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Cleveland Clinic Journal of Medicine

All sulfa drugs are not created equal

Sarcoidosis with diffuse purplish erythematous plaques on the hands

Can my patient with a 'sulfa allergy' receive celecoxib or other nonantimicrobial sulfonamides?

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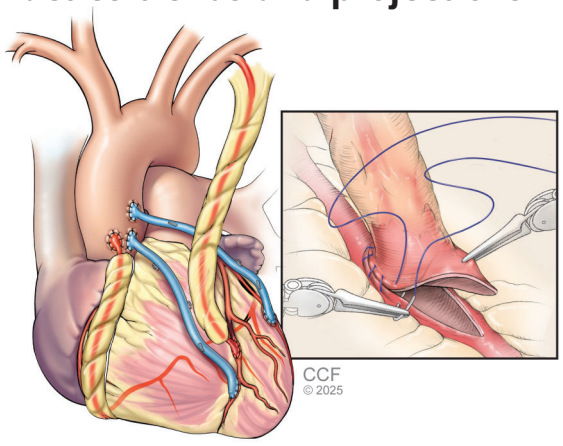

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All sulfa drugs are not created equal

I frequently hear from patients in clinic that they are "allergic to sulfa antibiotics" or have been told to avoid sulfa medications. This concern may be noted in the patient's electronic medical record (EMR), and various prescribed sulfa-containing medications may be flagged with an avoidance warning in their EMR or by a dispensing pharmacy's drug database due to concern about cross-reactivity. This chain of events can result in the unnecessary avoidance of useful medications and the prescription of less-effective alternatives. As pointed out by Cline et al[1] in this issue of the *Journal*, there can be significant misinformation leading to a decision to avoid prescribing nonantimicrobial sulfonamides to all patients with a history of "sulfa antibiotic allergy."

First, is the patient's history of sulfonamide antibiotic allergy correct? Many patients conflate intolerances like diarrhea or queasiness with allergy. Some patients were told by their parents they had an allergic reaction to an antibiotic taken as a child, without the possibility of further clarification. Others may recall a rash at the time of taking an antibiotic, without a way of retrospectively knowing whether that "rash" was actually caused by the medication or by an underlying (perhaps viral) infection or other triggers. There are no fully validated ways, at present, to definitively diagnose allergy or hypersensitivity to antimicrobial sulfonamides using skin prick tests or in vitro testing.[2] Thus, an oral exposure challenge may be needed to confirm the allergy. If the initial presumed "allergy" was a severe hypersensitivity or anaphylactic reaction, this approach is generally avoided.

Allergic reactions to sulfonamide antimicrobials are not unusual. A study using EMR data reported an incidence of approximately 7%,[3] and the incidence is believed to be higher in patients with human immunodeficiency virus infection or systemic lupus erythematosus. Of these allergic reactions, most are cutaneous, with maculopapular eruptions being most common (37%), and slightly above 10% are severe.[2] Most of these reactions are, at least in part, T-cell mediated and generally delayed in time from the start of therapy. Immediate immunoglobulin E–mediated reactions occur less often.

Critical to the understanding of "sulfa allergy" is, as discussed by Cline et al,[1] the fact that sulfa is not the immunologic or allergic target, nor is the sulfonamide molecular moiety that is shared by the sulfonamide antimicrobials and the nonantimicrobial sulfonamides. Distinct nonsulfonamide chemical structures are immunologically targeted, resulting in immediate and delayed hypersensitivity reactions. These structures, while shared among the antimicrobial sulfonamides, are not present in nonantimicrobial sulfonamides like furosemide, probenecid, thiazides, celecoxib, and others.[4] Yet antibiotic and nonantibiotic sulfonamides continue to be frequently lumped together, despite a lack of data indicating that they share allergic cross-reactivity. Surprisingly, this includes inconsistent pharmaceutical package insert labeling approved by the US Food and Drug Administration, as discussed by Knowles et al.[5]

Some patients with a known allergic reaction to an antimicrobial sulfonamide may have an allergic reaction to a nonantimicrobial sulfonamide. This does not prove the case, however, for cross-reactivity and the need for *across-the-board* avoidance of all sulfonamides in antibiotic-allergic patients. In a conceptually important paper, Strom et al[6] reported that some patients have an allergic diathesis—it is not necessarily the drug alone that dictates the likelihood of an allergic response, it may be the patient's immune system. In their study of 969 patients allergic to an antimicrobial

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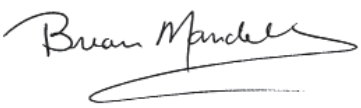
sulfonamide, the risk of an allergic response to chemically dissimilar penicillins (14%) was higher than the risk of an allergic response to nonantimicrobial sulfonamides (9.9%), and both were higher than the usual incidence of allergic reactions to these drugs in patients without an allergic history. And yet some nonantimicrobial sulfonamide drugs carry a warning label suggesting cross-reactivity. As an example, the label for celecoxib indicates that its use is contraindicated in patients with an allergy to antimicrobial sulfonamides, despite the above and the directly relevant data indicating its safe use in 28 patients with history of a "sulfonamide allergy," including some who tested positive for antimicrobial sulfonamide sensitivity by skin prick or in vitro assay.[7] But this can get complicated. For instance, some drugs like sulfasalazine may be metabolized into cross-reactive molecules that are like antimicrobial sulfonamides, and thus should be avoided.[8]

So while some caution is certainly warranted in patients with a clear allergic history, there is not an absolute need to avoid use of all sulfa-based drugs in all patients with a history of antimicrobial sulfonamide allergy.

Unrelated to the above, I sadly note the passing of John D. Clough, MD, on January 26, 2025. John was a Renaissance man who I was very fortunate to know as my friend, colleague, and mentor. He was nationally known as a clinical researcher and consultant rheumatologist. He chaired the Department of Rheumatology at Cleveland Clinic and then served as the head of Health Affairs. He directly preceded me as Editor in Chief of *CCJM* from 1996 to 2004, setting in motion several of the successful innovations that continue through today. He was an avid reader, author, musician (euphonium), band conductor, and composer. In his outpatient clinical practice, he presaged the use of the digital medical record. And he was so much more. To his family, parish, and so many friends he was a humble bedrock of strength and equipoise and a moral compass. To those of us who worked with him, it was with utmost respect and admiration that we watched him navigate the corporate waters, never afraid to speak truth to power with a keen analytic mind and a wry sense of humor. Our condolences go out to Mary and family—thank you for sharing John with us.



Brian F. Mandell, MD, PhD
Editor in Chief

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Effective but inaccessible antiobesity medications

To the Editor: We read with great interest the commentary on improving access to antiobesity medications by Dr. Burguera and colleagues published in the November 2024 issue.[1] This article highlighted the plague of unequal and inadequate access to the new glucagon-like peptide (GLP) 1 and dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist medications for weight loss. We would like to echo and highlight the lack of access to these medications in patients awaiting organ transplants.

Obesity is a leading risk factor for chronic kidney disease, metabolic dysfunction–associated steatotic liver disease (formerly known as nonalcoholic fatty liver disease), and congestive heart failure. Studies have shown that patients with obesity have a lower likelihood of being listed and undergoing a kidney transplant.[2] There are about 90,000 patients awaiting a kidney transplant, and 17 people die each day in the United States while awaiting an organ transplant.[3] Obesity in patients who have undergone renal transplant has been associated with a higher risk of delayed graft function, wound dehiscence, allograft rejection and loss, posttransplant diabetes, and cardiovascular disease.[2,4]

Burguera and colleagues[1] outlined the cost differences for these medications between countries, with individuals in some countries paying as much as 75% less for them. Insurance coverage and pricing in the United States have amplified the inequalities in access in our healthcare system, as some insurance companies have limited their coverage and expanded prior authorization requirements in an effort to reduce the number of patients eligible for these medications.[5] This further exacerbates disparities in access to solid-organ transplants, and particularly affects those who are already at a disadvantage in our healthcare system.

We add our voices to those of Dr. Burguera and colleagues[1] in a call to action to expand coverage and affordability of these medications as our patients' lives are at stake.

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Classic diabetic ketoacidosis and the euglycemic variant

To the Editor: I am writing to commend the review by Dr. Mehta and colleagues[1] on classic and euglycemic diabetic ketoacidosis (DKA), which highlights the evolving clinical challenges that clinicians face in diagnosis and management. I would like to offer a few reflections and questions that may further stimulate discussion on this important topic.

First, I value the authors' emphasis on identifying euglycemic DKA, which frequently manifests in an unconventional way—ie, with blood glucose levels that are normal or almost normal. This variation presents a diagnostic conundrum, particularly in patients who do not exhibit conventional hyperglycemia, as the authors note.[1] Although ketosis and an elevated anion gap are well-established diagnostic criteria for euglycemic DKA, further research is necessary to find early biomarkers or other clinical signs that could help differentiate euglycemic DKA from other conditions that might present similarly. For instance, future research could examine the function of high serum beta-hydroxybutyrate as an early signal.[2]

I also want to bring up the issue of euglycemic DKA care. According to the paper, this variation frequently affects people on sodium-glucose cotransporter 2 inhibitors, which might obscure hyperglycemia and thus complicate the clinical picture. The authors stress how crucial it is to diagnose euglycemic DKA in these patients in order to prevent delays in receiving the right care. However, considering the difficulties these patients have with fluid shifts and renal function, I would like to know if the authors have any thoughts on whether early intravenous insulin therapy or modifications to fluid management techniques would improve outcomes in these situations.[3]

Last, the article's mention of the significance of educating and raising clinician's understanding about euglycemic DKA is quite pertinent. I think there might be a chance to create more focused clinical guidelines or decision-support systems to help physicians recognize this variant sooner, especially as sodium-glucose cotransporter 2 inhibitors are being used more often in the treatment of diabetes. This might lessen the possibility of an incorrect diagnosis or postponed therapy.

Given the circumstances, I applaud the authors for their efforts to better comprehend this intricate clinical phenomenon and to improve our understanding of DKA in all its manifestations. As we continue to advance our methods for diagnosing and treating persons with diabetes, I am excited for more studies and conversations in this field.

Param Darpan Sheth, MBBS
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In Reply: First, we would like to thank Dr. Param Darpan Sheth for the commendations and, just as important, for the insightful and clinically important questions and comments.

There is no question that the earlier the diagnosis of diabetic ketoacidosis (DKA), the quicker the resolution of acute symptoms. To attempt to establish a quicker diagnosis, there must be a high degree of suspicion. Practically, a patient admitted to an emergency department will have a basic electrolyte panel: a low bicarbonate and increased anion gap are immediately identified. Checking for urine ketones, while quick, is not necessarily very helpful because sodium-glucose cotransporter (SGLT) 2 inhibitors induce ketosis and the turnaround time for serum ketones delays initiation of appropriate therapy.

Our recommendation is that the presence of low bicarbonate (< 20 mmol/L), increased anion gap, and blood glucose less than 200 mg/dL allows a presumptive diagnosis and requires starting a dextrose-containing intravenous fluid—normal saline if the potassium exceeds 5.5 mmol/L or Ringer's lactate if the potassium is lower. This will induce endogenous insulin secretion and provide the glucose to stop ketogenesis.

It is difficult to mandate insulin administration to non-endocrinologists, but it can be mandated that any patient with ketoacidosis and a blood glucose less than 200 mg/dL be given a nonpeaking insulin like glargine or degludec at a dose of 20% of the body weight in kilograms. This is based on the physiologic principle that any ketoacidosis requires a relative insulin deficiency in relation to glucagon, and administered insulin will go a long way to correct that imbalance.

The risk of hypoglycemia is very low given that any excess insulin is counterbalanced by the suppression of endogenous insulin secretion and the glucose infusion, as well as the fact that peakless basal insulins control hepatic glucose output but are poor at disposing of glucose from the circulation when used in low doses. In fact, national guidelines recommend the continuation of basal insulin during the treatment of full-blown DKA,[1] which is also indicated in our paper.[2] Even if the unmeasured ion comprising the increased anion gap is lactic acidosis, a basal insulin has been shown to be advantageous. Instituting an insulin infusion is indicated once the beta-hydroxybutyrate level has been established, and this would not be adversely affected by the presence of the basal insulin.

These approaches, based on the first laboratory tests on arrival in the emergency department, treat the physiologic basis of ketoacidosis from the start: lack of glucose and relative insulin deficiency and dehydration. And they do so with a very low risk of hypoglycemia. Of course, once capillary point-of-care ketone meters, which are under development, become less expensive and more universally available, delays in diagnosis will become moot.

The comment on ketones is quite germane. There is a very thin line between the advantages of ketonemia and the disadvantages of ketoacidosis. SGLT-2 inhibitors blur the line further. Ketones, being strong acids, will decrease bicarbonate. Therefore, starting SGLT-2 inhibitors in patients with a bicarbonate level less than 21 mmol/L is asking for trouble. As well, ketones are an efficient secondary fuel, requiring less oxygen to be metabolized to form adenosine triphosphate. However, this is done in muscle: a low creatinine de novo or in relation to blood urea nitrogen predicts a low muscle mass. The latter is important in the very elderly, in whom sarcopenia may be masked by muscle fibrosis, thus making weight a poor marker of sarcopenia. Unfortunately, creatinine loses its predictive value at presentation with ketoacidosis because of the associated dehydration.

With regard to guidelines, we could not agree more. The therapeutic measures discussed above are based on physiologic principles, and our approach is based on these principles, not on guidelines. With the wider use of SGLT-2 inhibitors in conditions without attendant hyperglycemia, it is important that relevant professional organizations recognize the greater frequency of ketoacidosis and develop a consensus and physiologically sound guidelines.

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Insomnia in older adults

To the Editor: I read with great interest the review on insomnia in older adults by Dr. León-Barriera and colleagues[1] in the January issue. The authors mention that up to 50% of older adults may have difficulty initiating or maintaining sleep, and that secondary causes of insomnia, such as sleep apnea, should be excluded. One of the important secondary causes of sleep-onset insomnia in adults is restless legs syndrome (RLS). Note that RLS is a misnomer, however, because the disorder can involve the upper extremity; restless *limb* syndrome is a more appropriate term. The prevalence of RLS increases with advancing age.[2] It is a clinical diagnosis made by asking patients if they have a creepy, crawling sensation in the legs or arms with an urge to move; if symptoms occur in the evening or night; if they have onset of symptoms at rest; and if the symptoms improve with movement.

León-Barriera et al[1] list mirtazapine, amitriptyline, and the over-the-counter antihistamine diphenhydramine among the agents that have been used for treatment of insomnia. However, these 3 drugs are important secondary causes of RLS, and prescribing them without excluding the diagnosis of RLS has the potential of making sleep-onset insomnia worse.

Recently updated guidelines[3] by the American Academy of Sleep Medicine have changed the recommendations for treatment of RLS, now favoring alpha-2-delta ligands like gabapentin and pregabalin as first-line drugs over dopamine agonists.

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In Reply: We appreciate the detailed response to our article on insomnia in older adults.[1] As Dr. Katyal points out, there are several underlying causes of insomnia that should be addressed before beginning therapy for primary insomnia. As we discuss in our article, before initiating therapy, it is important to screen for not only restless legs syndrome, but also sleep apnea, thyroid conditions, chronic pain, migraine, chronic obstructive pulmonary disease, asthma, congestive heart failure, gastroesophageal reflux disease, psychiatric conditions, and substance use disorders.[1] Our article discusses management of insomnia assuming it is primary insomnia—that is, where these other causes have been ruled out.

We thank Dr. Katyal for pointing out that the term restless *limb* syndrome is more appropriate, as the disorder can occur in the upper extremities as well. We appreciate and agree with the American Academy of Sleep Medicine recommendations[2] to use gabapentin and pregabalin to treat restless legs syndrome, but we should emphasize that these agents have no recognized role in the treatment of primary insomnia and can be hazardous in older adults due to their association with hip fracture and falls among frail and elderly patients.[3,4]

We concur that mirtazapine, amitriptyline, and diphenhydramine should be avoided for the treatment of primary insomnia. As our article states, amitriptyline and diphenhydramine are problematic in the elderly population because of their anticholinergic properties, and mirtazapine is not recommended except in the treatment of depression and insomnia associated with depression.[1]

Finally, we would like to reiterate that, in the case of primary insomnia in the elderly, no pharmacologic agent is considered first line, and providers should initiate treatment with cognitive behavioral therapy for insomnia whenever feasible.[1]

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Sarcoidosis with diffuse purplish erythematous plaques on the hands

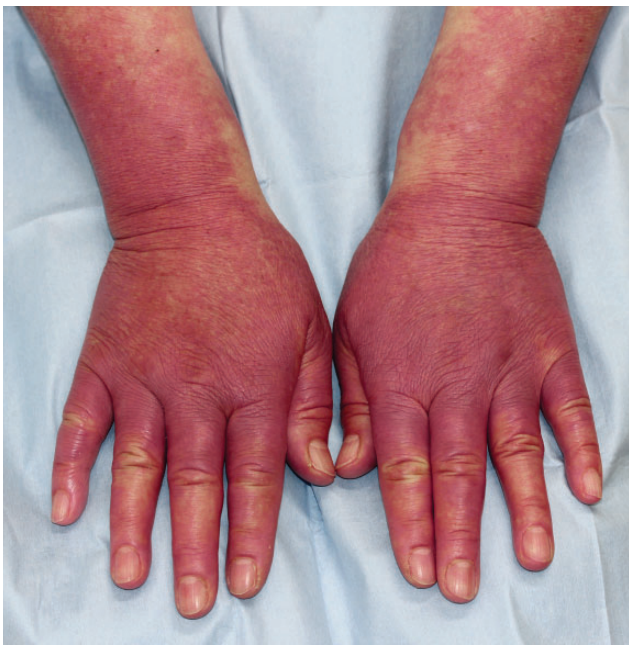

Figure 1. Diffuse purplish erythema on the dorsal surface of the distal forearms, hands, and fingers, with telangiectasia and swollen fingers.

A previously healthy 70-year-old woman presented in winter with a 1-month history of asymptomatic redness of the hands. She denied that the rash had been exacerbated by exposure to the cold temperatures. Physical examination revealed diffuse purplish erythematous plaques symmetrically distributed on the distal forearms and on the dorsal surface of the hands and fingers, with telangiectasia and swollen fingers (**Figure 1**). She had no other skin lesions.

