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A useful gap

Disseminated varicella zoster

Masked tinea

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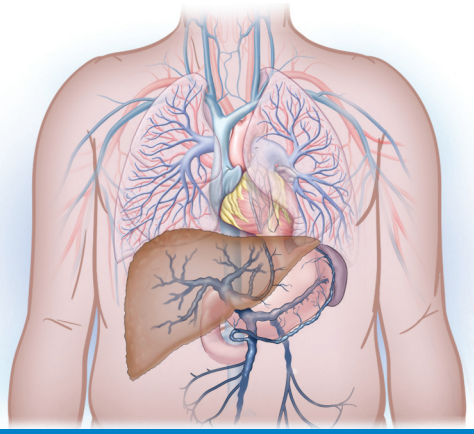

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A useful gap

We look initially at laboratory test results with specific intent, checking for major items of concern, alterations in organ function, side effects of medications, or monitoring of drug efficacy. Many results are straightforward, such as measures of blood cell production, kidney or thyroid function, and liver or muscle injury. There are also some derived subtleties included in routine laboratory reports that help put other test results in perspective, such as the red blood cell distribution width when evaluating the cause of anemia.[1] Looking at some of these derived "subtleties" can tip off clinicians to the presence of inapparent or subtle systemic pathophysiology, prompting additional focused laboratory investigations. The anion gap (AG) is a derived numeric that appears routinely on electrolyte lab reports, and I suspect is not routinely glanced at unless there is concern for an acid-base disturbance.

I trained in a nephrocentric internal medicine residency program, more specifically in a program that strongly emphasized the evaluation of acid-base and electrolyte status of every patient. I would characterize the AG for us in the 1980s as a "fifth vital sign" in the context of virtually every academic patient presentation. The lasting impact of that training struck a chord decades later, while I was teaching at a small hospital in Japan. In this hospital, they did not routinely order electrolyte panels. Sodium, bicarbonate, creatinine, and others had to be individually requested. The AG was not a vital sign, it was not even on the residents' minds as a uniformly useful tool. One day when discussing a patient with renal disease, Sjögren syndrome, and joint pain, we pursued the explanation for a low potassium. This led to finding a low bicarbonate and to a discussion on how to distinguish causes of acidosis. This launched us into doing daily discussions of acid-base problems, including the value of the AG.

I, a rheumatologist, remain amused decades later at the educational staying power of my residency training experience that permitted me to facilitate those discussions. There is little question in my mind that every one of my resident peers would still be equally comfortable in those teaching sessions. It is a striking example of how the internal culture and peer-driven expectations of a residency training program can exert a lasting impact on its graduates.

I am not certain of when the concept of the AG became inculcated into clinical practice. Many authors have cited as seminal the lectures of James Gamble,[2] although these are now long out of print and hard to find. His "Gamblegrams" illustrated the components of serum electroneutrality and the diagnostic value of monitoring the homeostatic changes that accompany metabolic perturbations. Our conceptual knowledge "bible" as medicine residents included the multiple writings of Emmett and Narins[3] and Gabow et al,[4] which were supplemented by the real-time teaching of our University of Pennsylvania faculty and the residency class the year ahead of us. It was an implicit expectation that we would pass this knowledge on to the next residency class, with the expectation of its full comprehension and practical implementation at residents' morning reports and in their clinical notes and daily presentations. Such was the culture of our training.

In routine laboratory assessment, not all cations and anions are measured. But by measuring Na^+, Cl^-, and bicarbonate, we account for 95% of cations and 85% of anions. The arithmetic difference between the 5% and 15% of those unmeasured charged molecules is the anion gap, and it is generally defined as between 3 and 9 mEq/L (with an estimated fluctuation in a given person of approximately 4). The AG taken in the context of the bicarbonate provides a window to detecting a change in the makeup of charged small molecules and (mainly) proteins. When the AG is

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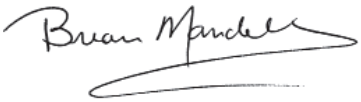
significantly elevated, it suggests the presence of an organic acidosis, even when the pH is normal. It can also be mildly elevated in the setting of a primary metabolic alkalosis due to increased lactate generation, and markedly elevated due to ingestion of exogenous anionic compounds.

In this issue of the *Journal*, Haber et al[5] review a less commonly discussed aspect of the AG, the significance of a low value. Apart from its value in teasing out the cause of an acid-base disturbance when elevated, a very low AG suggests a laboratory measurement error, or provides a clue to several possible clinically important protein abnormalities or ingestions that warrant specific investigation.



Brian F. Mandell, MD, PhD
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2023

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MEDICAL DERMATOLOGY THERAPY UPDATE III
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A new paradigm for adult ADHD

To the Editor: Adults with attention deficit hyperactivity disorder (ADHD) experience sustained attention deficits manifested with accompanying difficulties completing tasks.[1,2] While ADHD symptoms cause significant impairment, many affected adults remain untreated.[1] Efforts to improve recognition and management include the development of ADHD symptom scales for screening and treatment monitoring of these patients.[1]

In the recent commentary by Drs. Manos and Short,[2] task incompletion is regarded as the primary dysfunction in adults. Accordingly, the authors suggest that task completion should be used as a measure to track pharmacologic therapy response in these patients. This is conceptually plausible since several adult ADHD diagnostic criteria relate to task completion, eg, "reluctance to start or to persist with tasks requiring sustained mental effort."[3] Clinical assessments to help evaluate task completion difficulties include the use of continuous performance tests (CPTs), which can measure attention and require the individual to respond to targets (a measure of attention) and to inhibit response to non-targets (a measure of impulsivity).[4]

Marchetta et al[5] found a deterioration of time-on-task in adults with ADHD relative to controls. Babajanyan et al[3] noted 3 patterns that decreased task completion. These patterns included complete lapses in attention, partial attention to a task, and engaging in multiple tasks. However, disagreement exists on whether the ability to stay on task as measured by CPTs can accurately reflect the severity of ADHD. Baggio et al[6] examined CPTs as a marker of adult ADHD presentation and severity and reported small correlations between CPT variables and ADHD symptoms determined by a clinical interview: 51.7% of the sample were classified as likely to have ADHD by CPTs. The classification error was 80.3% for the inattentive subtype and 22.5% for the hyperactive subtype.[6]

While the utility of CPTs to assess or monitor ADHD in adults appears limited, task completion itself may be a more suitable clinical measure. However, this remains to be empirically demonstrated in reliability and validity studies before it can be widely implemented in clinical settings.

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Samantha Frigon
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To the Editor: In the July issue, Drs. Manos and Short[1] presented a new model through which to treat and determine efficacy of treatment for adult ADHD. I'd like to thank the authors for sharing a fresh lens into the clinical practice of this disorder. Their emphasis on using task completion as the unit of measurement in determining effectiveness of treatment, as well as strategies to write out a formal plan through which to delegate and complete tasks, was of note. I'd like to offer two suggestions.

First, while stimulants are widely regarded as the first-line treatment for adult ADHD,[2] I'd be remiss not to bring non-stimulant dopaminergics, such as atomoxetine and bupropion, into the conversation. In one study, only standard-dose atomoxetine resulted in moderate significant improvements vs placebo when assessing individual ADHD pharmacotherapies as a continuous measure,[2] while in another study, bupropion was found to significantly decrease ADHD rating scales by greater than or equal to 30% compared with placebo.[3] I believe these agents should also be considered prime candidates for the treatment of adult ADHD, especially for patients who tolerate amphetamines poorly or are at high risk for developing or relapsing into a substance use disorder.[2]

The recommendation of social scaffolding assumes the patient has access to the same variety of conveniences afforded to the likes of business executives with assistants and administrative offices tailoring their daily lives. A more accessible avenue for accountability would be to engage regularly with peer support groups. Peer support benefits include increased self-efficacy, enhanced coping strategies, and reduced social isolation.[4] A meta-analysis of 28 randomized controlled trials showed peer support outcomes for a range of mental illnesses significantly improved measures of psychiatric symptoms and measures of personal agency, self-esteem, and self-management of difficulties.[5]

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In Reply: The two reactions to our paper on adult ADHD were insightful. Both speak to two important issues that we highlighted in our article. The first issue, the problem of task incompletions, which we note as the central concern for adults with ADHD, is both a useful indicator of response to treatment and a helpful diagnostic measure. This issue is one that can be easily assessed in the clinical diagnostic interview. As noted by Frigon and Dr. Modesto-Lowe, the challenge is to establish a reliable and valid measure that captures the depth and significance of the problems that manifest as a consistent pattern of task incompletions. At present, there is no measure that captures the chaos in functional daily living that we identify as central to ADHD dysfunction. Thus, the best strategy to gather this information is a straightforward, in-depth, clinical interview.

The comments by Uche Nkanginieme lend support to our position that social scaffolding can successfully overcome the challenges of adult ADHD. In addition, Nkanginieme rightfully acknowledges that most adults are not given the support afforded more privileged individuals, such as the chief executive officer of a corporation. Instead, partners, peers, supervisors, and others often chastise and criticize rather than support adults with ADHD who require social scaffolding to successfully complete tasks and responsibilities. This failure of systems support is counterproductive for adults with ADHD. If all members of a team are to be successful, it is possible to build a system of support for those members, to design fail-safe measures that assist even the weakest link. Entities can build such an infrastructure through coaching, as Nkanginieme recommends. Such action requires us to rethink how people work as a team, with multiple individuals serving the same goal and agreed end points.

