Born again: The many lives of metformin

Petaloid dermatosis affecting the scalp and genitalia

Cutaneous metastasis from gastric carcinoma

Persistent rectal pain leading to diffuse pustules

Should coagulation abnormalities be corrected before minor invasive procedures in patients with cirrhosis?

Should I consider metformin therapy for weight loss in patients with obesity but without diabetes?

A practical guide for buprenorphine initiation in the primary care setting

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Born again: The many lives of metformin

Repurposing of medications—getting US Food and Drug Administration (FDA) approval to use an old drug for a new indication—is not a new drug-development strategy, as I have discussed before and as we saw most recently during the COVID-19 pandemic. As physicians, we can prescribe FDA-approved drugs to individual patients off-label. But off-label use has drawbacks. Insurance companies need not cover the cost of the drug. We may place ourselves at increased legal risk as a result of any untoward drug-related event. The pharmaceutical company cannot actively condone or promote off-label use without risking great financial penalty. Without moving through the normal regulatory approval process, the drug will likely not undergo rigorous safety and efficacy testing in the targeted patient population. In addition, there is often much to be learned about drug-disease-patient interactions from a well-conducted clinical trial that will enhance clinical care, as opposed to relying only on anecdotal accumulated experiences.

Achieving FDA approval for a new drug is an arduous process, with the overwhelming majority of tested compounds falling by the wayside without approval due to safety or efficacy concerns. Previously approved drugs, however, have the advantage of already running the gauntlet of preclinical animal toxicology, teratology, and drug-distribution studies, clinical dose-range studies, and safety observation from phase 3 clinical trials—and perhaps also from postmarketing surveillance and anecdotal safety reports. Thus, they are unlikely to fail for unforeseen safety reasons, unless there is a safety signal unique to the intended disease-specific population, and adequate efficacy must still be demonstrated.

There are multiple reasons why a specific drug may be selected for formal repurposing. Sometimes, during the drug’s initial development, when the mass of collected data is analyzed, information is gleaned that suggests an unanticipated beneficial off-target effect (eg, on blood pressure or low-density lipoprotein cholesterol levels, or on weight). Sometimes the structures of FDA-approved drugs are analyzed to see if they can “fit” into a computer-generated image of a desired target receptor or target site of enzyme activity. And sometimes postapproval clinical use in the real world or in postmarketing studies reveals a desired off-target effect in treated patients: semaglutide, originally approved for diabetes mellitus, is now also approved for obesity, and baricitinib, approved for rheumatoid arthritis, is now also approved for alopecia areata and COVID-19. As Rodriguez et al discuss in this issue of the Journal, metformin, the initial go-to drug for most patients with type 2 diabetes, should also be considered as an initial and adjunctive treatment for obesity, based on clinical experience and on the results of a large randomized, placebo-controlled diabetes prevention trial.

The story of metformin is what my friend and medical podcaster Adam Brown would call a “ripping yarn”—a Britishism for a thrilling tale. When I was in training, metformin and its classmate phenformin were the answers to pharmacologic trivia and acid-base questions related to the development of lactic acidosis in patients with diabetes. I never anticipated the prominent role that metformin would ultimately play in the management of diabetes and, increasingly, in a number of other disorders. But the versatility of the drug was recognized long before the 20th century.

Since the Middle Ages, herbalists have used extracts from the plant French lilac (Galega officinalis, “goat’s rue”) to treat worm infections, epilepsy, plague, and conditions of “thirst and frequent
urination” (aka diabetes). Substances isolated from the plant included several guanidines that were found to lower blood glucose levels, although some proved to have unacceptable toxicity. Galegine, one of the better-tolerated compounds, was studied in the 1920s and was shown to lower glucose slightly in normal volunteers, but more markedly in individuals with diabetes. With the discovery of insulin, research on these alternative compounds slowed. Several decades later, metformin (1,1-dimethylbiguanide hydrochloride) and other guanidines were tested in different clinical settings. During testing and use in treating influenza virus in the 1940s, metformin’s hypoglycemic effect was reconfirmed. (Note: Studies of metformin as an antiviral to treat COVID-19 were not without historical precedent.) French pharmacologist and physician Dr. Jean Sterne (1909–1997) laboriously investigated metformin’s hypoglycemic effects, leading to its registration in parts of Europe in 1957. Around the same time, the biguanide phenformin was developed in the United States. It was more potent than metformin, received FDA approval, and was heavily marketed. However, phenformin provoked lactic acidosis that was associated with a number of fatalities, which severely tarnished the biguanides, including metformin. Phenformin was ultimately removed from the US market in 1978.

Renewed interest in the hypoglycemic effects of metformin, which lacks phenformin’s propensity to elicit lactic acidosis, led to its FDA approval for type 2 diabetes. Then, several years later, it was shown to also reduce the frequency of cardiovascular events.

Metformin’s primary mechanism of action in lowering glucose is not entirely clear. It does not stimulate insulin release, but it has several demonstrated pharmacologic effects: it decreases gluconeogenesis in the liver, and it enhances insulin activity at least in part by stimulating glucose transport into skeletal myocytes. In what appears to be a concentration-dependent manner, metformin can affect mitochondrial function, reduce intracellular adenosine triphosphate, and ultimately increase the concentration of adenosine monophosphate-activated protein kinase (AMPK), a major sensor of energy stores and thus a modulator of several intracellular metabolic pathways and cellular functions. Increased AMPK can affect fat storage and decrease several transcription factors, including some that drive the synthesis of proinflammatory cytokines. Thus, it should be no surprise that metformin is being utilized and investigated in the treatment of polycystic ovary syndrome, fatty liver syndromes, rheumatoid arthritis, systemic lupus, and long COVID, as well as obesity.

Further study may provide even more lives for metformin.

Brian F. Mandell, MD, PhD
Editor in Chief

2023

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September 22
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October 13–15
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October 14
Chicago, IL

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November 4
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Beachwood, OH

CONTEMPORARY MULTIDISCIPLINARY CARE OF THE HEAD AND NECK CANCER PATIENT: UPDATES ON THE INNOVATIVE APPROACHES TO HEAD AND NECK CANCER TREATMENT
November 17
Cleveland, OH

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November 17
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DECEMBER

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Hongfang Liu, PhD – Mayo Clinic
Lucila Ohno-Machado, MD, PhD – Yale School of Medicine
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Marco Zenati, MD – Brigham and Women’s Hospital and Harvard Medical School
Petaloid dermatosis affecting the scalp and genitalia

A 41-year-old male presented with a 1-month history of pruritic lesions on his scalp, neck, and penis. He had attempted a 2-week course of terbinafine cream, with no improvement. The lesions were unaffected by exposure to sunlight. The patient also reported new-onset wrist stiffness and pain. He had been diagnosed with primary syphilis 9 months prior to presentation, with a reactive plasma reagin titer of 1:64, and had been treated with intramuscular penicillin G benzathine 2.4 million units.

Physical examination revealed annular and petaloid plaques with central clearing and raised borders on the scalp, right mandibular angle (Figure 1), and penis (Figure 2). No lesions were observed on the oral mucosa, palms, or soles. No lymphadenopathy or new-onset alopecia was present.

Clinically, the differential diagnosis included discoid lupus erythematosus, lichen planus, tinea infection, sarcoidosis, and annular secondary syphilis. Serology for human immunodeficiency virus was non-reactive, and cutaneous punch biopsy of the mandibular lesion was performed. Histologic sections revealed...
a brisk, mixed inflammatory infiltrate including numerous plasma cells within the superficial dermis to the mid-dermis. Staining for *Treponema pallidum* highlighted numerous spirochetes, consistent with syphilis. Repeat rapid plasma reagin testing was positive with a 1:256 titer.

Though not certain, we believed that this patient likely acquired a new case of syphilis after treatment of his previous infection, because he presented at 9 months after the primary diagnosis, and resolution of secondary syphilis typically occurs within 12 weeks. Therefore, he was given an intramuscular dose of 2.4 million units of penicillin G benzathine, with close follow-up recommended with the department of infectious diseases.

### SECONDARY SYPHILIS AND OTHER PETALOID DERMATOSES

**Clinical presentation**

Syphilis is a sexually transmitted disease caused by the spirochete bacterium *T pallidum*. While primary syphilis typically presents as a solitary, painless papule or ulcer in the genital area, secondary syphilis is a generalized infection often accompanied by systemic symptoms such as fever, malaise, headaches, sore throat, or joint pain. These acute symptoms typically begin 6 to 8 weeks after the appearance of the primary lesion and resolve within 12 weeks.

The most common cutaneous presentation of secondary syphilis is a generalized morbilliform rash, usually involving the palms and soles. However, secondary syphilis can present as annular secondary syphilis, which is also known as petaloid syphilis owing to its appearance resembling the petals of a flower. Lesions in annular secondary syphilis often occur close to the angle of the mandible and frequently spare the palms and soles. Secondary syphilis typically presents without lymphadenopathy and often affects the genitalia.

### MANAGEMENT OF PETALOID DERMATOSES

The differential diagnosis for annular plaques is broad and depends on clinical history, symptoms, and location and morphology of the lesions. Annular lesions on the head and neck could also be secondary to petaloid seborrheic dermatitis, tinea corporis, discoid lupus erythematosus, subacute lupus erythematosus, cutaneous sarcoïdosis, or granuloma annulare.

A thorough history and physical examination, relevant laboratory studies, skin biopsy, and potassium hydroxide preparation of these lesions are helpful in narrowing the diagnosis.

### TAKE-HOME POINTS

It is important for clinicians to consider petaloid secondary syphilis in the differential of annular lesions, as it can mimic other inflammatory and infectious etiologies.

### DISCLOSURES

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

### REFERENCES


Address: Taylor A. Bullock, MD, Department of Dermatology, A60, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; bulloct3@ccf.org
Cutaneous metastasis from gastric carcinoma

A 75-year-old man presented with a 3-month history of asymptomatic nodules with alopecia on the scalp. He said that 3 years before this presentation, he had undergone total gastrectomy with Roux-en-Y anastomosis and extended lymphadenectomy due to poorly differentiated, diffuse gastric adenocarcinoma with locoregional metastatic lymph nodes. For 24 weeks after that, he had received 8 cycles of chemotherapy with epirubicin, cisplatin, and 5-fluorouracil. At a 2-year follow-up, there was no evidence of recurrence or metastasis.

On examination, 2 round, smooth, pink, rubbery nodules were noted in the occipital region (Figure 1). The patient said that the nodules had gradually grown in size over the past 3 months.

Dermoscopy showed a round, pink nodule with thick linear and arborizing vessels, shiny white structureless areas, and loss of follicular openings (Figure 2). Biopsy of a nodule revealed adenocarcinoma with diffuse infiltration of carcinoma cells arranged as single cells and forming tubules and glands in the dermis and subcutis. On immunohistochemical study, the neoplastic cells were positive for cytokeratin 7, cytokeratin 20, caudal-type homeobox 2, and villin, and negative for special AT-rich sequence-binding protein 2. The patient was referred to the oncology department, where metastasis to the abdominal cavity and lymph nodes was identified. The patient refused further chemotherapy and died 1 year later.

Cutaneous metastases from visceral carcinomas are rare, with an overall incidence of 0.7% to 9%.1 The
SKIN METASTASIS, GASTRIC CANCER

scalp is one of the most frequent cutaneous sites of distant metastasis from visceral carcinomas, and most lesions have a nodular presentation.\(^2\) Alopecia neoplastica is a cutaneous metastasis due to underlying cancer spreading to the scalp, accounting for 4% of all cutaneous metastasis, and associated with a poor prognosis.\(^3\)

Alopecia neoplastica usually presents as single or multiple asymptomatic, reddish-violet or flesh-colored nodules with scarring alopecia, and is most prevalent in the frontal or parietal region of the scalp.\(^3\) It can also manifest as a plaque or patch.\(^3\) The primary tumor associated with alopecia neoplastica is most frequently in the gastrointestinal tract, followed by the breast, kidney, lung, and thyroid.\(^3\) Adenocarcinoma is the most frequent histologic subtype.\(^3\)

The diagnosis of alopecia neoplastica can be challenging, but timely pathologic examination is critical, and immunohistochemistry is helpful in determining the origin of the tumor. It must be distinguished from common and benign alopecia conditions. Alopecia neoplastica indicates a poor prognosis for cancer patients, and a comprehensive evaluation is needed to guide treatment.