Histopathologic examination of a skin biopsy specimen showed noncaseating granulomatous infiltrates of epithelioid histiocytes with mild lymphocytic infiltrates in the dermis (**Figure 2**). Radiography of the hands found no bone lesions. Laboratory testing showed a serum angiotensin-converting enzyme level of 30.4 U/L (reference range 7.0–25.0 U/L). Systemic

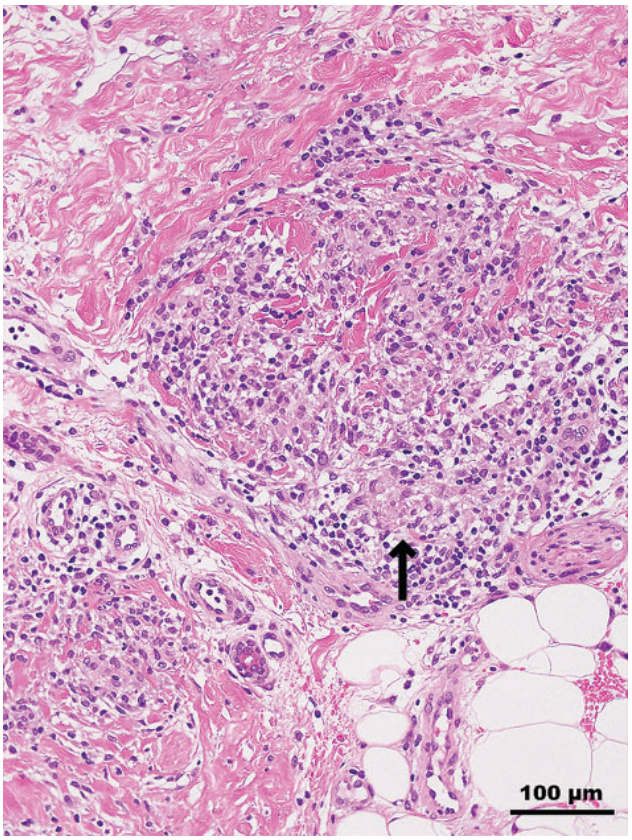

Figure 2. Histopathologic examination of a skin biopsy specimen revealed nodular histiocytic infiltration in the dermis, forming epithelioid granulomas (arrow) without evidence of necrosis (hematoxylin and eosin, original × 200).

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investigations identified supraclavicular and mediastinal lymphadenopathies and uveitis.

A diagnosis of sarcoidosis was made, and treatment with oral prednisolone (0.5 mg/kg daily) was started. The skin lesions abated in 2 months, and the prednisolone was tapered off. The nodal lesions also have disappeared or regressed, and the uveitis has improved.

CUTANEOUS MANIFESTATIONS OF SARCOIDOSIS

Sarcoidosis is a systemic disorder of unknown etiology characterized by noncaseating epithelioid cell granulomas that mainly involve the lungs (about 90% of cases), mediastinal and peripheral lymph nodes, eyes, and skin.[1] Involvement of the liver, spleen, central nervous system, heart, and bones occurs less often but is usually severe.

Cutaneous lesions specific for sarcoidosis, ie, those that display the histopathologic features of sarcoid granulomas, develop in up to 35% of patients with systemic sarcoidosis.[2] Less than one-third of patients with cutaneous manifestations have isolated cutaneous sarcoidosis without any systemic features.[1] The most common specific skin lesions include maculopapular sarcoidosis, nodular and plaque sarcoidosis, lupus pernio, scar or tattoo sarcoidosis, and subcutaneous sarcoidosis.[2]

Nonspecific skin lesions—those not caused by granulomas—also can occur in sarcoidosis and include erythema nodosum, prurigo, digital clubbing, erythema multiforme, pyoderma gangrenosum, and Sweet syndrome. Of these, erythema nodosum is the most common. However, there are many less common cutaneous manifestations of sarcoidosis, and, because of this varied morphology, sarcoidosis is considered one of the great imitators in dermatology.[2]

In this patient, the cutaneous lesion may have been lupus pernio, which causes indurated violaceous papulonodules and plaques on the nose, cheeks, and ears.[3] The fingers and toes can be affected as well. To the best of our knowledge, lupus pernio occurring only on the hands has not been reported. Differential diagnoses in this patient included vascular disorders, such as chilblains, Raynaud phenomenon, and acrocyanosis.

Delays in the diagnosis of sarcoidosis are common given its varying presentations. Sarcoidosis is diagnosed more easily and earlier when skin lesions are present because the skin is easily accessible for histopathologic confirmation.[4] However, this does not necessarily mean that it is easy to recognize a skin lesion as a manifestation of sarcoidosis. Because cutaneous sarcoidosis presents with varied morphology, it may present a diagnostic challenge.

A thorough skin examination and skin biopsy are necessary for diagnosing sarcoidosis. Laboratory tests can also be useful because at least 60% of patients diagnosed with sarcoidosis have an increased serum angiotensin-converting enzyme level.[2] A systemic workup to evaluate the extent of involvement should be undertaken in all patients with cutaneous sarcoid lesions, even in those with minimal skin involvement.

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: Can my patient with a 'sulfa allergy' receive celecoxib or other nonantimicrobial sulfonamides?

A: There is no cross-reactivity between antimicrobial sulfonamides and nonantimicrobial sulfonamides. For this reason, patients with a history of immunoglobulin (Ig) E–mediated (allergic or anaphylactic) reaction to a sulfonamide antibiotic can receive nonantimicrobial sulfonamides such as celecoxib, chlorthiazide, furosemide, and others without elevated risk of an IgE-mediated reaction compared with the general population.

SULFONAMIDE ALLERGY

Patients with a reported sulfonamide allergy are frequently encountered in clinical practice. A history of "sulfa allergy" is second in frequency to penicillin allergy and is reported in 3% to 6% of the general population.[1–4] Clarification of allergy status is particularly important because sulfonamide antibiotics remain first-line treatments for certain infections, including *Pneumocystis jirovecii*, *Toxoplasma gondii*, and *Stenotrophomonas maltophilia*.[5]

Adverse reactions to sulfonamides vary from mild and self-limited to potentially life-threatening, and may include any of the 4 hypersensitivity reactions from the Gell and Coombs classification (**Table 1**).[1,2] Cutaneous reactions are the most frequent, with maculopapular exanthemas being the most common type.[6] Cutaneous reactions to sulfonamides have also been reported in up to 30% of patients with human immunodeficiency virus.[1] Drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis, and other severe adverse reactions are fortunately less common.[5]

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CROSS-REACTIVITY BETWEEN SULFONAMIDES

Table 2 lists commonly prescribed antimicrobial and nonantimicrobial sulfonamides. These drugs all contain an SO_2NH_2 moiety (**Figure 1**), from which they derive the designation *sulfonamides*. Antimicrobial sulfonamides contain an arylamine group at the N4 position, which accounts for the drugs' antimicrobial function through competitive inhibition of a structurally similar compound needed for microbial processes. This arylamine group and another nitrogen-containing ring found in antimicrobial sulfonamides are the primary targets, or determinants, for allergic sensitization.[1,2]

Type I (immediate) hypersensitivity reactions occur when IgE binds and cross-links to a specific antigenic determinant. This results in the activation of mast cells and the release of inflammatory mediators, including histamine, leukotrienes, and others, which can manifest as pruritus, urticaria, angioedema, bronchospasm, vomiting, and hypotension. Thus, molecular structure determines IgE-mediated allergenicity and cross-reactivity. An index reaction to 1 antimicrobial sulfonamide agent precludes future use of other antimicrobial sulfonamides due to interclass cross-reactivity of the shared arylamine group's allergenic determinant.[7] A preferred label for this allergy would be *sulfonamide antibiotics*, to indicate that an alternative nonsulfonamide antibiotic should be used. Notably, these type I allergic reactions to sulfonamides are not directed at the SO_2NH_2 group after which the drug class is named.[2]

Nonantimicrobial sulfonamides include carbonic anhydrase inhibitors, selective cyclooxygenase-2 inhibitors, loop diuretics, sulfonylureas, thiazide diuretics, triptans, and other agents.[2] Although product information approved by the US Food and Drug Administration for

TABLE 1
Gell and Coombs classification of hypersensitivity reactions

Type	Hypersensitivity reaction	Immune mechanism	Description
I	Immediate hypersensitivity	Immunoglobulin E–mediated reaction driven by immunoglobulin E bound to mast cells or basophils or both	Engagement of immunoglobulin E with its appropriate antigen leads to degranulation and release of histamine, leukotrienes, and other inflammatory mediators (eg, anaphylaxis)
II	Cytotoxic antibody	Antigen-antibody interaction	Local production of anaphylatoxin (C5a) and recruitment of polymorphonuclear leukocytes lead to release of hydrolytic neutrophil enzymes and subsequent tissue injury (eg, immune cytopenia)
III	Immune complex	Immunoglobulin G and M antibodies bind to antigen	Antigen-antibody complexes deposit in the glomerular basement membrane, pulmonary basement membrane, or both, leading to tissue injury and organ damage (eg, serum sickness reaction)
IV	Delayed hypersensitivity	Cell-mediated immune response	T cells are activated by an antigen-presenting cell; when antigen is presented again, memory T cells activate leukocytes (macrophages, neutrophils, eosinophils), leading to an inflammatory response with possible tissue injury via reactive oxygen species, lysosomal enzymes, and inflammatory cytokines (eg, tuberculin skin test, Rhus dermatitis, Stevens-Johnson syndrome or toxic epidermal necrolysis)

nonantimicrobial sulfonamides may include warnings about possible cross-reaction with antimicrobial sulfonamides,[1] these drugs do not need to be withheld. Nonantimicrobial sulfonamides lack an arylamine group at the N4 position, so they do not cross-react with antimicrobial sulfonamides. For example, a patient with a history consistent with IgE-mediated reaction to the antimicrobial sulfonamide trimethoprim-sulfamethoxazole can receive celecoxib, chlorthiazide, furosemide, or other nonantimicrobial sulfonamides, as indicated.

Antimicrobial sulfonamide metabolites are most likely responsible for non–IgE-mediated reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis.[1,2,6] Because nonantimicrobial sulfonamides lack an arylamine group, they do not produce similar metabolites, which is the reason they do not cross-react in patients who have had non–IgE-mediated reactions to antimicrobial sulfonamides.

Patients who have had IgE-mediated or non–IgE-mediated reactions to antimicrobial sulfonamides may also receive medications or other agents that contain sulfates or sulfites, such as morphine sulfate, ferrous sulfate, potassium metabisulfite, and sodium bisulfite, as these are not sulfonamides. The same recommendation applies for dapsone, a sulfone, which also does not need to be withheld.

EVALUATION AND MANAGEMENT OF SULFONAMIDE ALLERGY

Sulfonamide allergy management depends on the type of reaction and the underlying immune mechanism. Patients who report a severe delayed immune-mediated reaction (eg, drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome or toxic epidermal necrolysis, acute generalized exanthematous pustulosis, drug-induced nephritis or hepatitis) should subsequently avoid the culprit drug, as this can be regarded as a contraindication to future use.[4,8–11] However, patients with more benign reactions or a suspected IgE-mediated allergy may be candidates for reevaluation.

Lack of validated testing

Clinical history combined with immediate hypersensitivity skin or in vitro testing can be used to confirm or rule out IgE-mediated allergic potential to penicillin;

TABLE 2
Commonly prescribed antimicrobial and nonantimicrobial sulfonamides

Antimicrobial	Nonantimicrobial	
	Class	Examples
Sulfacetamide Sulfadiazine Sulfamerazine Sulfamethoxazole Sulfanilamide Sulfapyridine Sulfasalazine Sulfathiazole	Carbonic anhydrase inhibitors	Acetazolamide
	Cyclooxygenase-2 inhibitors	Celecoxib
	Loop diuretics	Bumetanide Furosemide Torsemide
	Sulfonylureas	Glipizide Glyburide
	Thiazide diuretics	Hydrochlorothiazide Chlorthalidone
	Triptans	Rizatriptan Sumatriptan
	Miscellaneous	Diazoxide Tamsulosin Zonisamide Metolazone Probenecid

in vitro testing is generally not recommended based on poor sensitivity.[4] In contrast to penicillin, neither skin nor in vitro testing for sulfonamide allergy has been validated.[4,8] The reference standard to establish allergic potential vs tolerance is drug provocation, or direct oral challenge (DOC) with a test dose of the culprit drug.

In the absence of validated diagnostic testing, counseling for a reported "sulfa allergy" historically led to a recommendation of future sulfonamide drug avoidance. When a sulfonamide drug was clearly indicated, without an equally efficacious antibiotic that could be used, desensitization was performed to induce temporary tolerance.[4] This enabled administration of a sulfonamide antibiotic to treat an acute infection, but it did not clarify whether an allergic or anaphylactic potential was present. Although effective, these protocols were lengthy, costly, and at times impractical—especially for patients needing intermittent therapy, as serial desensitization was required for temporary tolerance for each antibiotic course.[8]

DOC for low-risk patients

Fortunately, guidance on the approach to sulfonamide allergy has evolved to reflect more recent data showing the safety and efficacy of performing DOC in properly selected low-risk patients. A simplified algorithm for reassessment, as opposed to avoidance or desensitization, which implies a presumption of lifelong IgE-mediated potential, enables allergy "delabeling" based on history-guided DOC as standard of care.

We have learned that rates of true or persistent type I hypersensitivity to sulfonamide antibiotics are lower than previously thought.[4] Accordingly, the 2022 Drug Allergy Practice Parameter update[4] recommends a 1-step DOC to trimethoprim-sulfamethoxazole for low-risk patients, defined as those with a history of benign cutaneous reaction (eg, morbilliform or urticarial rash), unknown or remote history, or nonsevere delayed (> 36 hours) reaction to a sulfonamide antibiotic. As an added precaution for patients with a reaction history within the previous 5 years, which makes them higher risk, a 2-step DOC, starting with 10% of the target dose, is recommended.

This protocol is an extension of the widely accepted PEN-FAST (penicillin allergy reported by patient, five years or less since reaction, anaphylaxis or angioedema, severe cutaneous adverse reaction, and treatment required for reaction) clinical decision tool that has been used to identify patients with reported penicillin allergy who are appropriate for DOC rather than immediate hypersensitivity skin testing, which recent data suggest has poor positive predictive value in low-risk patients.[11] Preliminary data for the SULF-FAST clinical decision tool have been promising, with high

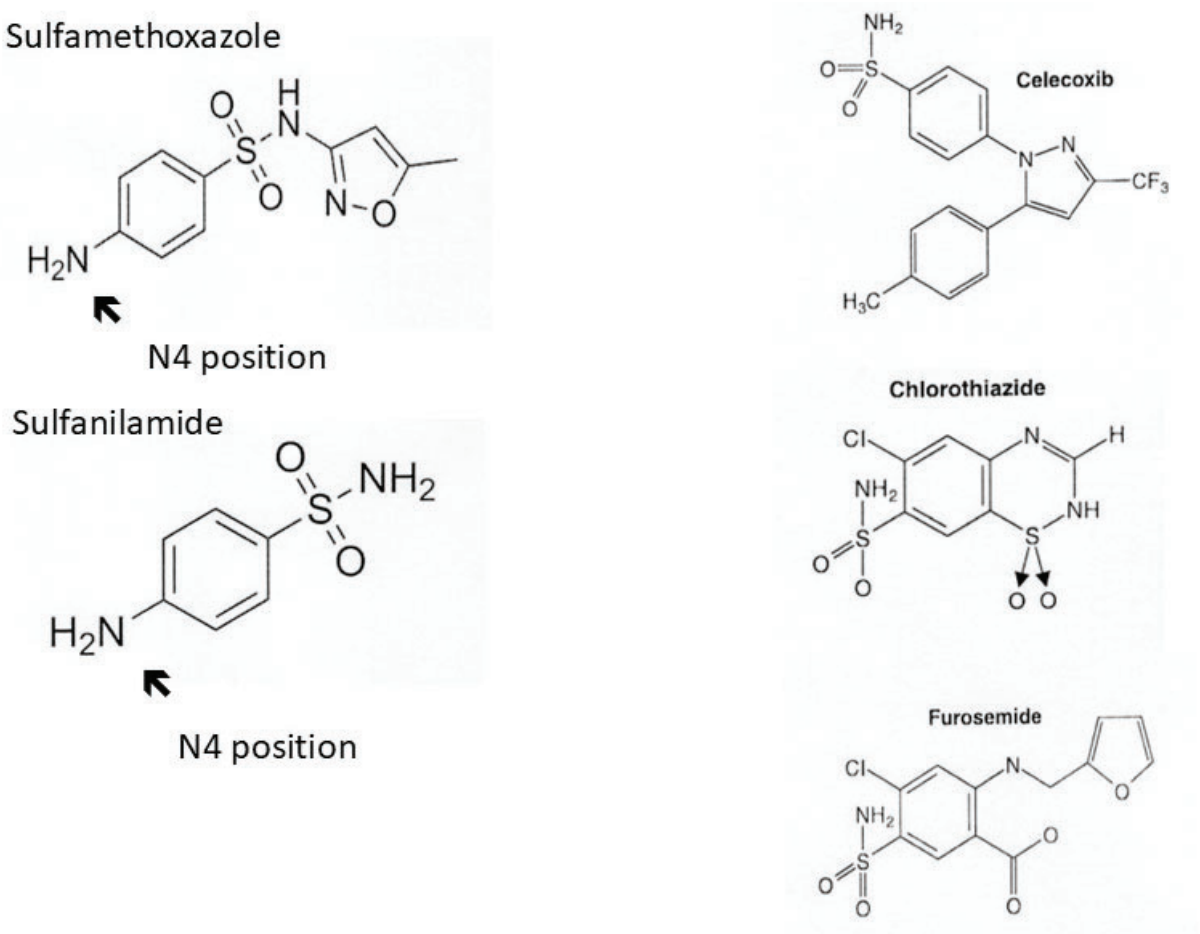

Figure 1. Chemical structures of antimicrobial and nonantimicrobial sulfonamides. Interclass reactivity and nonreactivity between antimicrobial and nonantimicrobial sulfonamides are shown. All sulfonamides contain an SO_2NH_2 moiety. Antimicrobial sulfonamides (eg, sulfamethoxazole and sulfanilamide) contain an arylamine group at the N4 position (arrow), which serves as the primary target for immunoglobulin E–mediated sensitization. Nonantimicrobial sulfonamides (eg, celecoxib, chlorothiazide, and furosemide) lack the arylamine group at the N4 position. For this reason, these drugs do not cross-react with antimicrobial sulfonamides.

specificity and negative predictive value; however, further validation is required before it is implemented more widely.[12]

Delabeling patients

Earlier studies were directed at delabeling patients with greater need for sulfonamide antibiotics, such as trimethoprim-sulfamethoxazole for *P jirovecii* prophylaxis in immunosuppressed populations, including patients with cancer, human immunodeficiency virus, or acquired immunodeficiency syndrome in whom the benefit of DOC outweighed the risk.[13] More recent data have shown similar levels of DOC safety and tolerance in the general population.[8,10,12] Proactive delabeling for "sulfa allergy" is not yet the standard of care as it is for penicillin. However, when there is an explicit need for sulfonamide antibiotic therapy, including anticipated immunosuppression due to a future organ transplant,[10] delabeling via DOC can be performed for both immunocompromised and immunocompetent patients categorized as low risk.[4]

THE BOTTOM LINE

Sulfonamide allergy is commonly encountered and is clinically important. Patients with a history of severe cutaneous or other serious delayed-type reaction (eg, drug reaction with eosinophilia and systemic symptoms or Stevens-Johnson syndrome) to an antimi-

crobial sulfonamide should be cautioned to maintain lifelong avoidance. Patients with a history of recent IgE-mediated (allergic or anaphylactic) reaction should empirically avoid all antimicrobial sulfonamides based on the risk of cross-reaction; however, nonantimicrobial sulfonamides do not need to be avoided. In addition, a 1- or 2-step DOC can be considered for properly selected low-risk patients. The allergy label should accurately reflect the restrictions above rather than broadly implicating all sulfonamides, as there is no evidence of cross-reactivity between antimicrobial and nonantimicrobial sulfonamides.

