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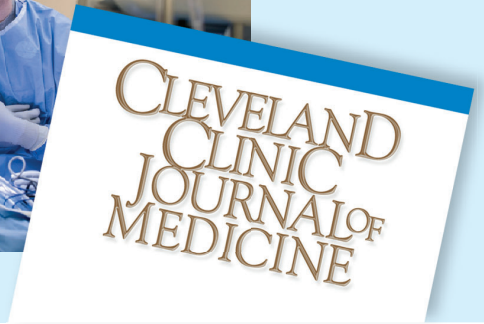

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CLEVELAND CLINIC JOURNAL OF MEDICINE

A tale of scale: Corticosteroids and pustular psoriasis

In this issue of the *Journal*, Wong and colleagues[1] describe a severe episode of generalized pustular psoriasis (GPP) in a 69-year-old man with known plaque psoriasis. The episode occurred after repeated courses of systemic corticosteroids for treatment of recalcitrant calcium pyrophosphate arthritis ("pseudogout").

Recognizing GPP is important, as a high proportion of patients with GPP are systemically ill, and may develop secondary infections with sepsis and multiorgan failure.[2,3] It is often considered a variant of plaque psoriasis—in different series, about 30% to 80% of patients had a history of plaque psoriasis[2]—but it can occur in isolation and has a pathobiology distinct from more routine psoriasis. The pathobiology seems unique, with a dependence on interleukin-36 that is of sufficient magnitude that the interleukin-36 receptor antagonist spesolimab has received regulatory approval specifically for the treatment of GPP flares.[4]

GPP is rare. It seems to be more common in Asian individuals and in women. Subsets of patients have been described with various propensities to recur or have a protracted course. Several case series have described probable precipitants, including infections, pregnancy, external stress, and medications. Best known to internists is the feared association of GPP with withdrawal of corticosteroid therapy prescribed for severe plaque psoriasis or other inflammatory conditions, as presented in this issue by Wong et al.[1]

Digging into the literature on the association of GPP with corticosteroids, given the rarity of this condition, with a few cases per 100,000 patients, it is not surprising to find that there is controversy surrounding the relative need to avoid corticosteroids in patients with psoriasis. Guidelines and textbooks have reinforced concern over the use and withdrawal of corticosteroids in patients with psoriasis, yet strong evidence that defines this association is hard to come by, and corticosteroids seem to be prescribed fairly often.

In 1968, Baker and Ryan[5] described 104 patients with GPP. In approximately one-third of the subset of these patients who had long-standing psoriasis and developed GPP, prior use of corticosteroids was implicated as a trigger for its onset. This and several smaller reports prompted widespread concern regarding corticosteroid treatment for psoriasis. Yet patients with psoriatic arthritis or severe psoriasis, or both, are frequently treated with systemic[6] or intra-articular corticosteroids while waiting for nonsteroid immunosuppressive medications such as methotrexate to take effect or for insurance approval of a newer biologic or targeted biochemical therapy. Gregoire et al[7] in 2021 described 516 patients with preexisting psoriasis who had been treated with systemic corticosteroids and had evaluable follow-up; the calculated flare rate was 1.4%. Attribution of corticosteroids as the cause is difficult, and no flares were described as GPP. One patient had erythroderma

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and responded to a course of corticosteroids. As seen in many of the papers attempting to analyze the relationship between corticosteroids and psoriatic flares, defining a "flare" can be difficult, especially in retrospective studies.

In a systematic review of the literature on psoriatic flares following corticosteroid treatment and withdrawal, Vincken et al[8] selected 21 studies that compared corticosteroid use with no use in patients with psoriasis or psoriatic arthritis. Between 3% and 26% of patients with psoriasis were prescribed corticosteroids in these studies. The 10 observational/interventional studies reviewed did not demonstrate an increase in psoriatic flares of any type after corticosteroid treatment. These included 2 randomized trials comparing the use and non-use of corticosteroids. Notably, the patients in the randomized trials also had received methotrexate or biologic therapy, which may have prevented flares. No information on pustular flares was presented.[8] The authors note in their discussion the metabolic and other risks of corticosteroid therapy, which I think should be highlighted in a patient population already at high risk for the complications from metabolic syndrome. However, the demonstrated benefits of faster disease control gained by adding short-term corticosteroid therapy to methotrexate or other disease-modifying medications should also be noted.

Thus, it seems that corticosteroid use or withdrawal may not be associated with psoriasis flares as often as many of us were taught. Some reported flares with tapering in the older literature may have reflected rebound of incompletely controlled disease on withdrawal of effective therapy, a phenomenon that may occur less often now due to co-administration of effective disease-modifying therapies. Yet we still see descriptions of patients who do have flares,[1] including rare pustular psoriatic flares related to medications. Examples are flares on withdrawal of corticosteroids and the odd but well-recognized occurrence of palmoplantar pustulosis associated with the use of tumor necrosis factor-alpha inhibitors. The perception, and perhaps the reality, that psoriasis flares are occasionally triggered by corticosteroids is reflected in a summary of the US Food and Drug Administration's Adverse Event Reporting System from 2016 to 2021[9]: prednisone was the leading reported drug for exacerbating or inducing psoriasis, excluding drugs approved to treat psoriasis.

So while caution, careful observation, and patient communication are prudent, the use of corticosteroids to calm severe psoriatic inflammation in skin and joints while awaiting the beneficial effect of a long-term anti-psoriatic medication may have a role in selected patients.

Brian F. Mandell, MD, PhD
Editor in Chief

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2024

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2023 Update in ambulatory general internal medicine

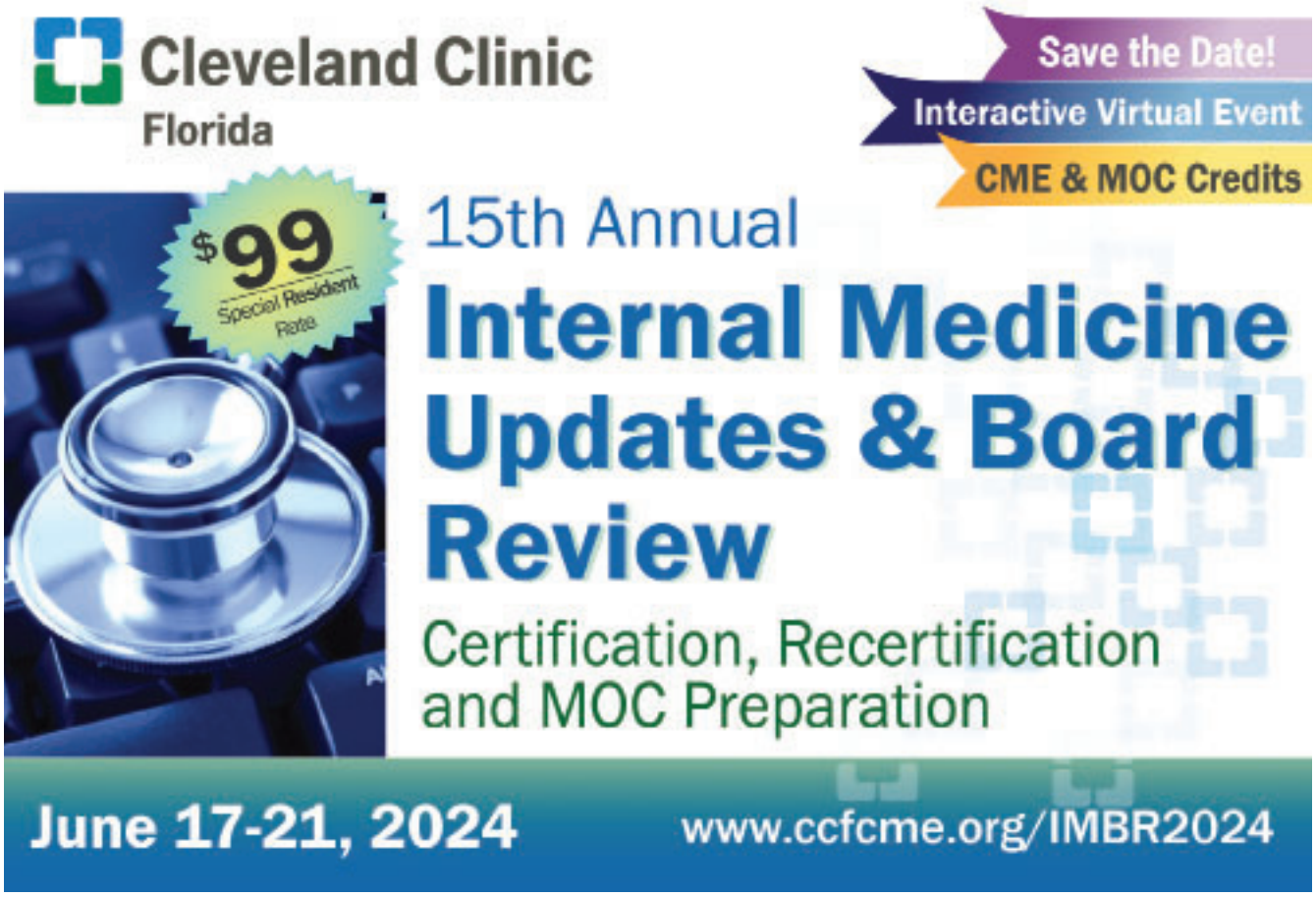
To the Editor: I am writing to express my gratitude for the insightful article "2023 Update in ambulatory general internal medicine" by Jason T. Alexander, MD, and colleagues[1] published in the January 2024 issue of the *Journal*.

The authors have succinctly addressed the challenges faced by internists practicing ambulatory medicine, emphasizing the overwhelming nature of managing acute concerns, chronic medical problems, and disease prevention within time-pressure constraints. Their review of 5 significant studies from 2022 and 2023 covering chronic kidney disease, secondary cardiovascular disease, kidney stones, obesity, and lipid management provides valuable insights for the ambulatory medical community.

The discussion about the use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, specifically empagliflozin, is enlightening. However, as highlighted in the Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY),[2] the benefits were most pronounced in patients with significant albuminuria. Given this, I wonder if there is a need for further clarification on the potential benefits of empagliflozin or alternative SGLT-2 inhibitors in patients without albuminuria.[3] A discussion on the potential benefits, risks, and cost, as suggested in the article, would be valuable in guiding clinical decisions.[4]

Furthermore, the authors provide an excellent overview of diet as secondary prevention, particularly emphasizing the superiority of a Mediterranean diet over a low-fat diet. However, it might be pertinent to explore the feasibility and accessibility of such dietary recommendations for patients, considering cultural and socioeconomic factors. This could aid in tailoring dietary advice to the needs of individual patients.[5]

In conclusion, the authors have done an admirable job in synthesizing complex medical information



for the benefit of practitioners in ambulatory medicine. I appreciate their efforts and hope for continued updates and discussions on the practical application of these findings in clinical practice.

Ashley Lim, Medical student
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doi:10.3949/ccjm.91c.03001

In Reply: We appreciate Ashley Lim's close read of our review. Regarding the use of SGLT-2 inhibitors in patients without albuminuria, as we point out, the EMPA-KIDNEY trial[1] was the first large randomized trial of SGLT-2 inhibitors to enroll patients with chronic kidney disease without albuminuria. Two other large randomized trials of SGLT-2 inhibitors have evaluated patients with chronic kidney disease with or without diabetes, but both required some degree of albuminuria.[2,3] Thus, we conclude that there is currently no convincing evidence to support using SGLT-2 inhibitors to prevent kidney disease progression in patients with chronic kidney disease without significant albuminuria. Given the higher rates of cardiovascular disease among patients with chronic kidney disease, managing cardiovascular risk (eg, reducing systolic blood pressure in patients with hypertension or initiating statin therapy)[4] should be prioritized over initiating SGLT-2 inhibitors for these patients until such evidence emerges.

Regarding the feasibility of recommending a Mediterranean diet over a low-fat diet for secondary prevention of major cardiovascular events, we share Lim's concern that many patients are not able to access, afford, or implement such a diet. Additional measures available to participants of the Delgado-Lista et al study,[5] including individual and group appointments with dietitians both in person and by telephone, are also unlikely to be available to the majority of patients who may benefit from a Mediterranean diet. Despite these limitations, we found that this study provides important insights into dietary recommendations that clinicians may use when counseling patients with previous cardiovascular disease.

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Steroid use triggers severe psoriatic reaction

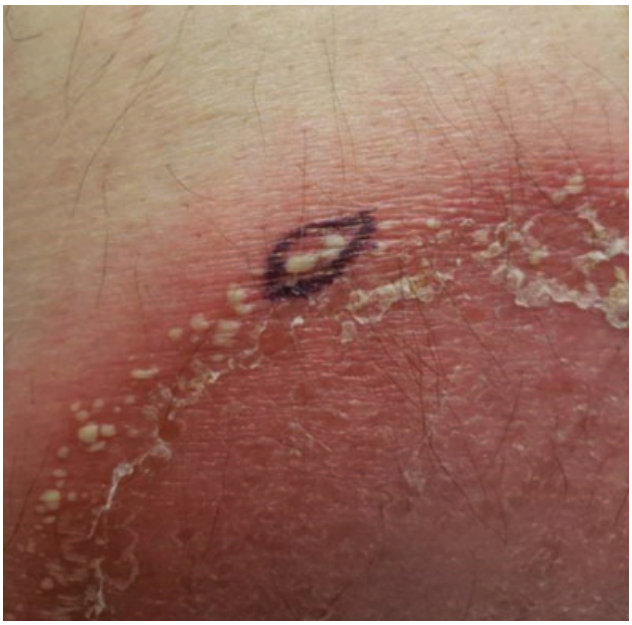

Figure 1. After tapering prednisone, the patient developed a circular plaque bordered with pustules superimposed on erythematous skin. The pustules expanded centrifugally.

A 69-year-old man with well-controlled plaque psoriasis who presented to the emergency department for unilateral wrist pain was found to have calcium pyrophosphate deposition disease. Symptoms improved with a 7-day course of oral prednisone 30 mg twice daily without tapering. Attempts were made to control his symptoms with other recommended treatments for calcium pyrophosphate deposition disease, including colchicine and intra-articular steroid injection, but the pain recurred and only prednisone provided relief. Nonsteroidal anti-inflammatory drugs were not started because the patient was on long-term anticoagulant therapy. Two rounds of prednisone 20 mg twice daily for 5 days with a 5-day taper to 7.5 mg daily were prescribed, with an intention to continue until a follow-up visit with a rheumatologist could be scheduled.

doi:10.3949/ccjm.91a.23060

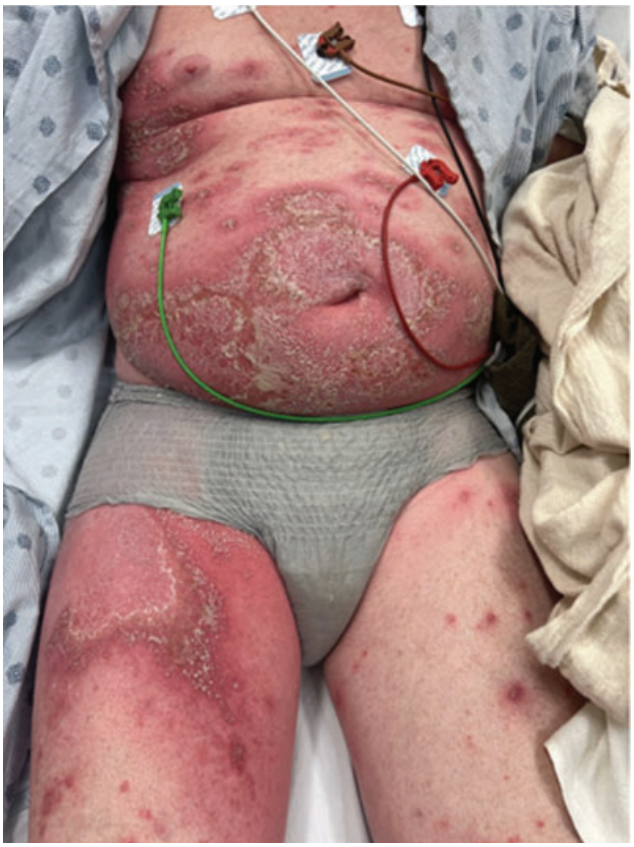

Figure 2. Widespread generalized pustular psoriasis involved both lower extremities and the torso.

