pressure leads to capillary fluid leak, basal membrane degeneration, inflammatory infiltrates, and a negative cycle of tissue degeneration and scarring. Poorly healing ulcers develop and can become chronically infected, leading to significant morbidity.

Postthrombotic syndrome

PTS is chronic venous disease that can occur in up to 50% of patients in the 2 years after DVT.[7] It is a consequence of venous obstruction or valvular damage. Either or both can result from chronic inflammatory processes and inadequate venous recanalization following a DVT.

Several diagnostic and severity scales such as the Villalta-Prandoni scale (**Table 1**)[8] are available to help diagnose and evaluate the severity of PTS. Venous ulcers can develop in up to 10% of patients in the 2 years following DVT.[9] The severity of disease often correlates with the proximity of the DVT. For example, disease is worse in iliocaval and iliofemoral DVT than in femoropopliteal and calf DVT. Adequacy of immediate management is also a factor.[5]

Nonthrombotic iliac vein lesions

Nonthrombotic iliac vein lesion (NIVL) refers to extrinsic compression of the iliac vein. Up to 66% of the general population may have an asymptomatic NIVL,[10] so a careful workup is needed to identify NIVL as the cause of disease. May-Thurner syndrome (also known as Cockett syndrome or iliac vein compression syndrome) is compression of the left common iliac vein at the site where it is crossed by the right common iliac artery.[11] In some patients, the close, persistent pulsing of the right common iliac artery causes chronic extrinsic compression of the left common iliac vein with intimal scarring and fibrosis. Similar variants can occur in all parts of a left or right iliac

TABLE 2

Clinical features of chronic venous outflow obstruction

Swelling affecting the whole leg, including the pelvis, groin, and hip
Venous claudication, often described as pain and heaviness of the whole leg that may be associated with shortness of breath and tiredness on walking due to reduced venous return
Persistent features of chronic venous insufficiency such as nonhealing venous ulcers despite adequate treatment, or absence of superficial and deep venous incompetence
History of venous thromboembolism, central venous catheterization, abdominal or pelvic surgery, and recreational intravenous drug use
The presence of dilated collateral veins in the groin, genitalia, abdomen, and pelvis

vein. Stenosis exceeding 50%, especially with surrounding fibrotic scarring and significant features of CVD, may benefit from intervention.[12] Up to 24% of the general population may demonstrate this potentially symptomatic variant with fibrotic scarring, yet only a small number develop this condition.[10]

Other causes

Benign and malignant lesions from an adjacent lymphadenopathy, uterine fibroids and cysts, or abdominal and pelvic cancers can lead to CVOO. Associated radiotherapy, central venous cannulation, trauma, and surgical treatment also may be implicated. Retroperitoneal fibrosis is treated pharmacologically, but endovenous intervention has been described for persistent venous symptoms.[13] Congenital absences of deep veins such as inferior vena cava atresia and those associated with Klippel-Trenaunay syndromes are rare.[14]

THE INITIAL ASSESSMENT

The initial assessment for patients with CVOO is the same as for CVD. The patient's symptoms and signs, associated with prolonged standing, worsen as the day progresses. Edema, skin changes, and ulceration tend to occur at the ankle where the venous pressure is at its highest in the blood column.

Even though no manifestations clearly point to CVOO as the cause of the patient's CVD, several clinical features listed in **Table 2** may increase clinical suspicion. Delis and colleagues reported[15] that 43.6% of patients with prior iliofemoral DVT developed venous claudication during follow-up. Differential diagnoses include ankle-swelling secondary to cardiac, hepatic, or renal failure; skin infection; arterial, neuropathic, and diabetic ulcers; pelvic venous reflux; lymphedema; and malignancy. Detailed assessment of thrombotic risk factors for patients with a history of venous thromboembolism is essential.

IMAGING: STRENGTHS AND LIMITATIONS

Duplex ultrasonography

Endovascular intervention is a promising option

Duplex ultrasonography is the first-line investigation for CVD of the lower limb, used to detect incompetence and obstruction of superficial and deep veins. It is noninvasive and economical and uses no ionizing radiation.

When CVOO is suspected, imaging of all the deep veins, including the iliac veins and inferior vena cava, is important. Imaging should demonstrate the presence of obstruction or significant reflux, or both. The presence of phasic flow in the common femoral vein may indicate that there is no significant CVOO.[16] Phasic flow refers to the normal pulsation of the venous flow, reflecting the cardiorespiratory cycle. Significant CVOO can interrupt the continuity of the blood column. Transvaginal duplex ultrasonography can help diagnose or rule out pelvic venous reflux.