**REFERENCES**


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Why 25-dehydroxyvitamin D is a negative acute-phase reactant

To the Editor: In previous publications, we presented evidence that 25-dehydroxyvitamin D (25[OH]D) in serum behaves as a negative acute-phase reactant, ie, that its concentration decreases in the presence of inflammatory states. Low levels may thus reflect low vitamin D stores or inflammation, complicating the clinical interpretation of test results.

We have recently become aware of the mechanism underlying this phenomenon: less than 1% of circulating 25(OH)D exists in unbound form, and the majority is tightly bound to vitamin D binding protein, while 10% to 15% is bound to albumin. Both are negative acute-phase proteins. As the serum concentrations of these proteins decrease, so does that of 25(OH)D. Similarly, the positive acute-phase behavior of copper is explained by the fact that it is bound to ceruloplasmin, a positive acute-phase protein.

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Persistent rectal pain leading to diffuse pustules

A 34-year-old male with a history of syphilis and with human immunodeficiency virus on a home regimen of dolutegravir and the combination of darunavir, cobicistat, emtricitabine, and tenofovir alafenamide presented to the emergency department with persistent rectal pain, yellow rectal discharge, widespread skin lesions, and episodes of fever, with a maximum temperature of 102.9°F (39.4°C). The rectal pain and discharge had started 1 week earlier, and 4 days after that, he developed skin lesions on the face that quickly spread to the rest of his body.

Examination of the skin revealed diffuse pustular lesions involving the face, chest, back, all 4 extremities, genitalia, and palms (Figure 1), and the patient was admitted to the hospital for further evaluation.

Figure 1. The patient presented with widespread diffuse pustular lesions, including the face and palms, diagnosed as mpox.
Examination of the anal region revealed multiple unroofed papules with serous drainage at the anal sphincter. Anal lesions were swabbed and sent for testing for mpox virus and herpes simplex virus. Results of laboratory testing revealed a white blood cell count of 13.1 × 10^9/L (reference range 3.5–10.5), a human immunodeficiency viral load of 22,700 copies/mL, and a CD4 count of 447 cells/mm^3 (500–1,200). Results of a quantitative rapid plasma reagin test were consistent with treated past syphilis infection.

Computed tomography suggested a perirectal abscess, with mucosal hyperenhancement around the rectum, mild circumferential perirectal edema, and outpouching along the left lateral rectal wall of less than 1 cm.

Owing to high suspicion for mpox (formerly monkeypox) virus infection, the patient was placed on isolation precautions and was started on tecovirimat 600 mg twice daily for 14 days, and doxycycline for proctitis. The patient's febrile episodes stopped on day 2 of hospitalization. Marked improvement in the anal discharge was noted on day 4, though the rectal pain persisted with bowel movements. The skin lesions improved, developing a hard crust and exhibiting decreased drainage. Days later, on hospital day 7, the lesion swab resulted positive for mpox virus.

## MPOX EPIDEMIOLOGY

As of February 1, 2023, the US Centers for Disease Control and Prevention reported more than 88,000 confirmed cases of mpox globally in more than 110 locations, over 90% of which have not historically reported mpox infections. Nearly 31,000 cases have been confirmed across the United States, including pediatric cases, and 33 fatalities were reported, the majority in severely immunocompromised adults.

Despite being first witnessed in captive cynomolgus monkeys, rodents and small forest mammals have been noted to be the attributed source of zoonotic transmission, with the first human case of mpox reported in 1970 in a 9-month-old child in the Democratic Republic of the Congo. In the United States, human cases of mpox have historically been described in laboratory workers, pet shop workers, and veterinarians after direct contact with an infected animal.

The exact mode of transmission is still under investigation, although it seems that human-to-human transmission is primarily due to contact with lesions, infected bodily fluids, or large respiratory droplets. Contact with recently contaminated objects or surfaces used by an infected individual is also considered a risk factor for transmission. With respect to the current (ie, 2022) outbreak, mpox cases have been concentrated in men who have sex with men.

## CLINICAL PRESENTATION OF MPOX

The clinical presentation of mpox often begins with a nonspecific prodromal period consisting of 1 to 5 days of fever, sweats, chills, headache, back pain, myalgia, and lymphadenopathy. Within 1 to 5 days from fever onset, a rash appears first as macules, followed by papules, then vesicles, and finally pea-sized hard pustules. These pustules become umbilicated, develop crust, and eventually desquamate, leading to resolution of the rash in 7 to 14 days.

However, in the current outbreak, patients may present with a less severe prodrome and increased prevalence of vesicular lesions in the genital and perineal regions. In addition, symptoms may include anorectal pain or pharyngitis. The differential diagnosis of pustular lesions consists of several infectious processes including mpox, herpes simplex virus, molluscum contagiosum, cutaneous cryptococcosis, cutaneous cytomegalovirus, syphilis, and lymphogranuloma venereum.

## MANAGEMENT OF MPOX

Many patients with mpox will recover within 2 to 4 weeks without any medical intervention. Severe cases can occur, more commonly in children and immunocompromised individuals, with a case-fatality rate of 1% to 11%. Tecovirimat is approved by the US Food and Drug Administration for the treatment of smallpox and may be considered for patients with or at increased risk of severe mpox through the Expanded Access Investigational New Drug Protocol for treatment of nonvariola orthopoxviruses like mpox during an outbreak. Vaccinia immune globulin intravenous, brincidofovir, and cidofovir are currently being evaluated. Mpox vaccination should be offered to individuals at high risk of exposure or after known or presumed exposure to mpox virus.

## PATIENT OUTCOME

The patient was discharged on hospital day 8 with continuation of his home antiretroviral medication, a 4-day course of oxycodone for pain management, and instructions to isolate from human contact for 4 to 6 weeks, until lesions had disappeared, and new skin had formed underneath all scabs.

His most recent follow-up with an outside derma-
tologist at 6 months after discharge revealed resolution of mpox lesions and postinflammatory hyperpigmentation of the involved sites.

**TAKE-HOME POINTS**

Mpox should be included in the differential diagnosis when assessing patients with new papulovesicular or vesiculopustular lesions. In contrast to previous outbreaks, the current outbreak is primarily driven by human transmission, may lack the characteristic prodrome or lymphadenopathy, and may present with anorectal pain or pharyngitis. While most cases are self-limited, tecovirimat may be considered in patients with severe disease.

**DISCLOSURES**

Dr. Andrasik has disclosed consulting for Bristol-Myers Squibb. Dr. Fernandez has disclosed consulting for Abbvie Pharmaceuticals, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Mallinckrodt, Novartis, and UCB; teaching and speaking for Abbvie Pharmaceuticals, Kyowa Kirin, Mallinckrodt, and Novartis; work as advisor or review panel participant for Abbvie Pharmaceuticals; research or principal investigator for Alexion; and awarded a grant from Pfizer to fund a medical dermatology fellowship position. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

**REFERENCES**


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

November 9-12, 2023
Cleveland Clinic Administrative Campus
3175 Science Park Drive, Building #4 | Beachwood, OH

Primary care clinicians face the almost overwhelming task of staying abreast of current research in the various medical disciplines and assessing it for clinical implications. This challenge, in turn, creates knowledge and competency gaps in many primary care clinicians.

This CME-certified, live symposium is designed to review best practices that highlight the latest therapies, procedures, and diagnostics in primary care, women’s health and behavioral medicine. Join us as we explore updates in Asthma Management, PrEP Therapy and HIV Management for Primary Care, and Weight Management. Engage in lively discussions covering Women’s Health in the Geriatric Population, Care of the LGBTQ+ Patient, and Reproductive Access in Today’s Climate. Watch as our faculty present Advanced Therapies in Mental Health Treatment, Clinical Management of Adolescent Depression, and Behavioral Addictions. All attendees will be given the opportunity to participate in our Glucose Monitoring Diabetic Workshop, and optional workshops will be available in Endometrial Biopsy and IUD Insertion, as well as MSK - Joint and Trigger Point Injections.

Learn How To
• Summarize the most recently published data from research and clinical trials and discuss their clinical implications for primary care medicine including the use of PrEP prophylaxis, treatment of asthma, hyperlipidemia, adolescent obesity, diabetes management and the use of supplements in patient care.
• Utilize clinical technology including Continuous Glucose Monitors in the care of patients including hands-on understanding of how they work, associated software integration and patient counseling.
• Critically appraise the benefits and risks and use of evidence-based guidelines for the management of Hormone Replacement Therapy, Osteoporosis, PCOS and breast and cervical cancer screening in patient care.
• Provide patient-appropriate, safe, effective women’s healthcare in special populations including geriatric and LGBTQ+ and understand limits to access to reproductive health care for all.
• Assess and care for patients with difficult to manage behavioral health disorders including treatment resistant depression, bipolar disorder and adolescent depression using both pharmacologic and non-pharmacologic treatment.
• Identify behavioral and substance addiction in patient care and employ evidence-based recommendations for management, as well as use of toxicology screens to manage risk and abuse.
• Identify indications for injection, risks and benefits and injection of major joints and trigger points including the knee and shoulder, carpal tunnel syndrome and trigger points in patient care.
• Counsel patients on the risks and benefits of IUD insertion/removal or EMB procedure and safely and effectively perform the procedures.

Who Should Attend
This activity is designed for family physicians, general internists, nurses, nurse practitioners, physician assistants, and other health care professionals who have an interest in primary care, women’s health and behavioral medicine.

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Q: If a patient has cirrhosis, should I correct coagulation abnormalities before a minor invasive procedure?

A 56-year-old man with a history of cirrhosis is hospitalized with decompensated liver cirrhosis, ascites, and encephalopathy. His hemoglobin is 9 g/dL (reference range 13.8–17.2), platelet count $40 \times 10^9$/L (150–400), and international normalized ratio (INR) 2.5 (0.8–1.1). Do I need to correct the patient’s elevated INR or thrombocytopenia before performing diagnostic and therapeutic paracentesis?

No. An elevated INR in patients with cirrhosis does not predict the risk of post-procedural bleeding, and no evidence suggests that correcting a prolonged INR with fresh frozen plasma will lower procedure-related bleeding.1 Transfusion of platelets to prevent bleeding in the setting of stable cirrhosis is not recommended for patients undergoing low-risk procedures such as paracentesis, thoracentesis, and liver biopsy.1,2

BLEEDING RISK WITH CIRRHOSIS: A TENUOUS BALANCE

In patients with cirrhosis, hemostatic system abnormalities are common and include thrombocytopenia, prolonged prothrombin time, prolonged activated partial thromboplastin time, elevated INR, and decreased fibrinogen. These abnormalities were once implicated in increased bleeding events, but it is now understood that changes in both prohemostatic and antihemostatic pathways contribute to a “rebalanced” hemostatic state,3 and because this balance is tenuous, patients with liver disease are also susceptible to thrombotic events.1

Prothrombin time, activated partial thromboplastin time, and INR are often elevated in the setting of cirrhosis because of low levels of coagulation factors produced by the liver and a concomitant decline in levels of protein C, protein S, and antithrombin.1 The INR is one component of the Model for End-Stage Liver Disease score,4 a commonly used prognostic model for cirrhosis. However, INR measurement, originally developed to standardize the prothrombin time for patients on warfarin, does not accurately reflect the hemostatic profile in patients with cirrhosis who are not taking warfarin.5 A meta-analysis of 29 studies demonstrated no significant association between periprocedural bleeding events and preprocedural INR.5

Thrombocytopenia is a common consequence of hypersplenism and decreased hepatic thrombopoietin production, but the bleeding risk may be balanced by elevated levels of von Willebrand factor; by decreased levels of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13), a potent inhibitor of von Willebrand factor; and by platelet activation by endotoxemia.3 There is no consistent association between thrombocytopenia and risk of bleeding in patients with cirrhosis who undergo low-risk procedures.1

Studies have identified an association between severe thrombocytopenia (a platelet count less than $50 \times 10^9$/L) and bleeding after percutaneous liver biopsy, dental extractions, percutaneous ablation of liver tumors, and endoscopic polypectomy, but the results of these studies were likely confounded by the use of prophylactic platelet transfusions.6 The risk of bleeding in patients with cirrhosis is determined by clinical and procedural factors unrelated to

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COAGULATION AND CIRRHOSIS

coagulation testing. Anemia, renal failure, and sepsis are known clinical predictors of bleeding in this population.\textsuperscript{1,3}

Invasive procedures are classified as having a low or high risk of bleeding, with low bleeding risk defined as a bleeding rate less than 1.5%. Procedures associated with low bleeding risk include paracentesis, thoracentesis, liver biopsy, and percutaneous ablation of liver cancer.\textsuperscript{1} Ultrasonographic guidance has been shown to reduce bleeding complications in certain procedures, most notably placement of a central line in patients with coagulopathy.\textsuperscript{1}

WHAT DO GUIDELINES RECOMMEND?