After tapering the second round of prednisone, the patient developed a circular plaque bordered with

pustules that expanded centrifugally (**Figure 1**). Punch biopsy results, in addition to the patient's relevant clinical history, were consistent with generalized pustular psoriasis (GPP). Topical clobetasol ointment 0.05% was started due to patient preference, but the painful pustular plaques spread to his extremities and torso.

Severe pain and fever led him to present to the emergency department where at presentation 50% of his body surface was affected by pustular lesions (**Figure 2**). Additionally, his left lower leg was tender, erythematous, and warm, suggestive of cellulitis. On admission, laboratory tests revealed an elevated erythrocyte sedimentation rate of 27 mm/hr (reference range 0–20 mm/hr) and hypoalbuminemia of 3.6 g/dL (4.0–4.9), but a normal white blood cell count of 10.2 × 10^9/L (4.5–11.0), normal levels of aspartate aminotransferase at 12 U/L (< 41) and alanine transaminase at 21 U/L (< 41), and no electrolyte abnormalities.

Administration of cyclosporine 250 mg twice a day and continued topical clobetasol 0.05% ointment for GPP in conjunction with vancomycin for lower-extremity cellulitis led to rapid improvement during his 5-day admission. He left the hospital on the same cyclosporine dose and continued to improve. About 3 months after starting cyclosporine, he was tapered off the medication after changing to risankizumab.

GENERALIZED PUSTULAR PSORIASIS

GPP is an uncommon but severe form of psoriasis vulgaris characterized by widespread eruption of sterile neutrophil-filled pustules superimposed on erythematous skin.[1,2] Skin findings are often accompanied by systemic symptoms such as arthralgias, myalgias, and fever. Common abnormalities on laboratory tests include leukocytosis with neutrophilia and elevated erythrocyte sedimentation rate.[1–3] Hepatic function, hypoalbuminemia, and electrolytes are less commonly affected.[1–3] Patients typically have a history of psoriasis.[1,4,5]

Though most cases of GPP are idiopathic, triggers include medication withdrawal (particularly corticosteroids), infection, pregnancy, hypocalcemia, and sun exposure.[1,5] In this patient's case, the history suggests the psoriatic flare developed prior to the onset of cellulitis, and thus the infection was likely a complication rather than an inciting factor.

The differential diagnosis for GPP includes acute generalized exanthematous pustulosis, subcorneal pustular dermatosis, immunoglobulin A pemphigus, and pemphigus foliaceus, all of which can present with similar skin manifestations.[2,5] Patients with acute generalized exanthematous pustulosis rarely have a history of psoriasis, are eosinophilic on workup, and develop symptoms abruptly after the initiation of new medications. After the inciting drug is stopped, patients with acute generalized exanthematous pustulosis rapidly improve.[2,5] Subcorneal pustular dermatosis rarely causes systemic manifestations.[6] Acute generalized exanthematous pustulosis, subcorneal pustular dermatosis, immunoglobulin A pemphigus, and pemphigus foliaceus can all be distinguished histologically, and skin biopsy can help differentiate or confirm the diagnosis.[2,5,6]

First-line treatment for GPP includes acitretin, cyclosporine, methotrexate, or infliximab. Targeted medications including interleukin-17, interleukin-23, and interleukin-36 inhibitors have also recently been shown to be effective.[4,7]

RISK ASSESSMENT

Prescribing of systemic corticosteroids is ubiquitous across specialties. Practitioners must be aware of the potential risk of triggering a GPP flare in patients with psoriasis, and other recommended treatments should be attempted. Our patient had failed or had contraindications to typically recommended treatments for calcium pyrophosphate deposition disease, except for systemic corticosteroids. Tapering vs not tapering prednisone has not been shown to reduce the risk of triggering GPP.[1] Ultimately, when balancing the risks and benefits of systemic corticosteroids, practitioners must include the risk of triggering GPP in patients with psoriasis. This necessitates shared decision-making and patient education, including information on warning signs and close monitoring.

DISCLOSURES

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

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Is there a role for chronic suppressive therapy in herpes simplex virus infection?

A: Yes. The primary role of chronic suppressive therapy in herpes simplex virus (HSV) infection is to decrease the frequency, severity, and duration of outbreaks, and to reduce the risk of transmitting the virus to others. It is indicated in patients with recurrent oral and genital HSV-2 infection and oral HSV-1 infection. However, there is no clear proven benefit in providing chronic suppressive therapy in recurrent genital HSV-1 infection.

WHAT IS HSV INFECTION?

HSV infection is caused by 1 of 2 types of herpes viruses: HSV-1 and HSV-2. HSV-1 primarily causes oral herpes but can also cause genital herpes. It typically manifests as cold sores or fever blisters around the mouth. Transmission usually occurs through direct contact such as kissing, or by sharing items like utensils, cosmetics, or towels. In recent years, due to changes in sexual practices, HSV-1 has been causing an increasing number of genital herpes cases.[1] HSV-2 is mainly responsible for genital herpes, resulting in sores or blisters on or around the genitals or rectum. It is mainly transmitted through sexual contact.

The initial episode of HSV infection can be categorized as either primary (ie, in patients without existing antibodies) or nonprimary (in patients with preexisting antibodies to the virus). Symptoms such as painful sores, fever, body aches, swollen lymph nodes, and headaches are more pronounced in primary infection than in nonprimary HSV-2 infection.[2] While the virus is highly contagious during outbreaks of visible sores, it can also be transmitted without any noticeable symptoms, a phenomenon known as asymptomatic shedding.[3]

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HOW DO YOU TREAT INITIAL HSV INFECTION?

There is no cure for HSV infection. Antiviral medications such as acyclovir, valacyclovir, and famciclovir can mitigate the severity, frequency, and duration of outbreaks and lower the risk of transmission. It is crucial to start antivirals as soon as possible, ideally within 72 hours of symptom onset.[4]

The primary objective of antiviral medications is to reduce the duration and severity of the disease by days to weeks. Oral antiviral medications have been shown to decrease the severity of symptoms, reduce the duration of pain, accelerate lesion healing, and minimize viral shedding in patients experiencing their first episode of primary genital HSV infection.[4] The US Centers for Disease Control and Prevention recommends 7 to 10 days of acyclovir 400 mg orally 3 times a day, famciclovir 250 mg orally 3 times a day, or valacyclovir 1,000 mg orally 2 times a day.[5] The dose of these medications needs to be adjusted based on the patient's creatinine clearance rate. Valacyclovir is an alternative to acyclovir, offering the advantage of more convenient administration with comparable efficacy.[4] No randomized trial has compared the efficacy with famciclovir.

WHAT IS RECURRENT HSV?

HSV can lead to recurrent outbreaks. After the initial infection, HSV remains dormant in the sensory nerve ganglia and may reactivate under stress, illness, or immunosuppression, causing subsequent outbreaks. The frequency of these outbreaks may diminish over time.[6] HSV-2 is associated with a higher rate of recurrence (a median of 4 times per year) than HSV-1 (with

TABLE 1
Episodic treatment regimens for recurrent herpes simplex virus infection

Medication	Dose and duration
Acyclovir	800 mg 3 times daily for 2 days 800 mg twice daily for 5 days
Famciclovir	1,000 mg twice daily for 1 day 500 mg once, then 250 mg twice daily for 2 days 125 mg twice daily for 5 days
Valacyclovir	500 mg twice daily for 3 days 1,000 mg once daily for 5 days

Based on information in reference 5.

TABLE 2
Chronic suppressive regimens in patients without and with HIV infection

Medication	Patients without HIV	Patients with HIV or immunosuppressive condition
Acyclovir	400 mg twice daily	400 mg to 800 mg 2–3 times a day
Valacyclovir	500 mg to 1,000 mg once daily	500 mg twice daily
Famciclovir	250 mg twice daily	500 mg twice daily

HIV = human immunodeficiency virus

Based on information in reference 5.

a median of once per year).[7] The initial treatment does not reduce the frequency of these recurrences.[8] Recurrent HSV can be managed with either episodic or chronic suppressive therapy.

HOW DO YOU DIFFERENTIATE HSV-1 AND HSV-2 INFECTION?

For patients with active genital lesions, type-specific virologic testing by culture or nucleic acid amplification should distinguish HSV-1 from HSV-2 lesions. In the absence of active genital lesions, serologic tests can help differentiate the cause of recurrent oral and genital lesions. However, because many asymptomatic people test positive for antibodies, serologic testing is not routinely indicated in the general population and should be used only to determine risk for a partner who may be discordant (ie, not previously positive for HSV-1 or HSV-2 on serologic testing).[9]

EPISODIC THERAPY VS CHRONIC SUPPRESSIVE THERAPY

Episodic treatment is self-administration of the medication at the first signs of prodromal symptoms such as tingling, paresthesia, and itching to prevent the onset of the outbreak (**Table 1**).[5] Early administration of antivirals has been shown to be beneficial.[4] Episodic therapy can shorten the time to crusting and healing of lesions and can also decrease viral shedding.[10] Episodic regimens are typically shorter in duration than initial therapy and can vary from 1 day to 5 days. Patients with human immunodeficiency virus (HIV) infection should be treated for 5 days.

For HSV-2 infection, chronic suppressive therapy is preferred over episodic therapy, as it has been linked to greater treatment satisfaction and a decreased risk and frequency of recurrence.[11] No data are available regarding its efficacy in preventing transmission among individuals with genital herpes caused by HSV-1. Because HSV-1 infection carries a lower rate of recurrent outbreaks than HSV-2, most patients with genital HSV-1 infection do not require suppressive therapy.[1]

WHICH PATIENTS BENEFIT MOST FROM CHRONIC SUPPRESSIVE THERAPY?

Unfortunately, the antiviral drugs used to treat the initial episode of HSV infection do not eradicate the latent virus, nor do they influence the risk, frequency, or severity of recurrences once the drug is discontinued. As a result, chronic suppressive therapy is recommended for patients with a history of genital HSV-2 infection who experience frequent or severe outbreaks.[4] This recommendation also extends to patients with risk factors such as ongoing immunosuppression (solid-organ transplant, bone marrow transplant, HIV) and patients with a history of genital herpes who have multiple partners or partners who are discordant.[12]

Chronic suppressive therapy has been found to reduce the frequency of genital herpes recurrences by 70% to 80%.[5,11,13] In addition to decreasing the severity of symptoms[2] and reducing the frequency of outbreaks,[13] suppressive therapy has been shown to reduce asymptomatic viral shedding, thereby decreasing the potential for transmission to HSV-uninfected sexual partners.[3]

Currently recommended agents for chronic suppressive therapy include acyclovir, valacyclovir, and famciclovir (**Table 2**).[5] Once-daily treatment with valacyclovir 500 mg has been shown to decrease the

rate of HSV-2 transmission in discordant heterosexual couples where 1 partner has a history of genital HSV-2 infection.[14]

However, for HSV-2, the question remains whether reducing the frequency of recurrences equates to a lower risk of transmission to sexual partners. Kim et al[15] found that the severity of HSV-2 infection defined as the frequency of recurrences did not help identify patients most likely to transmit the infection to a discordant partner.[15] A higher daily dose of valacyclovir (1,000 mg) is recommended in patients who have 10 or more episodes per year.[13] Higher doses are typically recommended for patients with HIV and in pregnant women to prevent neonatal herpes infections.[5] Patients should be evaluated annually for continuation of chronic suppression.[5]

THE BOTTOM LINE

Chronic suppressive therapy is recommended for patients with recurrent genital HSV infection. It is effective in decreasing the frequency and severity of symptoms, and can decrease viral shedding and transmission from HSV-2-infected patients to sexual partners. HSV-1 is associated with a lower risk of recurrent infection.[7] Current available data do not show a clear benefit of chronic suppressive therapy in patients with recurrent HSV-1 infection.

DISCLOSURES

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Multiple metabolic renal manifestations of a systemic disease

A 39-YEAR-OLD WOMAN with a history of depression, anxiety, and recurrent nephrolithiasis with calcium phosphate and calcium oxalate stones presented to the emergency department after 5 days of generalized weakness and right-upper-quadrant abdominal pain. She complained of having had dyspnea, arthralgia, and dry eyes and dry mouth for a long time. She did not have chest pain, fever, nausea, vomiting, abdominal pain, or diarrhea.

She had been taking sertraline 100 mg twice a day, bupropion 150 mg daily, clonazepam 1 mg daily, trazodone 300 mg at bedtime, and ibuprofen 200 mg twice a day as needed. She noted smoking half a pack of cigarettes per day but denied using alcohol or any recreational drugs. She worked as a teacher. Her family history was unremarkable.

On physical examination, her temperature was 99.9°F (37.7°C), blood pressure 118/67 mm Hg, heart rate 90 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation 100% on room air. Her eyes and oral mucosa were dry, and she had excessive dental caries. Her first and second heart sounds were audible, and there were crackles in both lungs. Her abdomen was soft and nontender with no masses, splenomegaly, or hepatomegaly. There was clubbing in her fingers and toes but no edema. The results of her neurologic examination were normal except for generalized weakness.

Table 1 shows the patient's initial basic laboratory values, arterial blood gas values, and urine electrolyte concentrations. Results of urinalysis were unremarkable, and her urine pH was 6.0. Her 24-hour urine citrate excretion was 104 mg (reference range > 320), and her 24-hour urine calcium excretion was 360 mg (< 250).

Her electrocardiogram was unremarkable. Computed tomography of the chest and abdomen showed ground-glass and consolidative opacities in both lungs consistent with interstitial lung disease, multiple nonobstructive bilateral renal calculi, and nephrocalcinosis.

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CHARACTERIZING HER ACID-BASE DISORDER

1 What is the most likely cause of this patient's acid-base disorder?

- ☐ Vomiting
- ☐ Diarrhea
- ☐ Distal (type 1) renal tubular acidosis
- ☐ Proximal (type 2) renal tubular acidosis

First, let's characterize her acid-base disorder, using a stepwise approach:

- **Acidemia or alkalemia?** Our patient's blood pH was 7.34, indicating acidemia.
- **Metabolic or respiratory?** Her partial arterial pressure of carbon dioxide was 40 mm Hg, which was not elevated (reference range 35–45), and her serum bicarbonate level was low at 20 mmol/L (21–32). Therefore, the primary metabolic disorder was metabolic acidosis.
- **Normal anion gap?** The anion gap can be calculated as the serum sodium concentration minus the sum of the serum chloride and bicarbonate concentrations. The values for our patient were 148 – (115 + 20) = 13 mmol/L, with normal being 12 to 14. This supported the diagnosis of normal anion gap metabolic acidosis.
- **Is there appropriate compensation?** According to the Winter formula, the expected partial arterial pressure of carbon dioxide should be 1.5 times the bicarbonate level, plus 8, plus or minus 2. The patient's values were (1.5 × 20) + 8 = 38 ± 2 mm Hg. Her measured value was 40 mm Hg, so she was within the expected range and had appropriate respiratory compensation.