Despite its first-line role, duplex ultrasonography has relatively low sensitivity (67%) and specificity (70%).[17] Among its limitations, duplex ultrasonography may provide an inadequate view of the iliac veins in approximately 20% of cases,.[18] Views may also

be inadequate in patients who have obesity or bowel gas,[18] and operator skills and interoperator variability may affect the results.

Magnetic resonance and computed tomographic venography

Magnetic resonance venography and computed tomographic venography help to define the anatomy of the abdominal and pelvic veins and surrounding structures and assess for venous obstruction and dilation, and the presence of collateral veins. In CVOO, these imaging options help confirm the diagnosis and plan treatment,[18] but neither technique is ideal. Nephrotoxic contrast is used in computed tomographic venography and contrast-enhanced magnetic resonance venography. Magnetic resonance venography protocols such as time-of-flight techniques and balanced steady-state free precession[19] do not use contrast.

Computed tomographic venography also exposes patients to ionizing radiation. In a retrospective study, researchers found NIVL on conventional venography in 30.6% of patients with unexplained lower limb swelling and pain who had undergone nondiagnostic duplex ultrasonography, magnetic resonance venography, and computed tomographic venography.[16] Magnetic resonance venography and computed tomographic venography are highly sensitive and specific for the diagnosis of iliocaval and iliofemoral DVT, but sensitivity appears to diminish in identifying CVOO.[20,21]

Venous ulcers can develop in up to 10% of patients in the 2 years after DVT

Ascending contrast venography

Ascending contrast venography, historically the mainstay technique for the diagnosis of CVOO, has been superseded by noninvasive duplex ultrasonography and computed tomographic and magnetic resonance venography. Contrast venography is now usually used in interventional procedures. The sensitivity of single-plane venography in detecting venous stenosis greater than 70% is reportedly only 45% despite the use of multiple views.[22] Besides being invasive, ascending contrast venography is also limited by the use of nephrotoxic contrast and radiation.

Intravascular ultrasonography

Intravascular ultrasonography is regarded by many as the gold standard for the detection of CVOO. The technique, which uses an ultrasound probe at the tip of a catheter, delineates intravenous lesions better than other venographic techniques,[22] especially if there are intraluminal webs that would not otherwise be visible. In the Venogram vs IVUS for Diagnosing Iliac vein Obstruction (VIDIO) trial, intravascular ultrasonography identified significant lesions not detected by 3-view venography in 26.3% of patients.[23] The findings led to a revision of treatment plans in 72% of cases.[23] Further, clinical improvement after stenting was best predicted by the stenotic area measured at baseline by intravascular ultrasonography, with 54% estimated as the optimal stenosis threshold for interventional treatment.[24]

Other important roles of intravascular ultrasonography include treatment planning, sizing and placement of stents, and detection of in-stent restenosis.[21,22] However, it is invasive and costly.

MANAGEMENT STRATEGIES

The objective of treating CVOO is to reduce the risk of PTS and can range from compression therapy to surgical revascularization. Whatever treatment strategy is indicated, close follow-up is part of the management plan.

First steps

Early and adequate administration of therapeutic anticoagulation and adherence to therapy after an episode of acute DVT are associated with a decreased incidence of PTS.[25] Other preventive measures, although not proven, include wearing compression hosiery[26] and walking and exercising as soon and as much as the patient is able.[25] These measures reduce the propagation of thrombus and recurrence of DVT, and they improve recanalization of the obstructed veins, reducing the risk and severity of PTS.[25,26]

Early thrombolysis

Early removal of thrombus in DVT re-establishes patency and reduces inflammatory processes caused by the heavy thrombus load that can lead to valvular damage and vein-wall fibrosis. Theoretically, this reduces the risk of PTS.

For iliofemoral DVT, there is conflicting evidence to support catheter-directed or pharmacomechanical thrombolysis in appropriate patients. These strategies are associated with a reduced risk of developing severe PTS but an increased risk of bleeding.[27,28] Systemic thrombolysis is rarely used. Widely recognized guidelines, including those from the National Institute for Health and Care Excellence (NICE),[29] the European Society for Vascular Surgery,[30] the Society for Vascular Surgery, and the American Venous Forum,[31] recommend consideration of early endovascular removal of thrombus for selected patients with iliofemoral DVT. The patient criteria for thrombolysis of acute iliofemoral DVT recommended by NICE, and similar to other organizations' guidelines, are:

- Symptoms lasting less than 14 days
- Good functional status
- A life expectancy of 1 year or more
- A low risk of bleeding.