For patients with cirrhosis, current guidelines recommend a conservative approach to prolonged INR, thrombocytopenia, and fibrinogen deficiency.

Prolonged INR: Avoid fresh frozen plasma

Correction of prolonged INR with fresh frozen plasma to decrease procedure-related bleeding is not recommended in the European Association for the Study of Liver clinical practice guidelines on bleeding and thrombosis in patients with cirrhosis.\textsuperscript{1} In a combined retrospective and prospective study of 100 patients, Yousef et al\textsuperscript{7} found that fresh frozen plasma transfusion corrected prothrombin time in only 12.5% of patients in the retrospective groups and 10% of patients in the prospective groups. A Cochrane review on the use of prophylactic fresh frozen plasma demonstrated no benefit in procedure-related bleeding in patients with cirrhosis.\textsuperscript{9} Possible consequences of fresh frozen plasma transfusion include increased portal hypertension as a result of increased blood volume, transfusion-associated circulatory overload, transfusion-related acute lung injury, and allergic or anaphylactic reactions. Given the risks, transfusion of fresh frozen plasma to correct prolonged INR in cirrhosis should be avoided.\textsuperscript{1}

Thrombocytopenia: Case-by-case decision

Studies that evaluate the efficacy of platelet transfusion or thrombopoietin receptor agonists to prevent bleeding in patients with cirrhosis are lacking. The American Gastroenterological Association recommends against routine use of platelet transfusions or thrombopoietin receptor agonists for procedures such as paracentesis, thoracentesis, variceal banding, colonic polypectomy, endoscopic retrograde cholangiopancreatography, and liver biopsy.\textsuperscript{1}

In vitro studies have established that in patients who have cirrhosis and platelet counts greater than 56 × 10\textsuperscript{9}/L, platelet-dependent thrombin formation is preserved.\textsuperscript{1,9} This finding is the theoretical basis for guidelines that recommend avoidance of platelet transfusion or thrombopoietin receptor agonists when the platelet count is greater than 50 × 10\textsuperscript{9}/L. In patients with platelet counts less than or equal to 50 × 10\textsuperscript{9}/L who are undergoing a high-risk procedure (eg, endoscopic retrograde cholangiopancreatography, endoscopic polypectomy, ligation of esophageal varices), transfusion of thrombopoietin receptor agonists may be considered on a case-by-case basis,\textsuperscript{1} and decisions can be made with the guidance of a hepatologist or a hematologist. Additional prospective studies are needed to determine the efficacy of platelet transfusion or thrombopoietin receptor agonists to prevent bleeding in patients with cirrhosis.

Fibrinogen deficiency: Routine correction not recommended

Fibrinogen is necessary for clot formation and can be increased by administration of cryoprecipitate. Although fibrinogen levels below 100 mg/dL are associated with bleeding in patients with cirrhosis, this association may reflect the severity of disease rather than a cause.\textsuperscript{1,10} A retrospective study evaluating the effect of cryoprecipitate transfusion for critically ill patients with cirrhosis and hypofibrinogenemia failed to demonstrate reduced bleeding with routine cryoprecipitate transfusions.\textsuperscript{7,11} Given the lack of evidence that cryoprecipitate transfusion prevents bleeding and avoids the high cost of cryoprecipitate, routine correction of fibrinogen deficiency to prevent procedure-related bleeding is not recommended.\textsuperscript{1}

Viscoelastic testing: Unsupported in nonsurgical settings

Thromboelastography and rotational thromboelastometry are types of viscoelastic testing (VET) that evaluate the rate, stability, and strength of blood clot formation and the rate of dissolution in whole blood.\textsuperscript{12} VET is thought to represent in vivo hemostasis better than more traditional coagulation testing such as INR, prothrombin time, and activated partial thromboplastin time. Used routinely during liver transplant surgery, VET is associated with decreased use of blood products without an increase in bleeding adverse events.\textsuperscript{12} The strategy is increasingly favored for evaluation of coagulopathy in cirrhosis because of unclear benefit associated with following and correcting traditional coagulation markers such as INR.

In a meta-analysis, Shenoy et al\textsuperscript{12} compared standard of care based on platelet and INR guidelines
vs. VET-guided preprocedural transfusions. In the VET group, 14.4% required platelet transfusions and 22.2% required fresh frozen plasma, compared with 64.7% and 55.6% in the standard-of-care group. Decreased preprocedural transfusions in the VET group did not result in increased postprocedural bleeding events or mortality. However, the analysis was unable to define common VET-based transfusion thresholds among the studies included. The authors recommended against the use of VET in patients with cirrhosis undergoing nonsurgical procedures such as paracentesis, thoracentesis, or liver biopsy, citing limited availability of the technology and specialized training required to use it.

THE BOTTOM LINE: MORE STUDIES NEEDED

Because of rebalanced hemostasis, traditional laboratory testing such as prothrombin time, activated partial thromboplastin time, INR, and platelet counts are unhelpful in predicting the risk of bleeding in cirrhosis. Studies have demonstrated that correction of INR with fresh frozen plasma in this patient population is often ineffective in normalizing the INR and preventing postprocedural bleeding. The threshold level of thrombocytopenia at which platelet transfusions and thrombopoietin receptor agonists are beneficial in cirrhosis is unknown. Similarly, the cutoff for transfusion of cryoprecipitate for decreased fibrinogen levels has not been elucidated, and routine administration of cryoprecipitate for prevention of postprocedural bleeding is not recommended.

DISCLOSURES

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

REFERENCES

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Q: Should I consider metformin therapy for weight loss in patients with obesity but without diabetes?

A: Yes. Evidence supports the weight-loss effects of metformin in adults with obesity and without type 2 diabetes. The magnitude of metformin-induced weight loss is modest but clinically significant, and it is achievable at low cost with an agent that has proven long-term safety, few serious adverse effects, and well-documented favorable non-glycemic effects. To date, metformin is the only pharmacologic weight-loss intervention to demonstrate long-term effects.1

Thus, in the absence of contraindications, metformin should be seriously considered as an off-label initial therapy and as an adjunct to antiobesity medications approved by the US Food and Drug Administration for the management of obesity, particularly in the presence of specific concomitant conditions, as will be discussed here.

■ SUPPORTING EVIDENCE

The main sources of evidence for weight loss with metformin in people without type 2 diabetes come from the Diabetes Prevention Program trial (DPP)2 and its long-term follow-up, the Diabetes Prevention Program Outcomes Study (DPPOS).1

The DPP, a 3-arm randomized controlled trial, compared the effects of intensive lifestyle intervention, metformin 1,700 mg/day, and placebo in 3,234 participants with prediabetes. The primary outcome measure was prevention or delayed onset of type 2 diabetes, with weight loss reported as a secondary outcome.2 The mean weight and body mass index (BMI) of the overall population in the study was 94.2 ± 20.3 kg and 34 ± 6.7 kg/m², respectively. During the initial 2.8-year follow-up, the metformin group experienced an average weight loss of 2.1 kg, compared with 5.6 kg in the lifestyle intervention group, and 0.1 kg in the placebo group.2

Weight loss is maintained

Unlike the weight loss experienced in the intensive lifestyle intervention group, weight loss in the metformin group was maintained throughout the DPP and DPPOS follow-up periods (N = 2,766 participants). Those on metformin had an average 2.5-kg weight loss over time, while the lifestyle intervention group progressively regained weight, with a final average weight loss of 2.0 kg after 10 years of follow-up.3

Approximately 30% of participants randomized to metformin lost more than 5% of their body weight in the first year, and a post hoc analysis demonstrated that their mean weight loss relative to baseline was 6.2% after 15 years of follow-up, compared with 3.7% in the lifestyle intervention arm. Adherence and weight loss during the first year of treatment with metformin were relevant predictors of long-term weight-loss maintenance.1 Because the DPP and DPPOS were not designed primarily to assess weight loss, caution must be exercised when interpreting these data.

To date, the largest evaluation of weight loss with metformin as a primary outcome in patients without diabetes is the preliminary phase of the Biguanides and Prevention of the Risks in Obesity trial,4 with 324 participants with abdominal obesity (inclusion criterion was waist-to-hip ratio, not BMI) and no diabetes. Participants were randomized to receive metformin 1,700 mg/day or placebo. After 12 months of treatment, metformin had a significantly better effect on weight...
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( mean −2 kg, 95% confidence interval [CI] −3.0 to −1.1, vs placebo −0.8 kg, 95% CI −1.6 to 0.1, \( P < .06 \)).

Higher degrees of insulin resistance
A more recent nonrandomized, real-world study assessed the efficacy of metformin for weight loss in 154 patients with obesity and no diabetes compared with 45 control participants. The mean weight loss in the metformin group was 5.8 kg (± 7.0), whereas controls gained 0.8 kg (± 3.5 kg) on average (\( P < 0.0001 \)). Both absolute and relative weight loss increased with higher degrees of insulin resistance, as measured by the Matsuda index and HOMA index. The study provides good real-world evidence on the use of metformin in patients with obesity and no diabetes, but the control group comprised patients who chose not to use medication as a means of reducing weight. Consequently, the possibility of innate bias should be considered when interpreting the results.

A meta-analysis that included 21 trials and 1,004 participants analyzed the effect of metformin on BMI in different populations and found that in patients with obesity, BMI was reduced by 1.3 units (weighted mean difference [WMD] −1.31; 95% CI −2.07 to −0.54). A subanalysis found that metformin had the most pronounced effect in the population with BMI greater than 35 kg/m² (WMD −1.12; 95% CI −1.84 to −0.39), at doses higher than 1,500 mg/day (WMD −1.01; 95% CI −1.29 to −0.73) for at least 6 months (WMD −1.09; 95% CI −1.71 to −0.47). Evidence regarding the timeframe in which weight loss might be expected to occur is inconsistent. Commonly, however, in trials with longer follow-up periods, weight loss generally starts after 4 weeks of treatment with metformin and occurs mainly during the first 6 to 12 months of continuing metformin therapy.

SPECIFIC POPULATIONS

Prediabetes
In the DPP trial, the incidence of diabetes was 58% lower (95% CI 48% to 66%) in the lifestyle intervention group and 31% lower (95% CI 17% to 43%) in the metformin group compared with placebo. However, metformin proved to be particularly effective for preventing or delaying diabetes in the subgroups of participants with higher BMI (≥ 35), younger age (< 60), and higher baseline fasting blood glucose and hemoglobin A1c, and in women with a history of gestational diabetes. This particular effect has been shown to be durable after 15 years of follow-up. In these populations, the role of metformin goes beyond its weight loss effects, and its use should be encouraged with the dual goal of promoting weight loss and preventing or delaying the onset of type 2 diabetes.

PATIENTS TREATED WITH ANTIPSYCHOTIC DRUGS
Most antipsychotic drugs are associated with weight gain. It has been reported that 75% of patients receiving antipsychotic agents increased their baseline weight by more than 7%. Atypical antipsychotics have greater potential for inducing weight gain, and among them, clozapine and olanzapine are the agents most associated with weight gain, followed by risperidone and quetiapine. These are also the agents for which the literature on metformin’s weight-attenuating and weight-loss effects is more abundant. However, there does not appear to be an antipsychotic drug-specific beneficial effect of metformin, and it is rather the magnitude of weight gain that drives metformin efficacy.

Several trials have demonstrated beneficial effects of metformin in reversing or preventing weight gain associated with antipsychotic drug therapy. A meta-analysis including 12 studies and 743 participants confirmed that metformin is effective in treatment of weight gain associated with these agents. The mean weight loss was 3.27 kg (95% CI −4.66 to −1.89; \( Z = 4.64; P < .001 \)), and metformin resulted in significant reduction in BMI (−1.13; 95% CI −1.61 to −0.66) compared with placebo.

Weight gain can be associated with other medications, including some anticonvulsants, antidepressants, and systemic glucocorticoids, but evidence regarding the utility of metformin in those groups of patients is lacking.

Polycystic ovary syndrome
In women with polycystic ovary syndrome, metformin therapy has been shown to increase ovulation, menstrual frequency, fertility, and rates of live birth. A meta-analysis comparing orlistat with metformin in women with polycystic ovary syndrome found that both had similar favorable effects on BMI, with a mean decrease in BMI of 3.4 to 4.55 with metformin, and 4.48 to 5.7 with orlistat (difference −0.65%, 95% CI −2.03 to 0.73).