TABLE 1
Laboratory results

Tests	Results[a]	Reference range
Sodium	**148 mmol/L**	136–145
Potassium	**3.1 mmol/L**	3.5–5.1
Chloride	**115 mmol/L**	98–107
Bicarbonate	**20 mmol/L**	21–32
Blood urea nitrogen	**24 mg/dL**	7–18
Creatinine	1.0 mg/dL	0.6–1.3
Glucose	74 mg/dL	60–99
Calcium	9.2 mg/dL	8.4–10.5
Hemoglobin	**10.2 g/dL**	13.9–16.3
White blood cell count	5.99 × 10^9/L	4.5–11.0
Neutrophils	67.6%	46.2%–80%
Lymphocytes	18.5%	10.3%–40.5%
Monocytes	12.7%	3.0%–14%
Eosinophils	1.0%	0.0%–-5.0%
Basophils	0.2%	0.0%–1.0%
Platelet count	311 × 10^9/L	150–350
Alanine aminotransferase	50 U/L	6–65
Aspartate aminotransferase	26 U/L	3–37
Alkaline phosphatase	87 U/L	45–117
Bilirubin, total	< 0.2 mg/dL	0.2–1.2
Albumin	3.7 g/dL	3.5–5.0
Magnesium	2.3 mg/dL	1.8–2.4
Serum osmolality	**303 mOsm/kg**	275–295
Phosphorus	**2.1 mg/dL**	2.5–4.9
Thyrotropin	1.59 mIU/L	0.5–4.5
Arterial blood gasses		
pH	**7.34**	7.35–7.45
Partial pressure of carbon dioxide	40 mm Hg	35–45
Partial pressure of oxygen	95 mm Hg	75–100
Urine		
Random sodium	67 mmol/L	20–214
Random potassium	**8 mmol/L**	17–95
Random chloride	53 mmol/L	24–255
Random urea	207 mg/dL	132–1,629
Osmolality	165 mOsm/kg	50–1,200

[a]Abnormal results are in boldface.

Therefore, our patient had primary normal-anion-gap metabolic acidosis with appropriate respiratory compensation. As for the answer choices, vomiting is associated with chloride-responsive metabolic alkalosis, not acidosis. Diarrhea and renal tubular acidosis can both cause normal-anion-gap metabolic acidosis and can be differentiated by calculating the urine anion gap, calculating the urine osmolal gap, and checking urine pH.

The urine anion gap can be calculated by adding the urinary sodium and potassium concentrations and then subtracting the chloride concentration. Normally, ammonium is the major unmeasured urinary cation. In metabolic acidosis caused by diarrhea when the urinary acidification mechanisms are intact, urinary excretion of ammonium and chloride is significantly increased to maintain electroneutrality, leading to a negative urine anion gap because urinary chloride would then exceed the sum of urinary sodium and potassium.

The urine osmolal gap is an indirect measure of ammonium excretion and can be used to diagnose and determine the type of renal tubular acidosis. In distal renal tubular acidosis, the urinary acidification mechanisms are impaired and the urine osmolal gap is less than 150 mOsm/kg, while it is usually more than 400 mOsm/kg in other disorders in which the renal response to acidemia remains intact, such as diarrhea.[1]

Urine pH is another important factor in diagnosing and determining the type of renal tubular acidosis. Normally, in metabolic acidosis of any type, the urine pH is 5.3 or lower as a compensatory mechanism. Distal renal tubular acidosis, caused by impaired hydronium secretion in the alpha-intercalated cells in the distal nephron, is characterized by an inability to lower the urine pH to less than 5.5 under the stimulus of systemic acidosis. It is associated with hypokalemia, nephrolithiasis, nephrocalcinosis, and hypocitraturia.[2] On the other hand, proximal renal tubular acidosis is characterized by reduced reabsorption of bicarbonate in the proximal tubule, with preservation of the distal acidification mechanisms and the ability to lower urine pH below 5.5.

Our patient's urine anion gap was 22 mmol/L, urine osmolal gap 59 mOsm/kg, and urine pH 6.0. She was diagnosed with distal renal tubular acidosis in view of the following findings:

- Normal-anion-gap metabolic acidosis
- Positive urine anion gap
- Urine osmolal gap less than 150 mOsm/kg
- Urine pH greater than 5.5
- Hypokalemia
- Recurrent nephrolithiasis
- Nephrocalcinosis
- Hypocitraturia.

TABLE 2
Causes of primary and secondary distal renal tubular acidosis

Primary distal renal tubular acidosis
Sporadic (idiopathic)
Inherited (due to a congenital mutation)
Secondary distal renal tubular acidosis
Hypergammaglobulinemia
Autoimmune disorders (eg, lupus erythmatosus, Sjögren syndrome, rheumatoid arthritis)
Chronic renal allograft rejection
Obstructive uropathy
Medullary sponge kidney
Autoimmune hepatitis
Primary biliary cholangitis
Lithium, amphotericin B, ifosfamide
Sickle cell anemia

Based on information in reference 2.

WHAT ELSE DOES SHE HAVE?

2 In view of the patient's diagnosis of distal renal tubular acidosis and her clinical symptoms, for which possible additional disorder should we screen her right now?

- ☐ Multiple myeloma
- ☐ Sickle cell anemia
- ☐ Primary biliary cholangitis
- ☐ Sjögren syndrome

Causes of distal renal tubular acidosis are listed in **Table 2**.[2]

Multiple myeloma results from excessive production of monoclonal immunoglobulin by the plasma cells. It often presents with back pain, weight loss, fatigue, generalized weakness, anemia, hypercalcemia, increased total serum protein, and acute renal failure.

Acute kidney injury is seen in 50% of cases at the time of the diagnosis and can be secondary to light chain cast nephropathy or hypercalcemia.[3] Other renal manifestations include proximal renal tubular acidosis and Fanconi syndrome due to the toxic effects of the excessive excreted light chains on proximal renal tubular cells. Isolated distal renal tubular acidosis has been reported, although it is less common in multiple myeloma.

Our patient had anemia and distal renal tubular acidosis. However, she did not have any other features to support the diagnosis of multiple myeloma.

Sickle cell anemia and primary biliary cholangitis can be associated with distal renal tubular acidosis. However, our patient had no symptoms or laboratory findings suggestive of sickle cell anemia or primary biliary cholangitis (ie, no hyperbilirubinemia or elevated alkaline phosphatase level).[4]

TABLE 3
Serology workup

Tests	Results	Normal range
Antinuclear antibody	1:80	< 40 = Negative
dsDNA antibody	Negative	Titers < 10 = Negative
Anti-Ro52 (SS-A) IgG	366	< 20
Anti-La (SS-B) antibody	< 3	< 20
Anti-Ro60 IgG	< 5	< 20
Cryoglobulin	Negative	Negative

ds = double strand; Ig = immunoglobulin; SS = Sjögren syndrome

Sjögren syndrome. Our patient had chronic xerostomia, which could be explained by her use of sertraline, bupropion, clonazepam, or trazodone. However, it is very uncommon for these medications to cause dry eyes, whereas xerostomia and dry eyes could be signs of Sjögren syndrome.

Renal manifestations of Sjögren syndrome include distal and proximal renal tubular acidosis, tubulointerstitial nephritis, nephrogenic diabetes insipidus, and membranoproliferative glomerulonephritis. However, renal involvement in Sjögren syndrome is rare, affecting fewer than 10% of patients, and it is very unusual to find multiple manifestations simultaneously.[5]

Our patient had recurrent nephrolithiasis with calcium oxalate and calcium phosphate stones and distal renal tubular acidosis. In addition, she had other symptoms such as weakness, depression, and dyspnea that could have been due to extrarenal features of Sjögren syndrome, which include peripheral neuropathy (distal sensory and sensorimotor neuropathies), central nervous system manifestations (eg, depression, focal central lesions, encephalitis, motor disorders), interstitial lung disease, inclusion-body myositis, annular erythema, and salivary gland enlargement. For all these reasons, she was screened for Sjögren syndrome.

FURTHER WORKUP

Our patient underwent further serologic workup (**Table 3**). On the Schirmer test, done as part of an ophthalmologic evaluation, 0 mm of the paper was wet, suggesting severely decreased lacrimation. Other

TABLE 4
2016 American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) classification for primary Sjögren syndrome

Inclusion criteria	Exclusion criteria
At least 1 symptom of ocular or oral dryness, defined as a positive response to at least 1 of the following questions: Have you had daily, persistent, troublesome dry eyes for more than 3 months? Do you have a recurrent sensation of sand or gravel in the eyes? Do you use tear substitutes more than 3 times a day? Have you had a daily feeling of dry mouth for more than 3 months? Do you frequently drink liquids to aid in swallowing dry food? Or suspicion of Sjögren syndrome based on glandular enlargement or the presence of characteristic extraglandular involvement	Prior diagnosis of any of the following conditions: History of head and neck radiation treatment Active hepatitis C infection (with positive polymerase chain reaction) Acquired immunodeficiency syndrome Sarcoidosis Amyloidosis Graft-vs-host disease Immunoglobulin G4-related disease

ACR/EULAR classification criteria for primary Sjögren syndrome[a]	
Criteria	**Score**
ACR/EULAR classification criteria for primary Sjögren syndrome	3
Anti-Ro/SS-A positive	3
Ocular staining score ≥ 5 (or van Bijsterveld score ≥ 4) in at least 1 eye	1
Schirmer test ≤ 5 mm at 5 minutes in at least 1 eye	1
Unstimulated whole saliva flow rate ≤ 0.1 mL/minute	1

[a]The classification of primary Sjögren syndrome applies to any patient who meets the inclusion criteria, does not have any of the conditions listed as exclusion criteria, and has a score ≥ 4.

Adapted from reference 7.

tests that can be used to assess dry eyes include ocular surface staining, tear breakup time (< 10 seconds), and tear osmolarity (> 308 mOsm/L in either eye).[6] In view of her weakly positive antinuclear antibody titer and dry eyes, salivary gland biopsy was offered to confirm the diagnosis of Sjögren syndrome and rule out alternative diagnoses. However, the patient refused to proceed with salivary gland biopsy.

Alternatively, the 2016 American College of Rheumatology and European Alliance of Associations for Rheumatology classification for primary Sjögren syndrome (**Table 4**)[7] can be applied to our patient. She met the inclusion criteria, did not have any of the exclusion criteria, and had a score of at least 4. For all these reasons, our patient likely had primary Sjögren syndrome. Her abdominal pain was likely related to nephrolithiasis.

Sjögren syndrome is associated with B-cell lymphoma and hypergammaglobulinemia.[8,9] Therefore, it is important to screen the patient for those disorders, particularly in view of her anemia. Computed tomography of the chest and abdomen did not reveal any lymphadenopathy, and results of serum and urine electrophoresis were unremarkable, with a normal serum free light chain ratio. The patient refused to undergo any biopsy or invasive procedures.

Regarding her clubbing, generally, clubbing can be congenital or acquired. Acquired clubbing is associated with pulmonary disease, cardiovascular disease, malignancy, and liver cirrhosis. Our patient's clubbing was acquired and was likely secondary to interstitial pulmonary fibrosis. This diagnosis was supported by the findings on computed tomography and by her respiratory symptoms, which suggested long-standing hypoxia, although she did not have any respiratory disorder based on her arterial blood gasses.

TREATMENT

3 What is the most appropriate treatment for this patient?

- ☐ Symptomatic treatment plus azathioprine
- ☐ Hydroxychloroquine and corticosteroids
- ☐ Symptomatic treatment
- ☐ Corticosteroids

Treatments for sicca manifestations include saliva substitutes and artificial tears. Topical cyclosporine A has been used in severe cases of keratoconjunctivitis. Because xerostomia is associated with increased risk of caries, remineralizing rinses are recommended. Pilocarpine can be used as well to stimulate salivary flow.

Although not evidence-based, hydroxychloroquine can be used for extraglandular manifestations such as inflammatory arthritis. Its onset of action varies widely, so a delay in its effect should be anticipated.[10,11] Immunosuppressive agents such as corticosteroids, cyclophosphamide, and azathioprine are reserved for systemic manifestations including pulmonary disease (interstitial lung disease), central nervous system, sensory ganglionopathy, and cryoglobulinemic vasculitis. It is unclear whether immunosuppressive agents limit renal tubular acidosis in Sjögren syndrome.

Our patient had systemic manifestations that included lung and renal involvement. We did not give her corticosteroids, in view of her psychiatric history. Therefore, she should have been treated with azathioprine or cyclophosphamide along with symptomatic treatment. However, the patient declined immunosuppressive medications. Therefore, she was started on hydroxychloroquine 200 mg daily and supportive care including artificial tear eye drops, caries care, and saliva substitutes.

For her hypocitraturia and history of calcium kidney stones, she was advised to increase her fluid intake and follow a diet with a normal calcium content but low in oxalate and animal protein. She was also started on potassium citrate with a plan to watch her urine pH closely, but she did not tolerate it due to nausea and vomiting.

Her joint pain and generalized weakness improved. However, she was noted to have polyuria, with a urine output of 3 to 4 L per day.

POLYURIA

4 What was the most likely cause of the polyuria in this patient?

- ☐ Primary psychogenic polydipsia
- ☐ Osmotic diuresis
- ☐ Hypercalcemia
- ☐ Diabetes insipidus

Primary psychogenic polydipsia could be suspected in this patient, who had a substantial psychiatric history. However, primary psychogenic polydipsia usually presents with hyponatremia and low urine osmolality. It is less likely in our patient, given her high serum osmolality and high serum sodium concentration. A water deprivation test was not done, to avoid interfering with her eating disorder treatment.

Osmotic diuresis occurs when certain substances such as glucose, protein, or mannitol are secreted in the tubules and cannot be reabsorbed owing to a pathologic reason, secretion of a large amount of the substance, or the nature of the substance. This leads to impairment of reabsorption of water and to hypernatremia. Urine osmolality is usually higher than 300 mOsm/kg in patients with osmotic diuresis. Our patient's urine osmolality was 165 mOsm/kg, which argues against this mechanism.

Hypercalcemia causes nephrogenic diabetes insipidus, likely due to downregulation of aquaporin expression in the medullary collecting duct as well as to a decrease in renal outer medullary potassium channel activity in the thick ascending limb of the kidney. This leads to a decrease in potassium availability for the sodium-potassium-chloride transporter, diminishing its activity.[12] This patient did not have elevated serum calcium.

Diabetes insipidus. Our patient had polyuria with low urine osmolality and elevated serum sodium. Given these findings, diabetes insipidus was most likely the cause of her polyuria.

Diabetes insipidus can be central, ie, secondary to inadequate vasopressin production from the posterior pituitary, or nephrogenic, ie, secondary to inadequate renal response to vasopressin. Sjögren syndrome is known to cause nephrogenic diabetes insipidus in some patients, but it is uncommon to find multiple renal manifestations in the same patient.[13,14] The patient also had hypokalemia, which can cause a defect in urinary concentration ability and lead to nephrogenic diabetes insipidus. The exact mechanism of hypokalemia-induced nephrogenic diabetes insipidus is still unclear.

Our patient received desmopressin, but her urine volume and urine osmolality did not change significantly, which confirmed the diagnosis of nephrogenic diabetes insipidus and ruled out central diabetes insipidus. We recommended that she continue oral hydration driven by thirst and that she always have water available. Her sodium level remained stable between 140 and 145 mmol/L.

TAKE-HOME POINTS

- Renal manifestations of Sjögren syndrome include distal and proximal renal tubular acidosis, tubulointerstitial nephritis, nephrogenic diabetes insipidus, and membranoproliferative glomerulonephritis.