After clearance of thrombus, diagnostic venography and intravascular ultrasonography can be performed to assess for an underlying lesion. If an underlying lesion is found, balloon angioplasty with potential stenting can decrease the risk of reocclusion and the development of CVOO.

Conservative measures

A large, randomized control trial demonstrated no superiority of compression therapy over no compression therapy.[32] Nevertheless, graduated compression therapy remains standard practice for the treatment for CVD and CVOO. Graduated compression stockings improve venous return and microcirculation by increasing the efficiency of venous flow and emptying of the lower limb through external pressure.[33] Multilayered compression bandaging may be required to aid ulcer healing. Patients should be counseled to remain mobile, exercise, elevate their legs at rest, and lose weight. Prolonged standing increases columnar venous pressure and should be avoided. Some patients may need to consider significant lifestyle changes, including occupational adjustments or even a change of jobs.

Next step: Endovenous intervention

If conservative measures do not relieve the patient's symptoms, then endovenous intervention (**Figure 3**) should be considered before open surgical revascularization. Shared decision-making with the patient includes discussion of the benefits and risks of intervention compared with no intervention, the need for long-term surveillance, potential secondary interventions, and the importance of adher-

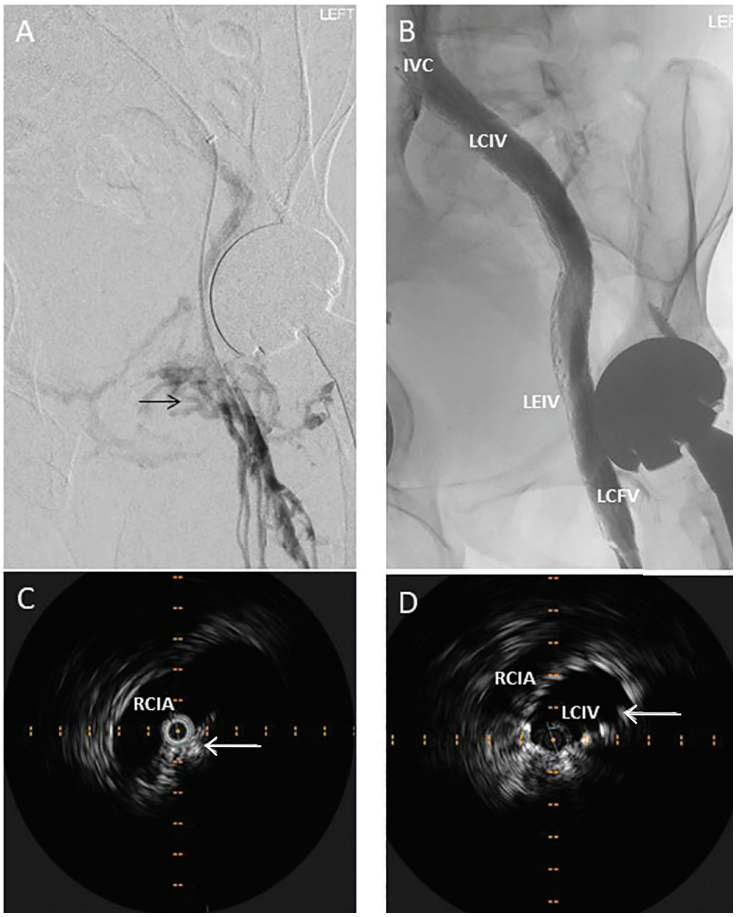

Figure 3. Contrast venography and intravascular ultrasonography of a 44-year-old man with obstructed left iliofemoral vein secondary to postthrombotic syndrome just before and after stenting. (A) Prestenting contrast venography shows complete obstruction of the left iliofemoral vein. The venous return of the left leg is through collateral veins (black arrow). (B) Poststenting contrast venography shows patent left iliofemoral vein following balloon angioplasty and stent placement with disappearance of the collateral veins. (C) Prestenting intravascular ultrasonography of the left common iliac vein shows that the vein (white arrow) is obstructed and compressed by the right common iliac artery (RCIA). (D) Poststenting intravascular ultrasonography of the left common iliac vein (LCIV) at the same level as in C shows the lumen of the vein is patent and maintained by the stent (white arrow). (IVC = inferior vena cava; LCFV = left common femoral vein; LEIV = left external iliac vein)

ence—possibly long-term—to a period of anticoagulation therapy. Endovenous stenting has been used in a significant number of cases only in the last 5 to 10 years, so long-term surveillance and outcome data are lacking. Nevertheless, stenting is an essential step, as balloon angioplasty alone disrupts the fibrotic tissues of the obstruction but is insufficient to maintain luminal patency.[34]