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vOka vaccine-associated disseminated varicella zoster

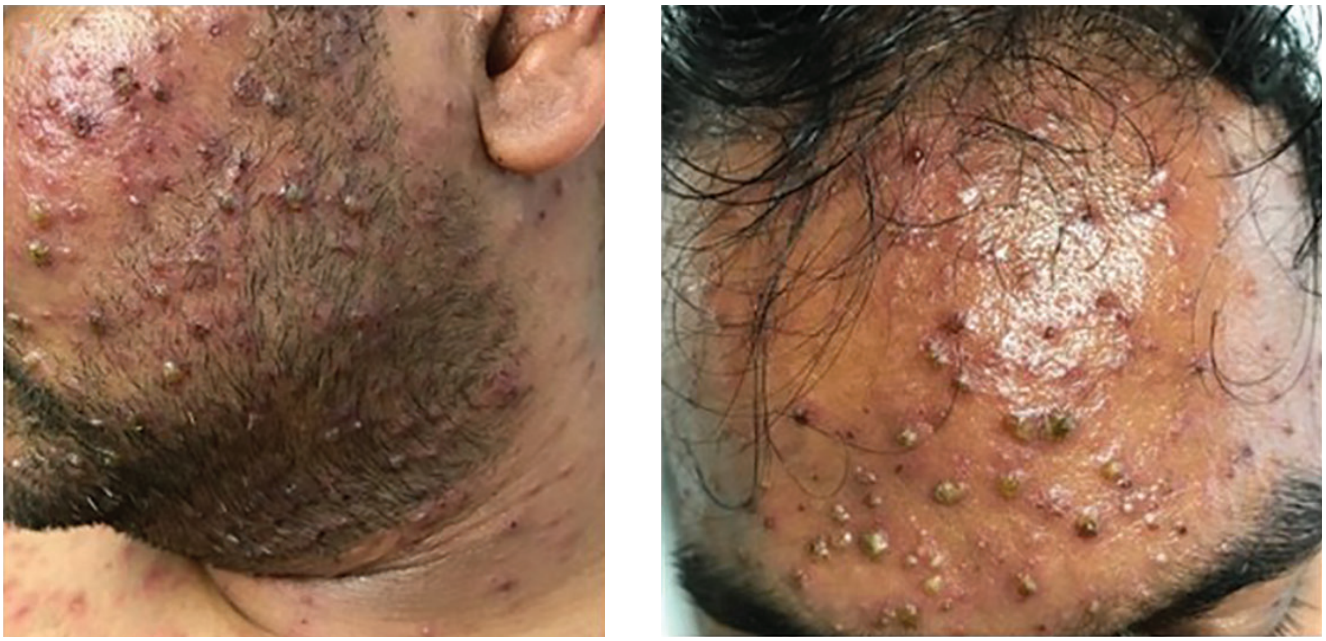

Figure 1. Diffuse vesicular lesions on the patient's face, forehead, and scalp at presentation.

A 34-year-old man presented to the emergency department with a 3-day history of rash, fever, diarrhea, and vomiting. He was being treated for seronegative rheumatoid arthritis with methotrexate 20 mg/week, prednisone 12 mg/day, and etanercept 50 mg/week. He said that 1 month prior he had received the live attenuated varicella vaccine (vOka) and that he had no previous history of varicella.

Physical examination revealed diffuse vesicular lesions, involving his entire torso, scalp, extremities, palms, soles, and hard palate (**Figure 1**). His temperature peaked at 41.1°C (105.9°F). Laboratory studies showed a hematocrit of 33% (reference range 39.5–50.2), thrombocytopenia with a platelet count of 51 × 10^9/L (141–377), an elevated aspartate aminotransferase of 185 U/L (15–46) an elevated alanine transaminase 234 U/L (< 50), and total bilirubin of 2.2 mg/dL (< 1.4).

Fluorescence resonance energy transfer polymerase chain reaction testing of fluid from an unroofed lesion identified vaccine-strain varicella zoster virus (Kay Radford, US Centers for Disease Control and Prevention, email, August 31, 2021). His skin lesions and laboratory abnormalities improved with intravenous acyclovir, though he was left with residual scarring. The improvements occurred over the course of about 7 days, with full healing requiring weeks.

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The differential diagnosis for diffuse vesicular lesions is broad, with most etiologies being immunologic conditions. However, associated infections include varicella, disseminated herpes simplex, eczema herpeticum, echovirus, coxsackievirus, and orthopoxviruses, including the mpox virus.[1]

Worldwide, more than 150 million doses of varicella vaccine have been distributed since its licensure in 1995.[2] Most adverse events after varicella vaccination are mild and consist of transient rashes, local reactions, or transient low-grade fever. Serious adverse events are infrequently reported (approximately 1 report per 100,000 doses from 2006 to 2020), and laboratory-confirmed cases of vaccine-associated varicella zoster, meningitis, and encephalitis have been rarely reported.[3]

Disseminated varicella zoster after vaccination with the live attenuated varicella vaccine is a serious and very rare complication, though it generally responds to antiviral therapy. However, over the past 25 years, 6 fatalities caused by vOka have been documented, all occurring in children or adults with immunodeficiency.[2]

The 2022 American College of Rheumatology guidelines for vaccination in patients with rheumatic and musculoskeletal diseases provide guidance on holding immunosuppressive medications and delaying vaccine.[4] The recommendations in our patient's case suggest that the methotrexate and prednisone should have been held 4 weeks before and after vaccination, and that the etanercept dose should have been deferred 1 week before and for 4 weeks after vaccination.[4] A report from the Infectious Disease Society of America highlights the importance of avoiding live attenuated varicella vaccine in highly immunocompromised patients when possible and of pausing the use of immunosuppressive therapies in patients who merit such vaccinations.[5]

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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Masked tinea

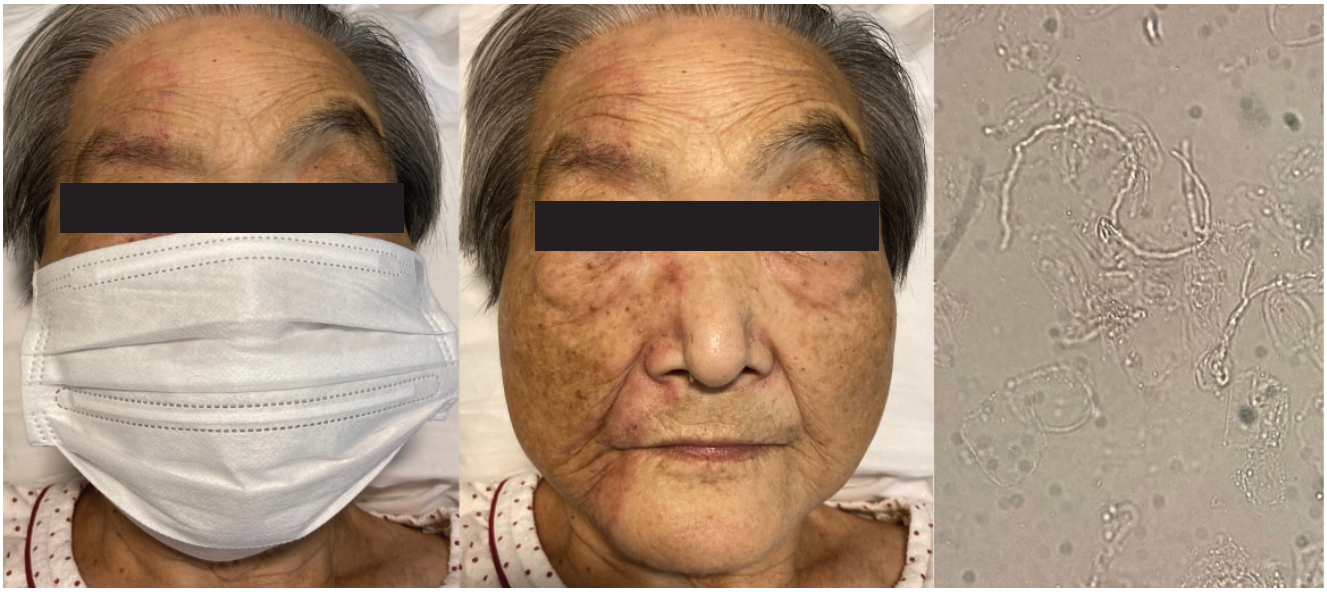

Figure 1. During her hospitalization for rehabilitation, the patient was masked. On hospital day 22, she complained of itching on her face. Removal of the mask revealed erythema on the right side of her face. Analysis of the lesions with potassium hydroxide confirmed tinea faciei.

A 91-year-old woman was admitted to the hospital with a 1-month history of anorexia. On admission, there were no significant abnormal findings, including in the face and mouth. She had been taking colchicine for gout, and this medication was suspected as the cause of anorexia. Colchicine was thus discontinued, her anorexia rapidly improved, and her hospitalization continued for rehabilitation. She wore a mask during this time.

On day 22 of hospitalization, the patient complained of itching on the face. Therefore, we asked her to remove her mask for examination. On removal of the mask, we noted a painless rash that extended from the forehead to the mandible on the right side of her face. The rash had well-defined borders, with small eczematous lesions at the margins and fine scaling (**Figure 1**). Differential diagnoses such as cellulitis, herpes zoster, seborrheic dermatitis, or contact dermatitis were ruled out because the lesions were painless, without blisters, and with distinct borders.

Microscopic study of a lesion preparation using potassium hydroxide showed tinea faciei, a filamentous fungal infection (**Figure 1**). She also had tinea pedis on both feet. Topical terbinafine ointment was prescribed, and the lesions improved within 2 months.

TINEA AND MASKS

Our patient's tinea faciei was likely attributable to her wearing a mask every day for almost the entire day, in addition to her touching her feet and face. Prolonged mask-wearing has been reported to be a risk factor for

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facial dermatitis[1] and may trigger skin temperature elevation, sweating, and irritation, which could result in the development of tinea faciei.[2]

To prevent tinea faciei, changing the face mask daily, avoiding wearing a mask continuously more than 6 hours a day, and washing the face and hands may be recommended based on a previous report.[2]

The diagnosis in our patient was delayed because large areas of tinea faciei were hidden by the patient's mask. Indeed, mask-related diagnostic delays have been reported in cases of facial dermatologic diseases such as facial skin tumors.[3,4] In particular, hospitalized patients would seem at high risk for delayed diagnosis of facial skin problems since medical staff rarely ask patients to remove their masks during rounds.

Lesions on the patient's forehead could have been detected earlier, as the mask did not cover the forehead. However, physicians did not recognize the lesions, perhaps because of cognitive bias based on a low suspicion for the development of tinea faciei, but also perhaps because the yellow and dark skin color of the patient's face made recognition of the lesions more difficult.

Our patient's case should serve as an alert to pay more attention to facial skin problems that may not be visible because of masks, and to examine the patient's face without the mask. Scheduling regular head-to-bottom examination in patients hospitalized for long periods may help prevent this kind of infection.