POTENTIAL MECHANISMS
Some evidence suggests that the mechanisms underlying metformin’s effects on body weight are much broader than its insulin-sensitizing effects. Additional proposed mechanisms include the following:
• Appetite suppression through increased secretion
of glucagon-like peptide 1 and peptide YY, and increased hypothalamic leptin sensitivity

- Alteration of the gut microbiome
- Induced expression and secretion of growth-differentiating factor 15, which reduces food intake, body mass, fasting insulin, and glucose intolerance.\(^{14,15}\)

Although most studies have used metformin in its immediate-release formulation, there is sufficient evidence to suggest no differences between immediate-release and extended-release formulations in terms of their weight-loss properties or the secretion of substances that potentially underlie this effect.\(^{16}\)

**SAFETY AND SIDE EFFECTS**

When metformin is used and prescribed appropriately, serious adverse events are extremely rare. The most common side effects are gastrointestinal—diarrhea, nausea, flatulence, vomiting, and abdominal discomfort. These are less frequent with postprandial use and with extended-release than immediate-release formulations. Given the lack of prospective data on the effect of metformin on weight loss, it is unclear whether weight loss is associated with gastrointestinal side effects. Since the magnitude of weight loss during the DPP (and its maintenance during the DPPOS) was directly related to adherence to metformin therapy,\(^{17}\) such an association seems unlikely.

The main contraindication associated with metformin is severe renal impairment, defined as an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m\(^2\). In patients with eGFRs between 30 and 60 mL/min/1.73 m\(^2\), the accepted recommendation is to reduce the dose, but no specific dose adjustments or maximum doses have been validated in clinical trials.\(^{18}\) If metformin is being considered as a weight-loss strategy in patients without diabetes, the following approaches are reasonable:

- eGFR less than 45 mL/min/1.73 m\(^2\): refrain from starting metformin
- eGFR 45 to 60 mL/min/1.73 m\(^2\): prescribe a maximum total daily dose of 1,500 mg (or 1,700 mg if prescribing an immediate-release formulation)
- eGFR 30 to 45 mL/min/1.73 m\(^2\) and already on metformin therapy: adjust to a maximum daily dose of 1,000 mg.

Chronic metformin use has been associated with a decrease in serum vitamin B12 levels without clinical manifestations. Reported in approximately 7% of patients, it is attributed to interference with vitamin B12 absorption. It is rarely associated with anemia and appears to be reversible with discontinuation of metformin or with vitamin B12 supplementation, or both.\(^{19}\)

**COST**

Metformin is widely available, with an average price of about $10 for a 90-day supply. There are no studies of the cost-effectiveness of metformin as a weight-loss intervention. However, cost-effectiveness analysis of metformin as a diabetes prevention strategy in the DPP concluded that, compared with placebo, it was "extremely cost-effective (that is, improved outcomes at a low incremental cost) or even cost-saving (improved outcomes and reduced total costs)."\(^{20}\)

**BOTTOM LINE**

It is well known that a small but sustained reduction in body weight (3% to 5%) is associated with improved glucose metabolism, blood pressure, and lipids, and is a strong predictor of diabetes prevention. Available evidence supports the use of metformin as an initial and adjuvant weight-loss medication, especially in the presence of prediabetes, severe obesity (BMI ≥ 35), use of antipsychotic drugs, or polycystic ovary syndrome. It should be considered a long-term treatment, particularly in patients who demonstrate a good response. The aim is to achieve a dosage of 1,500 mg/day or more (or adjusted by renal function), leveraging extended-release formulations and slow titration.

**REFERENCES**


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Q: When should pharmacologic therapies be used for uremic pericarditis?

A: Renal replacement therapies are the mainstay of treatment for uremic pericarditis and should be initiated as soon as possible. But when symptoms are refractory or fail to improve, pharmacologic therapies should be considered.

Uremic pericarditis, a condition with significant morbidity and mortality, was common at one time and initially reported in as many as 41% of patients with end-stage renal disease (ESRD) undergoing dialysis.1–3 With advancements in dialysis methods and earlier initiation of dialysis, the incidence has been reduced to approximately 5%, although this is still considerable given the number of people with ESRD.1,4

Uremic pericarditis is distinguished from dialysis-associated pericarditis based on the timing of clinical signs and symptoms of pericarditis in relation to renal replacement therapy. Uremic pericarditis is defined as the onset of clinical signs and symptoms of pericarditis before renal replacement therapy or within 8 weeks of initiation, and dialysis-associated pericarditis involves the onset of clinical manifestations after 8 weeks of renal replacement therapy.4 This is an arbitrary temporal designation and reflects the belief that dialysis-associated pericarditis is predominantly related to inadequate dialysis.5

PATHOPHYSIOLOGY OF UREMIC PERICARDITIS

The pathophysiology of uremic pericarditis is thought to involve metabolic alterations including hypoproteinemia, hyperuricemia, hypocalcemia, hyperparathyroidism, and accumulation of other toxic metabolites that exacerbate endothelial permeability.5,6 Dialysis-associated pericarditis is further highlighted in patients with inadequate dialysis secondary to lack of adherence or low-flow rates related to access issues or higher catabolic states.4 Circulating immune complexes have been implicated as pro-inflammatory toxins responsible for serositis, which is not specific to the pericardium.7

In addition to the inflamed pericardium, uremia places patients at a higher risk of bleeding and coagulopathy as a result of platelet dysfunction, an altered coagulation cascade, and activation of the fibrinolytic system.5 However, studies have not found a relationship between the degree of azotemia (or biochemical abnormalities) and the development of uremic pericarditis or dialysis-associated pericarditis.4 There are few adequate animal models for pericarditis, further challenging our understanding of the development of a pathophysiologic mechanism. A recently developed mouse model using inflammasome activation highlights the potential for biologic agents.8

SIGNS AND SYMPTOMS

Clinical features of uremic pericarditis include chest pain that typically occurs in the anterior chest, particularly in the recumbent position, that worsens with inspiration and can be associated with a pericardial rub, which is common in patients with uremic pericarditis and present in up to 83% of episodes.1,3,4 In severe cases, cardiac tamponade may be present in up to 16% of patients with dialysis-associated pericarditis.10 Therefore, the initial evaluation should involve excluding tamponade along with assessment for acute coronary and aortic syndromes, as patients on dialysis are at higher risk for major cardiovascular events.3
The diagnosis may be corroborated by findings on electrocardiography such as widespread concave ST elevation with PR depression, reciprocal ST depression, and PR elevation in lead aVR. In the case of pericardial effusion, low-voltage QRS complexes and classic electrical alternans may be found. Sinus tachycardia is a common but nonspecific finding, reflecting pain or a preload-dependent state. Overall, analysis has demonstrated specificity but minimal sensitivity of these findings, limiting their clinical utility. Echo-cardiography characterizes pericardial effusion but has limited utility for detailed pericardial assessment. Cardiac computed tomography and cardiac magnetic resonance imaging have become increasingly adapted to identify morphologic features of pericardial inflammation.

In the case of a pericardial effusion requiring drainage, pericardial fluid analysis may provide additional diagnostic information. Uremic effusions are generally transudative, while exudative effusions could suggest either hemorrhagic conversion or an underlying systemic inflammatory disorder that contributed to renal injury (such as glomerulonephritis related to vasculitis or systemic lupus erythematosus).

**RENAL REPLACEMENT THERAPY**

In treating uremic pericarditis, the removal of uremic toxins entails either initiation of dialysis in patients with chronic kidney disease or intensification of dialysis in those with ESRD. There is no known difference in response to dialysis in patients with uremic pericarditis than in those with dialysis-associated pericarditis, although the 2 entities differ in that 1 requires initiation of dialysis while the other depends on the technical features of the dialysis method.

For patients without an adequate response to the initiation of dialysis, intensifying the frequency (to 5 to 7 days a week) or the duration of chronic dialysis is recommended. In patients with dialysis-associated pericarditis, adequate dialysis dosing is imperative, and this includes ensuring adherence and adequate access flow, as well as addressing access issues. Resolution of clinical pericarditis has been reported to occur in 87% of patients within 2 weeks of starting chronic dialysis.

There may be differences in removal of relevant toxins between hemodialysis and peritoneal dialysis. A small case series demonstrated improvement in patients with pericarditis and hemorrhagic effusions refractory to appropriate hemodialysis once peritoneal dialysis was initiated.

**Complications**

While the rate of hemorrhagic pericardial effusion is low, systemic anticoagulation should be avoided when possible owing to the risk of hemorrhagic conversion, especially in the context of possible uremic platelet dysfunction, which can be difficult to quantify with routine laboratory assessment. In the context of myocardial infarction treated with anticoagulation, older series have demonstrated a higher rate of hemorrhagic pericardium, though incidence and guidance for modern anticoagulation methods are less clear.

In patients presenting with severe complications of uremia (e.g., encephalopathy, severe refractory acidosis, symptomatic pericardial effusion) and high degrees of azotemia, dialysis needs to be initiated slowly, with low flow rates to avoid disequilibrium syndrome. Meanwhile, in patients with larger pericardial effusions, judicious ultrafiltration must be done with close hemodynamic monitoring to ensure adequate cardiac filling.

**GUIDING THERAPY**

It is important to note the progression of techniques and evaluation of dialysis over time and various reasons for considering transition of modality. While there are no standard clinical or laboratory criteria to determine the success of dialysis, intensive dialysis should be continued until resolution of symptoms and resolution of pericardial friction rub. Multimodality imaging is increasingly used to assess pericardial disease, and imaging-guided therapies are used in cases of clinical suspicion for pericarditis without obvious findings of an associated effusion on echocardiography. These methods provide quantitative and qualitative data on pericardial disease and can elucidate underlying causes.

Late gadolinium enhancement and T2 short tau inversion recovery sequencing in magnetic resonance imaging are of particular interest when assessing pericardial and myocardial inflammation. Emerging data in recurrent pericarditis support modifying therapies in response to findings on cardiac magnetic resonance imaging, particularly in patients taking multiple anti-inflammatory therapies that can falsely decrease inflammatory markers. Serial follow-up imaging studies can be compared along with serologic measures of inflammation (C-reactive protein and erythrocyte sedimentation rate) to assess the adequacy of therapy, together with careful clinical assessment. This cardiac magnetic resonance imaging-guided response to therapy allows for the tailoring of treatment strategies.
in response to pericardial inflammation and edema resolution. Additionally, factors such as low systolic blood pressure, leukocytosis, high-grade fever, and large pericardial effusions have been reported as predictors of dialysis failure.

**PERICARDIAL INTERVENTIONS**

Infrequently, pericarditis remains refractory to intensive dialysis treatment. If patients develop tamponade physiology or pericardial effusions do not improve within 2 weeks of intensive dialysis, pericardial drainage is indicated. Patients with a large pericardial effusion—especially if associated with tamponade physiology—are not ideal candidates for urgent dialysis because of potential hemodynamic effects of ultrafiltration. In these situations, a pericardial window is a useful temporizing strategy before ultrafiltration and toxin removal can be achieved. Pericardiocentesis may be safely performed under echocardiographic guidance, with a 1.2% rate of major complications. Nonetheless, the introduction of the often unnecessary risk and insufficient durability of needle drainage has led to the procedure being largely reserved for acutely unstable patients as a bridge to surgical drainage.

A pericardial window procedure is usually preferred over the high-risk formal pericardectomy. While a
pericardial window offers the advantage of obtaining pericardial biopsy to rule out other causes of pericarditis, it does not eliminate pericardial inflammation until the uremic state is resolved with simultaneous dialysis. In patients with constrictive pericarditis or large recurrent pericardial effusions despite pericardial drainage, pericardiectomy serves as definitive therapy.

**PHARMACOLOGIC THERAPY IN PATIENTS WITH RESIDUAL KIDNEY FUNCTION**

When symptoms are refractory or fail to improve with maximally tolerated dialysis, pharmacologic options for uremic pericarditis are limited by their nephrotoxicity (in patients with residual renal function or possible renal recovery), the need for dosing adjustments, and bleeding risk. Unlike other forms of pericarditis, first-line anti-inflammatory therapies such as nonsteroidal anti-inflammatory drugs are generally avoided in patients who are not dialysis-dependent, especially in high-dose regimens. However, they may be used at the lowest effective dose for the shortest possible duration. The European Society of Cardiology guidelines include a class III recommendation against the use of colchicine in patients with advanced kidney disease, and a creatinine clearance cutoff of 30 mL/minute is usually adopted. Corticosteroids have been used with varying benefit, with...
low doses mainly considered in patients unable to use nonsteroidal anti-inflammatory drugs.