DISCLOSURES

Dr. Lang has disclosed consulting for Astra Zeneca, Celldex Therapeutics, Genentech, and Novartis, and teaching and speaking for Sanofi Regeneron. 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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CME MOC

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Hyperglycemic crises in adults: A look at the 2024 consensus report

ABSTRACT

Hospital admissions for diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS), the most severe hyperglycemic emergencies in patients with diabetes, have increased considerably over the past decade. The previous version of the American Diabetes Association's consensus report on the diagnosis and treatment of DKA and HHS was published 15 years ago. The updated consensus report (June 2024) introduces revised criteria for the diagnosis and resolution of DKA and HHS, as well as new recommendations for assessment, management, and prevention.

KEY POINTS

The new report's most relevant update incorporates quantitative beta-hydroxybutyrate measurement (ideally through bedside testing) into DKA and HHS diagnostic criteria, and also recommends its use when assessing severity and determining DKA resolution.

Managing mild and uncomplicated moderate DKA with subcutaneous insulin in a noncritical care setting, when clinically appropriate, is now recommended.

Treatment pathways for DKA and HHS have been simplified and now focus only on 3 main areas—fluids, insulin, and potassium; eliminate the use of arterial blood samples to assess acid-base status; and unify some parameters between DKA and HHS management.

The new report provides the first HHS resolution criteria, updates DKA resolution criteria, and emphasizes the use of clinical judgment when making management decisions.

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Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are the most serious hyperglycemic emergencies in diabetes.[1] Recent data show that hospital admissions for both conditions have increased substantially over the past decade,[2] underscoring the importance of early diagnosis and effective management.

The first consensus statement on hyperglycemic crises in adults was published by the American Diabetes Association in 2001[3] and was updated in 2009.[4] Here, we review the 2024 consensus report and compare current recommendations with previous guidelines.[5]

WHO WROTE THE CONSENSUS REPORT?

An international panel of experts representing the American Diabetes Association, American Association of Clinical Endocrinology, European Association for the Study of Diabetes, Joint British Diabetes Societies for Inpatient Care, and the Diabetes Technology Society reviewed the literature from 2009 to mid-2023 to provide an updated evidence-based consensus report. Published in June 2024, the report covers the epidemiology, pathogenesis, diagnosis, treatment, and prevention of DKA and HHS in adults. It is directed to the full spectrum of clinicians who care for patients with diabetes and to individuals with diabetes.[5]

WHAT ARE THE MAIN RECOMMENDATIONS?

The updated consensus includes the following recommendations for diagnosing and managing DKA and HHS.

Diagnosis

The diagnosis of DKA requires the presence of 3 criteria: (1) diabetes or hyperglycemia (D criterion), with a glucose level of 200 mg/dL or greater or a prior history of diabetes; (2) ketosis (K criterion), with a beta-hydroxybutyrate level of 3.0 mmol/L or greater or urine ketones at 2+ or higher; and (3) metabolic acidosis (A criterion), with pH less than 7.3, a bicarbonate concentration less than 18 mmol/L, or both.

The diagnosis of HHS requires the presence of 4 criteria: (1) hyperglycemia, with a plasma glucose level of 600 mg/dL or greater; (2) hyperosmolarity, with a calculated effective serum osmolality greater than 300 mOsm/kg or total serum osmolality greater than 320 mOsm/kg; (3) absence of significant ketonemia, with beta-hydroxybutyrate less than 3.0 mmol/L or a urine ketone strip of 2+ or lower; (4) absence of acidosis, with pH of 7.3 or greater and bicarbonate concentration of 15 mmol/L or greater.

Direct measurement of beta-hydroxybutyrate is strongly recommended for diagnosing DKA and monitoring treatment, using either serum samples in a central laboratory or capillary blood with point-of-care testing devices. Although both are acceptable methods with comparable precision, point-of-care testing offers easier testing and quicker results, potentially reducing admission duration and DKA recovery time. If beta-hydroxybutyrate determination is not available, a urine ketone strip of 2+ or higher will meet this criterion.

Anion gap is not recommended as a first-line diagnostic criterion, but it may have some value if ketone measurement is unavailable.

Management

Categorizing DKA severity helps guide decisions on the required level of care:

- Individuals with mild DKA (beta-hydroxybutyrate ≤ 6 mmol/L, pH > 7.25, bicarbonate ≥ 15 mmol/L, normal mental status) can be managed in a regular or observation nursing unit
- For those with moderate DKA (beta-hydroxybutyrate ≤ 6 mmol/L, pH 7.0–7.25, bicarbonate 10 to < 15 mmol/L, normal or drowsy mental status), management in a step-down or intermediate care unit is suggested
- Those with severe DKA (beta-hydroxybutyrate > 6 mmol/L, pH < 7.0, bicarbonate < 10 mmol/L, stupor or coma), HHS, or a concomitant critical illness should be managed in an intensive care unit.

DKA and HHS management involves administering intravenous fluids, insulin, and electrolytes, along with treating the precipitating cause. During treatment of DKA, capillary blood glucose should be checked every 1 to 2 hours, and electrolytes, phosphate, creatinine, beta-hydroxybutyrate, and venous pH should be checked every 4 hours until DKA resolution. For HHS, blood glucose, creatinine, electrolytes, and serum osmolality should be measured every 4 hours.

TABLE 1
2024 consensus report criteria for resolution of diabetic ketoacidosis and hyperglycemic hyperosmolar state

Resolution criteria[5]	
Diabetic ketoacidosis	**Hyperglycemic hyperosmolar state**
Plasma or capillary beta-hydroxybutyrate < 0.6 mmol/L AND Venous pH ≥ 7.3 OR Bicarbonate ≥ 18 mmol/L	Serum osmolality < 300 mOsm/kg AND Blood glucose < 250 mg/dL AND Urine output > 0.5 mL/kg/hour AND Cognitive status improved

Patients without cardiac or renal compromise should receive isotonic saline or balanced crystalloid solutions at 500 to 1,000 mL per hour for the first 2 to 4 hours. Once intravascular volume is restored, subsequent fluid replacement depends on hemodynamics, fluid balance, and sodium concentration.

Dextrose 5% to 10% should be added once glucose is less than 250 mg/dL to prevent hypoglycemia and permit insulin administration to continue until ketonemia resolves (**Table 1**).[5] For HHS, glucose reduction should not exceed 90 to 120 mg/dL per hour to avoid cerebral edema; sodium decline should not exceed 10 mmol/L in 24 hours, and osmolality should fall no more than 3.0 to 8.0 mOsm/kg per hour to minimize neurologic risks. Smaller fluid boluses (eg, 250 mL) should be considered in older adults and individuals with heart or kidney failure.

Insulin therapy for severe DKA should begin as soon as possible, either through a fixed-rate intravenous insulin infusion started at 0.1 units/kg per hour or by a nurse-driven insulin infusion protocol with a variable rate. Insulin should be adjusted to maintain glucose levels around 200 mg/dL and continued until ketoacidosis resolves (**Table 1**).

Most individuals with uncomplicated mild or moderate DKA can be treated with subcutaneous

TABLE 2
Changes in diabetic ketoacidosis diagnostic criteria between 2009 consensus statement and 2024 consensus report

Diagnostic criteria	2009 Consensus statement[4]	2024 Consensus report[5]
Plasma glucose (D criterion)	Glucose > 250 mg/dL	Glucose ≥ 200 mg/dL OR History of diabetes, irrespective of the presenting glucose value
Ketosis (K criterion)	Serum ketones: positive Urine ketones: positive	Beta-hydroxybutyrate ≥ 3 mmol/L OR Urine ketone strip ≥ 2+
Metabolic acidosis (A criterion)	pH ≤ 7.3 Bicarbonate ≤ 18 mmol/L Anion gap > 10	pH < 7.3 with or without bicarbonate < 18 mmol/L Anion gap was removed as a diagnostic criterion

TABLE 3
Changes in hyperglycemic hyperosmotic state diagnostic criteria between 2009 consensus statement and 2024 consensus report

Diagnostic criteria	2009 Consensus statement[4]	2024 Consensus report[5]
Hyperglycemia	Plasma glucose > 600 mg/dL	Plasma glucose ≥ 600 mg/dL
Hyperosmolality	Calculated effective serum osmolality > 320 mOsm/kg	Calculated osmolality: Effective[a] > 300 mOsm/kg OR Total[b] > 320 mOsm/kg
Absence of significant ketosis	Serum ketones: Small Urine ketones: Small	Beta-hydroxybutyrate < 3 mmol/L OR Urine ketones < 2+
Absence of significant acidosis	pH > 7.3 Bicarbonate > 18 mmol/L	pH ≥ 7.3 AND Bicarbonate ≥ 15 mmol/L
Mental status	Stupor or coma	Removed as a diagnostic criterion

[a]Effective osmolality calculated as 2[sodium (mmol/L)] + glucose (mmol/L)

[b]Total osmolality calculated as 2[sodium (mmol/L)] + glucose (mmol/L) + urea (mmol/L)

rapid-acting insulin analogues every 1 to 2 hours, with close nursing supervision.

For HHS, a fixed-rate intravenous insulin infusion should be started at 0.05 units/kg per hour. If there are mixed features (hyperosmolality with significant ketonemia or acidosis), the condition should be treated as DKA and a fixed-rate intravenous insulin infusion should be started at 0.1 units/kg per hour.

For patients already taking basal insulin at the time of hospitalization for DKA or HHS, basal insulin can be continued at the usual dose and adjusted as needed during hospitalization, in addition to the continuous intravenous insulin infusion. This may reduce rebound hyperglycemia and prevent recurring DKA.

To transition from intravenous to subcutaneous insulin, an estimation of the total daily insulin requirement is needed, considering hypoglycemia risk and anticipated nutritional intake. Estimations can be based on weight (estimating a total daily dose of 0.3–0.6 units/kg per day), preadmission insulin dose,

TABLE 4
Main changes in treatment recommendations between 2009 consensus statement and 2024 consensus report

		2009 Consensus statement[4]	2024 Consensus report[5]
Fluids	Type	Isotonic saline (0.9% NaCl) during the first hour Subsequently, use 0.45% NaCl if serum sodium is high or normal; continue 0.9% NaCl if serum sodium is low Change to dextrose 5% with 0.45% NaCl when glucose reaches 200 mg/dL in DKA and 300 mg/dL in HHS	Isotonic saline or balanced crystalloid solutions, with subsequent choice of fluids depending on fluid balance, hemodynamics, and sodium concentration 0.45% NaCl is indicated only if osmolality is not declining in HHS despite adequate fluid and insulin therapy Add dextrose 5% or 10% when glucose reaches < 250 mg/dL for both DKA and HHS
	Volume	15–20 mL/kg/hour or 1–1.5 L in the first hour Subsequently, 250–500 mL/hour	500–1,000 mL/hour during the first 2–4 hours Subsequently, adjust rate as clinically appropriate
	Time to correction of estimated fluid deficit	24 hours	24–48 hours (replace 50% of fluid deficit in the first 8–12 hours)
Insulin	Initial	Both DKA and HHS: 0.1 units/kg in IV bolus, followed by FRIII at 0.1 units/kg/hour OR FRIII at 0.14 units/kg/hour	Moderate and severe DKA: FRIII at 0.1 units/kg/hour (consider 0.1 units/kg IV bolus if IV access is delayed) OR Nurse-driven insulin infusion protocol Mild and moderate DKA: Subcutaneous rapid-acting insulin analogue 0.1 units/kg every 1 hour or 0.2 units/kg every 2 hours HHS: FRIII at 0.05 units/kg/hour Mixed DKA/HHS: treat as DKA
	Initial glucose goal for dextrose initiation	DKA: < 200 mg/dL HHS: < 300 mg/dL	DKA and HHS: < 250 mg/dL
	Maintenance after dextrose initiation	Decrease infusion to 0.02–0.05 units/kg/hour until resolution	Decrease infusion to 0.05 units/kg/hour until resolution
	Glucose goal until resolution	DKA: 150–200 mg/dL HHS: 200–300 mg/dL	DKA: 150–200 mg/dL HHS: 200–250 mg/dL
Potassium	Low	< 3.3 mmol/L: give 20–30 mmol/hour and postpone insulin therapy until serum potassium > 3.3 mmol/L	< 3.5 mmol/L: give 10–20 mmol/hour and postpone insulin therapy until serum potassium > 3.5 mmol/L
	Normal	3.3–5.2 mmol/L: give 20–30 mmol in each liter of IV fluid to maintain serum potassium of 4–5 mmol/L	3.5–5.0 mmol/L: give 10–20 mmol in each liter of IV fluid to maintain serum potassium of 4–5 mmol/L
	High	> 5.2 mmol/L: do not give potassium but check serum potassium every 2 hours	> 5.0 mmol/L: do not give potassium but check serum potassium every 2 hours

DKA = diabetic ketoacidosis; FRIII = fixed-rate intravenous insulin infusion; HHS = hyperglycemic hyperosmolar state; IV = intravenous

or in-hospital insulin requirements. A basal-bolus regimen is recommended, starting basal insulin at least 1 to 2 hours before stopping the insulin infusion.

Potassium should be measured at baseline, 2 hours after starting insulin, and every 4 hours thereafter until resolution of DKA. Potassium replacement should start after serum levels fall below 5.0 mmol/L to maintain levels between 4 and 5 mmol/L. If potassium levels are lower than 3.5 mmol/L at presentation, replacement should begin at a rate of 10 mmol per hour, and insulin therapy should be postponed until a potassium level higher than 3.5 mmol/L is reached.

Routine bicarbonate and phosphate administration is not recommended. Bicarbonate should be considered only in severe acidosis (pH < 7.0), and phosphate replacement should be considered if levels are under 1.0 mmol/L, particularly if muscle weakness or cardiac or respiratory impairment is present.

Patient education

Before discharge, all patients admitted with DKA or HHS should receive education focused on both the current event and overall diabetes management, including injection techniques, glucose monitoring, and urine or blood ketone testing.

WHAT IS DIFFERENT FROM PREVIOUS GUIDELINES?

Updates in the diagnosis of DKA and HHS are summarized in **Table 2** and **Table 3**, respectively, and DKA and HHS treatment updates are summarized in **Table 4**.[4,5]

Diagnosis of DKA

D criterion. Reducing the glucose cutoff to 200 mg/dL or greater is reasonable, as this level is typically diagnostic of diabetes in the general population, and there is no justification for it to be different in the context of DKA (**Table 2**). Adding a history of diabetes as an alternative to glucose values (and irrespective of them) allows for the inclusion of patients with euglycemic DKA. Mentioned in the 2009 consensus report, euglycemic DKA has become more common with the advent of sodium-glucose cotransporter 2 inhibitors. Use of these agents has been shown to increase the risk of euglycemic DKA in individuals with type 2 diabetes and in those with type 1 diabetes using them off-label.[6,7]

K criterion. This is a major update, as it involves the key diagnostic feature of DKA. The recommendation to measure beta-hydroxybutyrate is largely based on the pathophysiology of ketosis in DKA, in which the ratio of beta-hydroxybutyrate to acetoacetate rises from a physiologic 1:1 to up to 10:1. Then, during resolution, beta-hydroxybutyrate is oxidized to acetoacetate, causing its levels to decrease long before those of acetoacetate. Since the nitroprusside reaction (used to measure ketones semiquantitatively in urine and blood) measures only acetoacetate, it can underestimate the degree of ketosis at presentation but overestimate it during resolution.[8,9] Both tests have similar sensitivity, but beta-hydroxybutyrate is more specific for DKA diagnosis. Additionally, drugs can interfere with urine ketone testing[10]; in particular, false positives can be seen with commonly used medications like captopril and valproic acid. Therefore, the preferred method for assessing ketosis, both at diagnosis and during treatment, is quantitative assessment of beta-hydroxybutyrate, when available.

A criterion. The 2024 consensus removed the anion gap criterion to better account for the various factors influencing acid-base status in individuals with DKA. While an increased anion gap indicates a net gain in ketoacid anions, the accumulation of ketoacids in the extracellular fluid results in bicarbonate loss, which may not be immediately apparent due to extracellular volume contraction. Hyperglycemia-induced diuresis and natriuresis cause marked volume contraction, affecting the determination of the severity of metabolic acidemia, as standard calculations are based on concentrations rather than total content.[10] There is also associated hyperventilation due to acidosis, all of which contribute to the frequent occurrence of mixed acid-base disorders in individuals presenting with DKA.

Severity of DKA

Quantitative beta-hydroxybutyrate is now recommended for assessing DKA severity, with the introduction of quantitative cutoffs for mild and moderate (3–6 mmol/L) and severe DKA (> 6 mmol/L). Anion gap is no longer a severity criterion for DKA. The new consensus suggests assigning the level of hospital care based on DKA severity at presentation, including the possibility of managing mild DKA in the general ward. Not all criteria must be met to classify a patient as mild, moderate, or severe; clinical judgment and resource availability should ultimately determine severity and guide decisions on admission and level of care.

Diagnosis of HHS

The 2024 consensus report lowers the effective serum osmolality cutoff for diagnosing HHS and introduces total serum osmolality as a new criterion (**Table 3**). Including urea (ie, using total serum osmolality) in the diagnostic criteria, despite it not being an effective

osmolyte, accounts for the severe dehydration commonly seen in these patients.[11]

Mental status impairment is no longer a diagnostic criterion. Although past studies linked osmolality with mental status, many individuals, though very ill, do not necessarily have mental impairment, so this is no longer a requirement for diagnosis of HHS.[4,11]

Quantitative cutoffs were added for the allowed ketonemia in the diagnosis of HHS, and the bicarbonate level was lowered from 18 to 15 mmol/L to allow for a degree of acidosis that can occur due to insulinopenia.

Treatment of DKA and HHS

One key change (**Table 4**) involves the choice of fluids for initial resuscitation, now suggesting balanced crystalloids (when available) because their use is associated with faster recovery, less hyperchloremic metabolic acidosis, and shorter hospital stay.[12,13] Additionally, suggested fluid replacement speed and time are more conservative in the new consensus report, likely due to an older, more comorbid patient profile.

The 2009 consensus report introduced the concept of managing mild DKA with subcutaneous insulin, but the strength of the evidence now supports a formal recommendation of using it as an alternative to intravenous infusion in mild and uncomplicated moderate DKA,[14,15] thus avoiding the need for an intensive care unit admission.

Resolution criteria for DKA and HHS are outlined in **Table 1**. Criteria for DKA were updated to incorporate quantitative beta-hydroxybutyrate, and HHS criteria were established for the first time. The report also offers guidance on treating DKA and HHS in special populations, including older adults, those on sodium-glucose cotransporter 2 inhibitors, patients undergoing dialysis, pregnant patients, and those with COVID-19.