DISCLOSURES

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should midodrine be used as an intravenous vasopressor-sparing agent in septic shock?

A 55-year-old male presents to the emergency department with dysuria, fevers, and chills. His temperature is 38.3°C (101.8°F), blood pressure 75/46 mm Hg, and heart rate 113 beats per minute. Laboratory test results show a white blood cell count of 17.0 × 10^9/L (reference range 4.5–11.0) and serum lactate 4 mmol/L (> 2). Urinalysis shows 50 to 100 white blood cells per high-power field (0–3), as well as nitrites and leukocyte esterase. He is given 3 L intravenous fluids and is started on intravenous meropenem. Two hours later, his blood pressure is 81/50 mm Hg. Should we use midodrine rather than an intravenous vasopressor (IVP) for blood pressure support in this patient with septic shock?

A: No. While some research suggests that midodrine may be used to wean down IVPs in select patients during the recovery phase of septic shock, there are no robust data to suggest that midodrine can be used to avoid or delay IVP therapy or intensive care unit (ICU) admission in patients with septic shock in intermediate-care or general medicine hospital units.

SEPTIC SHOCK

Septic shock is defined as "a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality,"[1] and is clinically recognized by persistent hypotension, hyperlactatemia (often serum lactate > 2 mmol/L), and the need for IVPs to maintain a mean arterial pressure (MAP) of 65 mm Hg or higher.[1]

The epidemiology of septic shock has been historically difficult to study, but studies have estimated that sepsis affects approximately 1.7 million adults annually in the United States and is present is 30% to 50% of hospitalizations that result in death.[2,3] Mortality rates for septic shock have been estimated to be at least as high as 41%.[4] Current standard-of-care treatment for septic shock includes fluid resuscitation, antimicrobials, IVPs to maintain an MAP of 65 or higher, and intravenous corticosteroids if there is an ongoing requirement for multiple vasopressors.[5]

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WHY ALL THE INTEREST IN MIDODRINE?

Many of the treatments for septic shock require a higher level of care and more frequent monitoring in the ICU, which results in increased use of healthcare resources and increased costs. Thus, hospitalists and intensivists have been interested in IVP-sparing therapies for septic shock to improve both clinical and economic outcomes. Midodrine, an oral alpha-1 adrenergic receptor agonist with US Food and Drug Administration approval for symptomatic hypotension, produces a predictable, dose-dependent increase in blood pressure.[6] Midodrine has favorable pharmacodynamic and pharmacokinetic characteristics, with rapid absorption following oral administration,[6] and approximately 93% bioavailability.[7] Additionally, side effects are minimal, most notably paresthesia, piloerection, shivering, bradycardia, and urinary retention.[8]

WHAT DO THE DATA SHOW?

Only a few studies have addressed our question. A placebo-controlled, double-blind, randomized pilot trial conducted in 2 medical ICUs recruited adult patients hospitalized with sepsis who had an MAP of less than

TABLE 1
Studies of midodrine in the treatment of septic shock

Authors	Study design	Patient population	Outcomes
Lal et al[9]	Pilot, placebo-controlled, double-blind, randomized trial	Adult medical ICU patients hospitalized with sepsis; mean arterial pressure < 70 mm Hg despite sepsis treatment	Decreased duration of IVPs (P = .19) Decreased total IVP requirement (P = .59) Shorter ICU length of stay (P = .36) Similar hospital length of stay (P = .41)
Whitson et al[7]	Single-center retrospective cohort study	Patients hospitalized with septic shock requiring at least 24 hours of IVPs who demonstrated a period of clinical stability	Decreased IVP duration (P < .001) Decreased ICU length of stay (P = .017) Reduction in total IVP days and ICU patient days over year of study
Adly et al[10]	Single-center retrospective control study	Resuscitated patients with septic shock who demonstrated clinical stability on low-dose IVP for at least 24 hours	Reduced IVP (norepinephrine) duration (P = .001) Shorter IVP weaning period in septic shock recovery phase (P < .001) Decreased mortality (43.3% vs 73.3%, P = .018)
Santer et al[11]	Randomized, double-blind, placebo-controlled trial	Hypotensive adult patients on single-agent IVP unable to be weaned from IVPs for at least 24 hours	No difference in time to IVP discontinuation (23.5 vs 22.5, P = .62) No difference in ICU length of stay (6 days vs 6 days, P = .46) No difference in time to ICU discharge readiness (5 days vs 5 days, P = .64) No difference in ICU readmission rate (1.5% vs 4.5%, P = .62) Increased rates of bradycardia (7.6% vs 0%)

ICU = intensive care unit; IVP = intravenous vasopressor

70 mm Hg despite receiving antibiotics and sepsis-dose fluids (30 mL/kg crystalloids).[9] Patients in the intervention group (n = 17) received a total of 3 doses of oral midodrine 10 mg every 8 hours in addition to the usual sepsis care, including subsequent initiation of IVPs. The study reported a decreased median duration of IVPs in the midodrine group, decreased total IVP requirement in the first 24 hours of ICU stay, and shorter ICU length of stay when compared with the standard-of-care cohort.[9]

The results of the study were not significant, but the study was not powered to detect statistically significant differences between the groups. Thus, it could not be concluded that midodrine can be used in early treatment of septic shock or that it is associated with improved outcomes. However, the study did prove the feasibility of conducting a large clinical trial to study the use of oral midodrine in early sepsis.[9]

Whitson et al[7] investigated a similar clinical scenario and conducted a single-center retrospective cohort study to describe the feasibility and utility of oral midodrine to replace IVPs in the recovery phase of septic shock. The investigators identified patients admitted with septic shock who had already received at least 24 hours of IVPs and were demonstrating clinical stability as evidenced by stable or decreasing doses of IVPs. The clinical team administered midodrine concurrently with IVPs in select patients, and doses of midodrine were incrementally increased until IVPs were no longer needed. Importantly, the administration, dosing, and tapering of midodrine were made on an individual-patient basis and were not protocol-driven. In the patients who received midodrine with IVPs, the study found a 24% decrease in IVP duration and a 20% decrease in ICU length of stay, as well as a reduction of 121.5 total IVP days and 222.3 ICU patient days over the year that the study lasted.[7]

Adly et al[10] similarly conducted a prospective controlled study in septic shock patients who demonstrated clinical stability on low-dose IVPs for at least

24 hours.[10] Select patients were randomized to receive midodrine 10 mg three times daily in addition to IVPs, and the investigators reported decreased IVP duration, shorter IVP weaning time, and decreased mortality risk in the intervention group.[10] However, this study was unblinded and did not have enough power to detect a true difference with the use of midodrine.

The MIDAS (Effect of Midodrine vs Placebo on Time to Vasopressor Discontinuation in Patients With Persistent Hypotension in the Intensive Care Unit) trial[11] is the largest randomized clinical trial to date investigating midodrine as an adjunct to standard treatment in shortening the duration of IVP requirement for patients with vasodilatory shock in the ICU. This study recruited 132 hypotensive adult patients on single-agent IVP treatment who were unable to be weaned from IVPs for at least 24 hours; 66 patients received oral midodrine every 8 hours in addition to standard of care treatment. The investigators found no significant difference between the intervention and placebo groups in time to discontinuation of IVPs, time to ICU discharge readiness, or ICU or hospital length of stay. Bradycardia was an adverse event significantly more common in the midodrine group.[11]

Table 1 summarizes findings of the studies discussed here.[7,9,10,11]

THE BOTTOM LINE

Research and robust data are lacking regarding the use of midodrine as an adjunctive IVP-sparing treatment option in septic shock. Most studies have evaluated midodrine in the recovery phase of shock. A major limitation of many of these studies is that midodrine was administered every 8 hours, while its half-life is shorter at 3 to 4 hours, resulting in large swings in plasma concentrations of the medication and limiting confidence in these trials, both positive and negative.

Though midodrine has few side effects and is relatively safe, it should not be used in septic shock treatment to delay ICU admission or IVP initiation. Oral midodrine may be used to wean IVPs in select patients with septic shock already in the ICU, though the characteristics of patients who may benefit from midodrine are not quite clear. There is no definitive evidence that midodrine is effective for the treatment of hypotension in critically ill patients.

DISCLOSURES

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should I start an SGLT-2 inhibitor in my patient with heart failure and chronic kidney disease?

A 57-year-old male is admitted to the cardiology inpatient service for acute decompensated heart failure. He has a history of heart failure with reduced ejection fraction (HFrEF) with a left ventricular ejection fraction of 35% and stage 4 chronic kidney disease (CKD). His estimated glomerular filtration rate (eGFR) is 27 mL/min/1.73m^2. Should I start him on a sodium-glucose cotransporter 2 (SGLT-2) inhibitor?

A: Large-scale trials have demonstrated the beneficial impacts of SGLT-2 inhibitors in patients with CKD and heart failure, and thus they should be utilized with the goal of rendering renoprotective and cardiovascular benefits. The potential risks and benefits must be weighed, and patients should be monitored closely for adverse events and significant changes in renal function.

Heart failure and CKD are both increasing in prevalence globally, corresponding with an aging patient population with shared comorbidities. These 2 medical conditions are seen commonly in the primary care, cardiology, and nephrology settings, and they often co-exist.[1] They have complex interactions, with progression of kidney disease increasing the risk of major adverse cardiovascular events.[1] Moreover, patients with both heart failure and CKD have a significantly increased morbidity and mortality risk, with previously limited treatment options. With the emergence of new medications to treat HFrEF, it is necessary to critically evaluate the data regarding these medications in patients with additional medical comorbidities.

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WHAT ARE THE CARDIOVASCULAR AND RENAL BENEFITS OF SGLT-2 INHIBITORS?