**CONSIDERATIONS IN END-STAGE RENAL DISEASE WITHOUT RESIDUAL KIDNEY FUNCTION**

In patients with declared ESRD in whom worsening renal function is not necessarily a concern, there are still multiple issues that can be concerning, such as drugs that may be variably cleared through dialysis, significantly reducing efficacy. In patients with uremic platelet dysfunction, bleeding is an important concern, particularly when pericardial effusions are present, as is the risk for hemorrhagic conversion. Further, patients with advanced chronic kidney disease often have multiple comorbidities, experience worsening of concomitant coronary artery disease or heart failure, and have difficulty with volume and blood pressure management due to corticosteroids. These examples demonstrate how traditional treatment strategies involve risk and emphasize the need for nonpharmacologic and alternative therapies in this vulnerable population.

**BIOLOGIC AGENTS**

Newer therapies for the management of recurrent pericarditis including anakinra and rilonacept have not been robustly explored for use in patients with uremic pericarditis.

Anakinra is not dialyzable, but there is a recommendation for every-other-day dosing in patients with a creatinine clearance rate less than 30 mL/minute. This adjustment is based on pharmacokinetic studies and aims to reduce the development of drug-neutralizing antibodies, infection from immunosuppression, and gastrointestinal side effects including hepatotoxicity.

Rilonacept does not appear to need dose adjustment in patients with impaired kidney function. It is worth noting that residual cardiovascular risk in patients with impaired kidney function appears to be driven significantly by inflammation, as has been quantified with measurements of high-sensitivity C-reactive protein and interleukin-6.

With this in mind, the role for targeted immunomodulatory therapies in the treatment of uremic pericarditis needs further study. However, these agents have already shown promising results in the management of recurrent pericarditis, with substantial decreases in pericardial inflammation and resolution of edema on cardiac magnetic resonance imaging (Figure 1).

**THE BOTTOM LINE**

Management of uremic pericarditis requires a thoughtful, multidisciplinary approach that involves the patient and a team of internal medicine, nephrology, and cardiology clinicians. Renal replacement therapies are the mainstay of treatment and should be initiated as soon as possible. Pharmacologic therapy should be deferred initially because of the risk of side effects and the unclear evidence regarding efficacy prior to adequate dialysis. When symptoms are refractory or fail to improve, pharmacologic therapies should be considered (Figure 2).

**DISCLOSURES**

Dr. Klein has disclosed serving as advisor or review panel participant for Cardiol Therapeutics, Kiniksa Pharmaceuticals, and Pfizer; consulting for Kiniksa Pharmaceuticals and Pfizer; and intellectual property rights for Vifor. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

**REFERENCES**


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A practical guide for buprenorphine initiation in the primary care setting

ABSTRACT

Buprenorphine is a safe and effective treatment for opioid use disorder but remains underutilized because a major challenge of conventional buprenorphine initiation (termed induction) is that the patient must already be in opioid withdrawal. Previous legal barriers and clinician lack of familiarity with the unique pharmacology of buprenorphine have also limited its use. In this review, we outline changes regarding buprenorphine prescribing laws and physician perceptions of buprenorphine. We also review buprenorphine pharmacology and novel low-dose buprenorphine induction procedures that can be adopted in primary care settings to improve treatment acceptability, retention, and outcomes.

KEY POINTS

- Buprenorphine can be prescribed in the primary care setting, which can help improve treatment access and retention.
- Standard induction of buprenorphine requires that patients be in mild to moderate opioid withdrawal.
- Low-dose buprenorphine induction permits safe initiation of buprenorphine regardless of whether the patient is in withdrawal or has recently used opioids.

Buprenorphine is a safe and effective treatment for opioid use disorder (OUD) but remains underutilized owing to previous prescribing limitations, lack of physician familiarity with the unique pharmacology of buprenorphine, and the need for the patient to be in opioid withdrawal before initiating treatment. Low-dose buprenorphine induction (LDBI) is a recent treatment protocol that can be adopted in primary care settings to improve treatment acceptability, retention, and outcomes.

OUD is characterized by compulsive opioid use regardless of negative consequences. Individuals with OUD suffer a 15 to 20 times greater risk of mortality than that of the general population and at an unprecedented epidemic level. As of 2020, the US Centers for Disease Control and Prevention reported that 2.4 million people in the United States suffer from OUD, with only 6% to 7% likely to receive pharmacotherapy.

Until recently, prescribing buprenorphine was limited by the Drug Abuse Treatment Act of 2000 and required completion of an 8-hour training course or addiction board certification to apply for a designated license (X-waiver) to treat. In 2021, the 8-hour training requirement was removed, though an X-waiver was still required, and clinicians were still limited by monthly patient caps. In December 2022, the Consolidated Appropriations Act of 2023 was signed into law, entirely eliminating the X-waiver requirement and monthly treatment caps, allowing clinicians to treat as many patients as they can support with buprenorphine.

As of June 27, 2023, all who prescribe controlled substances must fulfill at least 1 of the...
following requirements before applying for or renewing their Drug Enforcement Administration registration: 8 hours of training on opioid or substance use disorders; board certification in addiction medicine or addiction psychiatry from the American Board of Medical Specialties, American Board of Addiction Medicine, or American Osteopathic Association; or graduation within 5 years in good standing from a medical, advanced practice, or physician assistant school in the United States that included at least 8 hours of opioid or substance use disorder curriculum. This easing of prescribing limitations presents an opportunity to expand buprenorphine treatment in primary care, thus increasing access to treatment for OUD. In this article, we review existing evidence supporting the use of buprenorphine in the primary care setting, provide an accessible overview of buprenorphine pharmacology, and describe buprenorphine induction protocols that can be adopted in primary care settings.

SHOULD PRIMARY CARE CLINICIANS PRESCRIBE BUPRENORPHINE?

Prior studies have found that primary care physicians (PCPs) regularly encounter patients with OUD and believe buprenorphine is an effective treatment for OUD, but do not always feel prepared to prescribe buprenorphine. One investigation found that 82% of individuals newly diagnosed with OUD had visited a PCP in the preceding 12 months. Another study in rural New England found that more than 80% of family physicians regularly encountered patients with OUD in their practice. Most of these physicians (73%) believed that they had a professional responsibility to treat OUD. More recently, a survey of physicians’ perceptions of pharmacotherapy for OUD found that 53 and 52 of 127 respondents indicated that buprenorphine decreases opioid cravings and fatal overdoses, respectively. Despite the interest of PCPs in treating OUD with buprenorphine and having some knowledge of this medication, they may not yet feel comfortable prescribing buprenorphine. A cross-sectional survey of PCPs found that approximately 80% of respondents were very or somewhat comfortable identifying OUD. However, only 36.9% were very or somewhat comfortable treating OUD with pharmacotherapy. Physician respondents identified lack of access to behavioral treatments and lack of experience with pharmacotherapy for OUD as the main reasons for feeling uncomfortable. The authors concluded that identifying comprehensive models of care and improving physicians’ sense of self-efficacy (one’s belief that one can succeed at a certain task) could help expand access to buprenorphine treatment through PCPs.

The treatment of OUD in primary care clinics typically involves medications such as buprenorphine in conjunction with services to address psychosocial needs. Data from rural and community primary care settings that prescribe buprenorphine demonstrate superior treatment retention relative to designated buprenorphine clinics. Though this model has been implemented in the United States to varying degrees, 91% to 99% of opioid agonist treatment is prescribed by PCPs in France. French primary care settings have improved OUD outcomes with decreased fatal opioid overdoses and overall mortality, suggesting that PCPs with proper buprenorphine training are well poised to have an enormous impact on the trajectory of patients with OUD.

BUPRENORPHINE: PHARMACOLOGY AND FORMULATIONS

Pharmacology

Successful buprenorphine induction requires familiarity with its unique pharmacologic properties. Buprenorphine is a semisynthetic opioid with partial agonism at the mu-opioid receptor (MOR), antagonism at the kappa-opioid receptor, and agonism at the opioid receptor-like 1 receptor. There is controversy about the action of buprenorphine on the delta-opioid receptor, with some sources describing it as an agonist and others as an antagonist. Kappa-opioid receptor antagonism is thought to play a role in the antidepressant and antiaddictive properties of buprenorphine. Human and animal models show that kappa-opioid receptor activation by stress neuropeptides produces dysphoria and drug-seeking behaviors. There is current interest in studying buprenorphine and other kappa-opioid receptor antagonists as adjuncts to treat depression and drug-seeking behaviors. Buprenorphine’s actions at the MOR and opioid receptor-like 1 likely account for its rewarding and analgesic properties, while its action at the MOR decreases opioid cravings and withdrawal and is therefore considered the most pharmacodynamically significant in the treatment of OUD.

When binding to the MOR, buprenorphine acts as a partial agonist with high receptor affinity and potency, which can pose both clinical advantages and challenges. Because of the partial agonism
at the MOR, buprenorphine demonstrates beneficial ceiling effects for respiratory depression, euphoria, and physiologic dependence that offer high clinical safety with relatively infrequent overdoses reported.2,16–19 Buprenorphine’s affinity for the MOR is about 120 times higher than that of oxycodone and 6.2 times higher than that of fentanyl16,20,21 and can therefore quickly and easily displace these opioids from the MOR.20 As a result of the ability of buprenorphine to displace almost all other opioids, in conjunction with its partial opioid-agonist activity, patients starting buprenorphine are at high risk of experiencing precipitated withdrawal.16 Precipitated withdrawal is characterized by the rapid onset of opioid withdrawal and occurs when the partial MOR agonist buprenorphine displaces a full MOR agonist, such as heroin, leading to a relative withdrawal despite a high percentage of MORs still being occupied.2,16

**Formulations**
Buprenorphine is available in a wide variety of formulations (Table 1)22,23 and is often paired with naloxone (an opioid antagonist) as a deterrent for...

### Table 1

**Buprenorphine formulations and indications**

<table>
<thead>
<tr>
<th>Generic name and administration route</th>
<th>Brand name</th>
<th>Dose formulations</th>
<th>US Food and Drug Administration indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine hydrochloride for intravenous or intramuscular administration</td>
<td>Buprenex injection</td>
<td>0.3 mg/mL</td>
<td>Acute moderate-to-severe pain</td>
</tr>
<tr>
<td>Buprenorphine transdermal system</td>
<td>Butrans</td>
<td>5 μg/hour</td>
<td>7.5 μg/hour</td>
</tr>
<tr>
<td>Buprenorphine buccal film</td>
<td>Belbuca</td>
<td>75 μg</td>
<td>150 μg</td>
</tr>
<tr>
<td>Buprenorphine extended-release injection for subcutaneous use</td>
<td>Sublocade</td>
<td>300 mg/1.5 mL monthly after induction for first 2 months</td>
<td>100 mg/0.5 mL maintenance dose monthly (can increase to 300 mg)</td>
</tr>
<tr>
<td>Buprenorphine sublingual tablets</td>
<td>Subutex</td>
<td>2 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>Buprenorphine/naloxone sublingual film</td>
<td>Suboxone</td>
<td>2 mg/0.5 mg</td>
<td>4 mg/1 mg</td>
</tr>
<tr>
<td>Buprenorphine/naloxone sublingual tablets</td>
<td>Suboxone</td>
<td>2 mg/0.5 mg</td>
<td>8 mg/2 mg</td>
</tr>
<tr>
<td>Buprenorphine/naloxone sublingual rapid-dissolve tablets</td>
<td>Zubsolv</td>
<td>0.7 mg/0.18 mg</td>
<td>1.4 mg/0.36 mg</td>
</tr>
</tbody>
</table>

Based on information in references 22 and 23.
misuse.\textsuperscript{2,22} Though naloxone has very limited oral bioavailability, it becomes highly bioavailable through insufflation (“snorting”) or intravenous injection, thus precipitating opioid withdrawal and reversing opioid overdose.\textsuperscript{2,22} It was believed that naloxone would therefore precipitate withdrawal if consumed intranasally or intravenously in combination with buprenorphine, but it should be noted that buprenorphine still has a binding affinity that is 10 times higher than naloxone.\textsuperscript{24} Although selecting the ideal formulation of buprenorphine for induction can seem daunting for the novice prescriber, we describe below a practical guide for induction.