HOW WILL THE NEW CONSENSUS CHANGE DAILY PRACTICE?

This 2024 consensus report represents a highly anticipated update in the management of hyperglycemic emergencies. It incorporates substantial changes, 2 of which we believe directly call for changes in daily clinical practice: the inclusion of direct measurement of beta-hydroxybutyrate for diagnosis, severity assessment, management, and resolution of DKA, and the exclusion of the anion gap from the aforementioned scenarios.

Ketonemia is the hallmark of DKA, with beta-hydroxybutyrate serving as the primary marker. Given the availability of direct beta-hydroxybutyrate measurement, its use should be strongly considered, as it is associated with reduced time to recovery and greater cost-effectiveness compared with urine ketone assessments.[16] Portable ketone meters have been widely available for more than a decade and are standard of care in many countries.[17,18] When portable meters are not available, central laboratory measurement of beta-hydroxybutyrate is an alternative. We believe that efforts should be made to ensure all hospitals caring for individuals with DKA have access to direct beta-hydroxybutyrate measurement.

Approximately 30% of patients with DKA present with mixed acid-base disorders, and resuscitation with isotonic saline (the most frequently used fluid worldwide) often results in associated hyperchloremic metabolic acidosis during treatment. Therefore, using anion gap to assess treatment adequacy and resolution is unjustified whenever beta-hydroxybutyrate measurement is available. The resolution of DKA depends on the adequate suppression of ketonemia, and measurement of beta-hydroxybutyrate now represents best practice in monitoring treatment response. However, in settings where beta-hydroxybutyrate measurement is not available, we believe that normalization of anion gap is still a good surrogate marker for DKA resolution.

DISCLOSURES

Dr. Morey-Vargas has disclosed teaching and speaking for Asofarma. 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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REVIEW

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Cardiovascular disease in people living with HIV: Risk assessment and management

ABSTRACT

Almost 40 million people worldwide are living with human immunodeficiency virus (HIV) infection. With treatment advances, HIV infection is now a manageable chronic disease for those with access to medical therapy. People living with HIV have a significantly higher risk and earlier onset of cardiovascular disease (CVD) owing to chronic inflammation and other biochemical factors, as well as overlapping social determinants of health and nonbiologic risk factors. Knowing that patients living with HIV develop coronary artery disease much earlier than the general population, careful attention must be given to assessment and management of their cardiovascular risk.

KEY POINTS

- Because people living with HIV present with coronary artery disease about 10 years earlier than the general population, maintaining a higher index of suspicion for CVD, even in younger patients, is important.
- Consider adjusting calculated CVD risk up 1.5 to 2 times and setting lower lipid targets and a lower threshold for starting statin therapy.
- Selection of lipid-lowering agents must take into account any potential interactions with antiretroviral therapy medications; a multidisciplinary approach can be helpful.

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Almost 40 million people worldwide, including more than 1 million people in the United States, are currently living with human immunodeficiency virus (HIV) infection.[1,2] Over the past 50 years, scientific and policy advances have dramatically improved life expectancy for people living with HIV such that it is now a manageable chronic disease for those with access to medical therapy. As this population ages, clinicians must remain vigilant regarding comorbidities for which they are at heightened risk.

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Specifically, people living with HIV have a significantly higher risk of developing cardiovascular disease (CVD). Globally, this risk is up to 2 times higher compared with individuals without HIV.[3] While the concept that "undetectable equals untransmissible" is a tremendous breakthrough for people living with HIV, it is important for clinicians to remember that increased CVD risk persists even with control of the virus to undetectable levels. Herein, we review the epidemiology and proposed mechanisms of this phenomenon and discuss screening, management, and other considerations in treating people living with HIV.

CVD RISK PERSISTS DESPITE VIRAL SUPPRESSION

A model constructed using the data of more than 10,000 individuals being treated for HIV from a cohort of the AIDS Therapy Evaluation in the

Netherlands suggested that, by 2030, 73% of people living with HIV will be 50 or older and 78% will have been diagnosed with CVD.[4] Irrespective of viral suppression, this population has an increased relative risk of myocardial infarction, ranging from 20% to 100%, compared with people not living with HIV.[5] Studies have shown that patients with HIV are also at increased risk for stroke, sudden cardiac death, heart failure, pulmonary hypertension, and myocardial fibrosis.[3,6–9]

The increased CVD risk in persons living with HIV persists even for patients taking viral suppressive therapies.[10] A virtual cohort of the Veterans Aging Cohort Study—a multisite, longitudinal, prospective study—examined more than 80,000 patients living with HIV and noted that risk for acute myocardial infarction was higher in patients living with HIV in every age group.[11] Importantly, this elevated risk remained when the analysis was restricted to patients with viral suppression. The Veterans Aging Cohort Study was relatively unique in that the patients were all male, the median age was 49 to 50, and 74% to 79% were Black or Latino.[12] Similarly, a meta-analysis found that having HIV conferred a 61% increased relative risk of CVD in those not on antiretroviral therapy (ART).[13] When limited to patients on ART, the relative risk of CVD was 2 times higher compared with patients without HIV.

PROPOSED MECHANISMS

The factors that contribute to the increased risk of CVD for patients with HIV infection are varied and not completely understood. Other recent studies reported that chronic inflammation and immune dysfunction persist even when the virus is well controlled.[14]

Lessons from studies of chronic inflammation in the general population

We know that chronic inflammation is linked to atherosclerosis. JUPITER (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin)[15] showed that rosuvastatin reduced the incidence of cardiovascular events in patients with normal low-density lipoprotein cholesterol (LDL-C) but elevated high-sensitivity C-reactive protein (hs-CRP). Notably, chronic inflammatory biomarkers associated with atherogenesis are elevated in people living with HIV compared with those without HIV.[14]

IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)[16] analyzed the correlation of this dual target (LDL-C and hs-CRP) and the primary composite end point of cardiovascular death, major coronary event, and stroke for patients randomized to simvastatin monotherapy or a combination of simvastatin and ezetimibe.[17] In a substudy that used the IMPROVE-IT data of 18,144 patients who had diabetes mellitus at randomization, simvastatin plus ezetimibe significantly increased the likelihood of achieving the predefined targets for LDL-C (< 70 mg/dL) and hs-CRP (< 2 mg/L). Further, a recent meta-analysis of randomized controlled trials showed that statins can be effective in reducing hs-CRP in patients with CVD, although further studies are warranted to clearly prove the beneficial effect of statins on hs-CRP.[18]

In a primary analytic cohort of the FOURIER study (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk), Bohula et al[19] explored whether the association of inflammation and risk of cardiovascular events persisted even at very low levels of LDL-C. In patients with LDL-C less than 20 mg/dL 1 month after randomization, the 3-year primary event rate for patients with hs-CRP of less than 1, 1 to 3, and more than 3 mg/L was 9.0%, 10.8%, and 13.1%, respectively. This further supports the concept of an inflammatory risk for CVD. A secondary analysis from the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial[20] further supported this relationship between hs-CRP reduction and cardiovascular risk reduction.

While IMPROVE-IT, FOURIER, CANTOS, and JUPITER did not specifically focus on people living with HIV, the physiologic lessons learned regarding inflammation and treatment of CVD appear to be generalizable.

HIV-specific mechanisms

Hyperlipidemia. HIV infection itself is associated with a proatherogenic inflammatory state.[21] The prevalence of hyperlipidemia in patients living with HIV ranges from 28% to 80%, compared with 10% to 11% among the general US population.[22,23] Further, REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV),[24,25] a large randomized, 12-country, multicenter trial, found that a daily statin (pitavastatin calcium) reduced major adverse cardiovascular events by 35% compared with placebo in people living with HIV aged 40 to 75 who had low to moderate CVD risk (with normal-range LDL).

HIV proteins. Even in patients with undetectable viral load on ART, low-level transcription of HIV genes encoding viral regulatory proteins continues.[26] Such proteins, like transactivator of transcription protein and negative factor, have been shown to induce endothelial dysfunction as well as inflammation.[27] Envelope glycoprotein 120, an HIV surface glycoprotein that helps the

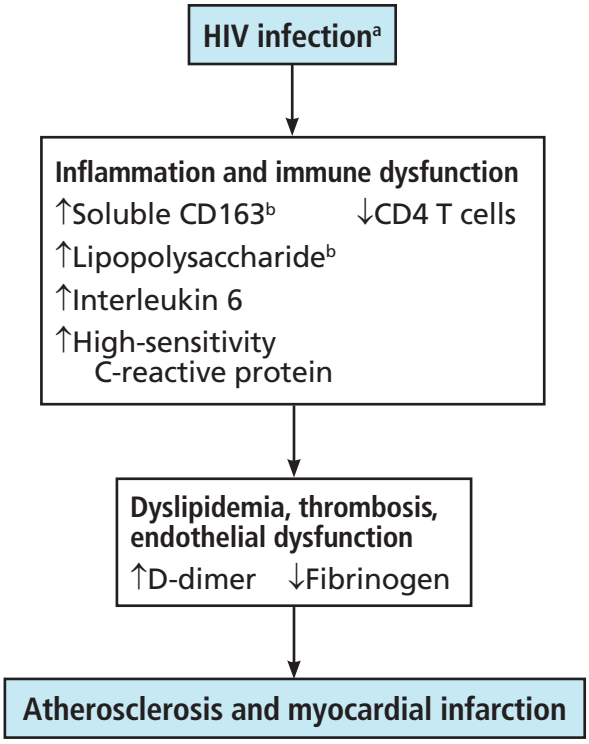

Figure 1. Mechanisms of atherosclerosis and myocardial infarction in people living with HIV.

[a]Traditional cardiovascular risk factors, such as smoking, and older therapies for treating people living with HIV also contribute to the development of atherosclerosis and myocardial infarction.
[b]Markers of microbial translocation from the gut.

HIV = human immunodeficiency virus

Based on information from reference 35.

virus enter target cells, has been shown to stimulate production of the vasoconstrictor endothelin-1, which has been associated with cardiac morbidity and mortality.[28]

Cytomegalovirus infection. CD8 T-cell expansion and inflammation linked to cytomegalovirus coinfection is another mechanism that has been proposed for the enduring elevated cardiovascular risk in patients with HIV, even on ART.[29]

CD4 T-cell depletion and gut microbial translocation. Depletion of CD4 cells is associated with higher rates of myocardial infarction, ischemic stroke, heart failure, and peripheral artery disease.[5] Replication of HIV in the gastrointestinal tract can severely reduce CD4 cells and thus lead to decreased function of the epithelial barrier.[30] This allows microbial translocation and, in turn, a chronic inflammatory response. It is postulated that both the subsequent susceptibility to opportunistic infections from the depletion of CD4 T cells in the gut mucosa and microbial translocation lead to chronic states of inflammation.[5]

Nonbiochemical factors

It is important to acknowledge the myriad of nonbiochemical factors that may disparately affect people living with HIV and contribute to CVD risk. Owing to overlapping social determinants of health and other risk factors, the prevalence of cigarette smoking is 2 to 3 times higher in people living with HIV than in those not living with HIV.[31]

Further, transgender people are disproportionately impacted by HIV. The US Centers for Disease Control and Prevention reports an HIV prevalence of 9.2% in transgender people compared with less than 0.5% in adults overall.[32] Studies have noted that metabolic changes asoociated with gender-affirming hormonal treatment may increase the risk of accelerated CVD.[33,34] These factors, along with systemic healthcare factors that contribute to diminished access in these and other vulnerable groups, highlight the complexities of increased CVD risk.

Even after adjusting for these and other various risk factors, however, studies have shown that people with

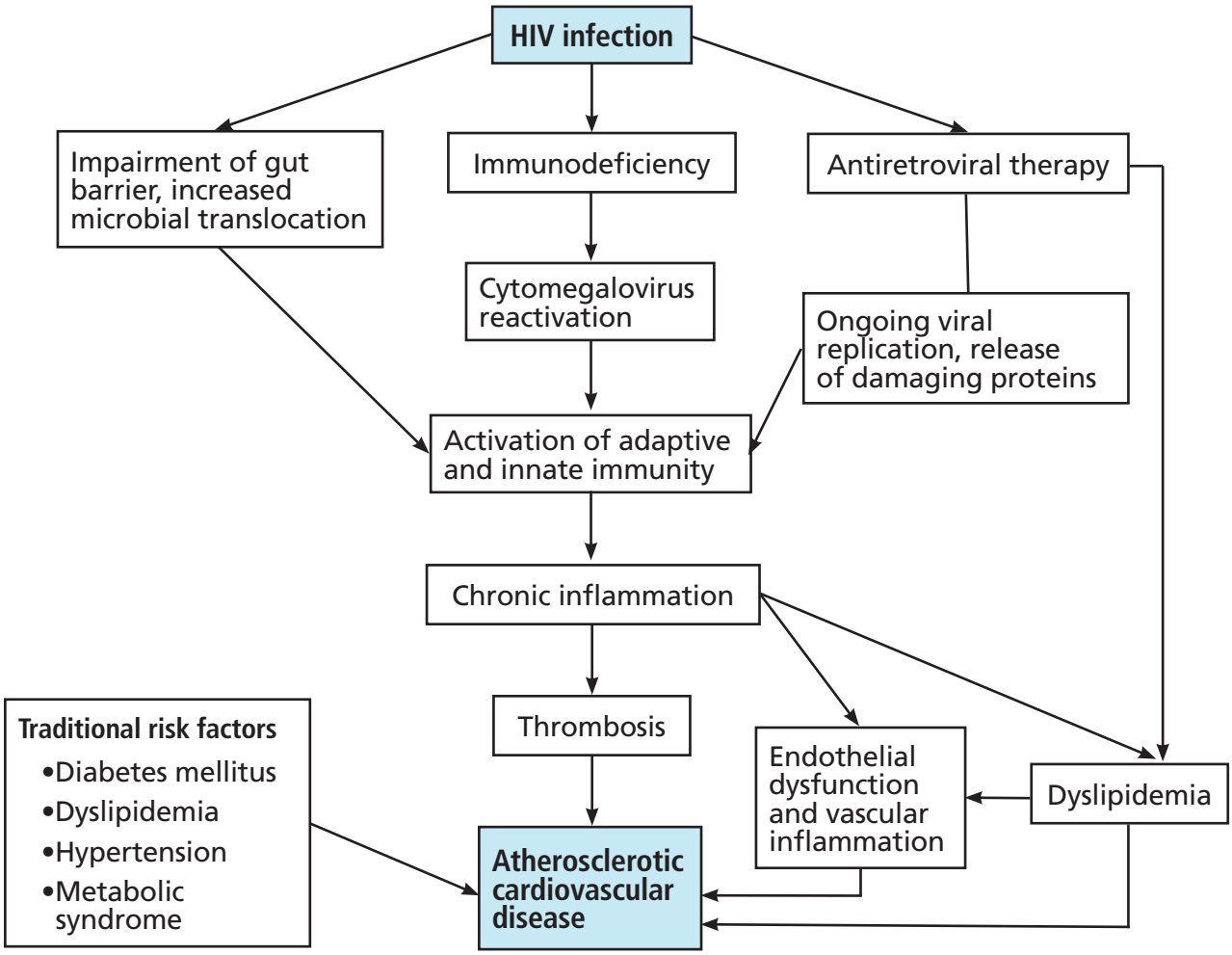

Figure 2. Pathophysiology of human immunodeficiency virus (HIV)–associated atherosclerotic cardiovascular disease.

Based on information from reference 36.

HIV still have significantly higher CVD risk due to overlapping risk factors. **Figure 1** illustrates the interplay of mechanisms of atherosclerosis and myocardial infarction in patients living with HIV.[35] **Figure 2** shows the proposed pathophysiologic mechanisms involved with HIV-associated atherosclerotic CVD.[36]

EARLIER ONSET OF CVD

An early study found that people living with HIV presented with coronary artery disease when they were about 10 years younger than patients without HIV.[36,37] Further studies found these patients were more likely to have low thrombolysis in myocardial infarction risk scores and single-vessel disease but higher rates of restenosis after percutaneous coronary intervention.[36,38,39] The incidence of restenosis after drug-eluting stent placement in patients with HIV was 19% vs 10% in those not living with HIV—with CD8 count and C-reactive protein levels somewhat correlated.[38,39]

ART AND COMORBIDITIES

Early studies suggested ART as a possible contributing factor to the increased risk of CVD in people living with HIV. More recent studies, however, have noted that this is not the case with newer ART regimens. Herein, we examine the historical progression of evidence.

Dyslipidemia

Combination ART–associated dyslipidemia was first described in patients using protease inhibitors, regimens

with nucleoside reverse transcriptase inhibitors, and nonnucleoside reverse transcriptase inhibitors, with duration of exposure being associated with increased CVD.[40] Part of this has been attributed to some component of the initial return of appetite and weight gain in these patients once they started ART. The historic DAD (Data Collection on Adverse Events of Anti-HIV Drugs) trial,[41] a comprehensive examination of CVD adverse events associated with ART, found an association between ART and dyslipidemia.

Older ART drugs, including abacavir, ritonavir, and lopinavir, have more cardiotoxic effects, including left ventricular dysfunction or altered lipid or glucose metabolism.[42] Specifically, older protease inhibitors like ritonavir are known to induce hypertriglyceridemia and other adverse effects such as dyslipidemia, hyperglycemia, and overt diabetes mellitus.[42] In addition, protease inhibitors boosted by ritonavir, as well as some first-generation nucleoside reverse transcriptase inhibitors and nonnucleoside reverse transcriptase inhibitors, have been shown to affect lipid parameters, such as increased total cholesterol, LDL-C, and triglycerides.[43,44] One study found that exposure to the protease inhibitors lopinavir-ritonavir and indinavir or the nucleoside reverse transcriptase inhibitors abacavir or didanosine was associated with increased risk of myocardial infarction.[42] This risk in patients taking abacavir appears, in some studies, to be linked to increased platelet reactivity and endothelial dysfunction.[36]

Further, different classes of ART can have differing effects on the development of adipose tissue. For example, some integrase inhibitors have been associated with weight gain, and some first-generation nucleoside reverse transcriptase inhibitors and protease inhibitors have been shown to correlate with the development of lipodystrophy.[43,44]

Newer ART medications, such as the C-C chemokine receptor 5 antagonist maraviroc and the integrase inhibitor raltegravir, are more favorable with respect to effect on lipid levels.[22] One recent study showed that switching from a protease inhibitor to the newer integrase inhibitor bictegravir was associated with improvement in lipid markers.[45] In particular, patients with the worst baseline lipid profiles had significant improvements, and those who switched from protease inhibitors to bictegravir also saw improvements in triglycerides. Dolutegravir, another integrase inhibitor, has a more neutral effect on lipids compared with efavirenze or ritonavir-boosted darunavir.[46]

Overall, initiation of ART may negatively impact lipid levels (including LDL, triglycerides, total cholesterol, and high-density lipoprotein), and this change is likely multifactorial. Lipid monitoring in patients living with HIV is imperative for CVD risk reduction.