Initial trials first detailed the beneficial impact of SGLT-2 inhibitors in patients with type 2 diabetes mellitus, demonstrating their ability to reduce heart failure hospitalizations.[2] Additional studies, including the landmark Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial,[3] expanded on these findings by evaluating SGLT-2 inhibitors in patients with confirmed HFrEF, regardless of the presence or absence of diabetes. The trial showed that patients with HFrEF had a lower risk of worsening heart failure or death from any cardiovascular cause when compared with placebo,[3] and this was validated in patients with more advanced HFrEF in the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction.[4] More recently, trials evaluating SGLT-2 inhibitors in patients with heart failure with preserved ejection fraction have demonstrated a reduction in cardiovascular deaths or hospitalizations for heart failure compared with placebo, thus improving the armamentarium for clinicians in this difficult to treat disease.[5]

These studies suggested possible beneficial effects of SGLT-2 inhibitors on progression of renal dysfunction in addition to a positive impact in patients with heart failure, but did not specifically evaluate SGLT-2 inhibitors in patients with CKD. Consequently, these drugs are often used conservatively in patients with impaired renal function. Further studies explored the

renoprotective effects of SGLT-2 inhibitors, including a meta-analysis that evaluated 3 separate trials and more than 34,000 patients and showed that SGLT-2 inhibitors reduced progression of renal disease by 45%.[6] This reduction in progression of renal disease was demonstrated irrespective of the presence of known atherosclerotic cardiovascular disease, indicating direct renal protection by SGLT-2 inhibitors.[6]

WHAT eGFR IS VALIDATED FOR SGLT-2 INHIBITORS IN CHRONIC KIDNEY DISEASE?

The recent Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY)[7] further evaluated SGLT-2 inhibitors in patients with CKD. This trial included patients with an eGFR between 20 and 45 mL/min/1.73m^2 regardless of the degree of albuminuria, or patients with an eGFR between 45 and 90 and a urinary albumin-to-creatinine ratio of at least 200. Primary outcomes included progression to end-stage renal disease (ie, initiation of dialysis or transplant), death from renal causes, sustained decline in eGFR of 40% or greater, or cardiovascular death. The trial showed a 28% lower risk of progression of kidney disease or cardiovascular death in patients taking empagliflozin vs placebo.[7]

In the context of these data, the 57-year-old male in our scenario should be placed on an SGLT-2 inhibitor. He is within the eGFR range of the study population included in EMPA-KIDNEY[7] and would likely benefit from an SGLT-2 inhibitor from both a cardiovascular and a renoprotective standpoint.

WHAT IS THE UNDERLYING MECHANISM OF ACTION OF SGLT-2 INHIBITORS?

Clinicians and researchers alike are encouraged by the prospect of revolutionizing the management of comorbid cardiovascular disease, CKD, and diabetes, while simultaneously hypothesizing about the pathophysiologic mechanism of their pleiotropic effects. SGLT-2 inhibitors block sodium and glucose reabsorption in the proximal tubule, thereby increasing the delivery of sodium to the distal tubule and downregulating the renin-angiotensin-aldosterone system.[8] This increased delivery of sodium to the macula densa (ie, natriuresis) activates tubuloglomerular feedback, thus reducing single nephron filtration and opposing glomerular hyperfiltration via afferent arteriole vasoconstriction.[8] This initial reduction in glomerular hyperfiltration has been postulated to lead to long-term preservation of kidney structure and function and to a lower risk of kidney disease progression.

WHEN SHOULD A CLINICIAN INITIATE SGLT-2 INHIBITORS?

While SGLT-2 inhibitors had historically been started in the outpatient setting, the Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized trial[9] evaluated the effects of starting empagliflozin in patients admitted with acute heart failure and found a statistically significant benefit in terms of symptomatic improvement, death from any cause, and heart failure events, and the benefit persisted months after randomization.

When initiating SGLT-2 inhibitors, clinicians must keep in mind that these medications have not been validated in patients with end-stage renal disease (eGFR < 15), those on dialysis, or those with previous renal transplant. While diuresis is not the predominant mechanism of SGLT-2 inhibitors in improving cardiovascular outcomes, adjustment of concomitant diuretic therapy may often be needed after starting SGLT-2 inhibitors.

The most commonly prescribed SGLT-2 inhibitors include empagliflozin (starting dose 10 mg daily), dapagliflozin (starting dose 5 mg daily), and canagliflozin (starting dose 100 mg daily). While some differences were seen in studies of these drugs, their long-term outcomes have not been compared directly in randomized controlled trials.

WHAT ARE THE SIDE EFFECTS TO BE AWARE OF?

Clinicians should monitor patients for adverse effects including acute kidney injury, euglycemic ketoacidosis, hyperkalemia, urinary tract infection, hypotension, dehydration, risk factors for lower-limb amputation (seen specifically with canagliflozin), Fournier gangrene, and volume depletion.[10] Clinicians should note that after initiation of SGLT-2 inhibitors, there is an acute, dose-dependent reduction in eGFR of about 5 mL/min/1.73m^2 in the first 2 to 4 weeks, similar to that seen with other classes of renin-angiotensin-aldosterone system inhibitors, and this reduction typically stabilizes thereafter. If such a drop in eGFR is noted, abruptly stopping these medications is not advisable, as patients may require time to benefit from SGLT-2 inhibitors. Patients can be followed with laboratory testing, and a basic metabolic panel should be obtained 2 to 4 weeks after starting an SGLT-2 inhibitor to monitor these parameters.

Overall, many large-scale trials have demonstrated the beneficial impacts of SGLT-2 inhibitors in patients with CKD and heart failure, and thus they should be used for their renoprotective and cardiovascular bene-

fits. The potential risks and benefits must be weighed, and patients should be monitored closely for adverse events and significant changes in renal function.

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should you use compression duplex ultrasonography to detect deep vein thrombosis to evaluate unexplained fevers?

An 84-year-old female was admitted for pyelonephritis complicated by septic shock and Klebsiella pneumoniae bacteremia. She was treated with antibiotics and she clinically improved. However, she later developed daily fevers with temperatures up to 39°C (102.2°F) with a negative repeat workup for infectious disease. Should you consider venous thromboembolism (VTE) as a potential cause of her fevers?

A: The hospitalized patient with unexplained fever is a commonly encountered diagnostic challenge. These patients constitute a heterogeneous group that shares broad differential diagnoses and often the need for extensive and expensive testing.

Venous thrombosis of the extremities has been traditionally taught to be a cause of occult fevers, and its diagnosis can be reliably made using a noninvasive test, compression duplex ultrasonography (CDUS). Hence, the use of CDUS in the workup of unexplained fever has increased despite the paucity of evidence on safety and cost-effectiveness in this clinical context.[1,2]

Although CDUS is essentially a risk-free procedure that can be performed on virtually any patient, clinical reasoning based on the outcome of this test could lead to substantial harm. The most important risks are stopping the diagnostic process prematurely if CDUS identifies an incidental thrombus, and the unlikely, but possible, risk of false-positive results leading to inappropriate anticoagulation therapy. Given these potential risks and the substantial financial cost associated with CDUS, ordering this as an initial test is not advisable. We reviewed the literature to provide clinicians with recommendations on when to order CDUS of the extremities in the evaluation of hospitalized patients with unexplained fever.

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VENOUS THROMBOEMBOLISM AND FEVERS: CAUSATION VS MERE ASSOCIATION?

Thrombosis involves endothelial activation and inflammation, which has been hypothesized to be pyrogenic.[3] However, VTE risk factors (eg, malignancy, infection, recent surgery, autoimmune diseases) are associated with fevers even in the absence of thrombosis, possibly acting as confounding variables in the association between VTE and fevers.[4,5] Hence, it is important to revisit the traditional teaching that venous thrombosis of the extremities causes fevers.

The association between VTE and fevers has been frequently described in case series. The estimated prevalence is highly variable and ranges between 4.9% and 33.3% in recent studies (**Table 1**).[6–11] This wide range is likely related to different temperature cutoffs, sites of measurement, measurement timing and frequency, scope of investigation (venous thrombosis of extremity alone vs pulmonary embolism), and the extent to which patients were evaluated for other causes of fevers before attributing the fever to VTE.

Despite the attempt to rule out alternative causes of fever in some series, the possibility of unidentified etiologies threatens the claim that thromboembolic events are causally related to fevers. Two studies emphasized this concern after finding similar temperatures in patients diagnosed with VTE and unmatched patients

TABLE 1
Fever characteristics in case series of VTE

Study	Sample size (n)	VTE site	Temperature for fever definition	Frequency of fever/ VTE-related fever [a]	Exclusion of other causes [b]	Fever grade
Barba et al, 2011[6]	14,814	DVT	≥ 38.0°C	4.9%	No	
Stein et al, 2000[7]	363	PE	≥ 37.8°C	26.2%/11.8%	Yes	> 38.9°C was seen in 1.4%
Saad et al, 2018[8]	245	PE	≥ 38.0°C	25.7%/24.1%	Yes	
Kazmers et al, 2000[9]	175	DVT	≥ 37.8°C	9.1%	No	> 38.3°C was seen in 4.6%
Calvo-Romero et al, 2004[10]	154	PE	≥ 37.0°C	18.2%/18.2%	Yes	> 39.0°C was seen in 0.6%
Kokturk et al, 2005[11]	117	PE	≥ 37.2°C	53.0%/33.3%	Yes	> 37.9°C and > 39°C were seen in 13.7% and 4.3%

[a]When no attempt was made to exclude alternative causes, only the total frequency of fever is listed.
[b]This was done in varied ways, including querying discharge documentation, review of culture/radiographic data, and careful review of the entire chart.

DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism

who had negative testing.[4,12] In a prospective study evaluating computed-tomography angiography, Stein et al reported temperatures greater than 38.5°C (101.3°F) in 2% of patients with both positive (n = 191) and negative (n = 632) testing for pulmonary embolism.[12]

In a study by Kazmers et al,[9] oral temperatures were measured in 1,847 patients referred for venous doppler ultrasonography of the lower extremities. Fever [defined as temperature > 37.8°C (100.4°F)] was present in 9.5% of the 175 patients diagnosed with acute deep vein thrombosis (DVT) and 7.5% of the remaining 1,678 patients. This difference was not statistically significant. When temperature was analyzed as a continuous variable, the authors detected a statistically significant but clinically small difference between patients with and without thrombosis (mean temperatures of 37.0 ± 0.6°C and 36.9 ± 0.6°C, respectively; $P < .02$).[9]

The main limitation of these studies is that the study groups may have differed in characteristics other than the presence of thrombosis. For example, patients referred for CDUS who did not have DVT may have had a higher rate of cellulitis as an alternative cause of their symptoms. Despite the limitations, the results of the study by Kazmers et al[9] suggest that body temperature may be elevated by acute thrombosis, though this seems to happen only to a mild degree or only in occasional patients, given the similar mean temperature across both groups.