Growing evidence from nonrandomized clinical trials, including controlled prospective interventional studies and registries, supports the clinical efficacy and safety of endovenous intervention for CVOO. A double-blind randomized clinical trial compared medical treatment vs iliac vein stenting in 207 CVD patients with a median follow-up of about a year.[35] Endovascular treatment was safe and beneficial for symptom relief and quality of life.[35] For example, recanalization of the CVOO with stents achieved significant improvement in pain and swelling, venous ulcer healing rate, disease severity scores (such as the Venous Clinical Severity Score and Venous Disability Score), and health-related quality-of-life measures.

Up to 66% of the population may have an asymptomatic NIVL

A recent meta-analysis of 16 single-arm observational studies of endovenous stenting included 1,688 patients, 70.5% with PTS and the rest with NIVLs.[36] The reported primary patency ranged from 59% to 94%, and secondary patency ranged from 87% to 100%.[36] Encouraging data are also emerging for the long-term patency rate of endovenous stenting of CVOO.[37] Further, major societies and organizations support its use. The Cardiovascular and Interventional Radiological Society of Europe, the Society for Vascular Surgery, and the American Venous Forum recommend endovenous stenting for severe CVOO.[38,39] The American Heart Association[40] assigned a class IIb recommendation with evidence level B to endovenous stenting for CVOO, while the European Society for Vascular Surgery recommendation is class IIa with evidence level C.[41]

When to consider surgery

Open surgical bypass and reconstruction of deep veins are invasive procedures with significant morbidity risks, highly varied patency rates, and limited evidence.[42] Open surgical revascularization of CVOO should be considered only as a last resort in highly selected patients whose CVD symptoms remain severe despite conservative measures and endovascular intervention.

Follow-up and antithrombotic strategies

Poststenting surveillance is vital to ensure that significant in-stent restenosis and thrombosis are detected and treated early, while optimal antithrombotic therapy is continued to prevent or reduce these risks. Poststenting surveillance and antithrombosis are often based on society guidelines, consensus statements, local multidisciplinary teams, and the individual clinician's preference and experience. Seshadri Raju, MD,[43] a pioneer in iliofemoral stenting, suggests surveillance with duplex ultrasonography the day after the procedure, and again at 4 weeks, 3 months, and yearly thereafter. A recent multidisciplinary consensus acknowledged highly varied practices across institutions, but recommended intensive follow-up duplex ultrasonography in the first 6 months after endovenous stent placement: ie, at 2 weeks, 6 weeks, 3 months, 6 months, and annually thereafter, especially in the case of thrombotic lesions.[12]

NIVLs may require less-intense surveillance if early in-stent complications are not present. Most clinicians consider reintervention if in-stent restenosis occurs in more than 50% of the luminal area or if CVD symptoms deteriorate.

Like many other clinicians, we use therapeutic-dose low-molecular-weight heparin for the first 2 to 6 weeks after stenting. We then convert to a direct oral anticoagulant if surveillance duplex ultrasonography shows no significant in-stent restenosis and the patient's symptoms improve. Some clinicians may use antiplatelets alone for NIVLs. Longer-term antithrombotic strategies—varying in type, intensity, and duration—often depend on the patient's risk of venous thromboembolism. Overall, the intensity and duration of poststenting antithrombotic therapy is decreased for NIVL over PTS. In complex PTS cases, a multidisciplinary approach, including a hematology consult, is essential.

REFERRAL AND INTERVENTION

Patients seek medical attention for CVD through varying routes and with various care-

givers. They may consult first with primary care physicians and nurse practitioners who refer them to vascular specialists, dermatologists, and plastic surgeons. Some patients who develop PTS are already being followed for DVT by a vascular or hematologic clinician. Many clinics that specialize in leg ulcers are managed by nurses or allied healthcare professionals. For many patients with PTS, the index event was likely unrecognized by the patient or clinician, or was treated and the patient was then lost to follow-up. We are all aware of patients who present for the first time with CVD-associated skin changes and ulceration. In some instances, superficial venous incompetence is assessed and treated ahead of or simultaneously with CVOO management.

Although no clear evidence supports strict criteria for pursuing advanced imaging and referral for consideration of intervention,[10] it is generally recommended that patient selection for intervention consider severity of symptoms, failure of conservative measures, superficial venous reflux therapy, and episodes of recurrence, as well as age and general frailty. While there is no evidence that duration of the ulcer or severity of symptoms determines likelihood of successful intervention to relieve CVOO, we believe that patients with the most severe symptoms are likely to achieve the most clinical benefit.