\section*{STANDARD BUPRENORPHINE INDUCTION: METHODOLOGY AND CHALLENGES}

Clinicians face a peculiar challenge in initiating buprenorphine for OUD using a standard induction approach. If buprenorphine is started in the setting of recent opioid use, as is expected in patients with OUD, it will cause precipitated withdrawal as the partial MOR agonist buprenorphine displaces almost all other opioids, including full MOR agonists.\textsuperscript{16} Successful induction is therefore difficult, but can be accomplished when patients abstain from opioids before initiating buprenorphine or when LDBI guidelines are followed.

\subsection*{Method}

Standard buprenorphine induction requires that patients abstain from opioids and present with moderate withdrawal to initiate buprenorphine.\textsuperscript{19} Withdrawal should be measured by the clinical opiate withdrawal scale, an 11-item scale that is readily available online and in many clinical calculator applications.\textsuperscript{25} The patient’s clinical opiate withdrawal scale score should be greater than 12 prior to giving the first buprenorphine dose.\textsuperscript{2,17,19,26} Another challenge of the standard induction approach is that a 2-day process is recommended, with a maximum total dose of 8 mg on the first day.\textsuperscript{19}

Guidelines from the Substance Abuse and Mental Health Services Administration suggest giving a single starting dose of 2 mg to 4 mg buprenorphine sublingual if the patient is in adequate withdrawal,\textsuperscript{19} though we recommend starting with 2 mg. If the patient experiences precipitated withdrawal (marked by an abrupt worsening of withdrawal), symptoms should be treated, and induction reattempted 24 hours later.\textsuperscript{19} However, if withdrawal symptoms are instead partially relieved, another 2-mg or 4-mg dose is given after 2 to 4 hours.\textsuperscript{19} This process can be repeated until withdrawal symptoms are controlled, up to a total of 8 mg daily on the first day.\textsuperscript{19} The total dose received on the first day should then be prescribed for the next day, and the patient should return to clinic for the second day of induction.\textsuperscript{19} If the patient reports adequate symptom relief, the induction is complete.\textsuperscript{19} If symptoms are not yet controlled, the patient will resume the induction process of taking repeated 2-mg or 4-mg doses, with assessment of withdrawal symptoms every 2 to 4 hours.\textsuperscript{19} This process can be repeated as needed until a total of 16 mg of buprenorphine has been given on the second day, or until symptoms are controlled.\textsuperscript{19}

\subsection*{Challenges}

At a dose of 16 mg buprenorphine, it is believed that approximately 80% to 90% of MORs are occupied, and withdrawal symptoms should theoretically be controlled.\textsuperscript{27} Yet there is evidence that 16 mg may not suppress opioid cravings in severely dependent patients.\textsuperscript{27} Patients with severe OUD may require doses up to 24 to 32 mg (maximum approved dose) or even higher for adequate control of withdrawal and cravings.\textsuperscript{27-29}

It is important to note that when the standard induction protocol was developed, heroin (a short-acting opioid) dominated the illicit opioid supply.\textsuperscript{17,19} Patients only needed to abstain from heroin for 4 to 12 hours before experiencing adequate withdrawal to safely start buprenorphine.\textsuperscript{17,19} However, with the shift from heroin to fentanyl as the current prevalent illicit opioid, the abstinence time required has dramatically increased.\textsuperscript{2,16,17,21,26} The total abstinence time required depends on the type of opioid used, and ranges from 4 hours for heroin to 36 to 48 hours for methadone, and 3 days or more is often needed for fentanyl.\textsuperscript{2,16,17,21,26,30} Notably, fentanyl users may experience buprenorphine-precipitated withdrawal even after prolonged abstinence.\textsuperscript{16,21,31} Fentanyl is stored in adipose tissue with chronic high-dose use,\textsuperscript{2,16,21,26,31} and therefore demonstrates an unexpectedly long renal clearance time despite a half-life comparable to that of heroin.\textsuperscript{30} Fentanyl’s prolonged clearance time as the drug is slowly released from adipose tissue likely accounts for why patients using fentanyl are at higher risk of precipitated withdrawal compared with other opioids.\textsuperscript{32} The prolonged clearance time and requirement of multiple days of abstinence can prove difficult for patients and may lead to treatment dropout or relapse.\textsuperscript{2,16,17,21,31}

\section*{LOW-DOSE BUPRENORPHINE INDUCTION}

LDBI strategies are designed to avoid precipitated withdrawal and are feasible to implement in the pri-
LDBI was first described (in English) in 2016 by Hämmig et al. This method was based on previous research showing that doses of 0.2 mg of buprenorphine did not precipitate withdrawal in patients taking methadone for OUD. LDBI involves giving very small doses of buprenorphine, with gradual dose increases. When the patient continues using full-agonist opioids or illicit opioids concurrently with LDBI, this approach is called the Bernese method. Hämmig et al described 2 cases in which this approach was taken. In case 1, the patient received an initial buprenorphine dose of 0.2 mg, followed by slowly increasing incremental doses of buprenorphine while tapering heroin use. After multiple attempts with conventional induction, the patient was weaned with the Bernese method, and on day 9, the patient had been 4 days without heroin while taking 12 mg/day of buprenorphine, and tolerated this process much better. In case 2, the patient was titrated slowly to a dose of 24 mg of buprenorphine with ongoing full-agonist use over 29 days. On the first day, buprenorphine was increased to 4 mg, and on the second day, buprenorphine was increased to 8 mg. A methadone dose of 72 mg was administered after every successful induction of buprenorphine for the day for 3 days. Mild withdrawal was treated symptomatically. Methadone was fully discontinued on day 4 once stabilization was confirmed.

**Recommended protocols**

For patients using fentanyl in the outpatient setting, we recommend one of the 3 induction protocols that are available online from Penn Medicine’s Center for Addiction Medicine and Policy and summarized in Table 2. A 2022 case report of a patient with a 3-year history of treatment with a 72-mg daily dose of methadone who needed to switch treatments owing to age, excessive sedation, and inability to come into clinic regularly detailed LDBI over 3 days in the outpatient setting. A 2-mg/0.5-mg buprenorphine/naloxone sublingual film was cut into 4 parts (approximately 0.5 mg of buprenorphine each), and each piece was given in intervals of 30 minutes to 1 hour on the first day. On the second day, buprenorphine was increased to 4 mg, and on the third day, buprenorphine was increased to 8 mg. A methadone dose of 72 mg was administered after every successful induction of buprenorphine for the day for 3 days. Mild withdrawal was treated symptomatically. Methadone was fully discontinued on day 4 once stabilization was confirmed.

There are multiple LDBI protocols but no current standard protocols, with some more suitable protocols used in the supervised inpatient setting.
BUPRENORPHINE INITIATION

dosing, some institutions have endorsed off-label use of buprenorphine buccal films (dosed in micrograms and approved for pain). Penn Medicine’s Center for Addiction Medicine and Policy also describes this approach. There is no current consensus on optimal time to fully discontinue MOR agonists, though a cross-titration from the full MOR agonist to buprenorphine is most desirable. Once the patient is on 16 mg of buprenorphine or higher and 90% of MORs are occupied, abrupt cessation of full agonists should theoretically not cause clinically significant withdrawal. Though LDBI can seem complicated, it offers many clinical advantages. It decreases the risk of precipitated withdrawal, does not require that the patient already be in withdrawal to start buprenorphine, and may thus provide better treatment outcomes for patients, especially those using fentanyl. Additionally, the Bernese method of treating with LDBI while reducing full-agonist opioids is gaining popularity among patients.

### TIPS FOR MANAGING PRECIPITATED WITHDRAWAL

Even with appropriate precautions, precipitated withdrawal may occur during buprenorphine initiation. One theory of the mechanism of precipitated withdrawal proposes that an abrupt reduction in opioid tone in certain brain areas, including the locus coeruleus and mesolimbic areas, occurs and causes withdrawal. More specifically, neuroadaptations in MOR signaling caused by chronic exposure to high-dose opioids, followed by a sudden reduction of MOR occupancy by full MOR agonists, likely causes precipitated opioid withdrawal. Precipitated withdrawal—much dreaded and called “precip” by patients—constitutes a major risk to overcome during early induction.

Withdrawal symptoms can include diarrhea, abdominal cramps, anxiety, yawning, rhinorrhea, lacrimation, myalgias, arthralgias, diaphoresis, and mydriasis, and can be quantified using the Clinical Opiate Withdrawal Scale. The medications noted in Table 3 can be used to alleviate symptoms of precipitated withdrawal and can also be used to facilitate induction. One current recommendation for managing precipitated withdrawal is to give 2 mg of buprenorphine every 1 to 2 hours, a strategy that may have limited utility in patients using fentanyl.

Another approach involves using high-dose buprenorphine, often referred to as macroinduction. This method relies on using repeated doses of 4 to 8 mg of buprenorphine to saturate MORs and reverse withdrawal symptoms. A recent case report from an emergency department setting detailed using a total dose of 20 mg of buprenorphine on the day of induction as a rescue strategy for precipitated withdrawal. Alternatively, macroinduction itself has also been described as an induction strategy, with a rela-

### TABLE 3

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Hydroxyzine</td>
<td>25–100 mg orally every 6–8 hours as needed (maximum 400 mg/day)</td>
</tr>
<tr>
<td></td>
<td>Lorazepam</td>
<td>1 mg every 4–6 hours as needed (maximum 6 mg/day)</td>
</tr>
<tr>
<td>Hypertension, tachycardia</td>
<td>Clonidine</td>
<td>0.1–0.2 mg every 6–8 hours, taper if given for &gt; 7 days</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Loperamide</td>
<td>4 mg initial dose followed by 2 mg after each loose stool (maximum 16 mg/day)</td>
</tr>
<tr>
<td>Myalgias, arthralgias</td>
<td>Acetaminophen</td>
<td>1,000 mg every 6–8 hours</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>600 mg every 6 hours for up to 7 days (maximum 2,400 mg/day)</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>Ondansetron</td>
<td>4 mg every 6 hours as needed (maximum 16 mg/day)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Trazodone</td>
<td>25–100 mg nightly (maximum 300 mg)</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>Cyclobenzaprine</td>
<td>5–10 mg every 8 hours as needed (maximum 30 mg/day)</td>
</tr>
<tr>
<td>Gastrointestinal cramps</td>
<td>Dicyclomine</td>
<td>10–20 mg every 6–8 hours as needed (maximum 160 mg/day)</td>
</tr>
</tbody>
</table>

Based on information in references 36, 39, and 40.
tively low risk of precipitated withdrawal when given in various dose increments up to 32 mg in a single day.31 Macroinduction is typically used in emergency medicine settings and merits further study as it may not be suitable for the outpatient primary care setting given the intense monitoring that is required.39

### TAKE-HOME MESSAGES

The increasing prevalence of OUD in the United States has led to mortality rates increasing to epidemic proportions. Buprenorphine is a MOR partial agonist approved for treatment of OUD. Advantages of induction with buprenorphine include its partial agonist properties that provide a ceiling effect and decrease the risk of overdose. Historically, buprenorphine treatment has been underutilized owing to prescribing restrictions and legal and pharmacologic barriers. While restrictions have been removed, thus positioning PCPs to be key prescribers of buprenorphine, pharmacologic challenges such as the risk of precipitated withdrawal still exist. Hence, standard induction guidelines suggest that patients take their first buprenorphine dose only after the onset of opioid withdrawal, which can be challenging with many patients now using fentanyl and experiencing complex, prolonged withdrawal.

LDBI is an alternate strategy that involves starting at and repeating small doses of buprenorphine and slowly titrating to therapeutic doses. These protocols can be implemented in primary care settings, with patients being able to complete most of the induction at home. Initiation in the primary care setting can help patients continue treatment and improves access to much needed OUD treatment.

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### REFERENCES


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### DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.
34. Salapenka I, Konakanchi JS, Sethi R. Outpatient rapid microinduction of sublingual buprenorphine in 3 days from methadone for opioid use disorder. Prim Care Companion CNS Disord 2022; 24(6):21cr03150. doi:10.4088/PCC.21cr03150
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Mpox: Keep it on the differential

ABSTRACT
In its current global outbreak, mpox has exhibited several novel clinical presentations that clinicians should be aware of so they can recognize it if they see it. Although the case rate has decreased, mpox could linger at a low rate or resurface in other populations and thus should remain in the differential diagnosis in patients presenting with potential infections after intimate encounters.

KEY POINTS
In its worldwide outbreak in 2022, mpox was remarkably different from its historic profile, a viral zoonotic disease that inefficiently spread from person to person.