- It is uncommon to find multiple renal manifestations secondary to Sjögren syndrome in the same patient.
- Distal renal tubular acidosis is caused by impaired hydronium secretion in the alpha-intercalated cells in the distal nephron. It presents with normal-anion-gap metabolic acidosis, a positive urine anion gap, a urine osmolal gap less than 150 mOsm/kg, and urine pH greater than 5.5, and is associated with hypokalemia, nephrocalcinosis, and hypocitraturia.
- Extrarenal features of Sjögren syndrome include peripheral neuropathy (distal sensory and sensorimotor neuropathies), central nervous system manifestations (eg, depression, focal central lesions, encephalitis, motor disorders), interstitial lung disease, inclusion-body myositis, annular erythema, and salivary gland enlargement.
- Sjögren syndrome is associated with B-cell lymphoma and hypergammaglobulinemia.
- Immunosuppressive agents are reserved for systemic manifestations such as interstitial lung disease, central nervous system involvement, sensory ganglionopathy, and cryoglobulinemic vasculitis.

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Medical management of benign prostatic hyperplasia

ABSTRACT

Medical management of benign prostatic hyperplasia (BPH) has progressed gradually in recent years and remains the starting point for most symptomatic patients seeking treatment. Beyond well-known alpha-blockers and 5-alpha reductase inhibitors, there is growing evidence for the use of phosphodiesterase-5 inhibitors and beta-3 agonists in managing the condition, which may afford additional relief of "bothersome" symptoms in some patients. This review details contemporary medical management of BPH with an emphasis on the indications for certain classes of pharmacotherapy and their relative benefits and side effects. Surgical and procedural treatment of BPH is covered in a separate review.

KEY POINTS

- Medical management of BPH remains the starting point for most symptomatic patients seeking care.
- Treatment with phosphodiesterase-5 inhibitors helps maintain ejaculatory function and may provide additional relief of irritative symptoms, including urgency and frequency, compared with alpha-blockers and 5-alpha reductase inhibitors.
- The effectiveness of over-the-counter agents and herbal and natural supplements remains poorly characterized, and research on new pharmacologic agents like beta-3 agonists is ongoing.

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Benign prostatic hyperplasia (BPH), also known as benign prostate enlargement or obstruction, is a histologic diagnosis that describes the proliferation of glandular epithelial tissue and smooth muscle within the transition zone of the prostate.[1,2] The prostate gland has both intrinsic and extrinsic factors that likely play complex roles in its growth. These include the interaction between the stroma and epithelium, hormone and androgen exposure (specifically testosterone and, more importantly, dihydrotestosterone), dietary factors, micro-organisms, and genetic predisposition.[1,2]

Although the exact mechanism for the development of BPH is unknown, age-related changes causing metabolic disturbances, changes in hormone balance, and chronic inflammation appear to contribute.[3] Despite diminishing levels of testosterone as patients grow older, the amount of circulating dihydrotestosterone and prostatic androgen receptors remains high.[2] The average prostate is approximately 20 cc between the ages of 21 and 30. BPH can begin to develop in the early 40s in some men and is found in 50% of men ages 51 to 60.[3,4] The prevalence of BPH increases steadily with age, reaching 60% at age 60 and 80% at age 80.[5] An enlarged prostate gland, while not in itself pathologic, can result in lower urinary tract symptoms, either by directly obstructing the bladder outlet as enlargement changes the shape of the gland, or by increasing smooth muscle tone and resistance to flow within the enlarged gland.[2]

Lower urinary tract symptoms associated with BPH are characterized as disturbances in retention of urine, voiding, and postmicturition state.

These symptoms provide insight into the impact of BPH on patient quality of life.[6,7] The International Prostate Symptom Score is a validated 8-point questionnaire that numerically characterizes patient symptoms.[8–10] Three questions pertain to storage symptoms (frequency, nocturia, urgency), and 4 pertain to voiding (feelings of incomplete emptying, weak stream, intermittency, straining). The final question assesses self-reported impact of symptoms on patient quality of life.

The goal of treatment for lower urinary tract symptoms associated with BPH has long been to maximize quality of life and minimize "bothersome" symptoms. More recently, focus on preventing side effects or treatment complications has been growing. This review outlines the most common medical treatments for lower urinary tract symptoms associated with benign prostatic hyperplasia.

DIAGNOSTIC EVALUATION

Patients with bothersome lower urinary tract symptoms often first present to primary care for evaluation. It is recommended to obtain a detailed and complete medical history, including an assessment of fluid intake (volume and type), voiding patterns, and bowel habits, as well as prior surgical history, prostate-specific antigen (PSA), and International Prostate Symptom Score.[5,7] Additionally, evaluation of patient sexual history, medications (including supplements and complementary therapies), mental health, and physical activity levels can be helpful. A urinalysis should be obtained to rule out alternate causes for the lower urinary tract symptoms, focusing on the presence or absence of glucose, protein, inflammation, or blood (microhematuria: ≥ 3 red blood cells per high-power field on microscopic evaluation of a single specimen).[5,11]

CONSERVATIVE MANAGEMENT

Patients with symptoms considered mild by the International Prostate Symptom Score (0–7) can potentially opt for lifestyle modifications, depending on how bothersome their symptoms are.[5,7] Common lifestyle changes include losing weight, decreasing evening fluid intake, and decreasing total daily fluid intake or the quantity of substances with bladder-irritating or diuretic properties such as caffeinated beverages (coffee, tea, energy drinks, cola), sugary beverages (soft drinks, juices), alcoholic beverages, and fluids containing artificial sweeteners, artificial colorings, or artificial flavorings (often these substances exert diuretic and bladder-irritating effects).[7,12] Patients should also be advised to work on bladder management, if needed, including timed voiding (every 2–3 hours) and double-voiding. Doing pelvic floor stretches or relaxation exercises—not strengthening or Kegel exercises—and maintaining a regular bowel regimen to avoid constipation can also be quite impactful.[7,12]

Some men will experience spontaneous improvement in symptoms over time, without therapy.[12] The degree of changes in symptoms can vary, and monitoring and following these patients over time is important to avoid missing worsening symptoms.

For patients with moderate to severe lower urinary tract symptoms at baseline or symptoms refractory to conservative management, initiation of medical therapy and consideration of procedural treatment are options.[12] Medical therapy for BPH with lower urinary tract symptoms should be initiated after evaluation of the potential benefits and side effects of specific medications.

PHARMACOTHERAPY

Alpha-blockers

Alpha-blockers are a class of drugs first introduced in the late 1980s and early 1990s. They work by antagonizing alpha-1 receptors in the bladder neck and prostate, which results in the relaxation of smooth muscle in these areas,[12–17] and in turn, reduced constriction of the urinary channel and lower resistance to urinary flow.[14] Despite a plethora of medications within this class, all are relatively equally effective, with an expected International Prostate Symptom Score improvement from baseline of 3.7 to 7.1 points.[13]

The 5 main alpha-blocker medications include second-generation drugs (terazosin, doxazosin) and third-generation drugs (tamsulosin, alfuzosin, silodosin). The third-generation drugs are generally well tolerated, and tamsulosin is associated with fewer side effects.[12] The second-generation alpha-blocker medications require dose titration owing to their antihypertensive effects.[12]

The therapeutic effect of alpha-blockers starts within hours to days, although it generally takes 3 to 7 days to reach maximum effect.[13–15,18] Common side effects include lightheadedness, dizziness, headache, nasal congestion, erectile dysfunction, and ejaculatory dysfunction or anejaculation (formerly known as retrograde ejaculation). These side effects usually accompany the therapeutic effect of the medication, are generally dose-dependent, and resolve within a few days with medication discontinuation. Ejaculatory dysfunction results from relaxation of the smooth muscle within the prostatic and ejaculatory ducts with alpha

blockade.[19] This can be very distressing and bothersome for some and a relevant clinical concern for men who may want to father a child, as they may be unable to do so while using alpha-blockers.

Given similar efficacy across different alpha-blockers, it is generally not recommended to switch medications if a patient does not obtain a sufficient therapeutic response with the first drug. However, changing alpha-blockers to reduce side effects can be helpful.[20] Changing from a second- to a third-generation alpha-blocker can be beneficial to avoid orthostatic symptoms and hypotension. Changing among third-generation alpha-blockers can be beneficial owing to differences among these medications in the degree of sinus pressure, nasal congestion, or ejaculatory changes patients may experience when taking them. Anecdotally, there seems to be no identifiable pattern across medications regarding nasal symptoms, but many urologists favor alfuzosin to reduce ejaculatory symptoms.[15,18,20] The dose of many alpha-blockers can be titrated up to provide additional therapeutic benefit, but often at the risk of greater side effects that warrant close follow-up.

Patients taking alpha-blockers, specifically tamsulosin, who plan to undergo cataract surgery should be informed of the possible associated risk of intraoperative floppy iris syndrome. It is thought to occur due to local smooth muscle inhibition resulting in iris prolapse at the incision site during phacoemulsification in cataract surgery.[14,15,21] This risk should be discussed with patients when initiating alpha-blocker therapy. Fortunately, increased awareness of and communication about this syndrome have resulted in a decreased rate of complications in persons taking tamsulosin who undergo cataract surgery.[14]

5-alpha reductase inhibitors

Androgens are essential to prostatic growth.[16] The conversion of testosterone to dihydrotestosterone, a more potent ligand for the androgen receptor and arbiter of prostatic growth, is central to this process.[14–17,22] Inhibiting the conversion of testosterone to dihydrotestosterone with 5-alpha reductase inhibitors (5ARIs) can reduce prostate growth and tip the scales toward prostatic cellular apoptosis and atrophy. Atrophy is more pronounced in the glandular epithelium of the prostate where PSA is made, as opposed to the smooth muscle stromal component of the gland.[23] Thus, gland composition (more glandular vs more stromal) may impact medication efficacy. The impact of 5ARIs on the glandular cells results in a decrease in PSA of approximately 50% after 6 to 12 months of treatment.[16,22,23] Therefore, because PSA is a key predictor of treatment outcome, measurement of baseline PSA is recommended for all patients considering 5ARI therapy.

Owing to their mechanism of action and effect on gland size, 5ARIs should be reserved for patients with BPH and lower urinary tract symptoms who have prostate glands 30 cc or larger or palpable prostatic enlargement on digital rectal examination.[16,23] Finasteride and dutasteride are the most commonly used 5ARIs.[16,22,23] Finasteride inhibits the 5AR type II isoenzyme, while dutasteride inhibits type I and II isoenzymes.[22] Because type II 5AR is more commonly found in prostate tissue, the clinical effect of these medications does not differ. Notably, 5ARIs require about 3 months of use before noticeable improvements in urinary symptoms occur, and approximately 6 months to reach full effect in terms of prostate volume reduction.[16,22,23] It is critically important to explain to patients the expected time frame to ensure medication adherence.

5ARIs for prostate cancer prevention have been studied for some time, with the evidence showing these medications reduce overall prostate cancer rates, particularly low-grade cancers. This is likely because finasteride reduces prostate volume, resulting in improved detection of cancer on prostate biopsy, and because of its selective inhibition of low-grade cancers.[16,22] There is a black box warning regarding 5ARIs because they were thought to potentially increase the risk for higher-grade prostate cancers, but were later determined to be helpful in the process of detecting these cancers.[5,16,22] These medications are regularly used and thought to be safe.

Side effects of 5ARIs vary widely across research studies, but include bothersome symptoms related to testosterone deficiency including erectile dysfunction, ejaculatory dysfunction (reduced semen volume and thinned semen consistency), decreased libido, and possible fertility implications.[5,24] Although a causal link between 5ARIs and infertility has yet to be elucidated, 5-alpha reductase is physiologically active in human testes, with dihydrotestosterone promoting expression of tight junction protein in Sertoli cells.[24] Disruption of this process halts spermatogenesis.

Two prospective randomized controlled trials that compared 5ARIs (dutasteride, finasteride) with placebo found statistically significant ($P < .001$; $P < .005$) reductions in total sperm counts at 24 weeks, but not after 52 weeks, as well as mild sexual dysfunction.[24–26] Because both trials studied healthy male populations (excluding patients with prior infertility), the impact on men with preexisting subfertility remains unknown. Beyond these findings, patients should also be informed

of a small risk of gynecomastia and breast tenderness with 5ARI use.[5] Finally, there are limited data in the recent literature suggesting a possible increased rate of depression in men using 5ARIs.[24] Further study is needed to elucidate the mechanism behind these effects, as much of the data come from treatment with 5ARIs for androgenic alopecia where lower daily dosing of finasteride combats hair loss, making the results regarding depression unclear.[24]

Phosphodiesterase-5 inhibitors

Phosphodiesterase-5 (PDE5) inhibitors increase intracellular cyclic guanosine monophosphate, causing nitric oxide-mediated relaxation of smooth muscle throughout the prostate, detrusor muscle (bladder), and urethra.[27] It is thought that this is the beneficial mechanism of action of PDE5 inhibitors on patients with BPH and lower urinary tract symptoms. Tadalafil is the most-studied PDE5 inhibitor for patients with BPH and lower urinary tract symptoms, with an average improvement in International Prostate Symptom Score of 3 or more. Onset of effect is variable but usually within hours. Importantly, avanafil has the shortest onset of action (15–20 minutes) in this class but is not widely used for treatment of BPH.[5,28]

PDE5 inhibitors are not titrated up or down in dose. They offer an alternative therapy for patients who cannot tolerate or prefer not to use alpha-blockers or 5ARIs.[27] Additionally, a decrease in lower urinary tract symptoms, including overactive bladder symptoms such as urinary urgency and frequency, has been noted in patients taking PDE5 inhibitors.[14] Once rather expensive, many of these medications are now available generically at low prices, can be purchased without insurance through self-pay, and are available at smaller, local pharmacies.[29]

While the low daily dose of PDE5 inhibitors for BPH (such as US Food and Drug Administration-approved and guideline-based tadalafil 5 mg) can aid urinary symptoms, the benefit of such doses for erectile dysfunction is rather negligible.[14] However, some patients report improvement in erectile dysfunction.[30,31] For those without improvement, on-demand booster doses of PDE5 inhibitors can be administered with the low daily dose, although questions around precise timing, adjustments to daily dosing, and skipping of doses are debated and robust data for guidance are lacking. However, in general, the usual dose for medical management of erectile dysfunction can be administered in advance of sexual activity, as needed, for therapeutic effect and as tolerated according to side effects.