TAKE-HOME MESSAGES

CVOO, especially secondary to NIVLs and PTS, is increasingly recognized as an important cause of CVD. Growing evidence shows that endovascular intervention for CVOO is effective and safe. It achieves acceptable patency rates in many patients with severe CVD when conservative measures and treatment of superficial venous incompetence alone fail to relieve symptoms.

Patients with CVD—particularly those whose symptoms of CVD are inadequately relieved by conservative measures and treatment of superficial venous incompetence resistant to initial intervention—should be referred to a vascular center with experience in deep venous intervention for assessment and management of CVOO.

DISCLOSURES

Dr. Chung Sim Lim has disclosed receiving speaker fees from Boston Scientific. Dr. Harris 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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REVIEW

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Changing US trends in contraceptive choices

ABSTRACT

Long-acting reversible contraceptives (ie, intrauterine devices and the etonogestrel subdermal implant) have become increasingly popular methods of contraception because of their convenience and safety profile. At the same time, the use of depot medroxyprogesterone acetate, one of the most prescribed contraceptives in the United States since its approval in 1992, is on the wane. The history and pros and cons of these contraceptive methods are reviewed.

KEY POINTS

Depot medroxyprogesterone acetate (DMPA) must be administered by intramuscular injection (at a clinic) or subcutaneously (by the user) every 12 to 14 weeks.

Disadvantages to using DMPA include abnormal bleeding, weight gain, bone mineral density reduction, possible increased susceptibility to sexually transmitted infections, and ovulation delay after stopping use.

DMPA use has one of the highest discontinuation rates among all users of contraceptives.

Intrauterine devices (IUDs) (copper and levonorgestrel) are safe to use for nulliparity, pelvic inflammatory disease, heavy bleeding, and contraindications for estrogen therapy.

Contraindications for levonorgestrel IUDs include history of breast cancer, untreated cervical cancer, Müllerian anomalies, and gestational trophoblastic disease.

Over the past few decades, trends in the choice of contraceptive method have changed due to convenience, individual patient lifestyle, and adverse-effect profiles. Counseling patients on their best options can improve adherence and improve rates of unintended pregnancy.

This article examines the changing trends and reviews appropriate use of depot medroxyprogesterone acetate (17-acetoxy 6-methyl progestin; DMPA) and long-acting, reversible contraceptives (LARCs).

DMPA: A LONG-ACTING, REVERSIBLE CONTRACEPTIVE

DMPA is a long-acting, reversible progestational contraceptive without any estrogenic or androgenic activity. Although approved by the US Food and Drug Administration (FDA) in 1959 as a treatment for endometrial and renal cancers, it is now primarily used for contraception because of its ability to inhibit follicular maturation and ovulation.

Cancer risk an early but disproved concern

Subsequent to FDA approval for cancer therapy, DMPA was found to be a highly effective contraceptive at a 150-mg dose injected at 3-month intervals.[1] However, the FDA denied approval as a contraceptive agent in 1969, 1978, and 1983 because of safety concerns, primarily increased risk of endometrial, breast, ovarian, and cervical cancers found in animal studies.[2,3] However, the World Health Organization (WHO) later concluded no associated increased risk of breast, ovarian, or cervical cancers, and actually found substantially reduced endometrial cancer incidence and mortality.[4] This led to approval of

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DMPA as a contraceptive in 1992,[4–6] after which DMPA quickly gained acceptance as one of few highly effective contraceptives at the time with a low per-dose cost.

Subcutaneous route allows self-administration

In 2004, a subcutaneous form of DMPA was FDA-approved with a 30% lower dose (104 mg every 3 months), offering an improved pharmacokinetic profile while providing more stability and sustained absorption because of low solubility.[7] Although peak serum levels are lower, duration of action is the same as provided by the intramuscular injection.[8] Subcutaneous DMPA can be administered in the thigh or abdomen every 12 to 14 weeks and was initially designed for self-administration in developing countries where patients have limited access to healthcare.[9]

Noncontraceptive benefits

DMPA has been recommended for female patients with certain medical conditions or preferences for the following reasons.