Mpox is currently primarily affecting men who have sex with men and is mainly transmitted through direct contact with an infectious lesion.

Clinicians should keep mpox in the differential diagnosis for single, multiple, or diffuse genital, anal, or skin lesions, as well as pharyngitis and proctitis.

Patients with suspected mpox should also be tested for sexually transmitted infections including human immuno-deficiency virus (HIV), and should be offered HIV post-exposure or preexposure prophylaxis and mpox vaccine if appropriate.

Mpox, formerly known as monkeypox, is a viral zoonotic disease caused by the mpox virus. This review describes the epidemiology of the 2022 mpox outbreak, the clinical presentation and differential diagnosis of mpox, and its management and prevention.

RELATED TO SMALLPOX
The mpox virus is a double-stranded DNA virus in the genus Orthopoxvirus, family Poxviridae. This genus encompasses many poxviruses, including some that infect humans exclusively, some that infect various animal species exclusively, and some that are zoonotic. Other medically important orthopoxviruses include variola (the causative agent of smallpox, which was eradicated from nature in 1980), vaccinia (source of the modern smallpox vaccine), and cowpox (used by Jenner in 1796 to induce immunity to smallpox through inoculation).

There are two clades (subtypes) of mpox virus that have historically been described in different regions of Africa since the 1970s. Clade I virus has been responsible for zoonotic mpox disease in the Congo basin (Central Africa) and is thought to be more virulent, with mortality rates of approximately 10%. In West Africa, where clade II virus is the causative agent, the mortality rate has historically been low, less than 1%.

SHIFTING EPIDEMIOLOGY
 Animals to people
The epidemiology of mpox has shifted. From the 1970s, when it was first recognized in humans, until the early 2000s, mpox was an endemic zoonotic disease occurring sporadically in the rain forests of West and Central Africa among people who had direct contact with forest ani-
The clinical presentation of mpox has changed. The first case of mpox in the United States was recognized on May 17, 2022, in Massachusetts, and more cases were ultimately found in all 50 states over the subsequent months. The peak of the US outbreak was in early August, when the US Centers for Disease Control and Prevention (CDC) reported a 7-day average of 457 cases per day. As of June 23, 2023, there were 30,505 domestic cases and 88,026 worldwide.

In the United States, the mpox outbreak has been highly concentrated in certain populations. By far, most cases (95.8%) have been in cisgender men, most of whom identify as gay, bisexual, or other men who have sex with men. Racial and ethnic minorities have been disproportionately affected including Black communities (31.1% of cases) and Latin-American communities (29.9% of cases). Geographically, most cases have occurred in US states with large urban areas, particularly those with substantial lesbian, gay, bisexual, transgender, and queer or questioning populations.

**Usually sexually transmitted**

People are exposed to mpox virus primarily through direct physical—often intimate—contact with infectious lesions. Less commonly, mpox is transmitted through fomites, usually among close household contacts. Animal models demonstrate that mpox, like smallpox, can also be transmitted through respiratory droplets, but the contribution of this route of transmission to the current outbreak is thought to be negligible.

During the current outbreak, direct physical contact with infectious material from skin lesions or mucous membranes during sexual activity is considered the main risk factor for acquisition. While viral DNA has been detected in semen, saliva, urine, and feces, it is unclear whether contact with these fluids transmits infection, but there is mounting epidemiologic evidence that people with presymptomatic and possibly asymptomatic mpox are playing a role in spreading the disease, including a study that suggests that transmission can occur without a visible rash.

**The clinical presentation has changed**

The clinical presentation of mpox during the current outbreak has differed from the classic presentation described in endemic countries over the past several decades. Classically, mpox has been a systemic illness characterized by fevers, chills, and myalgias accompanied by a characteristic diffuse, centrifugal rash consisting of well-circumscribed, deep-seated pustules with central umbilication that were all in the same stage of development.
During the current outbreak, the clinical manifestations have been more protean. Key distinguishing features of the current outbreak are a wide range of severity of disease and, frequently, lesions at the site of inoculation.14

Recognizing mpox in immunocompetent patients
Patients with mpox may experience a range of symptoms, from asymptomatic isolated skin lesions without systemic illness to severe disseminated disease. In immunocompetent patients, infection tends to be less severe.

The incubation period can range from 4 to 21 days, with an average of 5.6 days from exposure to symptom onset and 7.5 days from exposure to rash onset.9 Prodromal symptoms are nonspecific and can include fever, lymphadenopathy, malaise, chills, pruritus, headache, myalgias, nausea, vomiting, or abdominal pain. Most patients experience at least 1 systemic symptom during their disease, but a minority have none.

The rash usually appears 1 to 2 days after prodromal symptoms begin. Of note: the appearance and distribution of the rash varies widely in the current outbreak. Patients may have a single lesion or multiple lesions at a single site (usually the site of inoculation), or disseminated lesions involving the extremities, trunk, or face. The lesion typically starts as a 2- to 5-mm red macule, progressing to a papule, then a vesicle, then a pseudopustule (filled with cellular debris with high amounts of virus). Finally, the lesion crusts over and the crust dries and falls off. The period from macule to reepithelization can be up to 14 days in immunocompetent hosts. New lesions may appear during the course of the illness, and thus can exist in different stages of development (Figure 1).15

Given that the main route of transmission during this outbreak is through sexual contact, inoculation frequently occurs in the genital area, anus, rectum, or oropharynx (Figure 2).16

Genital lesions. When genital inoculation occurs, patients may develop single, few, or many lesions on
the penis, scrotum, or pubis. The lesions are usually painful, but some patients report only mild itching or no symptoms. Most lesions heal without complication, but cases of severe edema leading to paraphimosis have been reported. Urethral involvement can lead to urethral strictures requiring urologic intervention. Confluent lesions can lead to ulcers or necrotic crusts.

**Anal or rectal lesions.** When inoculation occurs in the anus or rectum, patients may have external lesions on the buttocks, anal margin, or perianal skin that can cause significant pain with sitting or defecation. Isolated rectal mucosal disease without external rash has frequently been reported in men who have sex with men who participate in receptive anal intercourse. This manifests as proctitis, with symptoms that can include pain, tenesmus, and bloody or purulent discharge. Proctoscopy is usually not performed because it would be too painful, but friable tissue with pox lesions on the rectal mucosa has been described.\(^{17}\)

**Oropharyngeal lesions.** If oropharyngeal inoculation occurs, patients may have visible external lesions on the lips, vermilion border, or perioral area. However, external visible lesions are not always present. Lesions in the posterior oropharynx or tonsils may be the only manifestation in patients who have oral exposure. This can lead to ulcerative pharyngitis or tonsillitis, or in rare cases mass lesions that can threaten to block the airway.

**A link between mpox and HIV**

Severe manifestations and poor outcomes have been reported in people living with human immunodeficiency virus (HIV), particularly those with advanced HIV infection and acquired immunodeficiency syndrome (AIDS). A November 11, 2022, report cited an HIV prevalence of 57% in adults diagnosed with mpox,\(^{18}\) compared with 0.36% in the general adult population.\(^{19}\) It is not yet known whether HIV infec-

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**Figure 2.** Sites of mpox lesions in an observational cohort study in southern France. (A) Primary inoculation site showing an irregular pustule with necrotic crust of the right nipple. (B) Pustular lesions with a crusted center on the mucosa of the upper lip, close to the left oral commissure and left nasal orifice. (C) Pustules circumferentially distributed on the anal margin and perianal skin of varying sizes and stages of evolution, some with central necrotic crusts. (D) Perineally extended purpuric lesions. (E) Scrotal lesions of varying sizes and stages of evolution, with edema surrounding the larger ulcer-hemorrhagic ulcers. (F) Scattered papules, pustules, and umbilicated pustules surrounded by an erythematous halo on the back. (G) Reddened and swollen right palatine tonsil with a fibrin-covered ulcer. (H) Pustular lesion on the nose with a necrotic central crust, whitish deposit, and erythematous halo.

Adapted from reference 16.
tion affects an individual’s risk for acquiring mpox if the HIV infection is under control. It is plausible that there could be a biological mechanism for increased susceptibility to mpox in HIV-positive individuals, or that mpox and HIV both circulate in similar sexual-risk networks, thus increasing the overlap between the 2 conditions.

Severe mpox has often been reported in patients with low CD4 counts. A report from November 4, 2022, summarized findings from CDC clinical consultations for 57 patients hospitalized with severe mpox disease. Overall, 47 (82%) of the patients were living with HIV, but only 4 were receiving antiretroviral therapy, and 31 (72%) of 43 had a known CD4 count less than 50 cells per mm$^3$. Lesions in such immunocompromised hosts are often enlarging and nonhealing.

As of March 7, 2023, the CDC received reports of 52 deaths in persons with confirmed or probable mpox, including 38 deaths that were classified as mpox-associated, 3 that were classified as non–mpox-associated, and 11 that remained under investigation. Among the 38 mpox-associated deaths, information was available for 33 patients, and 31 (94%) of them were immunocompromised due to uncontrolled HIV.

Immunocompromising conditions other than advanced HIV infection may also predispose to severe mpox. The November 4, 2022, report noted severe disease in 2 patients undergoing chemotherapy for hematologic malignancy, 3 solid-organ transplant recipients, and 3 patients who were pregnant. Further investigations are needed to delineate the risk of severe disease in these populations.

Complications of severe mpox

Severe mpox can manifest as disseminated dermatologic disease with or without mucosal or organ involvement. In the 57 severe cases reported to the CDC, 39 (68%) of the patients had mucosal lesions (oral, urethral, rectal, or vaginal), 12 (21%) had pulmonary disease, 12 (21%) had ocular disease, 5 (9%) had muscle or bone involvement, and 4 (7%) had neurologic disease. About one-third of patients required intensive care.

Complications of severe dermatologic disease can include bacterial superinfections, viral superinfections (most commonly with herpes simplex virus), and the need for surgical debridement of necrotic tissue. Viremia in mpox disease occurs during initial spread of systemic infection. With pulmonary involvement, mpox has a range of manifestations including pulmonary nodules, severe pneumonia, or empyema. Ocular involvement is also protean and can present as conjunctivitis, blepharitis, periocular cellulitis, keratitis, or subconjunctival nodules, and can result in loss of vision.

**DIFFERENTIAL DIAGNOSIS**

The clinical presentation of mpox overlaps with those of other viral infections and sexually transmitted bacterial infections. The flulike prodrome is nonspecific, so before skin or mucosal lesions appear, the clinician should keep mpox in the differential diagnosis in the right epidemiologic context by obtaining a relevant sexual and exposure history.

**Molluscum contagiosum**

The classic deep-seated umbilicated pseudopustule of mpox is similar in appearance to those caused by molluscum contagiosum virus, another member of the poxvirus family but in a different genus than the orthopoxviruses.

Molluscum contagiosum can involve the trunk, extremities, groin, and genitals, as with mpox. It can occur in healthy children, adolescents, and adults. In adults and sexually active adolescents, it can be transmitted by intimate contact, as with mpox. However, molluscum contagiosum lacks the prodromal symptoms and takes on a more chronic time course, with most infections self-resolving in 6 to 12 months. However, in immunosuppressed patients (particularly in advanced HIV infection), molluscum contagiosum can appear more rapidly and diffusely and persist, increasing the clinical overlap between molluscum contagiosum and mpox disease.

**Herpesviruses**

When mpox is in the vesicular stage of development it can be difficult to differentiate from infection with herpesviruses such as herpes simplex virus and varicella zoster virus.

To evaluate for herpes simplex virus, the clinician should ask about previous oral or genital herpes attacks, since patients with oral or genital herpes often experience multiple subsequent outbreaks. In patients with no history of oral or genital herpes, primary herpes simplex virus infection can present with a prodrome and rash at the site of inoculation associated with tender lymphadenopathy, similar to mpox. The time course and evolution of the rash may help differentiate the 2 diseases: herpes simplex virus lesions progress from vesicles to erosions and ulcerations, while mpox lesions progress to firm pseudopustules.

Infection with varicella zoster virus, which causes chickenpox and shingles, can also mimic mpox. Shingles classically manifests as systemic symptoms associ-
MPox

ated with a dermatomal rash of erythematous, grouped vesicles with acute neuritis. In immunocompromised individuals, disseminated varicella virus infection may be considered if they have a diffuse rash.

Any rash that cannot be clinically identified with certainty should be sampled for polymerase chain reaction (PCR) testing for orthopoxvirus, herpes simplex virus, and varicella zoster virus.