Insulin resistance and metabolic impact

First-generation ART medications were associated with insulin resistance and metabolic syndrome, leading to a higher incidence of diabetes and elevated hemoglobin A1c levels in people living with HIV.[43] Historically, protease inhibitors have been associated with insulin resistance, but these agents may be less commonly used due to other toxicities, such as the possibility of hepatotoxicity, Stevens-Johnson syndrome, or elevated cholesterol, as noted above. First-generation thymidine nucleoside reverse transcriptase inhibitors also impacted fat distribution and caused weight gain, effects that may be responsible for a lingering occurrence of insulin resistance in aging patients who used these medications.[43]

Evidence suggests that certain HIV preexposure prophylaxis regimens may be associated with metabolic changes (although the evidence is from trials that were not specific to people living with HIV).[47,48] Specifically, initiation of tenofovir alafenamide fumarate for preexposure prophylaxis was associated with increased risk of hypertension and statin initiation, especially in patients 40 and older.[47] Another study examined tenofovir disoproxil fumarate and emtricitabine and found a modest reduction in cholesterol.[48] The participants in the first study were found to have weight gain, and the participants in the second study were found to have weight loss, which may be the independent driver regarding metabolic impact. These results may further inform future studies on the effects of ART drugs on metabolic function.

MANAGEMENT

Models underestimate CVD risk

The 2019 American College of Cardiology and American Heart Association guidelines[49] on primary prevention of CVD recognized HIV as a risk factor for CVD based on the presence of chronic inflammation. In doing so, these guidelines acknowledged that standard models for predicting CVD risk systematically underestimate CVD risk for people living with HIV.[10] A recent meta-analysis examined 9 major CVD risk-prediction models and found a general tendency for these models to underestimate risk in these patients.[50]

As such, the guidelines note that individuals living with HIV may benefit from a lower threshold for statin initiation or intensification, particularly those with intermediate risk (≥ 7.5% to < 20% 10-year atherosclerotic CVD risk).[49] Further, consideration of the

underlying HIV diagnosis may help to sway treatment decisions for patients with borderline (5% to < 7.5% 10-year atherosclerotic CVD risk) or intermediate risk.[51]

The American Heart Association scientific statement[52] for prevention and treatment of CVD for people living with HIV suggests that clinicians may consider adjusting calculated CVD risk assessments up 1.5 to 2 times for patients with HIV, particularly for those with certain HIV-associated risk-enhancing factors like prolonged viremia, delayed ART initiation, and low CD4 count. This was more specifically discussed in the European Society for Cardiology guidelines,[53] which also suggest an LDL-C goal of less than 70 mg/dL in people living with HIV.[53]

REPRIEVE, discussed earlier, examined strategies for CVD risk prevention in people living with HIV. The study's results led to the concept that patients living with HIV should begin statin therapy to reduce CVD risk and that this should be individualized and communicated with the patient as part of shared decision-making.[24] However, many patients with HIV who already meet criteria for statin use do not receive a prescription for them (28%) or are prescribed statin therapy below the indicated intensity (12%).[54]

Considerations when selecting lipid-lowering agents

Selection of lipid-lowering agents in patients on ART requires attention to potential drug-drug interactions. Ultimately, considerations should be patient- and case-specific and part of a multidisciplinary discussion with infectious diseases and pharmacy colleagues in the broader context of patient care.

Overall, we know that statin therapy can be administered safely in patients on ART.[55] Some illustrative examples can be useful. Lovastatin and simvastatin are contraindicated in patients being treated with protease inhibitors because of the increased risk of rhabdomyolysis.[56] One study suggested a higher risk for atorvastatin in patients taking both protease inhibitors and ritonavir,[57] and the Infectious Diseases Society of America recommends starting with a lower dose of atorvastatin in these patients.[58] Of note, proprotein convertase subtilisin/kexin 9 inhibitors have recently shown promise in reducing atherogenic lipid levels in patients living with HIV and may be of increased utility in the future as investigations continue.[59]

A NOTE ON HEART FAILURE IN PATIENTS WITH HIV

There is currently no difference in guidelines regarding treatment of heart failure in people living with HIV and those not living with HIV. Recent studies have, however, indicated that the increased risk of heart failure for patients living with HIV is not primarily mediated through atherosclerotic disease pathways.[60] With respect to HIV-associated cardiomyopathy, the prevalence of systolic dysfunction has decreased with the spread of ART, but the number of patients with HIV with abnormal diastolic function has increased.[61] One meta-analysis reported systolic and diastolic dysfunction incidence at 8.3% and 43.4%, respectively, in people living with HIV.[62] Direct HIV-induced myocardial damage may have been a predominant driver of systolic dysfunction before the widespread use of ART, hence, a relative decline.[61] Theories to explain the increase in diastolic dysfunction have included higher rates of inflammation, hypertension, or direct impact on myocardium.[63]

Mechanisms that have been proposed to explain the pathophysiology of HIV-associated cardiomyopathy outside of those behind atherosclerotic risk and acute coronary syndrome are, again, multifactorial.[61] Direct HIV-induced myocardial damage, alluded to above, is one such mechanism. It is theorized that inflammation in the myocardium may contribute to increased left ventricular mass, which is consistent with studies examining similar findings in patients with other types of inflammation, such as systemic lupus erythematosus and rheumatoid arthritis.[63] Moreover, chronic inflammation and immune dysfunction may lead to collagen deposition and fibrosis in the myocardium itself.[64] While cardiomyocytes lack HIV-1 receptor proteins (glycoprotein 120 and 24), cardiac interstitial cells may serve as viral reservoirs and mediate inflammation.[61,65] Other mechanisms include negative inotropic effects exerted by proinflammatory cytokines that contribute to reduced systolic function, autoimmune effects, and side effects from some ART medications.[61]

An approach to heart failure risk stratification for patients living with HIV could be beneficial going forward.[66] Chowdhury et al[67] are currently studying whether people living with HIV receive standard of care for heart failure compared with people not living with HIV, which could reveal areas for potential focus in the future.

AREAS FOR FUTURE WORK

The link between HIV infection and CVD risk is clear. What remains for discovery are the more granular factors that may increase risk in a subset of people living with HIV and how best to reduce this risk.[6,52] One study examined various biomarkers in people living with HIV in an attempt to create different cluster phenotypes.[68]

Those in the cardiac phenotype (for example, with elevated interleukin-1 receptor–like protein) were more likely to experience pulmonary hypertension, and those in the inflammatory phenotype (for example, with elevated C-reactive protein and interleukin-6) were more likely to experience diastolic dysfunction. Such studies that examine biomarkers with greater granularity may guide future therapies and screening.

To this end, further studies examining factors associated with HIV infection—including hepatitis C virus coinfection, CD4 count, years of sustained and elevated viral load, history of opportunistic coinfections, timing of ART commencement, and others—are warranted and may yield a more standardized approach to risk analysis and management.

Finally, it is crucial that patients living with HIV be included in trials that study cardiac risk factors to broaden the applicability of evidence to this population. This will greatly aid the collective understanding of how to reduce CVD risk and prevent adverse events in patients living with HIV.

TAKE-HOME POINTS

- Screening and treatment of CVD should be tailored to patients living with HIV due to their heightened risk profiles.
- Because we know that patients living with HIV develop coronary artery disease much earlier, assessment of CVD risk should be considered along with potentially lower lipid targets and a lower threshold for treatment. Selection of lipid-lowering agents must take into account any potential interactions with ART medications, and a multidisciplinary approach is helpful.
- Careful attention to other cardiovascular pathology is imperative for patients living with HIV, including diastolic and systolic heart failure.

DISCLOSURES

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Heart to heart: Progress in cardiovascular disease prevention for people living with HIV

Advances in the United States and in other high-resource settings have led to longer life expectancy for individuals living with human immunodeficiency virus (HIV) infection and more opportunities to investigate long-term complications of the infection and related treatments.[1] Globally, acquired immunodeficiency disease–related illnesses and bacterial infections remain the leading causes of hospital admissions for patients with HIV.[2] Yet in the United States and other resource-rich nations, simplified medication regimens, including combination pills and injectable therapies, have changed the landscape of inquiry to include cardiovascular diseases.[3]

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HISTORICAL CONTEXT

The well-considered article on cardiovascular disease in patients living with HIV by Ghandakly and colleagues[4] in this issue of the *Journal* is reminiscent of a time when structured treatment interruptions were considered an acceptable alternative to patients consistently taking their daily medications. The era saw patients and clinicians eager to press pause on the administration of medications with considerable toxicity and wishing to lessen the burden of what was then referred to as "pill fatigue." Combination therapies formulated into a single tablet were rare, leading to complexity in daily medication administration. Many patients took matters into their own hands and stopped medications, earnestly believing that the cure was worse than the disease. This was before the widespread uptake of the integrase strand transfer inhibitor class of antiretrovirals (eg, raltegravir, bictegravir, dolutegravir), which were highly effective and well tolerated, and novel nucleoside reverse transcriptase inhibitors (eg, tenofovir disoproxil, tenofovir alafenamide, emtricitabine) and nonnucleoside reverse transcriptase inhibitors (eg, doravirine, rilpivirine), which were easier to take, had fewer toxic effects, and were more likely to be effective against circulating resistant strains of virus. At the time, a few medications with limited use were becoming available, including injectable enfuvirtide and the C-C chemokine receptor 5 antagonist maraviroc.

However, many patients were relegated to using the medications discussed in the authors' article,[4] including lopinavir, efavirenz, and ritonavir, with their known interactions with many of the then-commonly used statins (lovastatin, simvastatin), and the metabolically damaging nucleoside reverse transcriptase inhibitors zidovudine, didanosine, and stavudine. When patients approached clinicians informing them of their drug holiday, there was no evidence to guide discussions about the risks and benefits of that decision. It was extremely difficult to choose between the risks of treatment and the risks associated with uncontrolled viremia.

A CHANGING LANDSCAPE FOR HIV TREATMENT

The paradigm-shifting 2006 study on CD4-count–guided interruption of antiviral treatment fundamentally changed the landscape of HIV treatment.[5] Episodic use of antiretrovirals in 1 arm of the study allowed for treatment interruption until CD4 lymphocyte counts decreased to less than 250 cells/mm^3. Highly active antiretroviral therapy was then resumed and maintained until CD4 counts surpassed 350 cells/mm^3.

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Rationales at that time for treatment interruptions included reduction in pill fatigue, medication-related toxicity (significant at the time), and cost reduction. Results of this group were then compared with a group of patients continuing medications without interruption. The study found that, after approximately 16 months, there was an increase in death from opportunistic infection in the treatment-interruption group, as well as an increase in death from any cause, including major cardiovascular, renal, and hepatic disease, with death from cardiovascular disease being more common than renal or hepatic causes. These findings suggested that an increase in immunodeficiency and related inflammation was more harmful to patients than the effects of highly active retroviral therapy.[5]

Subsequent pivotal work included proof that starting antiretroviral therapy early was superior to delayed initiation.[6] In the following years, several studies, including those recounted by the authors, were developed to better understand the effects of inflammation on cardiovascular and other systems.

STATIN THERAPY AND HIV

Ongoing investigations have informed the guidelines from the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents with HIV,[7] which have been developed in collaboration with representatives from the American College of Cardiology, American Heart Association, and the HIV Medicine Association. The guidelines provide recommendations on the use of statin therapy in primary prevention of atherosclerotic cardiovascular disease in people with HIV receiving care in the United States.[7] Key among them are the following:

- For persons age 40 to 75, when 10-year atherosclerotic cardiovascular disease risk estimates exceed 5%, starting a statin is recommended, given that HIV is a risk intensifier and available risk calculators underestimate associated cardiovascular risk
- Treatment in this age group is recommended with pitavastatin, atorvastatin, or rosuvastatin
- For those under age 40, data are insufficient to recommend for or against statin therapy.

There are drug-drug interactions among some of the recommended statins (eg, atorvastatin) and integrase inhibitors and protease inhibitors, and in these instances, dose adjustments or substitutions are recommended.[7] While REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV)[8] showed statins like pitavastatin reduced the risk of major adverse cardiovascular events in people living with HIV without preexisting heart disease, not all individuals tolerate statin medications. In addition to dietary and lifestyle modifications, nonstatin options for lipid lowering include fibrates, ezetimibe, niacin, omega-3 fatty acids, and proprotein convertase subtilisin/kexin (PCSK) 9 inhibitors. However, with the exception of PCSK-9 inhibitors, nonstatin therapies have not been shown to reduce major clinical events.[9]

After starting antiretroviral therapy, many patients experience weight gain, which may increase cardiovascular disease risk. Integrase inhibitors, in particular, can increase body mass index.[10] Patients who already live with metabolic syndrome and obesity may see a further increase in cardiovascular disease risk with weight gain.[11]

SOCIAL DETERMINANTS OF HEALTH, HIV, AND HEART DISEASE

Social determinants of health play a crucial role in influencing heart disease outcomes among marginalized groups, including transgender, African American, and Black, Indigenous, and People of Color populations. These determinants, such as socioeconomic status, access to healthcare, and systemic discrimination, contribute to disparities in obesity, tobacco use, and HIV, all of which are risk factors for heart disease. Higher risk for heart disease has been described in studies on lesbian, gay, bisexual, transgender, and queer or questioning (LGBTQ+) youth,[12] African American sexual minority women,[13] and transgender beneficiaries of Medicare.[14] Higher rates of tobacco use have been found in communities with intersectional identities, such as those who are Puerto Rican and LGBTQ+.[15]

SUMMARY

Emerging research highlights the interconnectedness between HIV and heart disease risk, underscoring the role of changing science and social determinants of health. People living with HIV face higher rates of cardiovascular issues due to chronic inflammation and metabolic changes. However, social determinants of health, as noted above, exacerbate these risks, particularly in individuals from under-resourced communities. Factors like limited access to preventive care and the stress of social stigma can hinder even the most effective treatments available for both HIV and heart health. Successful interventions will be those based in medical science and equity, thereby improving outcomes and reducing the burden of heart disease in those living with HIV.

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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Psychedelic-assisted therapy: An overview for the internist

ABSTRACT

Preliminary evidence suggests that psychedelic-assisted therapy—the enhancement of psychotherapy with psychedelics such as 3,4-methylenedioxymethamphetamine (MDMA) and psilocybin—may be efficacious for depression, posttraumatic stress disorder, substance use disorders, and other conditions. Therapeutic psychedelic research is advancing steadily, with psilocybin, MDMA, and lysergic acid diethylamide designated breakthrough therapies by the US Food and Drug Administration (FDA). However, in August 2024, the FDA declined to approve a New Drug Application for MDMA and asked its sponsor to conduct another phase 3 trial. Clinicians are urged to prepare for the possible return of psychedelics to medicine.

KEY POINTS

- Psychedelic-assisted therapy may hold therapeutic potential for some psychiatric conditions and substance use disorders.
- Response can vary, but psychedelics may offer durable effects for months or longer following a single administration.
- Psychedelics have a reassuring safety profile in highly controlled clinical trial settings, though they carry serious risks for some patients.

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Psychedelic compounds such as lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (MDMA, or Ecstasy), and psilocybin are drawing interest amid evidence that they may effectively treat psychiatric disorders and substance use disorders.[1] This interest is further fueled by evidence that psychedelics used in a psychotherapeutic setting may improve treatment-resistant conditions and provide benefits that last for months or longer after just 1 treatment session.

Because of the experimental nature of psychedelic-assisted therapy, internists may have little exposure to this modality. However, with possible US Food and Drug Administration (FDA) approval in the coming years and patients increasingly self-treating with psychedelics, the timing is right for clinicians to educate themselves about psychedelic-assisted therapy. This article reviews the potential effects, risks, and therapeutic applications of these powerful drugs, with a focus on MDMA-assisted therapy for posttraumatic stress disorder (PTSD) and psilocybin-assisted therapy for depression.

OVERVIEW OF PSYCHEDELICS

Psychedelic drugs can significantly alter perception, cognition, mood, affect, social relatedness, and sense of self or meaning. They are unique in that they profoundly affect consciousness without simultaneously inducing delirium.[1] Some of the most notable subjective effects of psychedelics are visual perceptual changes; hallucinations and pseudohallucinations; enhanced feelings of connectedness; and mystical experiences characterized by feelings of unity or oneness,

transcendence of time and space, and deep emotional and spiritual significance. More so than other drugs, the subjective effects of psychedelics are influenced by "set and setting," referring to one's mindset ("set") and the physical environment and social milieu ("setting") of administration.[2]

Classic vs nonclassic psychedelics

There is debate among researchers about which drugs should be classified as psychedelics. From a phenomenological standpoint, substances with a variety of pharmacologic mechanisms produce psychedelic subjective effects. For example, the effects of LSD are produced via serotonin 2A receptor agonism; ketamine, N-methyl-D-aspartate receptor antagonism; and MDMA, serotonin release into the synaptic cleft. However, some researchers argue that only compounds that produce these effects primarily via serotonin 2A receptor agonism (eg, LSD, psilocybin, dimethyltryptamine) are psychedelics. In a compromise between these competing views, primary serotonin 2A agonists are referred to as *classic* psychedelics, while compounds that exert similar effects via alternate pharmacologic mechanisms are termed *nonclassic* psychedelics.[3]

Underlying mechanisms are being explored

Over the past 2 decades, numerous studies have explored multiple psychedelic compounds for their effects on various mood, anxiety, and substance use disorders, with promising findings on efficacy and favorable safety profiles in research settings.[1] How psychedelics might be able to treat such diverse conditions remains unclear, but multiple potential explanatory hypotheses are currently under investigation.[4]

Functional neuroimaging studies suggest that psychedelics can disrupt the default mode network, a group of brain regions involved in self-referential thinking and introspection.[4] This network is often overactive in several psychiatric disorders and substance use disorders. Temporarily disrupting the default mode network may enable it to reorganize in a way that fosters more flexible thought patterns, facilitating more adaptive ways of thinking and behaviors.

Neurochemically, psychedelics seem to temporarily enhance neuroplasticity—the brain's ability to reorganize and form new neural connections—for weeks after their immediate effects have ceased. This increased neuroplasticity may promote learning and cognitive flexibility, which patients can use to develop new perspectives and facilitate lasting behavioral changes.

HISTORICAL PERSPECTIVE

Early medical use of psychedelics and subsequent regulation

Humans have used naturally occurring psychedelics such as psilocybin and mescaline for thousands of years, and knowledge from indigenous peoples' ritualistic use informs the delivery of psychedelic-assisted therapy.[5] Interest in therapeutic applications of psychedelics in Western medicine is not new. After Swiss chemist Albert Hoffman discovered LSD's psychoactive effects in 1943, his employer Sandoz disseminated LSD to physicians to identify potential clinical applications. Clinical use of LSD in the 1950s and 1960s showed promising results for alcohol use disorder, cancer-related psychological distress, and other conditions.[6,7] Hoffman identified psilocybin as the primary psychoactive compound in *Psilocybe mexicana* mushroom samples in 1958 and first synthesized psilocybin in 1959. Sandoz subsequently also disseminated it for psychiatric research.[8]

In the mid-1960s, the FDA began requiring that drugs be subjected to monitored clinical trials to establish safety and efficacy for specific indications. Amid growing public concern about nonmedical use of psychedelics and the patent for LSD expiring in 1965, Sandoz did not pursue these trials, so clinical use of psychedelics drew to a close.[9] In 1970, most psychedelics were designated under the Controlled Substances Act as Schedule I drugs (ie, no accepted medical use and a high potential for abuse) in the United States, erecting significant bureaucratic and cost barriers that essentially halted early research into psychedelics' therapeutic benefits.