YIELD OF COMPRESSION DUPLEX ULTRASONOGRAPHY IN EVALUATING UNEXPLAINED FEVERS

Two studies investigated the yield of venous doppler ultrasonography in patients being evaluated for unexplained fevers.[1,2] AbuRahma et al[2] retrospectively reviewed 89 patients undergoing a fever workup who had their lower extremities assessed for venous thrombosis. Acute DVT was diagnosed in 7 patients (7.9%), though only 5 patients (5.6%) met the study criteria to ascribe the fever to the thrombotic event.

Yoo et al[1] reviewed orders for 4-extremity venous Doppler ultrasonography in their vascular imaging laboratory. Out of 188 orders, 101 had fevers listed as the indication. Of these 101 orders, acute DVT was diagnosed in 11 patients (10.9%), though a more likely etiology for the fevers was found in 10 patients, leaving only 1 patient (1.0%) to have fever attributed to the DVT. These findings highlight the risk of premature closure if fever workup is terminated after identifying the presence of VTE.

UPPER-EXTREMITY COMPRESSION DUPLEX ULTRASONOGRAPHY

If CDUS is ordered to screen for DVT in patients with unexplained fevers in the absence of signs of venous thrombosis in any extremity, the question of which extremities to scan remains. In the study by

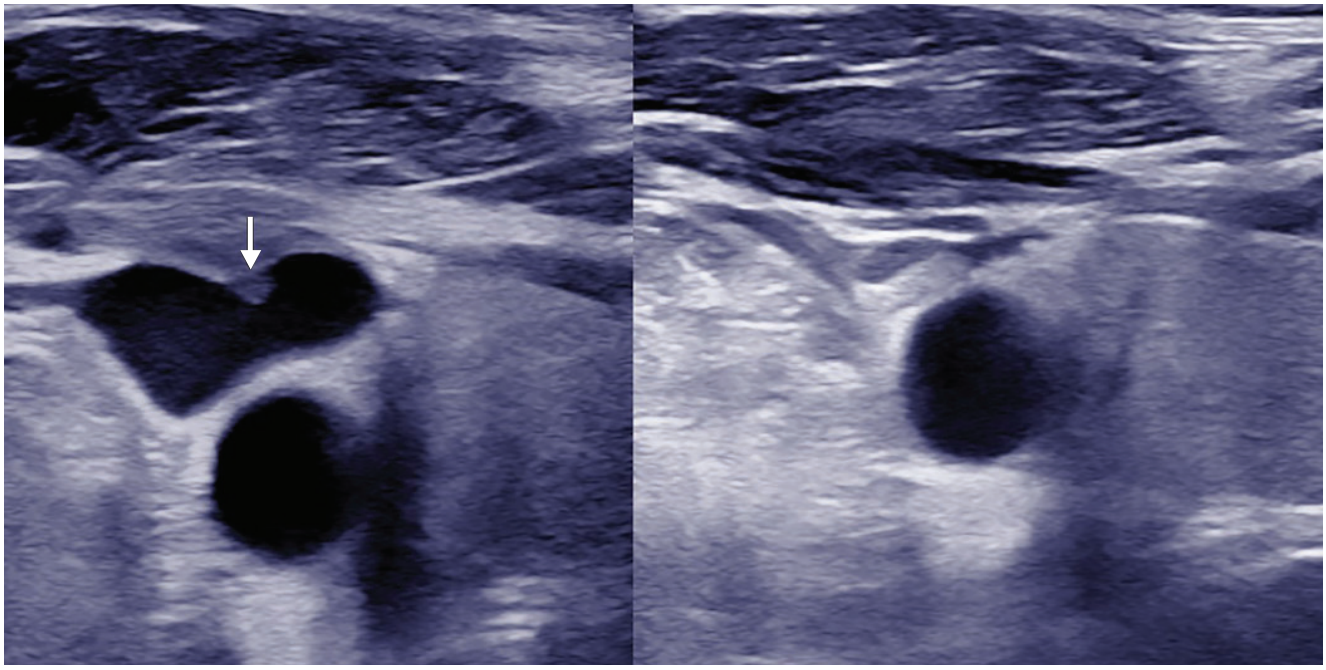

Figure 1. The left panel shows the right internal jugular vein with a scant amount of thrombus adherent to the anterior wall of the vessel (arrow). The right panel shows essentially complete compression of the right internal jugular vein on compression duplex ultrasonography.

Yoo et al,[1] which evaluated 188 orders for 4-extremity CDUS performed for various indications, 31 patients had acute DVT. Of the total number, 16 cases were only in the lower extremities, 11 were only in the upper extremities, and 4 were in both the upper and lower extremities. All 15 patients with upper-extremity DVT had a central venous catheter in place.[1] Furthermore, several studies suggest that central venous catheters and active cancer markedly increase the odds of upper-extremity DVT.[13,14] These findings suggest that upper-extremity Doppler ultrasonography in asymptomatic limbs should only be considered in individuals with increased pretest probability of upper-extremity thrombosis, such as those with an indwelling catheter or active cancer.

EVIDENCE SUMMARY

Overall, current evidence suggesting that VTE could cause fevers is weak, and in most cases where these two phenomena coincide, they are not causally related. Moreover, in the population presenting with unexplained fevers, the yield of venous Doppler ultrasonography is low. Hence, given the costs and potential harm associated with its use, we believe that venous Doppler ultrasonography should not be an initial test and should be ordered only when an exhaustive evaluation has been completed for more common causes of fever in the hospitalized patient. Caution should be taken before ascribing fevers to a venous thrombotic event. Lastly, when a decision has been made to use the test in asymptomatic extremities, we suggest scanning the lower extremities only, unless there are risk factors for upper-extremity venous thrombosis.

CASE CONTINUED

In our 84-year-old patient, CDUS was ordered and showed a small echogenic image suggestive of a venous thrombus where the patient had had an internal jugular vein catheter (**Figure 1**). Given the minuscule size of the thrombus and the presence of an alternative cause of the fever, ie, aspiration pneumonitis, the thrombus was thought to have been an incidental finding rather than the true cause of her fevers.

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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Inpatient glycemic management in noncritically ill patients: Updated guidelines

ABSTRACT

Hyperglycemia is common in hospitalized patients and is traditionally managed with scheduled and correctional doses of insulin. The authors present an overview of the latest (2022) guidelines from the Endocrine Society on inpatient hyperglycemia management in noncritically ill patients, which includes a role for newer diabetes technologies and nontraditional insulin and noninsulin therapies.

KEY POINTS

- The updated guidelines continue to endorse basal-bolus insulin as the preferred treatment for most noncritically ill hospitalized patients with hyperglycemia.
- Dipeptidyl peptidase 4 inhibitors with or without correctional insulin are now offered as alternatives in patients with mild hyperglycemia who do not have type 1 diabetes.
- For patients with type 1 or type 2 diabetes who have been using an insulin pump at home, the recommendations have changed to prefer continued use of insulin pumps and hybrid closed-loop pumps in the hospital.
- A new suggestion is the use of continuous glucose monitors in patients at risk of hypoglycemia, in addition to point-of-care blood glucose testing.

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Hyperglycemia, with or without underlying diabetes, affects nearly 40% of noncritically ill hospitalized patients.[1] Keeping blood glucose levels within a safe range can lower the risk of complications, infections, and death and shorten hospital stay. However, overly aggressive glucose control can lead to hypoglycemia, which has its own negative effects on health outcomes.

The Endocrine Society released guidelines for inpatient hyperglycemia management in 2012 for all inpatient healthcare professionals working in nonintensive care areas,[2] and updated them in 2022 to cover emerging diabetes technology, medications, and strategies to achieve glycemic control.[3]

WHO WROTE THE GUIDELINES?

A panel of 11 experts in endocrinology, internal medicine, primary care, nursing, pharmacy, and diabetes education and a patient representative collaborated to identify 10 key clinical questions, using the PICO format (patient or population, intervention, comparison, and outcome). A systematic review was conducted in July 2020 and updated in December 2021. Guidelines were developed using the GRADE method (grading of recommendations, assessment, development, and evaluation) to create 15 clinical recommendations.

WHAT ARE THE MAIN RECOMMENDATIONS?

The updated Endocrine Society guidelines[3] include the following key recommendations for adult patients who are hospitalized for noncritical illness:

Insulin therapy is preferred over noninsulin therapies in most hospitalized patients. In noncritical settings, the goal is to maintain glucose within the target range of 100 to 180 mg/dL.

Dipeptidyl peptidase 4 (DPP-4) inhibitors (gliptins) can be used in combination with correctional insulin or scheduled insulin therapy for select patients with well-controlled type 2 diabetes (hemoglobin A1c < 7.5%, prehospitalization insulin dose < 0.6 units/kg/day) with mild hyperglycemia (glucose level < 180 mg/dL).

Correctional insulin alone can be used to treat newly recognized hyperglycemia or diabetes that is well managed (with admission blood glucose < 180 mg/dL) with noninsulin therapy. However, scheduled insulin therapy (basal with bolus or correctional doses, or both) should be used for patients with persistent hyperglycemia (2 or more glucose readings ≥ 180 mg/dL in a 24-hour period).

Hyperglycemia associated with glucocorticoid use or enteral nutrition should be managed with neutral protamine Hagedorn-based or basal-bolus insulin regimens, or both, as neutral protamine Hagedorn and intermediate-acting corticosteroids share a similar pharmacokinetic profile, with overlapping onset and duration of effect.

Insulin dosing based on carbohydrate counting can be considered as an alternative to fixed prandial insulin dosing in patients with type 1 diabetes or insulin-treated type 2 diabetes. In this scenario, the prandial insulin dose is determined by dividing the grams of carbohydrate consumed by the patient's preestablished insulin-to-carbohydrate ratio.

Patients using an insulin pump before hospitalization can continue to self-manage their insulin pump while hospitalized, with oversight by experienced hospital personnel (which includes endocrinology care team members and knowledgeable nonendocrinology providers based on variations in practice resources, provider familiarity, and hospital policies). This is preferred rather than changing to subcutaneous basal-bolus insulin therapy.