Bleeding reduction. DMPA can improve mean uterine and fibroid volume for patients with heavy menstrual bleeding from leiomyoma.[10] In a study of female patients with diagnosed endometrial hyperplasia, DMPA was associated with regression in 92% of patients after 6 months of treatment.[5] It should be considered for patients with endometrial hyperplasia who have contraindications to surgery and want to preserve fertility.[11]

Female patients should be offered a wide range of contraceptive options and specific methods to fit their lifestyles

Cancer prevention. DMPA is an effective chemopreventive agent for women at high risk of developing endometrial cancer (eg, patients with Lynch syndrome).[6]

Pelvic pain reduction. DMPA has success rates similar to other medical therapies for endometriosis (eg, danazol, combination contraceptives, gonadotropin-releasing hormone analogues) in managing deep dyspareunia and nonmenstrual pelvic pain after 1 year of use.[12]

DMPA DRAWBACKS

DMPA has substantial drawbacks that have contributed to a decline in use.[13] It has the highest discontinuation rates among all contraceptives with side effects being the most common reason for stopping therapy.[14] However, DMPA continues to be commonly used in sub-Saharan Africa.[15]

Adherence to therapy is another challenge for DMPA therapy as clinic visits are required 4 times a year for intramuscular injection. A Planned Parenthood study followed 5,178 female patients prescribed DMPA: 57% returned for the second injection, 36% for the third injection, and only 23% continued therapy for 1 year.[16] The mean 1-year discontinuation rate has been reported to be 40% to 75%.[17]

Subcutaneous DMPA is associated with more injection-site reactions such as skin dimpling from lipodystrophy, and it is more expensive than the intramuscular form.[18]

Changes in menstrual bleeding

Effects on menstrual bleeding are often cited as one reason patients discontinue using DMPA.[9] Initially, progestin-only hormonal regimens can result in abnormal menstrual bleeding patterns; DMPA commonly causes spotting, irregular bleeding, and prolonged bleeding.[4] With prolonged use, DMPA is associated with amenorrhea, which many patients consider to be a benefit.[4,19] Reported rates are 52% to 64% at 12 months, and 71% at 24 months.

Combined hormonal contraceptives or estrogen supplementation may be used to manage bleeding in the short-term, but currently no effective long-term treatment methods have been identified.[4] Decreasing the administration interval to 10 weeks can reduce irregular bleeding for patients who have bleeding close to their next scheduled injection time. Very heavy and bothersome bleeding patterns warrant additional evaluation.

Ovulation delay

The DMPA clearance rate is variable. In overweight or obese patients, DMPA may be detected for up to 9 months after a single injection.[20] Generally, ovulation resumes within 14 weeks of DMPA discontinuation, although it may take up to 18 months.[21] On average, an additional 5 to 8 months is required to conceive after DMPA use compared with nonhormonal methods of contraception.[20]

Bone mineral density reduction

In 2004, the FDA added a black-box warning to the DMPA label, cautioning that prolonged use could result in loss of bone mineral density (BMD). Patients were advised to use long-term DMPA therapy only if they were unable

to use other contraception.[22] Compared with IUD users, DMPA users have more BMD reductions after 12 months of use.[23]

Hypoestrogenism from DMPA administration increases bone resorption over bone formation, contributing to the drug's skeletal effects.[24] Bone turnover markers, eg, alkaline phosphatase, increase within 12 months of DMPA use, suggesting increased bone resorption. In addition, glucocorticoid activity of DMPA decreases the proliferation of osteoblasts, leading to reduced bone formation.[25]

BMD loss appears to be more substantial in the initial 2 years of use, followed by a less intense nonlinear loss over the following years.[23] In adolescent girls, BMD values return to normal after DMPA is discontinued, with no differences noted compared with nonhormone users.[26] Perimenopausal patients who are vulnerable to a declining BMD may experience statistically significant bone loss with DMPA, increasing risk for developing osteoporosis.[9] However, a large study supported the safety of DMPA for use for 2 years or less, with only a modestly elevated absolute fracture risk in users compared with nonusers (adjusted hazards ratio 1.15 [95% confidence interval 1.01–1.31]).[27]

Use of DMPA beyond 2 years should not be absolutely contraindicated, as bone loss and fracture risk can return to baseline within 2 to 3 years after DMPA is discontinued,[28] especially in female patients with intact ovarian function. Although controversial, this recommendation is supported by the WHO and American College of Obstetricians and Gynecologists, regardless of patient age.[29] They recommend that providers discuss the black-box warning with patients, balancing the risks of using DMPA against the known health and social consequences associated with unintended pregnancy, particularly among adolescents.[29]

History of fracture is also not an absolute contraindication for DMPA use, and BMD monitoring is not recommended for current or previous DMPA users. However, it may be prudent to recommend lifestyle modifications, such as increasing physical activity, a diet rich in calcium, and vitamin D supplements.