Although MDMA was synthesized in 1912 by Merck chemists,[10] the company conducted no human testing, so it was not designated a Schedule I drug in 1970 because its psychoactive effects were still unknown. American chemist Alexander Shulgin re-synthesized MDMA and performed self-trials in 1976,[10] which led to therapists using MDMA as an adjunct in psychotherapy (permissible in some states at the time). Uncontrolled case series from that period suggested MDMA held therapeutic potential for multiple psychiatric conditions.[11] However, in 1984, once it learned of nonmedical use of MDMA, the US Drug Enforcement Administration announced plans to make MDMA a Schedule I drug. MDMA-assisted therapists attempted to halt this action via administrative hearings,[12] and the US Drug Enforcement Administration administrative judge overseeing the case concluded MDMA should be a Schedule III drug. However, the US Drug Enforcement Administration overruled this and placed MDMA into Schedule I in 1985.

Figure 1. Psychedelic treatment room, Cleveland Clinic Lutheran Hospital.

Renewed interest in therapeutic applications

Through considerable efforts of researchers and philanthropists who believed potentially useful medicines had become unnecessary casualties of the "War on Drugs," clinical trials exploring the therapeutic potential of psilocybin and MDMA were revived in the 2000s. Due to positive findings from these trials,[1] numerous biotechnology companies hoping to develop psychedelics as medicines have recently emerged.[13] Psychiatry has also warmed to the notion of psychedelics as medicines, with 81% of psychiatrists in a 2023 national survey agreeing they show promise in treating psychiatric conditions, and over half planning to incorporate psychedelics into their practices upon FDA approval.[14]

Research into therapeutic applications of psychedelics is now progressing after several decades of dormancy due to regulatory requirements and a lack of federal research funding.[15] In a promising sign, the FDA has granted breakthrough therapy status to LSD, MDMA, and psilocybin because they show potential for significant improvement over existing treatments. With this designation, pharmaceutical companies developing psychedelic treatments receive intensive guidance from the FDA on their drug development programs, and the FDA review process is accelerated.

Regulatory approval efforts

The field suffered a notable setback in August 2024, when the FDA declined to approve a New Drug Application for MDMA for PTSD despite positive findings from 2 phase 3 trials and asked its sponsor, Lykos Therapeutics, to conduct another phase 3 trial.[16] The FDA typically does not publicly disclose its reasoning for New Drug Application decisions, and Lykos Therapeutics has not publicly shared the complete text of the FDA's response letter. However, Lykos Therapeutics stated that the letter's contents "echo" critiques raised during a June 2024 meeting of an FDA Advisory Committee that recommended against approving MDMA.[17] Concerns raised about Lykos Therapeutics' trials during that meeting included ineffective blinding due to MDMA's psychoactive effects; failure to collect electrocardiograms, liver function tests, and data on participants' feelings of euphoria (to assess addictive potential); and risk of therapist sexual misconduct after a therapist in a phase 2 clinical trial in Canada engaged in a sexual relationship with a participant.[16]

Prior to this decision, it was believed by many in psychiatry that MDMA would become the first FDA-approved psychedelic. Due to the FDA's requirement of a new phase 3 trial, it now seems more likely that psilocybin will be approved by the FDA first. After a positive phase 2 trial,[18] Compass Pathways is conducting 2 phase 3 trials of psychedelic-assisted therapy for treatment-resistant depression. If these trials are successful, FDA approval could be granted in 2026.

TABLE 1
Essential concepts of psychedelic-assisted therapy

Set and setting	One's mindset ("set") and the physical environment ("setting") can strongly influence psychedelic subjective effects. Appropriate preparation by the practitioner, which includes building a strong therapeutic alliance and administering the psychedelic in a supportive environment, will minimize adverse experiences and enhance therapeutic efficacy.
Intention[24]	Defining and setting an intention for what one hopes to gain from a psychedelic experience may increase the likelihood of a powerful and therapeutic psychedelic experience.
Ego dissolution	Losing one's sense of self is a key feature of the psychedelic experience that can produce positive effects, such as feelings of unity, or negative effects, such as anxiety. This experience tends to be limited to classic psychedelics (psilocybin, lysergic acid diethylamide) and does not usually occur with MDMA.
Mystical experience	This transformational state, sometimes elicited by psychedelics, is marked by ineffability, ego dissolution, positive mood, transcendence of time and space, and feelings of unity with ultimate reality. The degree to which participants have a mystical experience has been positively correlated with therapeutic effect with classic psychedelics, but not with MDMA.
Challenging experience, bad trip	A negative psychedelic experience is marked by fear, dysphoria, paranoia, or confusion. Preparation, setting an intention, and taking a psychedelic under the care of a therapist can reduce the risk. Many who have had a challenging psychedelic experience ultimately report it was helpful, though some report long-term psychological harms.
Neuroplasticity	In this adaptive process, neuronal connections (eg, dendritic spines, synaptic proteins) change in response to a stimulus or experience. This can lead to formation of new neuronal connections or extinction of previously established ones. Psychedelics may enhance neuroplasticity for weeks after exposure.
Suggestibility[25]	The quality of readily and uncritically accepting and acting upon others' suggestions is enhanced by psychedelics and may be helpful for psychotherapy.

MDMA = 3,4-methylenedioxymethamphetamine

The Usona Institute has also reported positive findings in a phase 2 trial of psilocybin for major depressive disorder[19] and launched its first phase 3 trial in March 2024.

PSYCHEDELIC-ASSISTED THERAPY PARADIGM

Psychedelic-assisted therapy arose from combining LSD and psychotherapy in the 1950s, with the eventual addition of music during sessions.[20] Participants in psychedelic-assisted therapy clinical trials undergo preparation sessions to build therapeutic alliance with their therapists, set intentions for their psychedelic sessions, and receive psychoeducation about psychedelics. During psychedelic treatment sessions, participants are cared for by 1 or 2 psychedelic-assisted therapy–trained therapists. Psychedelic sessions occur in a therapeutically appointed space. Inside the treatment room there typically is calming artwork, a couch or a bed on which the participant may recline, and comfortable seating for the therapists, as sessions can last 6 to 8 hours (**Figure 1**). Patients wear headphones and listen to curated music playlists. Participants are also offered eyeshades to facilitate inward focus, with periodic discussion with their therapists occurring as needed.

The subjective effects of psychedelics vary widely, though it is not unusual for participants receiving high doses to report dramatic experiences, such as being reborn or being in the presence of God. Many trial participants report that psychedelic-induced mystical experiences are among the most meaningful and spiritually significant experiences of their lives.[21] Vital signs are collected throughout psychedelic treatment sessions, and participants undergo medical evaluations toward the session's end to ensure appropriateness for discharge. Once cleared, participants are released into the care of a responsible adult and instructed not to drive until the following day.

In the days to weeks after a psychedelic session, participants return for integration sessions to process their psychedelic experiences and consider how to translate resulting insights into durable behavioral change. For

TABLE 2
Potential acute effects and pharmacology of orally administered MDMA and psilocybin

	MDMA[30,31]	Psilocybin[18,19,48]
Potential acute psychological effects	Sense of well-being, relaxation, reduced anxiety, stimulation, euphoria, prosocial effects, heightened introspection, increased self-esteem, reduced fearfulness, increased empathy, altered sense of time, mystical experience	Elevated mood, stimulation, enhanced introspection, illusions, visual perceptual changes, hallucinations (auditory, olfactory, tactile, gustatory, and visual), synesthesia, alterations in sense of time, enhanced feelings of connectedness, anxiety, fatigue, affective lability, mystical experience
Potential acute physical effects[28,29]	Mydriasis; diaphoresis; increases in blood pressure, temperature, and heart rate; slight impairment in psychomotor performance; dry mouth; jaw clenching; bruxism	Mydriasis, elevated or slowed heart rate, elevated or decreased blood pressure, nausea, increased or decreased tendon reflexes, tremor, dysmetria
Most common adverse effects	Anxiety, jaw clenching, muscle tightness, reduced appetite, nausea, dizziness, excessive sweating, restlessness, feeling jittery, blurred vision, pyrexia, irritability, panic attack	Headache, nausea, visual perceptual effects, dizziness, fatigue, euphoric mood and mood alteration, anxiety, and paresthesia
Time to peak effects	1–2 hours	1–2 hours
Elimination half-life	8–9 hours	2–3 hours
Duration of acute effects	4–6 hours	6 hours
Primary neurotransmitters affected	Serotonin, norepinephrine, dopamine	Serotonin
Metabolism	Primarily hepatic, via cytochrome P450 (mainly CYP2D6)	Rapidly undergoes hepatic first-pass metabolism and dephosphorylation into psilocin (psychoactive metabolite); psilocin then undergoes phase I and phase II (primary) metabolism in the small intestine and liver, with metabolites eventually excreted renally

MDMA = 3,4-methylenedioxymethamphetamine

weeks after treatment, psychedelics appear to reopen critical periods for social learning[22] and enhance neuroplasticity.[23] This provides a rationale for the potential importance of integration sessions for prolonging therapeutic efficacy, although this claim requires further investigation. The number of psychedelic sessions in a treatment course typically ranges from 1 to 3 over several weeks, depending on the protocol and condition being treated.

Essential psychedelic-assisted therapy concepts are outlined in **Table 1**.[24,25]

MDMA-ASSISTED THERAPY FOR PTSD

MDMA is a nonclassic psychedelic; it acts primarily as a releaser and reuptake inhibitor of serotonin, norepinephrine, and, to a lesser extent, dopamine.[26] MDMA's effects tend to be less intense than those of classic psychedelics, despite frequently catalyzing powerful emotional experiences. It typically produces an increased sense of well-being accompanied by increased extraversion, empathy, and feelings of closeness with others. MDMA lends itself to enhanced introspection without the distraction of significant alterations in perception, body image, or sense of self.[27] Mild elevations in blood pressure, body temperature, and heart rate are expected during treatment sessions.[28]

Table 2 summarizes MDMA pharmacology, potential acute effects,[28,29] and the most commonly reported adverse events in clinical trials.[30,31]

Rationale for investigation of MDMA-assisted therapy

PTSD is marked by intrusion symptoms such as nightmares or flashbacks; avoidance of trauma-related thoughts, feelings, or external reminders; negative alterations in cognition and mood; and changes in

arousal and reactivity in people exposed to traumatic events. While trauma-focused therapies are considered first-line treatment, response rates are variable, dropout rates are high, and evidence quality of trials is generally poor.[32] Further, only 20% to 30% of patients respond to treatment with sertraline or paroxetine, the only 2 FDA-approved medications for PTSD.[32] Therefore, there is need for novel PTSD treatments.

MDMA may enhance therapeutic alliance via its prosocial effects while also facilitating a less-threatening experience of traumatic memories. It reduces activity in brain regions associated with fear and anxiety, which may allow severe emotional reactions to traumatic memories to be unlearned.[33,34] Similar to classic psychedelics, MDMA may also enhance or reopen critical periods of learning, which can facilitate behavioral change.

Functional unblinding in trials a challenge

Clinical trials of MDMA-assisted therapy for PTSD typically involve 2 or 3 treatment sessions, along with preparation and integration sessions. In randomized controlled trials, participants receive the same number of psychotherapy sessions whether they receive MDMA or placebo. Given the strong psychoactive effects of psychedelics, a common criticism of this line of research has been that most participants can easily distinguish whether they have received active drug or placebo (functional unblinding). In the most recent phase 3 trial of MDMA-assisted therapy for PTSD, 94% of participants receiving MDMA guessed they had received it, while 75% of participants in the placebo group were aware they had received placebo.[34]

Importantly, functional unblinding can occur due to a drug's psychoactive effects or side effects as well as its efficacy. This challenge is not unique to psychedelics; high rates are reported in trials of many commonly used psychiatric medications, including stimulants, benzodiazepines, antidepressants (primarily older ones due to more prominent side effects),[35] and antipsychotics.[36] Early MDMA trials used low-dose MDMA as an active placebo to reduce functional unblinding, but later studies switched to inactive placebo after low-dose MDMA was found to worsen PTSD symptoms for some participants. Low-dose MDMA also led to increased anxiety and re-experiencing of trauma during therapy without the emotional breakthrough necessary for processing conferred by high-dose MDMA, with some participants requiring benzodiazepine rescue treatments.[37]

Promising efficacy results

In a 2022 systematic review and meta-analysis,[30] all 5 eligible randomized controlled trials of MDMA-assisted therapy from 2011 to 2021 used the Clinician-Administered PTSD Scale (CAPS) to evaluate treatment effects (score range 0–80, with higher scores indicating more severe PTSD symptoms; CAPS score ≥ 50 signifies severe PTSD).[38] These trials involved 175 participants with baseline CAPS scores ranging from 44.0 ± 6.0 to 94.4 ± 20.2. Assessment of the primary end point occurred from 3 weeks to 2 months after the last MDMA session, with a 22-point greater reduction in baseline CAPS score occurring in participants receiving MDMA-assisted therapy than in controls (mean difference −22.03; 95% confidence interval [CI] −38.53 to −5.52).[30]

In a recent confirmatory randomized, placebo-controlled phase 3 trial of MDMA-assisted therapy for moderate or severe PTSD, after 3 treatment sessions, response rates at 18 weeks after baseline (6–8 weeks after MDMA session 3) were 86.5% and 69.0% for MDMA and placebo, respectively, while remission rates were 46.2% and 21.4%.[34] This translated to an effect size of 0.70 for MDMA vs placebo. (Effect size is a statistical measure used to quantify the magnitude of a difference between 2 groups' means, which provides a measure of the practical significance of study results. It is calculated as the difference between the 2 means divided by the pooled standard deviation, and is generally interpreted as follows: 0.2 small effect, 0.5 medium effect, and 0.8 or higher large effect.)

While no clinical trials have directly compared MDMA-assisted therapy with sertraline or paroxetine, at the primary end point of phase 3 trials for those medications, the effect sizes were smaller (0.45–0.56 for paroxetine and 0.31–0.37 for sertraline) than the effect size of MDMA in phase 2 trials (0.90) or the 2 phase 3 trials (0.91 and 0.70).[34,39] There have been no trials directly comparing MDMA-assisted therapy with traditional trauma-focused therapies. However, meta-analysis of randomized trials of trauma-focused therapies that included a control condition, rather than waitlist or treatment as usual, showed an effect size of 0.96 after 14 to 27 weeks of treatment.[40]

A dropout rate of 6.8% was observed among participants who received MDMA in phase 2 trials.[39] In contrast, in a recent randomized trial that evaluated 2 trauma-focused therapies for PTSD—prolonged exposure and cognitive processing therapy—dropout rates were 56% and 47%, respectively.[41] It is also notable that phase 2 trials for MDMA-assisted therapy included only participants who had previously been intolerant of or unresponsive to available treatments.[39] Therefore, MDMA-assisted therapy might offer the most public health benefit for PTSD in its potential for patients

not helped by existing PTSD treatments. Only head-to-head trials can provide an accurate assessment of comparative efficacy due to differences in study designs and study populations. Caution is warranted in any comparison of outcomes without head-to-head trials.

Low risk in clinical trial settings

MDMA has been well tolerated in clinical trials. Although adverse events are common, they have been primarily mild to moderate in severity. Serious adverse events have been rare. One clinical trial participant with a history of premature ventricular contractions experienced worsening contractions after receiving MDMA and was hospitalized, with full resolution and without long-term sequalae.[42]

Given that antidepressants can rarely worsen or induce suicidality, suicidal ideation and suicidal behaviors are important safety outcomes for psychedelic clinical trials. There have been no suicide attempts or completed suicides in clinical trials of MDMA. One trial participant with a history of suicide attempts was hospitalized for suicidal ideation 13 days after their second MDMA session and went on to complete the study.[30,42] In the most recent phase 3 trial of MDMA for PTSD, 2 participants in both the MDMA and placebo groups reported treatment-emergent suicidal ideation, and 1 participant in each group engaged in posttreatment nonsuicidal self-injuring behavior.[34]

MDMA appears to be physiologically safer in controlled settings than in recreational settings. While nonmedical MDMA use has caused rare deaths from hyperthermia or hyponatremia-related seizures, these are typically associated with multiple drug toxicity and dancing in high-temperature environments with likely overhydration.

MDMA's misuse potential is low compared with other commonly used psychoactive drug classes, but somewhat higher than that of classic psychedelics.[43] The existence of addiction to MDMA has been questioned.[44] Elements of addiction, including tolerance, cravings, and psychological dependence, have been reported with MDMA, but physical withdrawal symptoms such as dysphoria appear minor. Questions have been raised about whether these symptoms more accurately reflect subacute "comedown" effects rather than withdrawal. Clinical trials thus far have not yielded evidence of MDMA misuse among participants. While neuroimaging studies of nonmedical users of MDMA have raised concerns about serotonergic neurotoxicity, participants have typically been unusually heavy MDMA users. These studies have also suffered from likely confounding by use of multiple drugs and questions of purity, and have had only limited replicability.[45] Further investigation is necessary, but it is currently thought unlikely that exposure to a small number of MDMA-assisted psychotherapy sessions should cause appreciable risk in this regard.

PSILOCYBIN-ASSISTED THERAPY FOR DEPRESSION

Psilocybin primarily exerts its psychoactive effects via partial agonism at the serotonin 2A receptor. Depending on the dose, psilocybin can cause potentially intense perceptual alterations, with prominent effects on visual perception. Psilocybin can elevate mood, enhance introspection, and elicit vivid recollection of distant memories.[46] Heightened feelings of connectedness can also occur, but psilocybin tends to produce more of an inwardly focused experience compared with MDMA, with a higher rate of mystical experiences.[47]

Psilocybin elevates blood pressure and heart rate. While elevations are typically mild, self-limiting severe blood pressure elevations have been reported.[28] **Table 2** summarizes psilocybin's pharmacology and acute effects.[18,19,48]

Rationale for investigation of psilocybin-assisted therapy

Depression involves decreased mood; anhedonia; loss of motivation; disruptions in appetite, sleep, and functionality; and sometimes suicidal ideation or suicide. While antidepressants and psychotherapy are effective for many patients with depression, they are unhelpful or only partially helpful for a substantial minority, and symptomatic improvement is slow. Further, antidepressants can cause problematic adverse effects, including sexual dysfunction and emotional blunting. Treatment-resistant depression, most commonly defined as 2 failed antidepressant treatments, affects approximately one-third of patients with depression.[49] Modalities such as electroconvulsive therapy, transcranial magnetic stimulation, and ketamine or esketamine can be effective for patients with treatment-resistant depression, but there are multiple barriers to their use. Novel rapid-acting agents that produce durable antidepressant effects after only a few administrations would provide considerable improvement in comparison.