Continuous glucose monitoring with confirmatory bedside point-of-care blood glucose testing for adjustments in insulin dosing is recommended in patients with insulin-treated diabetes at risk of hypoglycemia, rather than point-of-care testing alone.

Targets. Patients with diabetes scheduled for elective surgery should aim for a preoperative hemoglobin A1c level less than 8% if feasible, and preoperative blood glucose concentrations in the range of 100 to 180 mg/dL.

Carbohydrate-containing oral fluids should be avoided preoperatively in patients with diabetes.

Inpatient diabetes education, ideally provided by diabetes care and education specialists, should be included as part of a comprehensive discharge planning process.

WHAT IS DIFFERENT FROM PREVIOUS GUIDELINES?

The new guidelines address emerging topics, particularly how to integrate diabetes technology into inpatient care by relying more on devices such as continuous glucose monitors and insulin pumps.

Glucose monitoring. The schedules for point-of-care blood glucose monitoring outlined by the 2012 guidelines still apply, ie, preprandial and bedtime checks if the patient is eating meals, or every 4 to 6 hours otherwise. The latest guidelines now suggest also using continuous glucose monitors in patients at high risk for hypoglycemia, regardless of whether the patient had been using one before admission. This addition is made possible by technological advancements over the past decade and growing evidence that continuous glucose monitoring is reliable and accurate in noncritical illness.[4–7] The new guidelines still recommend continuing routine point-of-care blood glucose checks with continuous glucose monitoring.

Insulin pumps. The 2012 guidelines suggested that patients with type 1 or type 2 diabetes who were using insulin pumps at home could keep using them in the hospital.[2] The new guidelines more clearly endorse pump therapy, based on results from observational studies on insulin pump use in eligible hospitalized patients, predominantly those with type 1 diabetes. These studies have demonstrated safety without any increase in hypoglycemia or diabetic ketoacidosis.[8–10]

Patients who had been using hybrid closed-loop delivery systems can continue using them in the hospital. These systems integrate continuous monitoring information directly into the insulin pump settings and can automatically suspend insulin delivery to prevent hypoglycemia, though data on their use in the hospital is limited.[11]

Scheduled basal-bolus insulin therapy is still the mainstay of inpatient glycemic management. However, the new guidelines also identify situations in which it is reasonable to deviate from scheduled insulin regimens in the hospital. In the past, noninsulin or oral therapies were recommended only in patients in stable condition resuming their home medications just before discharge.[2] While use of home noninsu-

lin therapies can still be considered during the discharge transition, the latest guidelines reflect newer data from randomized controlled trials showing that using DPP-4 inhibitors (whether new or continued) is reasonable and safe in hospitalized noncritically ill patients with mild hyperglycemia.[12–14] The updated guidelines also define criteria for patients with mild hyperglycemia who could be considered for correctional insulin therapy alone.

Some topics not addressed. The update does not address many of the topics from the 2012 guidelines that remain relevant. These include the indications for and the timing and routine targets of point-of-care blood glucose testing, recognizing and managing hypoglycemia, the role of nutritional therapy, and how to transition from continuous insulin infusion to subcutaneous insulin injections.[2]

WHAT IS THE EXPECTED CLINICAL IMPACT?

We hope that these recommendations will lead to improved inpatient glycemic control with fewer episodes of hypoglycemia. Each recommendation was assessed using the GRADE method to summarize available data and consider the certainty of evidence, patient values, balance of desirable and undesirable effects, resources and costs, equity, feasibility, and acceptability to key stakeholders.

DO OTHER SOCIETIES AGREE OR DISAGREE?

The 2022 Endocrine Society guidelines were cosponsored by the American Association of Clinical Endocrinologists, the American Diabetes Association, the Association of Diabetes Care and Education Specialists, the Diabetes Technology Society, and the European Society of Endocrinology. A representative from the American College of Physicians also served as a member of the writing panel. As there was significant collaboration in developing these guidelines, there is agreement among these societies.

The recommendations of the latest (2023) standards of care guidelines released by the American Diabetes Association also address diabetes care in the hospital and are consistent with the Endocrine Society recommendations.[15]

HOW WILL THIS CHANGE DAILY PRACTICE?

The guidelines continue to endorse basal-bolus insulin as the preferred treatment for most noncritically ill hospitalized patients with hyperglycemia. DPP-4 inhibitors with or without correctional insulin are newly offered as alternatives in patients with mild hyperglycemia who do not have type 1 diabetes. For those with type 1 or type 2 diabetes on an insulin pump, the recommendations have changed to prefer continuing pump therapy, and even allow for continuing hybrid closed-loop pump systems.

A new suggestion is to use continuous glucose monitors in patients at risk of hypoglycemia, in addition to point-of-care blood glucose testing. This suggestion lends support to adaptations made at some centers in response to the COVID-19 pandemic after the US Food and Drug Administration (FDA) granted emergency access to inpatient monitor use in 2020 to allow for remote monitoring of COVID-19 patients, preventing unnecessary exposure of healthcare workers and reducing use of personal protective equipment. This trend continued in 2022 when the FDA granted a breakthrough designation for the Dexcom CGM device in the hospital setting. Given these FDA allowances, many hospitals have already started to use continuous glucose monitoring data in conjunction with point-of-care blood glucose testing to guide inpatient therapy.

Overall, the endorsement of using insulin pumps and continuous glucose monitors in the latest guidelines increases the role of diabetes technology in the hospital.

WHEN WOULD THE GUIDELINES NOT APPLY?

These recommendations are specific to noncritically ill adults and do not apply in pediatric or critical care settings. The guidelines are not a substitute for clinical judgment, and we must consider the limitations of and contraindications to each new intervention.

Medication interference. A few medications are known to affect the accuracy of continuous glucose monitors: acetaminophen (> 1 g taken every 6 hours), hydroxyurea, and hydroxycarbamide interfere with the Dexcom CGM device, while ascorbic acid (vitamin C) in doses higher than 500 mg/day interferes with the Abbott Freestyle Libre CGM device.

Inability to self-manage. Insulin pump therapy in the hospital is self-managed, so patients must be willing and able to perform pump adjustments and deliver boluses. Any limitation on physical or mental capabilities that would prevent the patient from properly operating their pump would require switching to scheduled basal-bolus insulin.

Continuing to use an insulin pump is also not recommended in a patient with diabetic ketoacidosis or hyperosmolar hyperglycemic nonketotic syndrome.

For these patients, continuous intravenous infusion of regular insulin is the mainstay of therapy, in keeping with institutional protocols.

Contraindications, cautions for DPP-4 inhibitors. DPP-4 inhibitors should not be used in patients with a history of type 1 diabetes or pancreatitis and are not recommended during pregnancy and lactation. Dose adjustment may be necessary for patients with chronic kidney disease receiving sitagliptin, saxagliptin, or alogliptin. Saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease.

Practical considerations. Any new medication or technology added in the hospital that is intended to be continued after discharge must be accessible, affordable, and agreeable to the patient, considering their values and preferences.

Ultimately, feasibility and practicality are the largest barriers to incorporating the latest guidelines in the hospital setting. Centers need regular access to supplies and providers with expertise in diabetes technology to offer continuous glucose monitoring and to continue pump therapies, as well as access to diabetes care and education specialists to provide diabetes self-management education.

Given the high prevalence of diabetes and hyperglycemia in hospitalized patients, diabetes healthcare personnel and resources are important for improving patient outcomes. As always, the decision to involve endocrinology care team members is based on specifics of the patient's situation, the inpatient provider's knowledge and experience, and the hospital's resources and policies.

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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Evaluating a low anion gap: A practical approach

ABSTRACT

In teaching and in practice, little attention is given to a low anion gap. This oversight can result in a missed opportunity to diagnose acute or chronic disorders requiring treatment. In this article, we review the constituents of the anion gap, build a differential diagnosis for a low anion gap using case examples, and provide a stepwise approach to diagnostic testing to evaluate this abnormal finding.

KEY POINTS

Testing error is the most common reason for a low serum anion gap, so a patient should first undergo repeat serum electrolyte sampling to confirm the finding.

A decrease in negatively charged albumin lowers the anion gap. The effects of hypoalbuminemia on the anion gap can be accounted for using a correction formula. This correction is important because hypoalbuminemia may conceal an elevated anion gap metabolic acidosis.

An increase in an unmeasured cation, such as lithium, can lead to a low or negative anion gap. With early recognition, supratherapeutic lithium can be removed through hemodialysis.

An increase in a positively charged plasma protein lowers the anion gap; therefore, a low anion gap should prompt consideration of a monoclonal gammopathy.

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In teaching and in practice, when we talk about the anion gap, we usually focus on recognizing and evaluating an elevated anion gap, which frequently requires immediate intervention. Little attention, however, is given when a patient presents with a low or negative anion gap. Such oversight can result in a missed opportunity to diagnose acute or chronic disorders requiring treatment.

In this article, we review the constituents of the serum anion gap, outline a differential diagnosis for a low anion gap using case examples, and provide a stepwise approach to diagnostic testing for clinicians to evaluate a patient that presents with a low anion gap. This is not an exhaustive review of acid-base physiology,[1] but rather a practical starting point for generalists encountering this clinical problem.

WHAT MAKES UP THE ANION GAP?

The serum contains an equal number of positively charged cations and negatively charged anions. A "Gamblegram," named after physician James L. Gamble, offers a visual representation of each negatively and positively charged extracellular ion in the serum (**Figure 1**).

The anion gap is calculated by subtracting the sum of the serum chloride and bicarbonate concentrations from the serum sodium concentration (**Table 1**). The serum potassium contributes little to the total extracellular electrolyte pool and is often excluded from the calculation.[2] The value for sodium is nearly always higher than the combined value of chloride and bicarbonate, leading to the typically positive anion gap value.