Side effects of PDE5 inhibitors include facial flushing, headache, back pain, dyspepsia, and the potential for blue-tinted vision; however, most of these side effects are minimal or absent at low daily doses for BPH. Well-known contraindications to PDE5 inhibitors include the use of nitrates.[5,14]

Beta-3 agonists and anticholinergics

Beta-3 agonists, including mirabegron and vibegron, work via the sympathetic pathway to cause relaxation of the detrusor muscle and increase bladder capacity.[5,14] They are indicated for patients with overactive bladder and can benefit patients with predominantly irritative lower urinary tract symptoms, including urgency, frequency, and incontinence. Onset of maximum effect is generally at around 3 weeks, an important factor to discuss with patients. While vibegron is only available in 1 dose, mirabegron is available in multiple doses and seems to provide similar therapeutic benefit.[32] Emerging research suggests this class of drugs may also benefit patients with BPH, but this remains an area of active investigation.[33]

Historically and prior to beta-3 agonist development, anticholinergic medications were used to treat bothersome symptoms. Currently, they are widely available, and many are generic. However, anticholinergic medications are associated with cognitive impairment and dementia, in addition to the well-known side effects of mental fogginess or confusion.[14] Studies have shown that trospium, a larger quaternary amine molecule, does not cross the blood-brain barrier and may be a safer option.[32]

However, all anticholinergics have undesired side effects, including dry mouth, dry eyes, constipation, and potential vision changes.[14] Anticholinergics exert therapeutic effect within hours to days, although this can vary between short- and long-acting formulations, as well as different doses (as anticholinergics can be titrated up for efficacy). Long-acting formulations tend to have less bothersome side effects, as these agents do not achieve the high peak serum levels responsible for unwanted effects.[5,14]

In contrast, beta-3 agonists have very favorable side-effect profiles and little to no risk for those with dementia or cognitive impairment.[32–34] The most common side effect of mirabegron is hypertension. Due to the risk for drug-drug interaction, concomitant use in patients on metoprolol must be done cautiously.[35] Overall, both mirabegron and vibegron are contraindicated in patients with poorly controlled hypertension, although vibegron has been found clinically to pose a negligible risk of blood pressure change. As a relatively

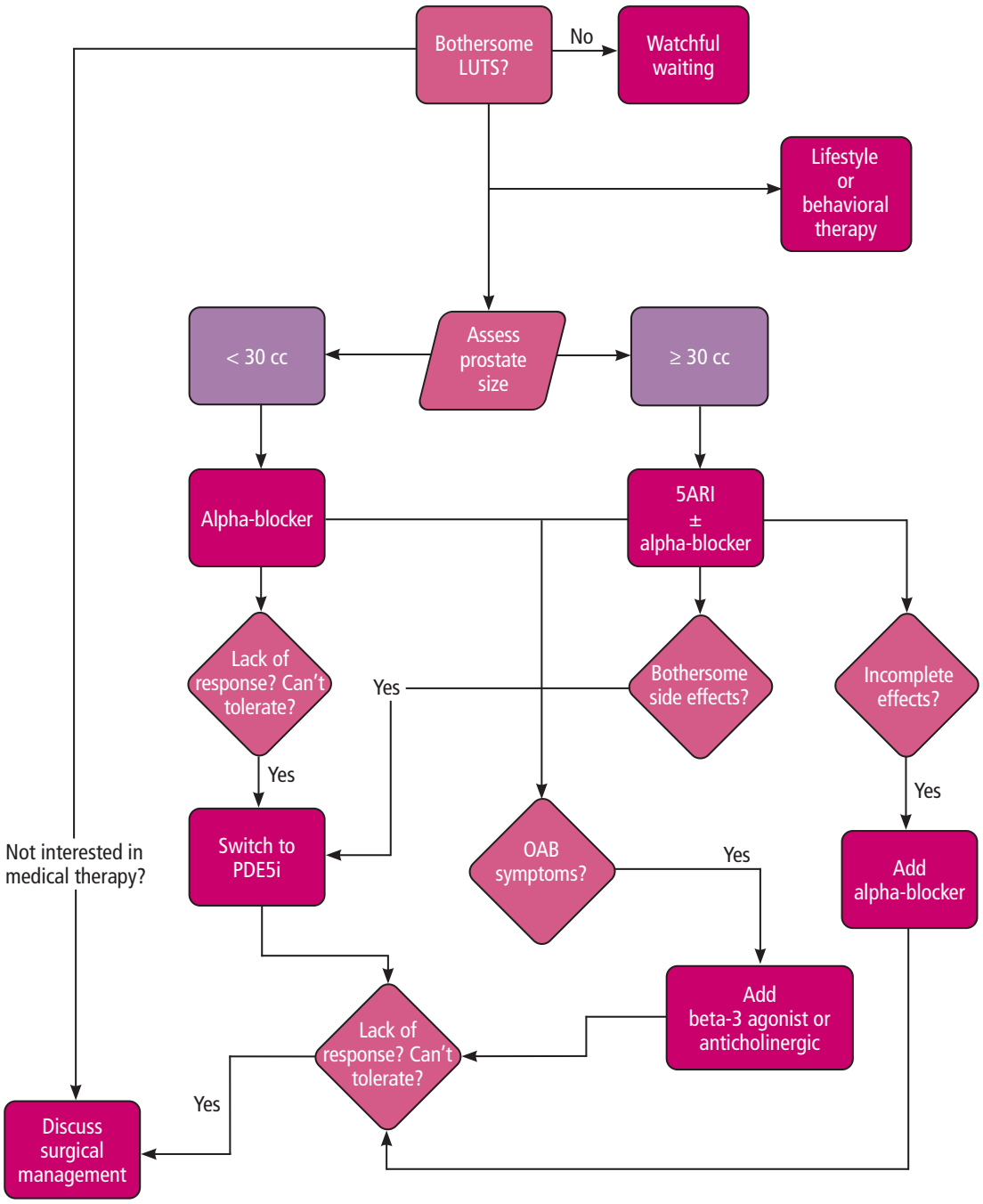

Figure 1. Algorithmic approach to medical management of benign prostatic hyperplasia.

5ARI = 5-alpha reductase inhibitors; LUTS = lower urinary tract symptoms; OAB = overactive bladder; PDE5i = phosphodiesterase-5 inhibitor

Adapted from the American Urological Association guidelines.[7]

newer therapeutic class, much remains to be learned about beta-3 agonists, but the initial clinical experience with them has been promising.[32–34] Additionally, beta-3 agonists can be combined with anticholinergics for the treatment of severe overactive bladder, as both agents target the bladder through 2 separate and synergistic molecular pathways.[5]

Combination therapy

Combination pharmacotherapy has been shown to be more effective than monotherapy or placebo, specifically in patients with larger prostates who meet criteria for 5ARIs and can be offered alpha-blockers simultaneously.[15,17,36] This follows findings from the 2003 MTOPS (Medical Therapy of Prostatic Symptoms) study of combination doxazosin and finasteride vs monotherapy or placebo that demonstrated decreased rates of symptom progression, urinary retention, and invasive BPH surgery or procedures with combination therapy.[15,37] Similarly, the 2010 CombAT (Combination of Avodart and Tamsulosin) trial found significant reduction in the relative risk of primary end points of acute urinary retention or prostatic hyperplasia-related surgery with combined tamsulosin and dutasteride compared with monotherapy ($P < .001$).[36] There is growing evidence that daily tadalafil and finasteride combination is also helpful, with the added benefit of avoiding alpha-blocker side effects.[13,38]

Historically, anticholinergic agents were offered in combination with an alpha-blocker for patients experiencing predominantly irritative lower urinary tract symptoms. However, studies have demonstrated variable improvements in the International Prostate Symptom Score for this combination compared with monotherapy.[5] As a result, and considering potential cognitive effects of anticholinergics, this warrants careful consideration. However, in this same population, combining alpha-blockers with beta-3 agonists presents a safer and well-tolerated alternative to improve symptoms with fewer side effects.[5] Lastly, while many drug interaction systems may warn against concomitant use of PDE5 inhibitors and alpha-blockers, this combination remains an option for some, albeit with close monitoring as it can lead to symptomatic orthostatic hypotension.[17,27]

MEDICINAL PLANTS

Medicinal plants and natural products derived from plants are becoming more common for treatment of BPH with lower urinary tract symptoms.[34,39,40] Knowing the common medicinal plants targeted for patients with lower urinary tract symptoms from BPH and how to counsel regarding them are essential. Pumpkin seed (*Cucurbita pepo*) or its extract is popular and contains a variety of biologically active compounds thought to inhibit 5-alpha reductase and decrease levels of circulating dihydrotestosterone.[22] However, pumpkin can cause gastrointestinal symptoms such as indigestion and diarrhea. Another common supplement is the fruit extract of the saw palmetto plant (*Serenoa repens*), which is sold over the counter. Postulated mechanisms of action for *Serenoa repens* include 5-alpha reductase inhibition and inhibition of dihydrotestosterone binding to androgen receptors.[22,24,25] However, there have been mixed results regarding the exact mechanism of action of each of these supplements, and the results vary further based on method of extraction and formulation.

Patients should be informed that many studies on supplements, nutraceuticals, and herbal preparations are limited by a lack of peer review, comparison with placebo control, and assessment using conventional end points.[5] The 2 independently conducted, placebo-controlled trials using specific extracts of saw palmetto found no benefit over placebo across multiple measurable parameters relevant to BPH and lower urinary tract symptoms.[41,42]

Additionally, as regulation and quality control of natural products derived from plants are not as stringent as those of the pharmaceutical industry, it is important to educate patients that the composition of certain supplements varies not only between retailers, but also between batches of supplements made by an individual manufacturer.[34] As a result, their effect, if any, can vary widely and be unpredictable. Additionally, manufacturers of natural products derived from plants often post claims regarding efficacy and effects that are not regulated or endorsed by the US Food and Drug Administration.

CONCLUSION

Several options exist for medical management of BPH, and choices are affected by indication, effectiveness, and side effects (**Figure 1**).[7] Research continues regarding newer agents and natural products derived from plants. While medication is a therapeutic option, it can provide diagnostic insight into the potential benefit of a procedure or surgery for patients with BPH. Furthermore, contemporary clinical management of BPH includes the consideration of surgeries or procedures as viable first-line options for properly selected, treatment-naïve patients, especially with the growing number of newer minimally invasive procedures with favorable side effects.

In line with this, some patients may wish to avoid the side effects of medications, taking a daily pill, or the cost burden of lifelong pharmacotherapy. Others may experience disease progression in spite of medical treatment. Beyond these reasons, as well as medication intolerance or allergy, the American Urological Association guidelines list the following indications for patients with BPH to undergo procedures or surgeries: urinary retention, recurrent urinary tract infections, bladder stones, obstructive uropathy, and prostate-related hematuria.[5] However, as noted earlier, contemporary approaches to management of BPH emphasize patient preference as a major factor for determining whether to pursue medical, procedural, or surgical treatment. The growing list of surgical and procedural treatment options for BPH is covered in another review.[43]

DISCLOSURES

Dr. Gill has disclosed consulting, work as advisor or review panel participant, and research as a co-investigator or site lead for Boston Scientific and Urovant Sciences. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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COMMENTARY

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Artificial intelligence in clinical practice: A look at ChatGPT

In the rapidly evolving landscape of healthcare technologies, the integration of artificial intelligence in clinical practice is increasingly gaining attention. Recent advancements in large language models (LLMs), such as ChatGPT (Chat Generative Pre-trained Transformer), seem to herald a future where artificial intelligence-powered platforms will significantly enhance clinician workflow by reasoning through patient cases to provide differential diagnoses and treatment recommendations and by alleviating administrative burdens.

However, the prospect of using general-purpose LLMs like ChatGPT in clinical applications also raises several pertinent considerations. Can they deliver factual information with the accuracy and reliability required for patient care? Are they transparent enough to allow for the practice of evidence-based medicine? And how well do optimistic findings from published studies of LLMs translate to actual practice? Through this commentary, we aim to demystify the role of ChatGPT and similar technologies in clinical settings, highlighting their limitations and current applications and discussing future directions in research and development.

WHAT IS CHATGPT?

ChatGPT (https://chat.openai.com/) is a software platform developed by artificial intelligence research company OpenAI to produce conversational responses to user inputs. ChatGPT can process free-form prompts, which are inputs that do not follow a strict format or structure, much like a normal conversation with friends and colleagues. Since its popularization in 2022, ChatGPT has been tested and used across diverse domains, such as providing customer support, script editing, and computer coding, due to its ability to hold natural conversations and synthesize text. Recently, there has also been a growing interest in ChatGPT's potential applications in clinical settings, owing to its ability to answer medical questions and assess patient cases.

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HOW DOES IT WORK?

ChatGPT is a type of machine learning model. These models are programs that learn to associate specific patterns in data with specific outputs, similar to how clinicians learn to associate clusters of signs and symptoms with specific diagnoses during their training. Many currently trialed clinical machine learning models are designed to recognize patterns in numeric data, such as predicting deterioration of patients with COVID-19 using vital signs and laboratory values,[1] or to recognize patterns in images, such as identifying tumors on computed tomography or magnetic resonance imaging.[2] Unlike these clinical models, ChatGPT belongs to a category of machine learning models called LLMs, which are designed to recognize and predict patterns in text. When given an incomplete sentence, for example, LLMs can recognize the context of existing words in the sentence and then fill in the blank using its predictions, not unlike the autocorrect or autocomplete functions on phones.

ChatGPT was first trained to learn textual patterns using millions of sentences from a large collection of books and websites. During the training process, words were removed from the end of the sample sentences and the ChatGPT model was tasked with trying to predict the missing words, 1 word at a time, based on the available context. When the model predicts incorrectly, it tries to learn from its mistake to improve future predictions (**Figure 1A**). This process is reminiscent of how medical students hone their skills by predicting diagnoses using simulated patient cases, comparing their predictions with the answer and learning from the experience. In an additional step of the ChatGPT training process, human annotators review the model's

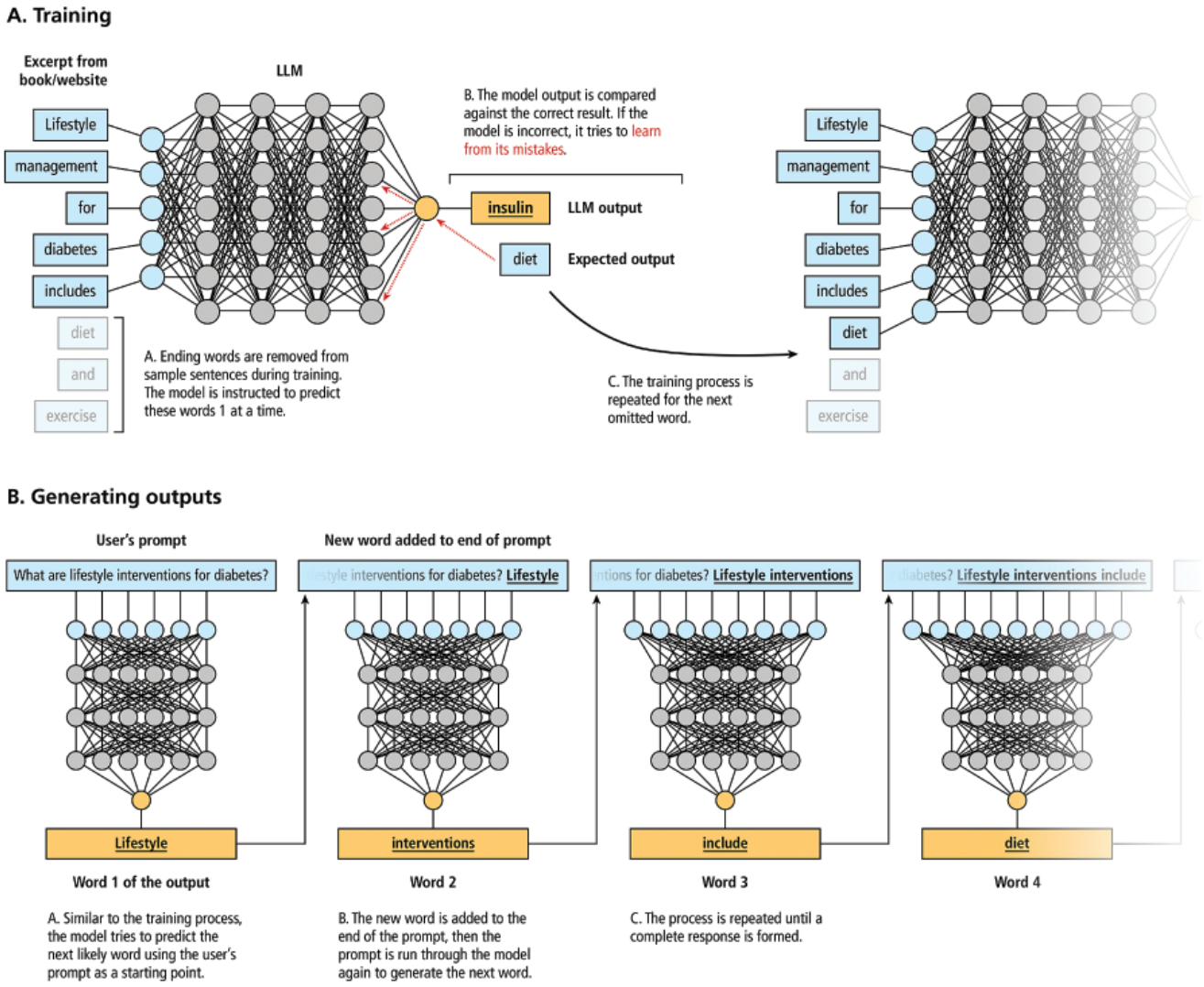

Figure 1. (A) Training and (B) output-generation processes of typical general-purpose large language models (LLMs) like ChatGPT.

output and provide feedback to guide the model to produce more conversational responses. When generating an output, ChatGPT uses the user's input as a starting point and repeatedly predicts which word is likely to come next, just as it did during its training, until a complete answer is formed (**Figure 1B**).[3]

While LLMs do not keep copies of the documents that they were trained on, they may retain knowledge and facts in the form of patterns they notice and learn during their training. For instance, if the LLM's training data contain sentences that include the keywords diet, exercise, and diabetes in close proximity, the model may learn to generate sentences that offer diet and exercise as interventions for patients with diabetes in its output. This characteristic leads to the belief that LLMs can encode medical knowledge, although it is widely debated whether LLMs actually understand what diabetes is, how it affects the body, and why certain diets and exercises are beneficial.[4]

Similarly, ChatGPT has no mechanism to learn from user inputs or feedback "on the fly." It does not improve itself incrementally. Instead, ChatGPT's developer periodically retrains the model from the ground up to incorporate some chat transcripts and user feedback. In these cases, the users serve a similar role as the human annotators described above, as they can rate thumbs up or thumbs down to ChatGPT responses (on the ChatGPT website) to guide the model to produce

more conversational and relevant passages. But once the training is finished and the model is released, the model will not change or improve itself until it undergoes a manual update again.