Significant efficacy findings

A meta-analysis of 9 clinical trials of psilocybin-assisted therapy for depression (1 or 2 treatment sessions) included 596 participants and evaluated antidepressant efficacy using multiple instruments, including the Hamilton Depression Rating Scale and the Montgomery-

TABLE 3
Conditions commonly excluded in psychedelic-assisted therapy trials

Psychiatric conditions
Bipolar disorder (personal or close family history)
Personality disorder (eg, antisocial, borderline, schizoid)
Psychotic disorder (personal or close family history)
Suicidal ideation (with intent or plan) or recent suicidal behavior
Nonpsychiatric conditions
Arrhythmia (clinically significant)
Type 1 diabetes, type 2 diabetes (uncontrolled)
Hepatic dysfunction, depending on psychedelic metabolism
Uncontrolled hypertension
Myocardial infarction (lifetime history)
Pregnancy or breastfeeding
QTc prolongation
Seizure disorder
Stroke (lifetime history)
Tachycardia
Unstable thyroid disease

Asberg Depression Rating Scale.[50] The standardized mean difference in depression outcomes between experimental and control arms was –0.78 (95% CI −1.06 to −0.51, $P < .00001$), signifying a large effect of psilocybin. The pooled response rate at primary end point (which, across included trials, ranged from 1 to 7 weeks after psilocybin administration) was 57% for psilocybin vs 22% for control. Remission was also higher in the psilocybin group compared with the control group (45% vs 14%). Large, statistically significant effect sizes for psilocybin were also observed in 2 open-label trials that had 6- and 12-month follow-ups (1.4 and 2.4, respectively).

Reassuring safety results

Adverse events are frequently reported in participants receiving psilocybin, though they are usually mild to moderate in severity. Serious adverse events have been rare in clinical trials. One participant sought psychiatric hospitalization for worsening depression after psilocybin treatment.[50] While recent research suggests psilocybin-assisted therapy reduces suicidality,[51] treatment-emergent suicidality remains an important area of interest.

The largest study of patients with treatment-resistant depression to date is a double-blind, randomized controlled phase 2 trial of a single psilocybin-assisted therapy session with 25 mg, 10 mg, and 1 mg (placebo dose) involving 233 participants.[18] From day 2 (first day after psilocybin) to week 3, incidence of suicidal ideation for the 25-mg, 10-mg, and 1-mg groups was 6%, 5%, and 3%, respectively. Incidence of nonsuicidal intentional self-injury during that period was 3%, 1%, and 0%, respectively. From week 3 to week 12, suicidal behavior was reported by 4% of participants in the 25-mg group (all had a history of suicidal behavior or nonsuicidal self-injury), compared with none in the other groups. The incidence of nonsuicidal intentional self-injury during that period for the 25-mg, 10-mg, and 1-mg groups was 0%, 1%, and 1%, respectively. Although not statistically significant, these differences warrant continued investigation into the potential for psilocybin-induced suicidality.

Psilocybin misuse has not been reported in clinical trials.

POST–REGULATORY APPROVAL CONSIDERATIONS

Should the FDA eventually approve a psychedelic, psychiatry will need to build the infrastructure and train the workforce necessary to deliver psychedelic-assisted therapy—a task that will likely take years. FDA Risk Evaluation and Mitigation Strategies for psychedelics will almost certainly require administration in a clinician's office with in-person monitoring by at least 1 licensed and trained psychedelic therapist. Due to logistical demands and training requirements, an initial bottleneck of psychedelic therapists should be expected.

With a round of MDMA-assisted psychotherapy expected to cost between $10,000 and $15,000,[52] coverage by insurers will also be essential to ensuring access.

While MDMA and psilocybin have favorable safety profiles in research settings, numerous populations with real and suspected risk of serious adverse effects from psychedelics are excluded from contemporary psychedelic clinical trials based on established safety guidelines (**Table 3**).[53] There is a significant need for clinical trials to determine the safety of psychedelic-assisted therapy in these populations, as it is unclear whether many of the potential exclusion criteria are necessary or simply based on theoretical but inaccurate risk appraisals.

Other issues to be addressed in trials include the following:

- Determine whether co-administering psychedelics and antidepressants affects efficacy and safety
- Identify psychedelic-assisted therapy's place in psychiatric treatment algorithms
- Incorporate personalized medicine into psychedelic-assisted therapy.

There is also considerable debate about the quantity and nature of psychological support that is necessary and sufficient during the psychedelic experience, as well as who should deliver it, a matter that could significantly impact treatment costs and access.

NONPSYCHIATRISTS' ROLE IN PSYCHEDELIC-ASSISTED THERAPY

If approved by the FDA, psychedelic-assisted therapy will be practiced primarily by mental health practitioners, but psychedelic-assisted therapy practitioners will likely look to internists, primary care physicians, and other physicians for guidance on the safety of psychedelics in older patients and patients with conditions that have been exclusionary in clinical trials. Oncologists and palliative care physicians may seek to become trained in psychedelic-assisted therapy themselves due to an increasing number of studies indicating psychedelics' potential to treat psychological distress associated with serious medical conditions.[1]

Further, since functional disorders are frequently seen across medicine and psychedelics may treat some of them,[54] there may be an important role for other specialists in conducting psychedelic-assisted therapy trials for these conditions and potentially delivering psychedelic-assisted therapy clinically someday. Notably, clinical trials are investigating psychedelic-assisted therapy for common pain disorders treated by internists, such as fibromyalgia, migraines, and irritable bowel syndrome.

LAST WORD

Psychedelic-assisted therapy may be a potentially significant medical advance, offering the possibility of durable therapeutic benefits with rapid onset for some patients with PTSD and depression following only a small number of psychedelic treatments. No psychedelic is currently FDA approved, but psilocybin could possibly gain approval in less than 2 years. If approved, it may be the first of many psychedelics to rejoin psychiatrists' armamentarium over the next decade. However, we have much to learn about optimizing these treatments in clinical settings and real-world patient populations.

DISCLOSURES

Dr. Barnett has disclosed serving as an advisor or review panel participant for CB Therapeutics, COMPASS Pathways, Cerebral, DynaMed, and Janssen Pharmaceuticals; ownership interest (stock, stock options in a privately owned company) in CB Therapeutics; serving as a research principal investigator for COMPASS Pathways and MindMed; consulting for Janssen Pharmaceuticals and TD Cowen; teaching and speaking for TD Cowen; and other activities from which remuneration is received or expected (editorial services- monetary reimbursement) for DynaMed. Dr. King has disclosed ownership interest (stock, stock options in a publicly owned company) in COMPASS Pathways. Dr. Mauney has disclosed serving as a research co-principal investigator for Tryp Therapeutics.

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Coronary artery bypass grafting: Practice trends and projections

ABSTRACT

Coronary artery bypass grafting, also known as CABG, is now in its sixth decade and continues to be the most frequently performed cardiac surgery in the world. This review summarizes evidence regarding the role of CABG in modern-day management of coronary artery disease and discusses the latest developments in perioperative care and outcomes. Future directions include expanding the use of multiarterial grafting, which has the potential to maximize patient longevity and lower risk for adverse events; offering patients less-invasive approaches; and enhancing operative recovery.

KEY POINTS

The collaborative multidisciplinary heart team approach should view percutaneous coronary intervention, CABG, and medical therapy as alternative and complementary treatments rather than as competing therapies; the risks and benefits of each option should be weighed for each patient.

CABG remains the standard of care for patients with complex multivessel disease and left main coronary artery disease, diabetes, or left ventricular systolic dysfunction.

Multiarterial grafting can offer better long-term survival and lower risk of adverse cardiac events for patients undergoing CABG.

Innovations that reduce the invasiveness of coronary surgery and hybrid coronary revascularization are reasonable alternatives in select patients with a preference for less-invasive revascularization procedures.

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Coronary artery bypass grafting (CABG) is performed in patients with ischemic heart disease to improve symptoms, quality of life, and life expectancy. Ischemic heart disease is a major health concern in the United States, affecting 20.5 million people and causing 371,506 deaths in 2022.[1,2] By 2060, the number of people in the United States with ischemic heart disease is expected to exceed 29 million.[3] The economic impact is substantial, with the annual cost of heart disease estimated at $239.9 billion.[2]

Around 650,000 revascularization procedures are performed in the United States annually, including 450,000 percutaneous coronary interventions (PCIs) and 200,000 CABG operations.[4,5] Although fewer revascularizations are done due to advances in medical therapy and appropriate-use criteria, progress contiues in CABG applications and the refinement of techniques, including maximizing longevity with multiarterial grafting, offering patients a less-invasive approach, and improving perioperative outcomes.

Herein, we provide a review of the current indications, techniques, outcomes, and future directions of CABG surgery.

OVERVIEW OF CABG

CABG was pioneered in the 1960s by René Favaloro, MD, to improve symptoms and survival in coronary artery disease.[6] Over the following decades, studies confirmed that CABG increases survival in patients with left main coronary artery and multivessel disease compared with medical therapy. In the early 2000s, PCI with drug-eluting stents emerged as a less-invasive

TABLE 1
Major CABG trials in multivessel disease

Study	Year	Comparison	Primary end point	Key findings
BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes)[10]	2009	Revascularization (CABG or PCI) plus intensive medical therapy vs intensive medical therapy in patients with diabetes	All-cause mortality at 5 years	Revascularization with intensive medical therapy not superior to intensive medical therapy alone CABG stratum: lower prevalence of myocardial infarction (10% vs 17.6%) and MACCE (22.4% vs 30.5%), no significant difference in all-cause mortality (13.6% vs 16.4%) or cardiac death (8% vs 9%) PCI stratum: no significant difference in myocardial infarction, MACCE, all-cause mortality, or cardiac death
FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease)[11]	2012	CABG vs PCI	All-cause mortality, nonfatal myocardial infarction, or nonfatal stroke	CABG superior to PCI: in CABG patients, lower 5-year primary composite end point (18.7% vs 26.6%), lower prevalence of myocardial infarction (6.0% vs 13.9%) and all-cause mortality (10.9% vs 16.3%), higher prevalence of stroke (5.2% vs 2.4%)
SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery)[12]	2013	CABG vs PCI (paclitaxel-eluting stents)	Composite MACCE (all-cause mortality, stroke, myocardial infarction, and repeat revascularization)	PCI inferior and not noninferior to CABG Lower 5-year MACCE (26.9% vs 37.3%); lower prevalence of cardiac death (5.3% vs 9%), myocardial infarction (3.8% vs 9.7%), and repeat revascularization (13.7% vs 25.9%); no significant difference in all-cause mortality (11.4% vs 13.9%) or stroke (3.7% vs 2.4%) for CABG and PCI, respectively
BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease)[13]	2015	CABG vs PCI (everolimus-eluting stents)	Composite of death, myocardial infarction, target-vessel revascularization	No significant difference in primary composite end point at 2 years (PCI 11% vs CABG 7.9%) At longer-term follow-up (median 4.6 years), PCI had significantly higher primary end point (15.3% vs 10.6%) compared with CABG owing to repeat revascularization and spontaneous myocardial infarction
STICH (Surgical Treatment for Ischemic Heart Failure) and STICHES (STICH Extension Study)[9]	2016	CABG plus medical therapy vs medical therapy alone in patients with left ventricular ejection fraction ≤ 35%	All-cause mortality	No significant difference in primary end point over 6 years; however, CABG with medical therapy resulted in significant improvement in long-term all-cause mortality out to 10 years compared with medical therapy alone (58.9% vs 66.1%) Cardiovascular mortality and morbidity were lower with CABG in both studies
FAME 3 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation)[14]	2021	Fractional flow reserve–guided PCI vs CABG in triple-vessel disease	MACCE (death from any cause, myocardial infarction, stroke, or repeat revascularization)	Fractional flow reserve–guided PCI not consistent with noninferiority to CABG: higher MACCE in fractional flow reserve–guided PCI arm compared with CABG (10.6% vs 6.9%) at 1 year

CABG = coronary artery bypass grafting; MACCE = major adverse cardiac or cerebrovascular events; PCI = percutaneous coronary intervention

TABLE 2
Major CABG trials in left main coronary artery disease

Study	Year	Comparison	Primary end point	Key findings
PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease)[15]	2011	CABG vs PCI (sirolimus-eluting stents)	MACCE (death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization)	No significant difference in primary end point at 2 years Higher ischemia-driven target-vessel revascularization in PCI group (9% vs 4.2%)
SYNTAX left main coronary artery subgroup[16]	2014	CABG vs PCI (paclitaxel-eluting stents)	Composite MACCE (all-cause mortality, stroke, myocardial infarction, and repeat revascularization)	No significant difference in primary end point at 5 years Increased stroke in CABG arm (4.3% vs 1.5%), higher repeat revascularization in PCI arm (26.7% vs 15.5%), and higher MACCE at 5 years in PCI with SYNTAX score ≥ 33 (46.5% vs 29.7%)
EXCEL (Evaluation of Xience Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization)[17]	2019	CABG vs PCI (everolimus-eluting stents)	Composite of death, stroke, myocardial infarction	PCI was noninferior to CABG for primary end point at 3 years, survival curves favored CABG at 5 years (22.0% vs 19.2%), and ischemia-driven revascularization was more frequent after PCI (16.9% vs 10%)
NOBLE (Nordic-Baltic-British Left Main Revascularization)[18]	2020	CABG vs PCI	Composite MACCE (all-cause mortality, nonprocedural myocardial infarction, repeat revascularization, and stroke)	CABG superior to PCI Lower MACCE for CABG (19% vs 28%) at 5 years, driven by lower nonprocedural myocardial infarction (3% vs 8%) and lower repeat revascularization in CABG patients (10% vs 17%)

CABG = coronary artery bypass grafting; MACCE = major adverse cardiac or cerebrovascular events; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With Taxus Stents and Cardiac Surgery

alternative. Despite PCI becoming more common, especially for patients with acute coronary syndromes, CABG remains the gold standard, particularly for patients with complex anatomy (ie, bifurcation disease and higher SYNTAX score—a score of coronary disease complexity, derived from the Synergy Between PCI With Taxus and Cardiac Surgery trial as criteria for treatment selection),[7] diabetes, and left ventricular dysfunction.[8,9] PCI is considered a valuable option for patients with fewer coronary lesions and for those who are poor surgical candidates.

CABG is one of the most studied cardiac surgical procedures, with extensive follow-up data (**Table 1** and **Table 2**).[9–18] Typical CABG patients are older, with more comorbidities, and often have undergone PCI. Most procedures involve multiple bypass grafts, usually 1 internal thoracic artery (ITA), and vein grafts. Arterial grafts, such as the right ITA and radial artery, can significantly improve long-term patency compared with vein grafts but are more technically challenging. Vein grafts often fail over time, leading to recurrent angina.

CURRENT INDICATIONS

The 2021 American College of Cardiology, American Heart Association, Society for Cardiovascular Angiography and Interventions guidelines[8] on coronary artery revascularization recommend CABG along with medical therapy in various clinical and anatomic scenarios to achieve symptom relief and improve survival (**Table 3**). However, recent studies and trials have sparked debate about the extent of the benefits of CABG in certain patient groups.

Seminal trials from the 1970s[19–21] confirmed the superiority of CABG over medical therapy for symptom relief and improved quality of life, with a landmark meta-analysis confirming the benefits of CABG, especially in individuals with more severe coronary artery disease.[22] These data solidified CABG as the gold standard for many patients with complex coronary anatomy.

The ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial[23] and subsequent meta-analyses have questioned the survival advantage of CABG in patients with normal or mildly reduced left ventricular function.[8,23] These studies often involved patients with a lower degree of disease complexity, the vast majority of whom received PCI. Additionally, a significant percentage of patients (21%) in the ISCHEMIA trial crossed over from medical therapy to intervention within a median follow-up of 3.2 years, often in the context of myocardial infarction.[23] This crossover and patient selection have complicated the direct comparison of long-term outcomes of CABG with other treatments. Recent evidence supports the safety of an initial medical approach with continued surveillance in select patients with low atherosclerotic burden. However, it does not negate the survival advantage of CABG in patients with multivessel coronary artery disease, an advantage long established by previous research.[22,24]

CABG is also indicated for symptom relief and improvement in quality of life, particularly for patients not adequately managed with medical therapy alone.[8]

CABG VS PCI: WHAT THE EVIDENCE SAYS

The comparison between CABG and PCI remains a focus of study owing to the continuous advances in medical technology and techniques, need for updated long-term data, and evolving nature of patient populations and their comorbidities. This comparison has been challenging due to selection bias in clinical trials and evolving clinical practices that outpace guideline recommendations. Recent landmark trials have provided clearer insights and helped refine recommendations for the optimal use of PCI and CABG based on patient-specific factors and long-term outcomes.[9–18]

Multivessel disease

Initial PCI vs CABG trials[25] primarily included patients with single- or double-vessel disease and normal left ventricular function, which had already been shown to have little prognostic benefit from surgery.[22] Later trials[9–18] shifted focus to patients with more complex conditions, such as multivessel and left main disease. Patients with a SYNTAX score of 22 or lower are generally well suited for PCI. Conversely, CABG is superior to PCI for the majority of patients with multivessel coronary artery disease with SYNTAX scores higher than 22 and for those with left main disease with SYNTAX scores of 33 or higher. In these later trials,[9–18] patients were assessed by a collaborative multidisciplinary heart team to determine their eligibility for equivalent anatomic revascularization. Based on clinical comorbidities and disease complexity, eligible patients were then randomized to receive either PCI or CABG. The results of major trials, like FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease),[22] SYNTAX,[23] and BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease)[24] have consistently shown that CABG should be considered the primary revascularization strategy for most patients with complex multivessel disease.[11–13]

Left main coronary artery disease

As for patients with left main coronary artery disease, the decision between choosing CABG over PCI is nuanced owing to inconsistent findings in different trials (**Table 2**).[15–18] To reconcile these conflicting results, an individual patient data meta-analysis[26] was conducted using data from 4,394 patients from 4 randomized controlled trials—SYNTAX,[12,16] PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease),[27] NOBLE (Nordic-Baltic-British Left Main Revascularization),[18] and EXCEL (Evaluation of Xience Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization)[28]—with a follow-up period of at least 5 years. In the study's time-to-event analysis, there was no statistically significant difference in 5-year all-cause mortality between patients treated with PCI using drug-eluting stents and those treated with CABG.[26] Although the Bayesian approach suggested that CABG may have a survival benefit over PCI, the absolute risk difference in all-cause mortality is likely less than 0.2% per year.