Syphilis

Mpox lesions can mimic the chancre lesion of primary syphilis, which is classically described as a painless papule at the site of inoculation that progresses to a 1- to 2-cm ulcer with a raised, indurated margin. Importantly, a chancre can appear at any site where inoculation occurs, including the perioral area and oropharynx. Disseminated mpox can mimic some manifestations of secondary syphilis including pustular syphilis. In immunocompromised patients, disseminated mpox can resemble malignant syphilis (lues maligna), a severe ulcerative form of secondary syphilis.

Mucosal manifestations

Isolated oropharyngeal mpox may be mistaken for bacterial tonsillitis or primary oral herpes, while mpox proctitis may be clinically indistinguishable from chlamydial proctitis (including lymphogranuloma venereum), gonococcal proctitis, or syphilitic proctitis.

Chancroid, others

A less common cause of genital ulcers is Haemophilus ducreyi, the causative agent of chancroid. The classic presentation of chancroid is a deep, undermined, purulent ulcer associated with painful inguinal lymphadenitis. Since 2011, fewer than 20 cases per year have been reported in the United States.

### TABLE 1

<table>
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<th>Sample site</th>
<th>Screening</th>
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| Blood                        | HIV-1/HIV-2 antigen-antibody immunoassay (screening test)\(^a\)  
Nontreponemal test (eg, rapid plasma reagin), reflexively followed by treponemal test, if positive  
Hepatitis C antibody\(^b\)  
Hepatitis B surface antibody, surface antigen, and core antibody\(^c\) |
| Urine                        | Gonorrhea and chlamydia nucleic acid amplification test |
| Rectum (if patient participates in receptive anal intercourse or has rectal symptoms) | Gonorrhea and chlamydia nucleic acid amplification test |
| Oropharynx (if patient participates in oral intercourse or has oropharyngeal symptoms) | Gonorrhea and chlamydia nucleic acid amplification test |
| Vagina, cervix (if patient participates in vaginal intercourse or has vaginal symptoms) | Gonorrhea and chlamydia nucleic acid amplification test |
| Lesion (when clinically unable to differentiate between mpox and herpesvirus) | HSV-1 and HSV-2 polymerase chain reaction test  
Varicella virus polymerase chain reaction test |
| Not recommended              | Serologic testing for HSV-1 and HSV-2 antibodies (does not distinguish current from previous infection)  
Serologic HSV or varicella virus polymerase chain reaction test (insensitive and nonspecific for dermatologic infection) |

\(^a\)HIV-1/HIV-2 antigen-antibody immunoassay will detect HIV about 17 days after HIV acquisition. For patients with a potential exposure < 17 days and concern for acute retroviral syndrome, send for HIV nucleic acid amplification testing (viral load). Caution in patients on preexposure prophylaxis, which can result in delayed seroconversion and indeterminate results on HIV differentiation assay.

\(^b\)Sexually active men who have sex with men should undergo hepatitis C virus screening at least annually.

\(^c\)Men who have sex with men without serologic evidence of immunity to hepatitis B should undergo vaccination.

HIV = human immunodeficiency virus; HSV = herpes simplex virus
Other dermatologic conditions that manifest with pustules should be considered in the right clinical context. These include infectious causes such as disseminated gonococcemia and noninfectious causes such as eosinophilic folliculitis (particularly in those with advanced HIV), pustular psoriasis, and acute febrile neutrophilic dermatosis (Sweet syndrome).

**TESTING FOR MPOX**
Diagnostic testing should be performed in all cases of suspected mpox. This can be done through consultation with public health authorities or by sending swabs to commercial laboratories. PCR testing for orthopoxvirus DNA should be performed on lesion samples.

Lesions should be vigorously swabbed to collect skin cells. Unlike lesions in herpes simplex virus infection that are easily “unroofed” during swabbing, mpox lesions will not unroof, and one should not attempt to unroof them with sharp implements, since accidental infections have occurred after needle stick.22 If there are multiple lesions, samples should be taken from at least 2 lesions. If no skin lesions are present, samples can be taken from sites of symptoms like the rectum or oropharynx. Samples should be clearly labeled with the site of collection in the case of multiple specimens.

The role of skin biopsy is limited, given the ease of PCR testing, but could be considered if PCR testing is unavailable or inconclusive.

**Cotesting for sexually transmitted infections**
Patients with mpox are frequently co-infected with other sexually transmitted infections. A CDC report in the early months of the 2022 outbreak noted that 25% of patients with mpox also had chlamydia, 28% had gonorrhea, and 8% had syphilis.21 A review of mpox cases at our institution in Philadelphia showed a 52% seropositivity rate for current or prior syphilis and 21% co-infection with gonorrhea or chlamydia for those who underwent testing, and the rectal gonorrhea positivity rate was 31% (unpublished data).

Therefore, the evaluation for mpox should include testing for sexually transmitted infections including HIV and syphilis, and triple screening (urine, rectal, oropharyngeal sampling) for gonorrhea and chlamydia. We recommend the tests listed in Table 1 for all potential mpox patients. Gonorrhea and chlamydia testing should be based on anatomy rather than gender identity: screening recommendations for cisgender females should be extended to all transgender males and gender-diverse people with a cervix, and recommendations for cisgender males should be extended to all transgender females and gender-diverse people with male anatomy.

**MANAGEMENT**

**Supportive care for mild disease**
Management of mild disease in immunocompetent patients is primarily supportive because many patients with mpox recover without medical intervention. Pain control is the main concern.

Over-the-counter medications such as acetaminophen or nonsteroidal anti-inflammatory drugs are recommended as first-line therapy. Topical steroids or anesthetics such as lidocaine can be considered for local pain relief, but should be used with caution on broken skin or draining wounds. Patients should use gloves when applying topical agents to avoid autoinoculation. Other adjunctive therapies can include oral antihistamines to control pruritus, or topical agents such as calamine lotion or petroleum jelly.

Prescription pain medications such as gabapentin or opioids can be considered for pain not controlled with the above interventions. However, the risk of unintended consequences of long-term use of opioids should be carefully considered.

For proctitis, stool softeners to reduce pain with bowel movements should be considered. Topical lidocaine and warm sitz baths with baking soda or Epsom salts may provide additional symptomatic relief, but
patients should drain the bath and disinfect the tub after use. In severe cases, patients may require hospitalization for pain management.

For pharyngitis, patients can try rinsing the mouth with saltwater every 6 hours. Prescription analgesic mouthwash (sometimes called “magic mouthwash”) can also be used.\(^{24}\)

**Antiviral therapy for severe disease, or high risk of severe disease**

Tecovirimat is an antiviral drug that inhibits the orthopoxvirus protein VP37, preventing viral exit from the host cell. Tecovirimat therapy should be considered for patients with severe disease or at high risk of it (Table 2). These recommendations may change as further research becomes available.

Studies are ongoing to determine the optimal duration of treatment. The current recommendation is to treat immunocompetent patients for 14 days, starting as soon as the infection is confirmed or if clinical suspicion is high. Dosing and counseling information for tecovirimat can be found in Table 3.

Because tecovirimat was originally developed as a treatment for smallpox to address bioterrorism concerns, US Food and Drug Administration approval was not sought for the treatment of mpox disease. Oral tecovirimat is currently available by a CDC expanded-access program through local health departments for those who cannot enter a clinical trial. To access tecovirimat through this program, clinicians or facilities need to register with the CDC.\(^{25}\) However, we recommend referring the patient to a clinical trial if possible, since additional data are needed on efficacy and other measures. Multicenter clinical trials to evaluate efficacy are in phase 3, including the National Institute of Allergy and Infectious Diseases-supported Study of Tecovirimat for Human Monkeypox Virus (STOMP).\(^{26}\)

### Advanced therapies

Patients with severe mpox disease should be managed in consultation with an infectious disease expert or the CDC mpox consultation team (CDC Emergency Operations Center: 770-488-7100).

Considerations for treating severe disease or risk for progression to severe disease include optimizing immune function by limiting immunosuppressive agents, initiating antiretroviral therapy for those with uncontrolled HIV, extending or repeating the tecovirimat course, or adding other antiviral medications such as cidofovir or brincidofovir, and vaccinia immune globulin intravenous. Trifluridine eye drops should be used for ocular involvement.

Guidance for treatment of severe mpox is being updated as more information becomes available, and current recommendations can be found on the CDC website.\(^{27}\)

### Infection Control in Healthcare Settings

In both inpatient and outpatient settings, patients with suspected or confirmed mpox should be assigned to single-occupancy rooms with private bathrooms if possible. Negative-pressure isolation is not required but can be used if available. Providers should wear personal protective equipment including gowns, gloves, and eye protection. Though there is currently no epidemiologic evidence that mpox is transmitted by the airborne route, a N95 respirator is also recommended to prevent the need to change the type of mask in the event that an aerosol-producing activity is performed.\(^{28}\)

### Infection Control at Home

While they are having symptoms of acute illness (eg, fever, systemic symptoms, and respiratory symptoms),
patients should isolate themselves and take the following precautions to avoid transmitting the virus to household contacts:

- Cover all lesions with clothing
- Avoid sharing clothing, towels, face masks, and other household items such as eating utensils
- Wear a well-fitting mask when in close proximity to others
- If sharing a bathroom, disinfect surfaces after use
- Practice frequent hand hygiene
- Avoid close contact with pets, given the risk of reverse zoonosis.29

After the acute illness has passed but the skin lesions are still resolving, patients should cover all lesions with clothing and continue to perform frequent hand hygiene, avoid sharing items, and wear a mask. Full isolation is no longer required when systemic symptoms have resolved. Skin lesions should be considered infectious until all scabs have fallen off and re-epithelialization has occurred, which is generally 2 to 4 weeks in immunocompetent hosts.

### HIV PROPHYLAXIS

All patients with mpox should be evaluated for HIV disease and prevention needs.

HIV-negative patients who present within 72 hours of a possible HIV exposure should receive nonoccupational postexposure prophylaxis with an approved antiretroviral regimen with appropriate baseline and follow-up HIV testing.

Patients who qualify for preexposure prophylaxis (Table 4) should be screened for HIV and started on preexposure prophylaxis expeditiously rather than treatment.

Since most cases of mpox during the current outbreak have been sexually acquired, we would consider a diagnosis of mpox as an indication for a discussion of preexposure prophylaxis, unless a nonsexual route of acquisition can be established.

#### VACCINIA VACCINATION

The live, nonreplicating, modified vaccinia Ankara vaccine has been offered to individuals at high risk for mpox. Between May and October of 2022, nearly 1 million doses were administered in the United States. Vaccination consists of 2 doses, 28 days apart, given subcutaneously or intradermally. Preliminary estimates suggest that the full 2-dose series is between 60% and 80% effective.30 Though modified vaccinia Ankara is considered a live vaccine, it is replication-deficient and thus does not produce infectious virus in humans and can be given to immunocompromised individuals.

#### CONDOMS ARE NOT EFFECTIVE PROTECTION AGAINST MPOX

Because mpox is transmitted through direct contact with infectious lesions, barrier protection (condoms) will only impede transmission by lesions on the genitals. For groin or suprapubic lesions, barrier protection will be insufficient. Patients should be counseled that condoms, while effective for STIs such as gonorrhea and chlamydia, should not be relied on as effective mpox protection.

#### LESSONS LEARNED, LESSONS TO BE LEARNED

The mpox outbreak occurred at a time when public health and medical communities were still reeling from the impact of COVID-19. Mpox presented similar but also distinct challenges. While strategies for testing, vaccine distribution, and rapid information dissemination could be applied to this new challenge,
mipox brought issues of stigma and homophobia to the forefront. For many, this stigmatization of mipox was reminiscent of the HIV-AIDS epidemic in the mid-1980s. While the public health response brought about some successes, there have certainly been lessons learned.

It is not yet clear what the future of mipox in non-endemic regions will be. Further clinical research is needed to characterize the epidemiology of mipox transmission including the extent to which asymptomatic individuals contribute to spread, and the risk for reverse zoonosis that could result in establishment of an animal reservoir in nonendemic regions. In addition, clinical trials are needed, designed to elucidate the optimal treatment strategies for the range of mild to severe disease. Finally, ensuring equitable access to mipox vaccination and treatments, not just in the United States but in developing countries through global assistance programs, will decrease the risk of re-emergence.

**DISCLOSURES**

Dr. Isacs has disclosed contributing medical chapters for UpToDate. The other author reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

**REFERENCES**


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