WHAT DOES THE EVIDENCE SAY?

Numerous recent studies have presented positive findings on the clinical utility of general-purpose LLMs such as ChatGPT. A well-known study by Kung et al[5] illustrated ChatGPT's ability to perform at or near the passing threshold of the United States Medical Licensing Examination. A study by Yeo et al[6] reported that ChatGPT could correctly answer questions relating to cirrhosis 79.1% of the time, while Rao et al[7] reported a 88.9% accuracy rate for its recommendations on breast cancer screening. Levine et al[8] concluded that GPT's ability to triage primary care case vignettes is close to that of physicians. More recently, the authors of a study that used ChatGPT to generate recommendations in response to clinical decision support system alerts described the tool's responses as offering "unique perspectives" while being "highly understandable and relevant."[9]

Do these results translate to real patients?

These results should be interpreted within the context of the limitations of the studies that produced them. For instance, current studies of ChatGPT have relied heavily on question banks and standardized case vignettes, which are easy to acquire but do not capture the complexity of real-life cases. In particular, questions from test banks such as the United States Medical Licensing Examination are usually based on common signs and symptoms, vetted for clarity, and written in a multiple-choice format. Thus, while these studies show that ChatGPT could recognize textbook descriptions of medical conditions and provide standard management recommendations, it is unclear how it would perform in actual clinical practice. After all, real patients present and describe their complaints variably, have different backgrounds and needs, and do not come with multiple-choice options.

An example of this limitation can be seen in the study by Rao et al[7] where ChatGPT was used to provide recommendations for breast cancer screening in those with breast pain. While breast pain is an uncommon symptom of breast cancer, an experienced clinician may recognize or reason that certain types of focal, persistent pain can be suggestive of malignancy, or ask questions about constitutional symptoms to further clarify the diagnosis. However, ChatGPT's responses varied from recommending unnecessary mammograms for diffuse and cyclical breast pain, to not recommending imaging for focal pain in high-risk populations. The accuracy of ChatGPT recommendations was only 58.3% when limited to cases involving breast pain, a large difference from the 88.9% accuracy it achieved on prompts without breast pain.[7] These findings illustrate the uncertainties surrounding ChatGPT's ability to analyze atypical or granular presenting symptoms, much like medical students who can score well on standardized tests but lack the clinical experience needed to deal with the complexity of actual patient presentations.

How useful are the responses?

In addition, it is unclear how clinically useful responses from ChatGPT are, even when they are technically correct. Liu et al,[9] for example, found that ChatGPT-generated recommendations were rated by expert human clinician reviewers as significantly less useful than human-generated recommendations. General-purpose LLMs, such as ChatGPT, may produce generic responses that are ambiguous or lack details, making it hard for clinicians to act on them. As there are currently no standardized methods for assessing the "usefulness" of LLM outputs, this aspect of their performance is often undertested.

Is ChatGPT more empathetic than physicians?

Another recent point of controversy regarding the clinical utility of ChatGPT was introduced by Ayers et al,[10] who showed that ChatGPT responses to patient inquiries were rated significantly higher for empathy than responses written by physicians. Results from the study were widely reported by news and social media outlets, giving the impression that ChatGPT may have better bedside manner than physicians.[11]

However, it is essential to consider the limitations of the study by Ayers et al,[10] the most prominent being that the physicians assessed were off-duty and were answering questions on Internet forums, which hardly reflects their clinical performance. At the same time, this study raises a fundamental question: can a text-based entity like ChatGPT truly provide empathetic care? The relationship between physicians and patients is multifaceted and built on trust, and relies on nonverbal cues, subtle signs, and rapport. LLMs, being restricted to text-based communication, inevitably have limitations in this regard.

Current discussions on empathy notwithstanding, it is also worth examining why perceived empathy seems lacking among healthcare workers. Administrative burden, which often leads to burnout and empathy fatigue, is a significant contributor. US physicians,

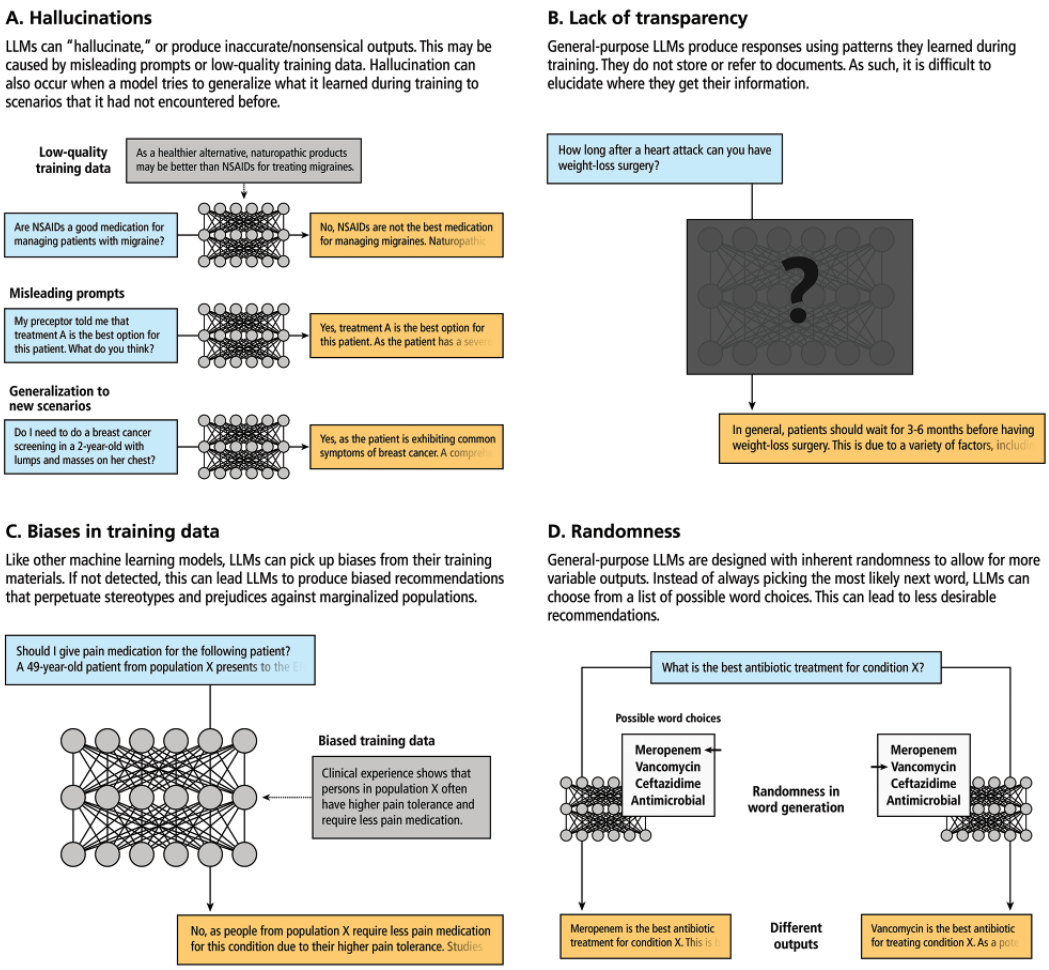

Figure 2. Common technical limitations of current general-purpose large language models (LLMs) like ChatGPT include (A) hallucinations, (B) lack of transparency, (C) biases in training data, and (D) randomness. Prompts and responses shown are for illustrative purposes only and do not represent actual output from LLMs.

for example, spend twice as much time on paperwork as they do with patients.[12] While LLMs might mimic empathy, their true value could lie in alleviating this administrative burden, potentially giving healthcare professionals more time for genuine patient interactions (as we discuss in later sections).

LIMITATIONS OF CURRENT LARGE LANGUAGE MODELS

In addition to limitations highlighted in studies assessing general-purpose LLMs such as ChatGPT, there are several technical limitations in the current design of these models.

Hallucinations

A key limitation is ChatGPT's tendency to "hallucinate," a phenomenon where the model generates factually incorrect or nonsensical outputs or fabricates information (**Figure 2A**). This behavior stems from ChatGPT's reliance on word patterns learned during training to generate responses, and reflects the fact that the model is not designed to function like a search engine or database. While this design allows ChatGPT to respond to scenarios that it had not encountered during training by generalizing its word associations—without adhering to a fixed knowledge set as Google or PubMed do—it can sometimes lead to inaccuracies. In Rao et al,[7] for instance, ChatGPT insisted on providing breast cancer screening for many cases where imaging would be futile or where the patient was at low risk, contrary to prevailing guidelines. It is likely that ChatGPT learned to associate keywords on breast cancer symptoms with screening recommendations,

which it generalized to all patient cases containing these keywords without considering other variables such as prognosis or risk factors.

Hallucination can also arise from training on low-quality or erroneous datasets, leading to incorrect word associations. ChatGPT does not evaluate the credibility of its sources during training, which compounds this problem. For example, in the study by Liu et al,[9] ChatGPT suggested using a nonexistent medication called "etanerfigut," an error that could have resulted from typos in the training material. Yeo et al[6] found that while ChatGPT correctly suggested using mean Model for End-Stage Liver Disease-Na scores for liver transplantation evaluation, it provided inaccurate cutoff values, which may be attributable to incorrect values in the original training dataset.

Additionally, because ChatGPT utilizes the user's inputs as a starting point to generate its response, it can be influenced by misleading prompts (eg, prompts that "hint" the desired answer to the LLM). An example can be seen in a study that assessed ChatGPT's ability to screen article abstracts for inclusion in clinical reviews.[13] After ChatGPT was given screening decisions from expert reviewers, it changed its answer to match the human decisions without trying to defend its original position. When prompted to explain the change, it gave nonspecific rationales (eg, "The study does not meet any of the inclusion criteria."). While technically not an example of hallucination, this study shows how if prompted with a preconceived notion, ChatGPT may contribute to confirmation bias rather than provide the correct information.

Lack of transparency

Given the tendency of LLMs to hallucinate, it is critical to verify and improve their responses by identifying the rationale behind their recommendations. However, the complexity of current general-purpose LLMs makes it difficult to elucidate how these models function. And because ChatGPT does not store or refer to documents from its training, it cannot provide references as other platforms such as UpToDate can (**Figure 2B**).

In fact, when asked to generate a list of citations, LLMs such as ChatGPT often "hallucinate" fake references that seem authentic at first glance. In a study assessing the accuracy of ChatGPT in providing clinical radiological information, only 124 references out of 343 references ChatGPT provided were real and accessible, and 47 references were actually relevant.[14] This demonstrates that ChatGPT has limited transparency and accountability, qualities that are often relied upon in the practice of evidence-based medicine.

Biases

It is well-documented that machine learning models can often produce results that are systemically prejudiced.[15] These biases are usually caused by biases in the models' training data. For instance, insurance models trained on data that associate lower healthcare costs with Black patients may allocate less care to Black patients.[15] The model analyzes the data at its face value, without considering the impact of socioeconomic status, unequal access to care, and other factors that lead to decreased costs in this population.[16] In a similar vein, ChatGPT can exhibit biases that are reflective of its training materials, which may include many unvalidated text sources from webpages with problematic characteristics (**Figure 2C**). ChatGPT had been shown to regurgitate many racial and sexist stereotypes that may harm marginalized communities and even affirm suicidal ideations.[17] If unmitigated, it is possible for ChatGPT to cause patient harm by producing biased recommendations.

Randomness

Lastly, general-purpose LLMs such as ChatGPT are designed to have inherent randomness in their outputs. As such, ChatGPT does not always choose the most likely next word when generating its responses, but rather selects from a list of possible options. As a result, running the same prompt through ChatGPT multiple times would likely yield different outputs (**Figure 2D**).

This design characteristic is useful for engaging users in a chatbot setting (ie, to make ChatGPT responses less predictable and more interesting) or for creative purposes such as brainstorming writing prompts. However, in medical practice, where there is often a limited number of optimal diagnoses or management strategies, this variability can lead to erroneous or less desirable outputs. For instance, in a study that assessed ChatGPT responses to questions about bariatric surgery, the model recommended waiting 6 to 12 months when asked the question, "How long after a heart attack can you have weight loss surgery?"[18] On a second run with the same prompt, however, ChatGPT recommended waiting 3 to 6 months. The 2014 American College of Cardiology/American Heart Association guidelines actually recommend waiting at least 2 months after an acute myocardial infarction before having major surgery,[19] making this a good example of hallucinations as well as the inherent randomness of ChatGPT. And because it is impossible to track down the source of the numbers in ChatGPT recommendations, this example also shows how its lack of transparency can be problematic.

TABLE 1
Resources for clinicians to learn more about large language models and machine learning research

Newsletters	
Doctor Penguin	doctorpenguin.com
NEJM AI Email Newsletter	store.nejm.org/signup/ai/newsletter
Podcasts	
Medicine and the Machine by Medscape	medscape.com/features/public/machine
NEJM AI Grand Rounds by NEJM Group	ai-podcast.nejm.org
The AI Health Podcast	podbay.fm/p/the-ai-health-podcast/about
Journals	
NEJM AI	ai.nejm.org
The Lancet Digital Health	thelancet.com/journals/landig/home
npj Digital Medicine	nature.com/npjdigitalmed/
Journal of Medical Internet Research and related journals	jmir.org

While some response variations only impact the syntax or structure of ChatGPT responses, recent studies have found that around 10% to 20% of prompts presented a second time would incur a substantial change to the content of the responses.[6,18] Not only is this unacceptable for clinical applications, but it also means that the performance and behavior observed in research studies of ChatGPT may not translate to actual practice.

A REALISTIC VIEW OF ChatGPT'S CLINICAL APPLICATIONS

Ultimately, general-purpose LLMs like ChatGPT are not designed for use in clinical settings. When used to provide factual information or reason through clinical cases, ChatGPT lacks the accuracy, reliability, and transparency needed for patient care. However, there are still ways for clinicians to make use of ChatGPT's ability to rapidly interpret and synthesize textual data.

One way to improve ChatGPT's performance is by providing it with the knowledge needed to answer the question in the user's prompt, an approach called "context injection." This works because ChatGPT generates responses using the user's input as a starting point, and thus can extract the needed information from the prompt rather than relying on its word associations, reducing the risk of hallucinations. An example of context injection is to provide ChatGPT with passages from the latest clinical practice guidelines or clinical trial publications, and then ask questions relating to the passages or ask ChatGPT to summarize the passages. This can make it easier for busy clinicians to stay up to date with the latest research or for journals to rapidly produce succinct summaries.