Furthermore, patients who underwent PCI had higher rates of spontaneous myocardial infarction (6.2%, 95% confidence interval [CI] 5.2%–7.3% vs 2.6%, 95% CI 2.0–3.4; hazard ratio [HR] 2.35, 95% CI 1.71–3.23; $P < .0001$) and repeat revascularization (18.3%, 95% CI 16.7%–20.0% vs 10.7%, 95% CI 9.4%–12.1%; HR 1.78, 95% CI 1.51–2.10; $P < .0001$)

TABLE 3
2021 American College of Cardiology, American Heart Association, Society for Cardiovascular Angiography and Interventions recommendations for CABG vs PCI

Indication	Criteria and recommendation	Class strength and level of evidence
Complex disease	Significant left main coronary artery disease with high complexity CABG is recommended over PCI to improve survival	Class 1, level B-R
	Multivessel disease with complex or diffuse coronary artery disease (SYNTAX score ≥ 33) It is reasonable to choose CABG over PCI to confer survival advantage	Class 2a, level B-R
Diabetes	Multivessel disease with LAD involvement CABG with left IMA to LAD is preferred to PCI to reduce mortality and repeat revascularizations	Class 1, level A
	Multivessel disease amenable to PCI, indication for revascularization, and poor candidate for surgery PCI can be useful to reduce long-term ischemic outcomes	Class 2a, level B-NR
	Left main coronary artery stenosis and low- or intermediate-complexity coronary artery disease in the rest of coronary anatomy Consider PCI as alternative to CABG to reduce major adverse cardiovascular outcomes	Class 2b, level B-R
Previous CABG	Refractory angina on guideline-directed medical therapy attributable to LAD disease CABG over PCI when IMA can be used as conduit to the LAD	Class 2a, level C-LD
	Complex coronary artery disease CABG over PCI when IMA can be used as a conduit to the LAD	Class 2b, level B-NR
Nonadherence to dual antiplatelet therapy	Multivessel disease amenable to treatment with either PCI or CABG CABG is preferred to PCI	Class 2a, level B-NR

CABG = coronary artery bypass grafting; IMA = internal mammary (thoracic) artery; LAD = left anterior descending coronary artery; LD = limited data; NR = nonrandomized; PCI = percutaneous coronary intervention; R = randomized; SYNTAX = Synergy Between PCI With Taxus Stents and Cardiac Surgery

Data from reference 8.

over the 5-year period compared with those who underwent CABG.[26] Notably, there was no difference in risk of stroke between PCI and CABG.

Eligibility

Typically, trials have limited follow-up periods, with 5 years being relatively short when long-term survival is a priority. Additionally, all trials comparing PCI and CABG are designed around the premise of equipoise between treatments, excluding patients with very complex coronary disease, significant comorbidities, and frailty that might favor one revascularization method over the other. Patients who cannot be included in trials are often followed in registries. A study using the OPTIMUM registry (Outcomes of Percutaneous Revascularization for Management of Surgically Ineligible

Patients With Multivessel or Left Main Coronary Artery Disease) found that reasons for surgical ineligibility varied and included poor distal target or conduit (18.9%), severe left ventricular dysfunction or nonviable myocardium (16.8%), severe lung disease (10.1%), frailty or immobility, prior sternotomy, and advanced age.[29]

There is also a large population that is ineligible for PCI. In a SYTNAX registry study in which registry patients constituted 41% of the study cohort, there were 5 times as many PCI-ineligible patients as CABG-ineligible patients.[30] Main reasons for PCI ineligibility included complex anatomy (70.9%), untreatable chronic total occlusion (22.0%), and inability to take antiplatelet medications (0.9%).[30] CABG in these patients had good outcomes. These results show a noteworthy prevalence of ineligible patients for both PCI and CABG, highlighting the importance of individualized treatment planning.

Current guidelines

When determining the optimal choice between PCI and CABG, several factors must be considered, including patient characteristics, disease stability, procedural risk, atherosclerotic burden and complexity, long-term efficacy, and patient preferences. The 2021 American College of Cardiology, American Heart Association, Society for Cardiovascular Angiography and Interventions guidelines[8] for coronary revascularization provide recommendations to guide decision-making in situations where CABG or PCI may be preferred (**Table 3**). There seems to be consensus that when it comes to complex anatomies, heavy atherosclerotic burden, and durability, CABG is the preferred modality. When feasible, PCI is a viable alternative in those who are poor surgical candidates and those with less-extensive coronary lesions.

Ultimately, the collaborative multidisciplinary heart team approach should view PCI, CABG, and medical therapy as alternative and complementary treatments rather than competing therapies. The multidisciplinary team should carefully weigh the risks and benefits of each option for each patient. This collaborative approach is recommended to provide the best possible outcomes for patients and is considered a Class 1 indication according to current guidelines.[8]

CABG TECHNIQUES

Off-pump vs on-pump CABG

Off-pump ("beating heart") CABG was introduced in high-risk patients to reduce the potential deleterious effects associated with cardiopulmonary bypass and aortic clamping. Despite several randomized controlled trials, there is no consensus on which technique is superior. The choice often depends on patient characteristics and expertise of the surgeon.

Patel et al[31] noted similar in-hospital mortality but varied longer-term outcomes in 3 of the largest contemporary trials comparing on-pump and off-pump CABG. The ROOBY (Randomized On/Off Bypass) trial reported increased 5-year all-cause mortality in the off-pump group, unlike the CORONARY (CABG Off or On Pump Revascularization) and GOPCABE (German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients) studies,[32–34] which showed no difference. Given the lack of a conclusive advantage of the off-pump approach, its use has declined in recent years, accounting for 17% of CABG procedures in 2012 but only 12% in 2021. It is favored for higher-risk patients and those with significant aortic atherosclerosis who have a high risk of perioperative stroke.[5,35] Factors favoring on-pump over off-pump CABG include the following:

- Small or diffusely diseased coronary arteries
- Suboptimal targets
- Intramyocardial coronary arteries
- Coronary endarterectomy
- Unstable hemodynamics
- Concomitant valve surgery.

Off-pump CABG or PCI should be considered when cardiopulmonary bypass presents a prohibitive risk or when there is severe calcification of the aorta, severe ascending aortic atherosclerosis, high risk for stroke, or liver cirrhosis.

Multiarterial grafting

The long-term survival benefit provided by CABG is largely determined by the durability of the grafts used and the bypassing of multiple important targets.[36,37] Using an ITA for bypassing the left anterior descending (LAD) artery is standard of care owing to its superior long-term outcomes compared with saphenous vein grafts, as reported in the seminal study by Loop et al.[38] Subsequently, in 1999, Lytle et al[39] found that using both left and right ITAs conferred a strong survival benefit compared with single ITA grafting. However, despite these findings, few use a second arterial conduit. Ten-year outcomes of ART (Arterial Revascularization Trial)[40] showed no difference in mortality or major adverse cardiac and cerebrovascular events. However, an as-treated analysis revealed notable 10-year survival benefit (HR 0.81, 95% CI 0.68–0.95) and a reduced composite of death, myocardial infarction, and stroke for multiarterial grafting (HR 0.80, 95% CI 0.69–0.93) compared with single-arterial grafting.[40]

Current consensus supports the superiority of arterial grafts over saphenous vein grafts in appropriately selected patients undergoing CABG.[41] Data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database show an increasing proportion of patients undergoing multiarterial grafting, from 10.9% in 2020 to 14.3% in 2021, with both bilateral ITA and radial artery use slowly increasing.[5]

Despite evidence supporting multiarterial grafting, the saphenous vein remains the most used conduit due to the ease of harvesting and length of the conduit. However, it has lower long-term patency. The "no-touch technique," which involves harvesting the vein with surrounding tissue to preserve its integrity, has shown comparable patency to ITA grafts but has a higher risk of wound complications given the significant prevalence of diabetes and obesity in the North American population.[41] In addition, patients are more likely to prefer a less-invasive approach.

Minimally invasive techniques

Over the past 3 decades, innovations in coronary surgery have led to the development of minimally invasive coronary surgery (MICS) CABG, robotic CABG, and hybrid coronary revascularization. These techniques aim to reduce the invasiveness of procedures and improve patient outcomes.

MICS CABG combines off-pump CABG with a minimally invasive method, such as left anterior small thoracotomy to avoid sternotomy, thereby reducing possible complications related to cardiopulmonary bypass and sternotomy (**Figure 1**).[42,43] Minimally invasive direct coronary artery bypass, the precursor of MICS, is applicable in patients with single-vessel disease in the proximal LAD or in those undergoing hybrid revascularization. MICS CABG allows multivessel grafting with various configurations and conduits, offering excellent procedural and short-term outcomes at experienced centers. The ongoing MIST (Minimally Invasive Coronary Surgery Compared to Sternotomy Coronary Artery Bypass Grafting) trial continues to evaluate whether MICS CABG leads to better recovery compared with conventional CABG.[43]

Robotic CABG differs from traditional approaches in that it involves harvesting the ITA and performing anastomosis to the LAD and other targets endoscopically or through a small incision, thereby reducing surgical trauma and potentially shortening recovery times.[44–46] Ideal candidates include those with single-vessel LAD disease or those being considered for hybrid revascularization, as these patients can benefit from the less-invasive nature of the procedure, leading to faster recovery and fewer perioperative complications. A systematic review reported 0.8% perioperative mortality, 11.5% conversion to larger incisions, and reduction in the morbidity associated with conventional surgical trauma.[44] High-graft patency was also reported (97.7% at < 1 month, 96.1% at < 5 years, and 93.2% at > 5 years).[45]

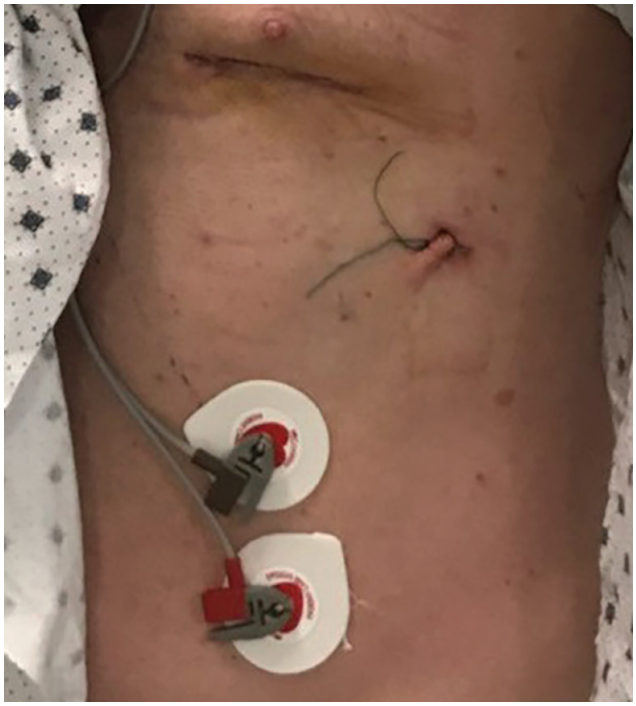

Figure 1. Surgical incision site located on the left anterior chest wall following a small thoracotomy for minimally invasive coronary artery bypass grafting. An accompanying chest drain incision site is seen inferolaterally.

Despite these promising results, robotic CABG is only available to a small proportion of surgical candidates at highly specialized centers. It accounts for only about 1% of total CABG procedures in the United States due to high costs, longer operative time, and the need for specialized training.[46] However, its use is likely to increase with greater procedural experience and wider availability.

Hybrid revascularization combines grafting the LAD with the left ITA using CABG (preferably MICS or robotic CABG) and PCI of non-LAD coronary stenoses.[47] The rationale includes the survival advantage of the left ITA-to-LAD graft, benefits of avoiding cardiopulmonary bypass and sternotomy, and restenosis rates of PCI-treated, non-LAD vessels comparable to occlusion rates of saphenous vein grafts. Limited data suggest hybrid revascularization offers durability,

symptom relief, and survival benefits over triple-vessel stenting, but may result in higher repeat revascularization rates in PCI-treated vessels.

In summary, minimally invasive techniques are promising but are limited to specialized centers. Further research is warranted to evaluate long-term outcomes and identify optimal patient selection for each technique.

Intraoperative management

The evolution of cardiopulmonary bypass has centered on enhancing biocompatibility and reducing hemodilution, leading to significant advances over prior cardiopulmonary bypass setups.[48] These newer systems provide considerable clinical benefits, such as significant reduction in postoperative atrial fibrillation, enhanced renal and myocardial protection, decreased systemic inflammatory responses, reduced cerebral gaseous microembolization, and better preservation of end-organ function. Concurrently, cardioplegia administration, using high-dose potassium to induce depolarized cardiac arrest, is essential to protect myocardial function and prevent ischemic damage during cardiopulmonary bypass. Cold potassium cardioplegia is used most often and has proven effective even in cases of severe ischemic cardiomyopathy.

Epiaortic ultrasonography and computed tomography are valuable tools for screening select patients for major atherosclerosis and calcifications in the ascending aorta. These methods greatly influence intraoperative management by allowing adjustments in the location of the aortic cannula to reduce the risk of atheroembolization. Additionally, specialized cannulas are used to minimize the risk of perioperative stroke or aortic dissection by reducing dislodgement of atheromatous debris during aortic manipulation.

Cerebral monitoring tools like near-infrared spectroscopy and electroencephalographic-based anesthesia depth monitoring are integrated to detect and manage potential neurologic complications, with ongoing research of their effectiveness.[48] Furthermore, transit time flow measurement serves as an essential intraoperative quality control measure, confirming graft patency and thereby enhancing both short- and long-term outcomes of CABG.

These developments highlight the continuous evolution of the CABG procedure and the optimization of surgical outcomes.

OUTCOMES CONTINUE TO IMPROVE

CABG is a safe procedure, with national in-hospital mortality below 2.1%, operative mortality below 2.7%, and centers of excellence maintaining operative mortality less than 1% for more than a decade.[5,49] These outcomes are consistent with global trends. Recent attention has been given to improving perioperative outcomes, which has driven differences between contemporary and early comparisons of CABG and PCI and has impacted early- and long-term mortality. In the FAME 3 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial,[22] 30-day mortality for CABG was 0.3%, identical to that of PCI[14] and 10 times less than what was reported in earlier trials.

Of all consecutively enrolled patients eligible for CABG (n = 153,208) documented in the Society of Thoracic Surgeons Adult Cardiac Surgery Database in 2021, including patients who underwent emergency and salvage CABG, the following major morbidities were reported: reoperation, 2.6%; deep sternal wound infection or mediastinitis, 0.8%; permanent stroke, 1.5%; prolonged ventilation (> 24 hours), 6.7%; renal failure (defined as a 3-fold increase in serum creatinine, serum creatinine > 4 mg/dL, or initiation of dialysis), 2.2%; new-onset atrial fibrillation, 26%; 30-day readmission, 9.1%; and postoperative hospital length of stay, 6 days (range 4–7).[5] Outcomes have improved over time, and centers of excellence are able to offer CABG with low morbidity and mortality despite referrals of older and sicker patients.

IMPORTANCE OF MEDICAL THERAPY AS AN ADJUNCT TO CABG

Optimal medical therapy affects postoperative outcomes, and adherence is important. Statins lower the risk of readmissions and late mortality from myocardial infarction or stroke. Furthermore, the adoption of modern nonstatin agents is expected to further reduce the risk of major adverse cardiovascular events in high-risk patients.[50]

The optimal antithrombotic therapy regimen after CABG is a topic of ongoing research. A recent meta-analysis of 38 studies involving 77,447 patients aimed to evaluate efficacy and risks of different antiplatelet regimens after CABG.[51] It compared dual antiplatelet therapy (DAPT) with single antiplatelet therapy and DAPT with clopidogrel vs DAPT with ticagrelor or prasugrel. The analysis demonstrated that, while DAPT is superior to single antiplatelet therapy in reducing mortality and major adverse events, it increases bleeding risks. Notably, DAPT with ticagrelor or prasugrel was found to be more effective than DAPT with clopidogrel in reducing mortality without affecting other outcomes. These findings suggest a need for personalized antiplatelet regimens after CABG based on individual risk profiles.

Guideline-directed medical therapy is critical in patients with reduced ejection fraction to enhance cardiac function, improve quality of life, and prevent further complications. This therapy includes renin-angiotensin-aldosterone system antagonists, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors.[52]

Last, starting and reinforcing other secondary prevention measures, including lifestyle changes, after CABG surgery are recommended.[8] Such measures include cardiac rehabilitation programs, personalized diet and exercise plans, and aggressive management of risk factors such as hypertension, diabetes, smoking, and chronic kidney disease. These changes, augmented by optimal medical therapies, help maintain long-term graft patency, enhance quality of life, and improve long-term prognosis.

FUTURE DIRECTIONS

The future of CABG depends on removing barriers to adopting beneficial practices and broadening access. Addressing discrepancies between current guidelines and actual practice and expanding the use of multiarterial grafting strategies and minimally invasive techniques in carefully selected patients are key. The clear volume-outcome relationships, especially with multiarterial grafting strategies, indicate a rapidly approaching era of coronary subspecialization.[53,54] Additionally, enhanced recovery protocols involving multidisciplinary teamwork, best practices implementation, continuous audits, and change readiness can accelerate recovery, shorten hospital length of stay, lower costs, and potentially increase survival rates.[55]

The public reporting scorecard needs revision to more accurately capture the scope and complexity of cardiac surgery practices, encouraging more hospitals to adopt best practices while minimizing risk aversion.[56] Accordingly, the American Association for Thoracic Surgery Quality Gateway aims to efficiently address gaps in outcomes reporting and quality assurance. By using advanced machine learning algorithms and high-performance computing, the American Association for Thoracic Surgery Quality Gateway provides real-time, risk-adjusted outcome predictions for all types of cardiac surgery, regardless of complexity, with lean data collection.[57]

Addressing disparities in access to CABG is also paramount. Current inequalities in healthcare call for strategies to make CABG more available and affordable, particularly in developing nations. This includes training local surgeons in advanced techniques, improving local healthcare infrastructures, and establishing collaborations with international cardiac surgery centers.[58] These factors will improve the care of many more patients requiring CABG.

In 2021, guidelines for CABG in patients with ischemic cardiomyopathy and heart failure were issued by the American Association for Thoracic Surgery expert consensus group.[52] They recommended a structured approach to revascularization, including use of mechanical cardiac support when necessary. The guidelines noted a lack of high-level evidence and emphasized the need for future research, particularly in optimizing perioperative mechanical cardiac support use, including right ventricular support, in this high-risk population.

Future research should prioritize optimizing treatment approaches for older patients, particularly because frailty is not currently integrated into risk-scoring models.

Last, newer medical therapies hold promise for stabilizing atherosclerotic lesions in the native coronary arteries, potentially improving long-term patency of bypass grafts.

TAKE-HOME MESSAGE

CABG remains the standard of care for patients with complex multivessel disease, left main coronary artery disease, diabetes, or left ventricular systolic dysfunction, offering durable long-term symptomatic relief and survival. PCI is a valuable alternative for poor surgical candidates and those with less extensive coronary lesions. Multiarterial grafting promises to maximize longevity, and less-invasive approaches have been developed. Ultimately, it is important for the collaborative multidisciplinary heart team to weigh the risks and benefits of each option for the individual patient to provide the best outcome.

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