Risk of sexually transmitted infections

Evidence indicates that DMPA may increase susceptibility to chlamydia, gonorrhea, herpes simplex, and human immunodeficiency virus (HIV).[4] Possible contributing causes are mucosal barrier disruption, inflammation, decreased humoral and cellular immune responses, and changes in the vaginal microbiome.[30–33] Consequently, the WHO issued a caution that women using progestin-only injectable methods of contraception should be strongly advised to use barrier protection (ie, male or female condoms).[4]

The Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial, conducted in sub-Saharan Africa, found that DMPA increased HIV transmission risk by 23% to 29% compared with the levonorgestrel IUD.[34] The authors concluded that the differences were not substantial, and the WHO used the results of this study to relax medical eligibility criteria for DMPA use in female patients at high risk for HIV infection. However, the study had a number of limitations, including lack of a control group of nonusers, casting doubt about the value of the results.[35] Further study is needed to provide clarity regarding HIV association.

Weight gain

Weight gain is a common concern for female patients starting contraceptive therapy. Most experts believe that DMPA use is more likely than other progestin contraceptives to lead to weight gain because of higher hormone levels and glucocorticoid activity.

Berenson et al[36] found that 36 months of DMPA use was associated with an average increase in body weight of 5.1 kg and an increase in body fat, percent body fat, and central-to-peripheral fat ratio compared with use of a combined hormonal contraceptive or nonhormonal method. Another study found a mean weight change over 12 months of 2.2 kg for DMPA users vs 1.0 kg for levonorgestrel IUD users.[37] In an unadjusted linear-regression model, DMPA use was associated with more weight gain than with use of a copper IUD.[36]

DMPA use has one of the highest discontinuation rates among all contraceptives

RECOMMENDATIONS FOR USE

DMPA is especially recommended as a contraceptive method for female patients with the following medical conditions and situations:

- Contraindications for estrogen-containing combined hormonal contraceptives, eg, migraine with aura (US Department of Health and Human Services Medical Eli-

gibility Criteria for Contraceptive Use [US MEC] category 1, ie, no restrictions), thrombogenetic variants (US MEC category 2, ie, advantages of using the method generally outweigh risks), and tobacco use in patients over age 35 (US MEC category 1).[38]

- DMPA does not appreciably affect blood pressure or increase risk of venous thromboembolism.
- Epilepsy: DMPA is associated with fewer antiepileptic drug interactions than combined hormonal contraceptives.
- Sickle cell disease: DMPA reduces the number of sickle cell crises.[39]
- DMPA can be used by female patients who have difficulty adhering to daily oral contraceptive regimens or have concerns about using implantable LARCs.

IUDS: NONHORMONAL AND HORMONAL

About 4.4 million women have an IUD in the United States,[40] where it has been available since 1968 and has been credited with national declines in overall unintended and teenage pregnancies.

Initial IUD had unacceptable risks

Adverse effects, changes in menstrual bleeding, and adherence are often cited as reasons for discontinuing DMPA

IUDs were initially made in a variety of shapes from different materials, including plastic and copper.[41] In 1971, the Dalkon Shield gained popularity, with an estimated 2 million users. However, this device was associated with significant rates of pelvic inflammatory disease, about 7,900 IUD-related hospitalizations, and 5 deaths, which were related to the multifilament-braided design of the IUD strings. In 1974, the device was removed from the market, and the manufacturer was responsible for approximately $500 million in compensatory and punitive damages, ultimately leading the company to file for bankruptcy. These events created controversy and distrust among patients seeking IUD contraceptive options.

Copper IUDS, an improvement

Alternate forms of IUDs have since been developed, including a copper-bearing version that debuted in the United States in 1988 (TCu380A or Paragard; CooperSurgical; Trumbull, CT).[42,43] Copper ions disrupt sperm motility and viability, and also increase white blood cell and prostaglandin levels within the uterus to prevent fertilization.

Copper-bearing IUDs are associated with increased cramping and heavier bleeding than the levonorgestrel IUD, but they remain an option for patients wanting nonhormonal LARC (eg, breast cancer survivors).[42]

Copper-bearing IUDs are currently the only LARC option approved for emergency contraception and can be inserted up to 5 days after unprotected intercourse. Evidence is emerging that the levonorgestrel IUD may also be effective for this indication.[43]

Levonorgestrel IUDs increasingly popular

IUDs containing the progestin levonorgestrel first became available in 2001, with rates of use increasing from 1.8% in 2002 to 9.5% in 2012 ($P < .001$), primarily in parous female patients who wanted to space additional pregnancies or who did not intend future pregnancies.[44]

Four levonorgestrel IUD options are now available: Mirena (levonorgestrel 52 mg, Skyla (levonorgestrel 13.5 mg, Kyleena (levonorgestrel 19.5 mg, and Liletta (levonorgestrel 52 mg). These hormone-containing IUDs are FDA-approved for use from 3 to 7 years, depending on the product.