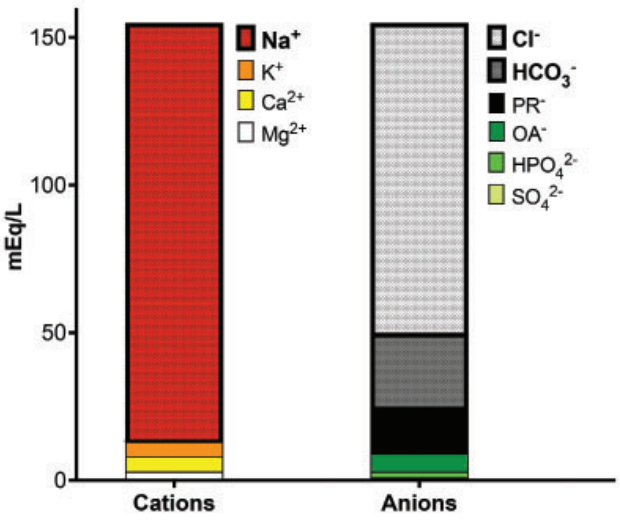

Figure 1. A "Gamblegram" showing the relative abundance of extracellular anions and cations. The serum cations are Na^+ (sodium), K^+ (potassium), Ca^{2+} (calcium), and Mg^{2+} (magnesium). The serum anions are HCO_3^- (bicarbonate), Cl^- (chloride), HPO_4^{2-} (hydrogen phosphate), SO_4^{2-} (sulfate), OA^- (organic acids), and PR^- (proteins). In this chart and in this article, for consistency, we use milliequivalents per liter (mEq/L) as the unit of measurement.

Note: Laboratories report anion gap in either mEq/L or millimoles per liter (mmol/L): 1 mEq/L is equal to 1 mmol/L multiplied by the valence charge of the ion. Since the anion gap calculation involves only variables with a valency of +1 or –1 (sodium, bicarbonate, chloride), the value in mEq/L will be identical to the value in mmol/L.

HOW LOW IS TOO LOW?

Until the 1980s, the reference range for the anion gap was between 8 and 16 mEq/L. When new serum electrolyte assays were introduced, the reference range was revised to between 3 and 9 mEq/L.[3] A low anion gap is defined as less than or equal to 3 mEq/L.[4]

CAUSES OF A LOW ANION GAP: CASE SCENARIOS

Testing error

A healthy 30-year-old patient has a chemistry panel measured during a routine checkup. The anion gap is 2 mEq/L.

Measurement error in serum chemistry is the most common cause of a low anion gap.[5,6] The anion gap is a derived number, dependent on 3 variables: the sodium, chloride, and bicarbonate concentrations. A preanalytical or analytical error in any of these can lead to a falsely low anion gap.[7,8]

TABLE 1
Three formulas for the anion gap

Anion gap = $Na^+ – (HCO_3^- + Cl^-)$
Anion gap = measured cations – measured anions[a]
Anion gap = unmeasured anions – unmeasured cations

[a]Here, "measured" refers to the cations and anions (sodium, chloride, and bicarbonate) typically included in the anion gap calculation, and "unmeasured" refers to any cations or anions that are not accounted for in the anion gap calculation.

Preanalytical errors arise during sample collection, transportation, and storage.[9] Analytical errors arise from measurement processes or poor quality control in the laboratory. If previous tests do not demonstrate a low anion gap, the patient should undergo repeat serum electrolyte sampling to exclude testing process error.

Decrease in an unmeasured anion (albumin)

A 50-year-old with a recent diagnosis of gastric cancer is admitted for nutritional support. The patient reports minimal oral intake over 2 months and appears cachectic. Laboratory values on admission and on serial measurement show an albumin of 2 g/dL and an anion gap of 2 mEq/L.

Negatively charged plasma proteins make up most of the unaccounted anions in the anion gap calculation, and albumin is the most abundant of these proteins. Therefore, serum albumin comprises most of the normal anion gap:

$$Na^+ – (HCO_3^- + Cl^-) = \text{anion gap} = \text{mostly albumin}.$$

Serum albumin concentrations may decrease due to malnutrition, impaired hepatic synthesis, acute or chronic inflammation, and urinary or gastrointestinal losses.[10] When albumin falls, so does the anion gap, as chloride anions rise to compensate for the loss of albumin anions to maintain serum electrical neutrality.[11]

Multiple studies have demonstrated a correlation between hypoalbuminemia and the anion gap. One published correction formula for hypoalbuminemia adjusts a patient's anion gap by adding 2.5 mEq/L to the calculated anion gap for each decrease of 1 g/dL in albumin from a normal baseline of 4 g/dL[12]:

$$\text{Corrected anion gap} = \text{measured anion gap} + [2.5\ (4 – \text{measured albumin})].$$

Our patient's anion gap of 2 mEq/L corrects to a normal value of 7 mEq/L when adjusted for a serum albumin of 2 g/dL.

Hypoalbuminemia can conceal an emergency

A 50-year-old patient with a gastric ulcer presents with acute abdominal pain. Laboratory testing shows an albumin level of 2 g/dL and an anion gap of 13 mEq/L.

When we adjust for the patient's albumin concentration of 2 g/dL and add 5 mEq/L to the calculated anion gap, the patient's corrected anion gap rises to 18 mEq/L. This elevated level may prompt targeted testing for an anion gap metabolic acidosis, including lactate measurement, abdominal imaging, or surgical consultation. Omitting this adjustment for albumin could lead the clinician to miss a metabolic acidosis indicative of an intra-abdominal catastrophe, such as a perforated viscus.[13]

Increase in an unmeasured cation

A 50-year-old patient with bipolar affective disorder presents with obtundation after an overdose of home medications. Admission laboratory tests and repeat measurements show an anion gap of 0 mEq/L.

Increases in cations such as potassium, magnesium, and calcium can lower the anion gap. However, increases in these electrolytes are usually noticed on direct measurement before reaching the point of markedly affecting the anion gap calculation.

Other cations that are not routinely measured, such as lithium, can result in a low or negative anion gap.[14] The excess positive lithium ions are balanced by a compensatory increase in negatively charged chloride ions. The sodium level remains the same, but the increased chloride causes a decrease in the calculated anion gap. In the right context, a low or negative anion gap should prompt serum lithium testing. With early recognition, supratherapeutic lithium can be removed through hemodialysis.[15]

Increase in a positively charged protein

A 70-year-old patient presents because of fatigue while riding a bicycle. Serial laboratory testing shows anemia, renal insufficiency, and an anion gap of 2 mEq/L.

A rise in positively charged plasma proteins can reduce the anion gap. Elevated positively charged proteins are counterbalanced by a compensatory increase in negatively charged ions, principally chloride. As chloride rises, the calculated anion gap falls.

The most common excess positively charged proteins are monoclonal immunoglobulins or light chains. Plasma cell dyscrasias such as multiple myeloma can produce positively charged immunoglobulin. The immunoglobulin G paraprotein has an isoelectric point higher than physiologic pH, resulting in a positive charge.[16] A low anion gap should therefore prompt investigation for a monoclonal gammopathy.

Conditions that cause polyclonal increases in immunoglobulin levels can exert similar effects on the anion gap if a portion of these immunoglobulins are positively charged. Patients with higher levels of circulating immunoglobulins, including those with chronic kidney disease,[17] cirrhosis,[18] and human immunodeficiency virus,[19] demonstrate an inverse correlation between their serum immunoglobulin levels and anion gap.

Chloride overestimation

A 70-year-old patient with osteoarthritis presents with nausea and tinnitus. The patient takes no medications other than over-the-counter aspirin for arthritis pain. Laboratory testing on admission and repeated during hospitalization shows a serum chloride concentration of 115 mmol/L and an anion gap of 0 mEq/L.

Chloride overestimation can occur when other halide ions such as bromide or iodide are erroneously read as chloride by ion-selective electrodes.[20] While these agents are infrequently used in modern practice, they can still be found in sedative agents or in combination with nonsteroidal anti-inflammatory drugs. Increased salicylate levels, as in the patient above, may also mistakenly register as chloride when newer chloride ion-selective electrodes are used.[21]

Pseudohyperchloremia from these conditions results in an overestimated chloride level subtracted from an accurately recorded sodium value, leading to a decreased anion gap. In the right clinical context, a low anion gap should prompt investigation for bromide, iodide, or salicylate ingestion. The elevated anion gap acidosis typical of salicylate poisoning may be masked by this artifactually low gap.[21]

Sodium underestimation

A 70-year-old patient presents for replacement of a dislodged gastrostomy feeding tube, which led to no enteral intake for 3 days. Laboratory tests on admission and repeated during hospitalization show a serum sodium concentration of 170 mmol/L and an anion gap of 0 mEq/L.

Hypernatremia can occur through impaired access to free water or urinary loss of free water. In severe cases, the patient's serum sodium concentration may exceed the upper limit of the laboratory assay (typically around 170 mmol/L), causing underestimation of the true sodium level. Underestimation of serum sodium can also occur in hyperviscosity states such as hyperproteinemia or hyperlipidemia due to difficulty with aspirating an adequate serum aliquot, which