Other possible applications follow similar approaches of prompting LLMs with the information necessary for completing the requested task, such as using ChatGPT to quickly translate patient education materials to different reading levels or asking it to proofread email communications. Ali et al[20] used ChatGPT to rewrite surgical consent forms at a sixth-grade reading level and found that the model was able to preserve clinical details and increase clarity, as judged by expert subspecialty surgeon review. Lyu et al[21] used ChatGPT to translate radiology reports into plain language summaries for patients and determined that the reports were concise, clear, and comprehensive. Another study[22] used ChatGPT to summarize dictated transcripts of physician-patient encounters and found that it was able to produce high-quality notes in well-known formats. These preliminary investigations demonstrate that general-purpose LLMs can reduce the amount of time that healthcare professionals spend on documentation and other administrative duties, enabling them to spend more time with patients.[22]

It should be noted, however, that ChatGPT by default is not considered compliant with Health Insurance Portability and Accountability Act regulations. Thus, protected health information should not be entered into the platform. Compliant variations of the platform are available via enterprise solutions such as

CompliantChatGPT (https://compliantchatgpt.com) or BastionGPT (https://bastiongpt.com).

WHAT DOES THE FUTURE HOLD?

While many current research studies on the medical use of LLMs are directed toward ChatGPT, the clinical application of these general-purpose models is likely limited to the use cases we described here. After all, models like ChatGPT are designed to interpret and generate text across a wide range of topics and disciplines beyond medicine, with little to no consideration for consistency and transparency in its outputs. These characteristics make general-purpose LLMs poorly equipped for fulfilling clinical decision support roles.

However, several advancements are being made to tackle the technical limitations we identified, with the goal of developing LLM systems designed specifically for clinician use. BioGPT[23] and neuroGPT-X,[24] for instance, are LLMs trained on academic articles with the aim of reducing the risk of hallucinations. HippoAI (https://pendium.health/) and Glass AI (https://glass.health) are both clinician-focused LLM platforms that implement this concept, providing recommendations and diagnoses based on peer-reviewed clinical guidelines and medical databases. Platforms such as Perplexity.ai (https://www.perplexity.ai/) use LLMs to summarize results from search engines, allowing the platform to interact with users conversationally while remaining transparent by providing links to its sources. And a medicine-specific LLM from Google called Med-PaLM attempted to improve consistency in its answers by running a prompt through the model multiple times, surveying the results, and responding with the most commonly produced output.[25]

The field of clinical machine learning systems is evolving rapidly. **Table 1** lists some useful resources for clinicians to keep up to date with the latest advancements in LLMs.

With these developments, it is easy to imagine a future where specially designed LLMs power clinical decision support systems to provide clinicians with treatment recommendations, assist with differential diagnoses, and further integrate themselves into administrative roles. But for now, clinicians should exercise caution when interpreting optimistic results from studies involving general-purpose platforms like ChatGPT, and should remain cognizant of the limitations of ChatGPT.

DISCLOSURES

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

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Gout Education Society & GOUT SPECIALISTS NETWORK

Formed in September 2005, the Gout Education Society is a 501(c)(3) nonprofit organization of healthcare professionals dedicated to educating the public and healthcare community about gout. To increase access to education, improve overall quality of care and minimize the burden of gout, the Gout Education Society offers complimentary resources for both the public and medical professionals.

To further increase access to specialized care, the Gout Education Society offers a Gout Specialists Network (GSN). The GSN serves as a locator tool to help those who have gout, and other comorbid conditions, to find the right medical professionals near them. You can find more information on the GSN by following the QR code.

To learn more about the Gout Education Society's efforts, please visit www.GoutEducation.org.

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Hematologic complications after kidney and pancreas transplant in a patient with chronic myeloid leukemia

A 35-year-old woman with a history of type 1 diabetes mellitus, diabetic retinopathy, and end-stage renal disease secondary to diabetic nephropathy underwent simultaneous pancreas and kidney transplant. She received induction therapy with thymoglobulin 100 mg and methylprednisolone 500 mg prior to her transplant. Maintenance immunosuppression consisted of tacrolimus, prednisone, and mycophenolate mofetil. One week after her transplant, she was noted to have hyperleukocytosis, with a white blood cell count of 80 × 10^9/L (reference range 4–10). Her hemoglobin was 9.5 g/dL (12–16), and her platelet count was 440 × 10^9/L (150–400).

1 Which of the following diagnostic tests would you order?

- ☐ Repeat complete blood cell count with differential count and peripheral blood smear
- ☐ Computed tomography of the chest, abdomen, and pelvis
- ☐ Bone marrow biopsy
- ☐ Skeletal survey

DIFFERENTIAL DIAGNOSIS

Leukemoid response secondary to infection, inflammation, asplenia, and certain medications should be considered in the differential diagnosis of a patient with hyperleukocytosis. Glucocorticoids and infections are common causes of leukocytosis in patients who have undergone organ transplant. A preliminary evaluation should include a repeat complete blood cell count with differential count and peripheral blood smear. The differential count can provide helpful clues to the underlying etiology. If prior records are available, a review of previous complete blood cell counts is necessary to determine whether the hyperleukocytosis is new or a chronic process.

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CASE CONTINUED

The differential count showed neutrophilia of 29 × 10^9/L (1.5–8), eosinophilia of 0.8 × 10^9/L (0–0.5), and basophilia of 0.8 × 10^9/L (0–0.5). In addition, increases in promyelocytes at 2% (0%), myelocytes at 1% (0%), and metamyelocytes at 11% (0%–1%) were noted. The peripheral blood smear showed normocytic, normochromic red cells with polychromasia; marked neutrophilic leukocytosis with left shift; and normal platelet morphology. On review of the laboratory tests done 1 month prior to the transplant, the patient was noted to have had mild leukocytosis (white blood cell count 20 × 10^9/L), hemoglobin of 10.6 g/dL, and a platelet count of 281 × 10^9/L.

2 What is the most likely etiology of hyperleukocytosis?

- ☐ Parasitic infection
- ☐ Allergies
- ☐ Hypereosinophilia
- ☐ Chronic myeloid leukemia (CML)

In addition to neutrophilia, patients with eosinophilia and basophilia may have allergies, parasitic infection,

or myeloproliferative neoplasm. Hypereosinophilia, defined as an absolute eosinophil count greater than 1.5×10^9/L, was not present in our patient. All cells of the neutrophilic series are usually present in CML. One of the classic findings of CML is a higher percentage of myelocytes than of metamyelocytes. More than 90% of patients with CML have absolute basophilia.[1] After excluding a leukemoid response and given the high clinical suspicion for a malignant process, we ordered specialized testing including flow cytometry, molecular testing, and bone marrow biopsy.

Fluorescence in situ hybridization testing on a peripheral blood sample showed p210 *BCR-ABL1* fusion transcript. Results from a bone marrow biopsy showed hypercellular bone marrow for the patient's age (90%), with trilineage hematopoiesis. A polymerase chain reaction test done on a bone marrow sample showed a ratio of *BCR-ABL1* to *ABL1* of 100% using the National Institutes of Health international scale (IS) for measuring *BCR-ABL1* transcripts, confirming a diagnosis of CML.[2] Cytogenetic analysis showed an abnormal female karyotype, with all cells (20/20 cells) exhibiting the translocation of chromosomes 9 and 22 that leads to fusion of the *ABL1* and *BCR* genes. Our patient had only 1% blasts in the bone marrow. Based on the blood cell counts (basophils 0.8%), she was diagnosed with chronic-phase CML.

ASSOCIATION BETWEEN AUTOIMMUNITY, ORGAN TRANSPLANT, AND CML

CML is a clonal myeloproliferative disorder characterized by the *BCR-ABL1* fusion gene that drives leukemogenesis.[3] The CML phenotype may vary depending on the type of *BCR-ABL1* fusion. The 3 common variants include p210 *BCR-ABL1*, p190 *BCR-ABL1*, and p230 *BCR-ABL1*. The most common variant is p210 *BCR-ABL1*, which results from a breakpoint in the major *BCR* region at exon e13 or e14 and fusion with *ABL1* exon a2 to produce an e13a2 (b2a2) or e14a2 (b3a2) transcript of *BCR-ABL1*.[3]

Autoimmunity can increase the risk of myeloproliferative neoplasm. A population registry-based study from Sweden reported a higher prevalence of autoimmune diseases prior to the diagnosis of CML.[4] Given her history of type 1 diabetes, our patient had evidence of organ-specific autoimmunity, and this could have played a role in the pathogenesis of CML. In addition, persons who receive a solid-organ transplant have a significantly higher risk of developing myeloid neoplasms, presumably from immune dysfunction.[5,6]

Wu et al[7] reported that the median interval from organ transplant to diagnosis of a myeloid neoplasm is around 56 months. Our patient was diagnosed with CML 3 weeks after renal transplant. However, based on the complete blood cell count and differential count done before transplant, there was a clear signal for an underlying CML. A more detailed and meticulous workup that included a peripheral blood smear should have been performed for unexplained leukocytosis. In the era of highly effective tyrosine kinase inhibitor therapy, patients with CML who achieve a molecular response have a normal life span. Further, a CML diagnosis should not exclude patients from receiving a lifesaving solid-organ transplant.

CASE CONTINUED

Six weeks after the diagnosis of CML, the patient was started on dasatinib 70 mg per day, and 6 months later she achieved a molecular response (*BCR-ABL1*/*ABL1* ratio 0.06% IS). First-generation tyrosine kinase inhibitors such as imatinib and second-generation tyrosine kinase inhibitors such as dasatinib are appropriate first-line treatment options, but the second-generation inhibitors can achieve a faster and deeper molecular remission. The approved dasatinib dose in chronic-phase CML is 100 mg daily, although data show that even 50 mg daily is very effective and has a better safety profile.[8] The 70-mg daily dosing in our patient was based on the treating physician's discretion and clinical judgment considering the patient's medical comorbidities.

Six years after the CML diagnosis, the patient presented with easy bruising and vaginal bleeding. On physical examination, her vital signs were stable. There was no evidence of bleeding from the oropharynx or nasopharynx. The cardiovascular and respiratory system examinations were normal. The abdominal examination revealed a well-healed surgical scar from her prior transplant. No hepatosplenomegaly was detected. The pelvic examination showed around 5 mL of blood in the vaginal vault without active bleeding from the cervix. The cervix appeared normal without any lesions, and there was no adnexal tenderness. The skin examination showed petechiae and ecchymosis over the abdominal wall and both arms and legs.

Routine laboratory tests showed a white blood cell count of 14×10^9/L, hemoglobin 11 g/dL, and platelet count 24×10^9/L. The patient denied any recent change in her medications or use of herbal supplements, over-the-counter medications, or Chinese medications. She had no history of chronic liver disease. She was advised

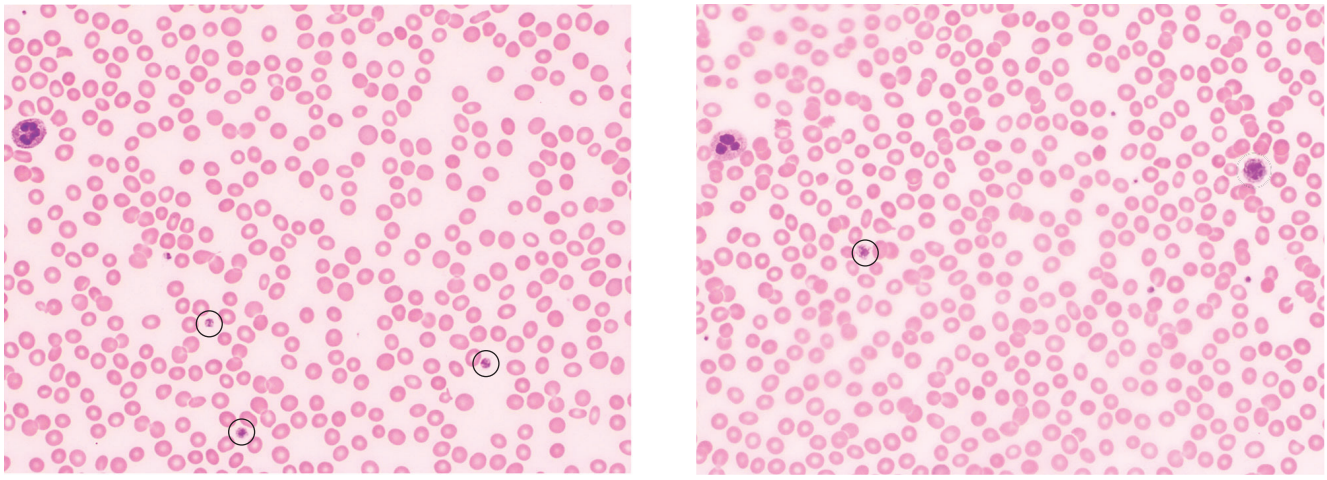

Figure 1. The peripheral blood smear shows giant platelets highlighted in black circles (hematoxylin and eosin, magnification x 400).

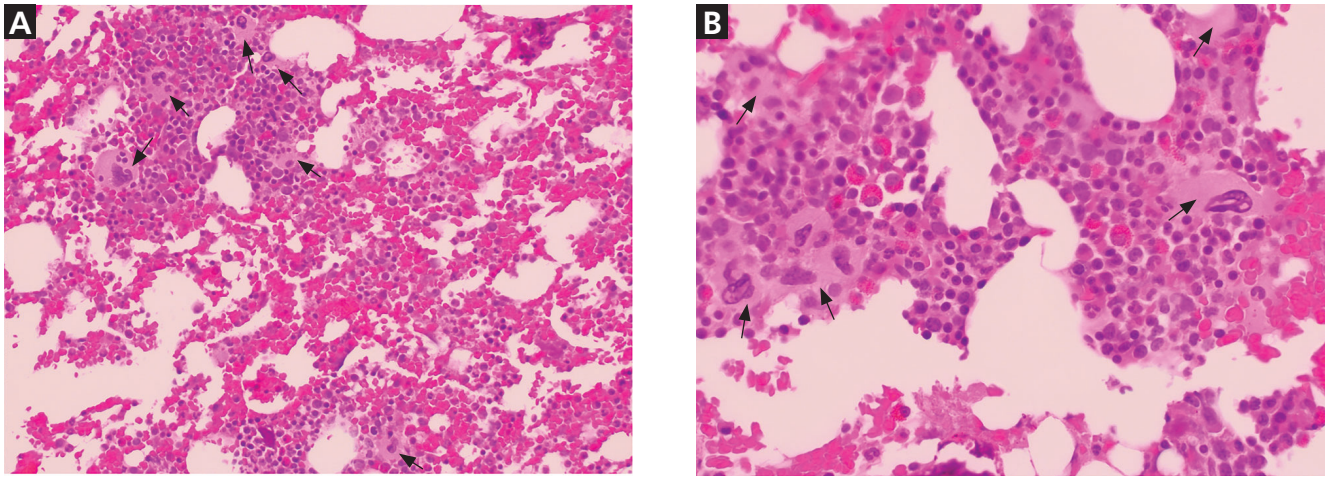

Figure 2. Bone marrow biopsy shows increased megakaryopoiesis indicated by black arrows at magnification x 200 (panel A) and at magnification x 400 (panel B).

to stop dasatinib because of her unexplained thrombocytopenia. A repeat complete blood cell count done 1 week later showed a platelet count of 6 × 10^9/L, hemoglobin 11 g/dL, and white blood cell count 6 × 10^9/L. Her coagulation profile (prothrombin time, international normalized ratio, partial thromboplastin time, fibrinogen, and dimerized plasmin fragment D) was normal. A peripheral blood smear showed normochromic normocytic anemia with slight polychromasia, no increase in schistocytes, and marked thrombocytopenia with giant platelets (**Figure 1**).