A trained professional must insert an IUD. Procedural and postprocedural risks include expulsion (5.8%) and uterine perforation (0.1%).[45,46]

Safe to use in many settings

As the risk for pelvic inflammatory disease with IUDs is extremely low, no prior screening for sexually transmitted infections is necessary for asymptomatic and low-risk patients. IUDs may be offered to patients diagnosed with pelvic inflammatory disease as a contraceptive method.[47,48] Removal of an IUD has no therapeutic benefit for patients being treated for pelvic inflammatory disease and is not recommended.

IUDs can be safely used in patients who are nulliparous (a practice supported by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics), have contraindications to estrogen therapy, want LARC without the need for regular medical visits, and have heavy menstrual bleeding.

Contraindications

Absolute contraindications for the levonorgestrel IUD include a history of breast cancer, Müllerian anomalies (involving an abnormal uter-

TABLE 1

Characteristics of commonly used contraceptive methods

Medical condition	DMPA	LNG-IUD	CHCs	Subdermal implant
Unintended pregnancy rates	≤ 1%[56]	< 1%	9%	< 1%
WHO effectiveness tier	2 (highly effective)[57]	1 (most effective)	2	1
Drug interactions	Minimal	Minimal	Several[58]	Minimal
Influence on blood pressure	Minimal	Minimal	Can cause mild increase	Minimal[59]
Venous thromboembolism	Minimal	Minimal	Slight increase in risk[57]	Minimal[60]
Weight gain	Yes[36]	Minimal	Minimal	Minimal[59,61]
Influence on bone density	Negative[23]	Minimal	Positive[62]	Minimal[63]
Endometrium	Antiproliferative[4,6]	Antiproliferative[50]	Antiproliferative[64]	Antiproliferative[65]

CHCs = combined hormonal contraceptives; DMPA = depot medroxyprogesterone; LNG-IUD = levonorgestrel-releasing intrauterine device; WHO = World Health Organization

Based on information in references 4, 6, 23, 36, 50, and 56–65.

ine cavity shape), untreated cervical cancer, and gestational trophoblastic disease with persistently elevated beta-human chorionic gonadotropin.[49]

The US MEC recommend against levonorgestrel IUDs in patients with endometrial cancer. However, recent evidence suggests that levonorgestrel IUDs can be used to treat patients with early-stage, low-risk endometrial cancer who want to preserve fertility or who are not good candidates for surgery.[50]

Adverse effects

The primary adverse effect of the 52-mg levonorgestrel IUD is unscheduled bleeding that may last up to 12 weeks after insertion; this should be discussed with patients during contraceptive counseling.[46]

Amenorrhea can also occur. A secondary analysis of the Contraceptive CHOICE Project found that it was reported by 4.9% of 1,802 52-mg levonorgestrel IUD users at 3 months, 14.8% at 6 months, and 15.4% at 12 months.[51]

Other levonorgestrel IUD dosages may have slightly different bleeding profiles.

Several studies have found that body fat mass and weight can increase with use of the levonorgestrel IUD. However, gains after 12 months of use were not significantly different from gains in copper IUD users in one study.[52]

SUBDERMAL ETONOGESTREL IMPLANT

The subdermal etonogestrel implant is another effective progestin-only LARC contraceptive option.[53] Inserted into the arm in an office procedure, it contains a single, radiopaque, extended-release rod that contains 68 mg of etonogestrel (a metabolite of desogestrel) and lasts for 3 years.[53]

The most common adverse effects are irregular bleeding, headache, and implant-site hematoma.[53] No changes in BMD or substantial weight gain were reported after 12 months of use.[54] Rates of discontinuation at 12 months for the subdermal implant are higher than for the levonorgestrel IUD or copper IUD, mostly due to menstrual cycle abnormalities.[55]

Comparisons of commonly used contraceptive methods are summarized in (**Table 1**).[4,6,23,36,50,56–65] More detailed recommendations can be found at websites for the US Centers for Disease Control and Prevention[66] and the US Medical Eligibility Criteria for Contraceptive Use.[67]

The DMPA label contains a black-box warning, cautioning that prolonged use may result in loss of bone mineral density

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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