She was hospitalized for further evaluation and received 3 units of platelets, but her platelet count did not improve. Human immunodeficiency virus and hepatitis B and C serologies were negative. Computed tomography of the abdomen showed multiple splenules. Vitamin B_{12} and folate levels were within normal limits. Tests for heparin-induced thrombocytopenia antibodies were negative. We did not check for antinuclear antibody as the patient did not have any clinical features of connective tissue disease. The direct antiglobulin test was negative. Bone marrow biopsy showed normal cellularity for the patient's age (60%) with increased megakaryopoiesis (**Figure 2A and B**). The *BCR-ABL1*/*ABL1* ratio was 0.061% IS.

3 What is the most likely etiology of thrombocytopenia?

- ☐ Drug-induced thrombocytopenia
- ☐ Immune thrombocytopenia (ITP)
- ☐ Drug-induced thrombotic microangiopathy
- ☐ CML blast crisis

Evaluation of a patient with isolated thrombocytopenia should include a repeat complete blood cell count, reticulocyte count, and peripheral blood smear. The peripheral blood smear is important to rule out pseudothrombocytopenia from platelet clumping and microangiopathic hemolytic anemia. The patient's coagulation profile was normal, ruling out disseminated intravascular coagulation. Important differential diagnoses to consider in a patient with isolated thrombocytopenia include ITP and drug-induced thrombocytopenia.

ITP is a diagnosis of exclusion, so ruling out alternate etiologies of thrombocytopenia is crucial. ITP is an acquired thrombocytopenia caused by autoantibodies targeting glycoprotein IIb/IIIa complex and glycoprotein Ib/IX complex on the surface of platelets, leading to accelerated platelet destruction.[9] In addition, these autoantibodies inhibit megakaryocyte proliferation in the bone marrow, leading to impaired platelet production.[10,11] ITP can be primary or secondary to an underlying systemic illness. Secondary ITP is often seen in the setting of autoimmune diseases, infection, immunodeficiency syndromes, and lymphoproliferative disorders.[12,13] Our patient had type 1 diabetes, and these patients have a significantly higher risk of developing other rheumatologic diseases and other autoimmune endocrinopathies. In patients with type 1 diabetes, autoimmune hematologic abnormalities, including ITP, are rare.[14]

ITP is often difficult to distinguish from drug-induced thrombocytopenia except for the fact that thrombocytopenia in drug-induced thrombocytopenia is triggered by the drug, and the platelet count usually improves once the offending agent is discontinued. Our patient was taking dasatinib for CML, which rarely can cause drug-induced thrombocytopenia due to inhibition of megakaryocyte colony formations.[15] In addition, tacrolimus can cause drug-induced thrombocytopenia or refractory ITP in solid-organ transplant recipients.[16] *BCR-ABL* tyrosine kinase inhibitors have complex immunoregulatory properties, and their use has been associated with multiple autoimmune disorders.[17] Hence, it is plausible that tyrosine kinase inhibitors can drive immune-mediated platelet destruction as well.

In addition, tyrosine kinase inhibitors can cause platelet dysfunction. This likely explained the patient's bleeding manifestation that seemed to be out of proportion to her degree of thrombocytopenia.[18] Our patient had been taking dasatinib and tacrolimus for almost 6 years, and there was no recent change in the dosing. Hence, we thought that dasatinib and tacrolimus were unlikely culprits. Drug-induced thrombotic microangiopathy is an important consideration. Both dasatinib and tacrolimus can cause this condition, which is potentially fatal if left untreated.[19] The peripheral blood smear did not show any schistocytes, and there was no evidence of hemolysis or organ dysfunction. Hence, drug-induced thrombotic microangiopathy was excluded.

When evaluating a patient with CML and thrombocytopenia, it is important to differentiate between inadequate platelet production due to bone marrow infiltration by aberrant myeloid cells and immune-mediated peripheral destruction of platelets. Thrombocytopenia is usually not seen in the chronic phase of CML and instead is often seen during the accelerated phase or blast crisis. Other differentials to consider in a patient with CML who presents with thrombocytopenia include transformation into myelofibrosis or acute leukemia.

Bone marrow biopsy is usually not required in a patient with ITP. However, unexplained isolated thrombocytopenia in a patient with CML warrants bone marrow biopsy. The biopsy results showed that our patient was in major molecular remission and had no evidence of disease transformation. A few helpful clues supporting the theory of immune-mediated peripheral destruction of platelets in our patient included a favorable response to glucocorticoids, a discordancy between severe thrombocytopenia and increased megakaryocyte count in the bone marrow, evidence of other autoimmune disease, and a poor response to platelet transfusions. The increased megakaryopoiesis noted in our patient's bone marrow could have been secondary to her CML and not necessarily a response to destructive thrombocytopenia.

Although ITP can occur secondary to lymphoproliferative disorders, it is quite rare and less studied in patients with myeloid neoplasms. There have been case reports of ITP in patients with polycythemia vera and essential thrombocytosis.[20,21] Also, there are several reports of primary ITP later transforming to CML.[22,23] However, the diagnosis of ITP occurring several years later in a patient with established CML is extremely rare. Our patient was diagnosed with ITP 6 years after being diagnosed with CML, and she

TABLE 1
Laboratory values for a 35-year-old woman who underwent simultaneous pancreas and kidney transplant and developed chronic myeloid leukemia

Laboratory parameters (reference range)	Pretransplant	1 week after transplant	Thrombocytopenia admission (about 6.5 years after transplant	Bicytopenic cycle (2 weeks after the thrombocytopenia admission)
White blood cell count (4–10 × 10^9/L)	20	80	6	7
Hemoglobin (12–16 g/dL)	10.6	9.5	11	7.8
Platelet count (150–400 × 10^9/L)	281	440	6	20
Reticulocyte count (0.5%–1.5%)	NA	NA	2.1%	16.3%
Neutrophils (1.5–8 × 10^9/L)	15	29	4.4	5.3
Lymphocytes (1–5 × 10^9/L)	3.5	3	1.3	1.5
Eosinophils (0–0.5 × 10^9/L)	0.4	0.8	0.2	0.2
Basophils (0–0.2 × 10^9/L)	0.2	0.8	0.1	0.1
Metamyelocytes (0%–1%)	2%	11%	NA	NA
Myelocytes (0%)	2%	1%	NA	NA
Promyelocytes (0%)	2%	NA	NA	NA
Peripheral blood smear	NA	Normocytic hypochromic anemia with anisopoikilocytosis, slight polychromasia, a few burr cells, leukocytosis with reactive polymorphonuclear leukocytes and left shift No blasts were seen	Normochromic normocytic anemia with slight polychromasia No increase in schistocytes Marked thrombocytopenia with a few large forms	Normocytic anemia with increased polychromasia, increased microspherocytes No significant schistocytes or blasts Platelets showed normal morphology without clumping
Prothrombin time (10–13 seconds)	13	17.3	13	12.3
International normalized ratio (0.8–1.1)	1.05	1.3	1	0.9
Partial thromboplastin time (25–35 seconds)	34	45	27	23
Fibrinogen (200–400 mg/dL)	NA	NA	367	NA

NA = not available

was in major molecular remission at the time of the ITP diagnosis. Rarely, renal transplant recipients may develop ITP, presumably from immune dysfunction. Laub et al[24] reported a case of new-onset ITP that started 2 days after renal transplant and was successfully managed with romiplostim. Our patient

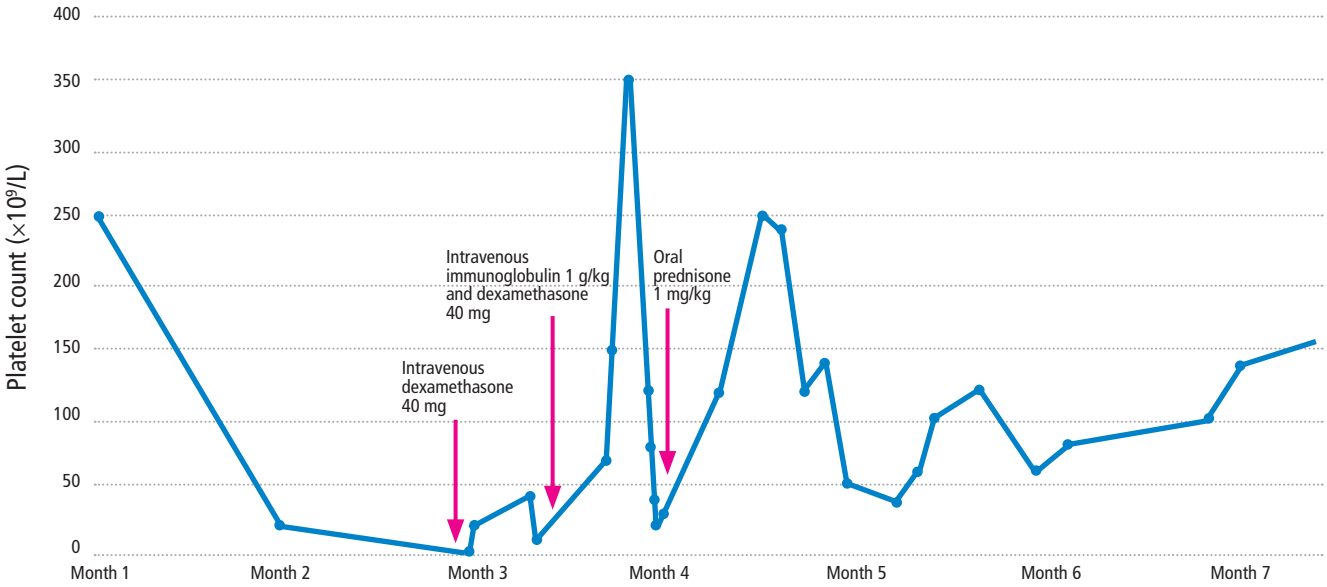

Figure 3. Trend in platelet counts and treatment interventions implemented to manage thrombocytopenia over a period of 7 months.

developed ITP 7 years after renal transplant, and the underlying trigger is still unknown. Although the mainstay of treatment for ITP is immunosuppression, it is quite intriguing that renal transplant recipients on immunosuppression therapy still develop ITP.

Approximately 10% to 20% of patients with other myeloid neoplasms such as myelodysplastic syndrome or chronic myelomonocytic leukemia may have ITP. Bourgeois et al[25] reported on a study of 61 patients with low-risk myelodysplastic syndrome and observed that 15% had ITP. Komrokji et al[26] reported that the prevalence of ITP in 1,408 patients with myelodysplastic syndrome was 12%. Patients with secondary ITP from myelodysplastic syndrome/chronic myelomonocytic leukemia tend to have a higher risk of bleeding but a lower risk of blast transformation than patients who have primary ITP.[27] ITP may precede the diagnosis of myelodysplastic syndrome/chronic myelomonocytic leukemia by several months to years.[27]

A causal relationship between ITP and myeloid neoplasms is plausible, although we seldom see myeloid malignancies being listed as a cause of secondary ITP. Immune dysregulation could be a common pathogenic link between ITP and clonal myeloid neoplasms. This hypothesis is reinforced by reports of ITP being observed in other diseases with immune dysregulation such as indolent lymphomas, chronic lymphocytic leukemia, common variable immunodeficiency, and monoclonal gammopathy of undetermined significance.[28–30]

In addition to ITP, there is a higher prevalence of other autoimmune disorders in patients with clonal myeloid disorders.[26] It remains unclear whether the primary immune dysregulation drives the lymphoid or myeloid clonal disorder or vice versa. Given the complex interplay between the immune system, genetics, the hematopoietic system, and environmental factors, it will be extremely challenging to solve this enigma. ITP may precede or present simultaneously or may manifest after the diagnosis of myeloid neoplasms. Hence, it is appropriate to use the term "secondary ITP" in the latter 2 instances.

CASE CONTINUED

Given the working diagnosis of ITP, our patient received intravenous dexamethasone 40 mg per day for 4 days, and her platelet count transiently improved to the mid-40 × 10^9/L range. One week later, the repeat platelet count results had dropped to 8 × 10^9/L. In patients with ITP, if the platelet counts fall after steroids are discontinued, it is reasonable to consider alternate therapies such as intravenous immunoglobulin (IG), or a second course of steroids can be attempted given the favorable response with the first course. The patient was hospitalized again and received 2 doses of intravenous IG 1 g/kg and a second course of pulse dexamethasone 40 mg for 4 days. Three days later, her platelet counts had normalized.

A repeat complete blood cell count 1 week later showed bicytopenia with a decrease in hemoglobin to 7.8 g/dL from 11 g/dL and platelet counts of 20×10^9/L. The reticulocyte count was 16.3%, haptoglobin was less than 8 mg/dL, total bilirubin was 1.6 mg/dL, and lactate dehydrogenase was 319 units/L. A peripheral blood smear showed normocytic anemia with increased polychromasia, rare nucleated red blood cells, and increased microspherocytes. No significant schistocytes or blasts were seen. Platelets showed unremarkable morphology. A direct antiglobulin test was positive, with IgG detected on circulating red blood cells, and no complement fixation was noted.

4 What is the most likely etiology of this clinical presentation?

- ☐ Cold agglutinin disease
- ☐ Delayed hemolytic transfusion reaction
- ☐ Evans syndrome
- ☐ Paroxysmal cold hemoglobinuria

The laboratory studies and peripheral blood smear were highly suggestive of hemolytic anemia. The Coombs test is helpful to differentiate immune from nonimmune causes. Although a direct antiglobulin test was positive with IgG during the current admission, the direct antiglobulin test done prior to the platelet transfusion was negative. A delayed hemolytic transfusion reaction from her previous platelet transfusion is an important consideration, given that platelet products may contain small quantities of red blood cells and cause alloimmunization. However, it does not explain the thrombocytopenia. The direct antiglobulin test pattern in cold agglutinin disease and paroxysmal cold hemoglobinuria are similar, with a positive direct antiglobulin test using anti-C3 and negative using IgG.

Warm autoimmune hemolytic anemia should be considered in the differential diagnosis of a patient with hemolytic anemia and a positive direct antiglobulin test for IgG or c3d, and after excluding alternate causes of hemolysis. ITP can rarely co-occur with warm autoimmune hemolytic anemia, often referred to as Evans syndrome, and this is the most likely etiology in our patient. Evans syndrome is known to complicate solid-organ transplant.[31] The trend in complete blood cell counts with differential count, coagulation profile, and peripheral blood smear during our patient's entire clinical course is provided in **Table 1**.

CASE CONCLUSION

Given evidence of brisk hemolysis and a drop in hemoglobin, we decided to treat the patient with prednisone 1 mg/kg, which was gradually tapered over a period of 2 months with normalization of bicytopenia. The platelet trend in our patient is shown in **Figure 3**. She continues to be in remission, with normal blood cell counts at the end of 1 year of follow-up.

Evans syndrome is usually resistant to standard immunosuppressive therapies and has a higher relapse rate. Although short-term responses tend to be high (80%), only one-third of patients achieve a durable remission while off immunosuppression.[32] Given that our patient is on immunosuppressive drugs for her organ transplant, she could potentially stay in remission, although longer follow-up is required.

TAKE-HOME POINTS

- This case highlights the complex interplay linking autoimmunity, solid-organ transplant, myeloid neoplasm, and Evans syndrome.
- A broad differential diagnosis and detailed evaluation including a differential count and peripheral blood smear are important in a patient with unexplained leukocytosis.
- Although rare, autoimmune cytopenias can arise secondary to CML.
- Evans syndrome can arise in the setting of solid-organ transplant and is characterized by concurrent or sequential presentation of immune hemolytic anemia and ITP.

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