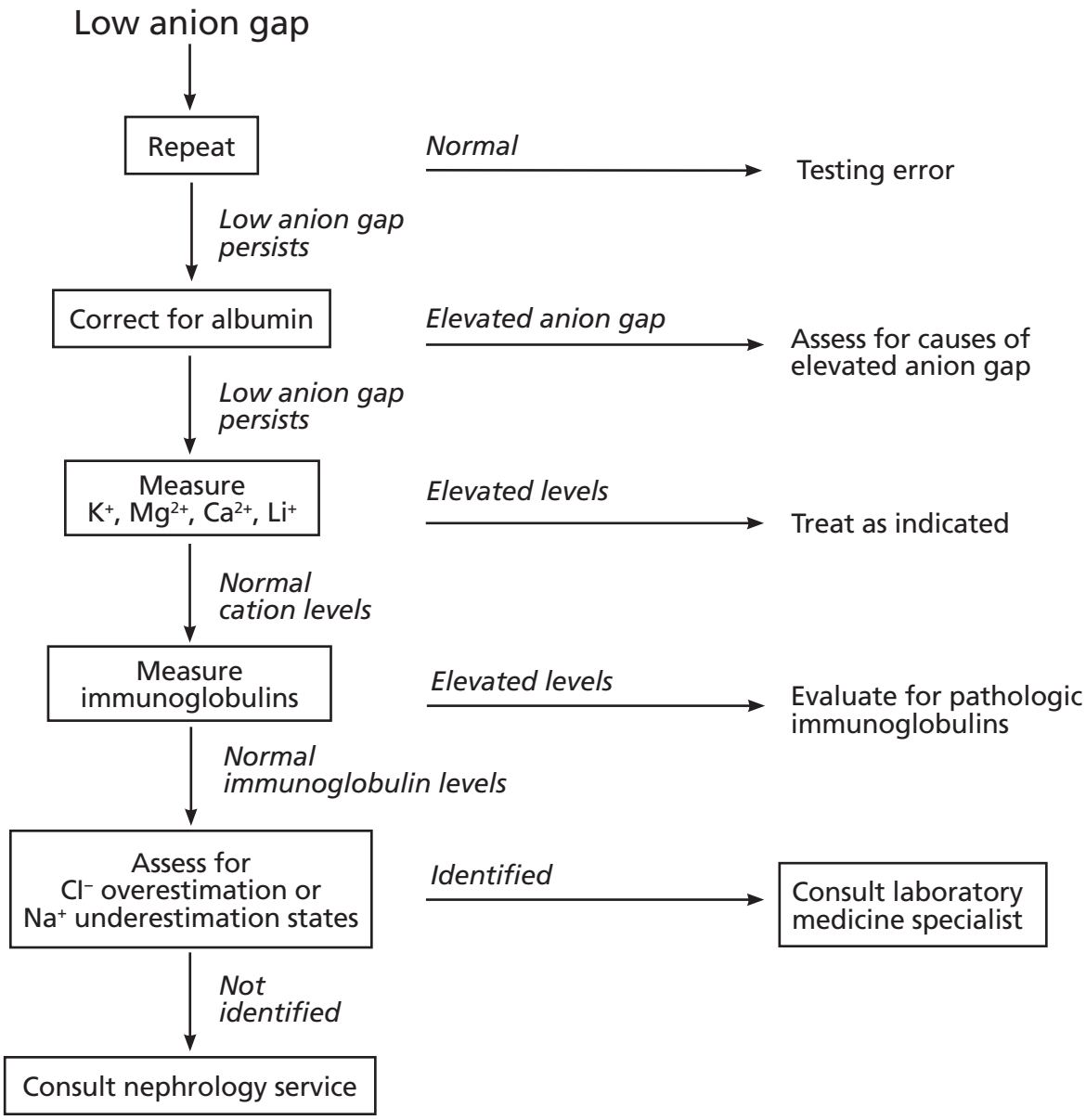

Figure 2. Stepwise approach to evaluating a low anion gap.

can be resolved by direct potentiometry.[22] In cases of pseudohyponatremia, accurately recorded chloride and bicarbonate values are subtracted from an underestimated sodium value, resulting in a decreased anion gap.

AN APPROACH FOR CLINICIANS

By understanding the components of the anion gap and how diseases and measurement techniques can affect the calculation, clinicians can direct initial diagnostic steps for a patient presenting with a low or negative anion gap (**Figure 2**). Nephrologists and laboratory medicine consultants are valuable collaborators for challenging or unexplained cases.

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DISCLOSURES

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

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: What is the most appropriate management of patients with acute decompensated heart failure who develop in-hospital hypotension?

A: Because the majority of patients with acute decompensated heart failure remain at high risk for in-hospital hypotension owing to low cardiac output and neurohormonal blockade from guideline-directed medical therapy,[1] we recommend a tailored approach to risk-stratify patients with acute decompensated heart failure that focuses on avoidance, early recognition, and management of symptomatic and clinically significant hypotension.

HYPOTENSION

Blood pressure varies widely within the course of hospitalization for acute decompensated heart failure, and elevated systolic blood pressure (SBP) allows for easier initiation of guideline-directed medical therapy,[2] whereas in-hospital hypotension is associated with unfavorable outcomes.[1,2]

Hypotension may be either absolute (eg, SBP less than 90 mm Hg or mean arterial pressure less than 65 mm Hg) or relative (eg, SBP drop more than 40 mm Hg) and becomes clinically relevant when persistent and associated with symptoms such as dyspnea, chest pain, syncope, headache, visual disturbances, emesis, or fatigue.[2] It is commonplace for patients with heart failure to experience transient blood pressure drops shortly after medication dosing, but symptoms usually subside with heart failure improvement.[2] Importantly, hypotension is not always a manifestation of shock, characterized by end-organ underperfusion.

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Factors that contribute to in-hospital hypotension

Numerous factors contribute to in-hospital hypotension in acute decompensated heart failure.[1,2] Lower effective circulating volume caused by diuretic use and third-spacing is a key precipitating element. Arrhythmias, which can either induce systolic dysfunction or exacerbate underlying cardiomyopathies, commonly present with acute decompensated heart failure. Impaired vasoreactivity due to comorbid conditions (eg, diabetes or amyloidosis) may amplify the heart failure-induced vasodilatory state.[1] Finally, hypotension may be a reflection of advanced pump failure resulting in inability to generate enough pressure to overcome the increased ventricular afterload and preload result-

ing from neurohormonal feedbacks (including sympathetic and renin-angiotensin system activation, as well as release of antidiuretic hormone).

Development of in-hospital hypotension in acute decompensated heart failure can limit the use of life-saving therapies and lead to malperfusion with consequent end-organ damage.[1,2] This is clinically relevant in patients with acute decompensated heart failure, where hypotension-induced kidney injury may prevent effective diuresis and require escalation to renal replacement therapy, thereby contributing to poor outcomes.[3]

Despite these factors, clinicians may accept in-hospital hypotension as a compromise to rapidly titrate guideline-directed medical therapy.[1] In fact, the STRONG-HF trial (Safety, Tolerability, and Efficacy of Rapid Optimization, Helped by N-Terminal pro-B-type Natriuretic Peptide Testing, of Heart Failure Therapies) met the composite primary outcome of reduced risk of all-cause death or heart failure readmission at 6-month follow-up, driven by reduction in the latter.[4] Therefore, early detection and correction of in-hospital hypotension is critical to mitigate patient risk and maximize benefits of guideline-directed medical therapy.

GUIDELINE-DIRECTED MEDICAL THERAPY: REAL-WORLD EXPERIENCE

Guideline-directed medical therapy underutilization is common for several reasons, including highly selected trial populations and the following[5]:

- Enterprise-level factors (restrictive pharmacotherapy policy, inadequate health information technology, inaccessible multidisciplinary care)
- Physician-level factors (knowledge or communication gaps, uncertainty about trial generalizability, concerns about contraindications, biased decision-making, clinical inertia)
- Patient-level factors (preference against changing therapies, suboptimal health literacy or adherence, lack of affordability, side effects, comorbidities).[5]

Importantly, acute decompensated heart failure complicated by cardiogenic shock, acute coronary syndrome, or worsening kidney function is common in registries, but patients with these scenarios were excluded from inpatient initiation trials.[1] Regardless, even trial-eligible patients remain undertreated.[5] Few multifold strategies to increase guideline-directed medical therapy utilization have been tested in randomized controlled trials, and even fewer were successful.[5]

Guideline-directed medical therapy and hypotension

Hypotension is a recognized adverse effect and reason for withdrawal of treatment among landmark trials.[1,5] Despite being a central safety criterion, it is important to note the heterogeneity of definitions, exclusion criteria, and incidence of adverse effects (**Table 1**).[6–23] Actually, lowering blood pressure is not always bad. Patients enrolled in the EMPHASIS (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure)[21] and PARADIGM-HF (Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure)[17] had lower mortality risk (all-cause and cardiovascular causes in both studies) and reduced risk of hospitalization even with greater blood pressure reduction after guideline-directed medical therapy. This may suggest that short-term blood pressure-lowering effects of guideline-directed medical therapy are a tolerable trade-off for the long-term beneficial neurohormonal blockade.

Angiotensin-receptor–neprilysin (ARN) inhibitors and carvedilol were studied in patients with acute decompensated heart failure and SBP greater than 100 mm Hg and greater than 85 mm Hg, respectively.[24] Patients with low SBP were more likely to discontinue therapy or have symptomatic hypotension. In contrast, stable patients with SBP greater than 100 mm Hg did not experience significant hypotension with sodium-glucose cotransporter 2 (SGLT-2) inhibitors.[25] Mineralocorticoid receptor antagonist trials did not have blood pressure exclusion criteria, and even patients with SBP less than 105 mm Hg had positive safety end points.[24]

HYPOTENSION IN ACUTE DECOMPENSATED HEART FAILURE: A PROPOSED APPROACH

We risk-stratify patients with acute decompensated heart failure and focus on avoidance, early recognition, and management of symptomatic and clinically significant hypotension (**Figure 1**). Initially, clinicians should proactively screen for signs of impending circulatory shock that would require immediate escalation of care. A cardiology consultation would be appropriate to guide judicious guideline-directed medical management in patients with subtle signs of early compensated shock, including restlessness, pale and clammy skin, nausea and vomiting, tachycardia, tachypnea, delayed capillary refill, and narrow pulse pressure. As the initial compensatory mechanisms start failing, physical (eg, obtundation, oliguria, cold extremities, peripheral cyanosis) and laboratory (eg, hypoxia, lactic acidosis, renal dysfunction, or liver injury) signs of crit-

TABLE 1
Hypotension in landmark randomized controlled trials of guideline-directed medical therapy

Trial	Medication	Hypotension	SBP drop	SBP cutoff exclusion	Notes
CONSENSUS[6]	Enalapril	0.05% (0% placebo)	SBP 10 mm Hg lower in both enalapril and placebo	None	5.5% discontinuation due to hypotension
SOLVD[7,8]	Enalapril	14.8% (7.1% placebo)	SBP 4.7 mm Hg lower, vs 4.0 with placebo	2.2% excluded for symptomatic hypotension during run-in period	During run-in period, 1.2% were at risk of serious hypotension and were hospitalized for 24 hours during the initiation of the drug
US Carvedilol Heart Failure Study Group[9]	Carvedilol	9% (4% placebo)	No significant SBP drop	SBP < 85 mm Hg	0.3% discontinuation due to hypotension
COPERNICUS[10,11]	Carvedilol	1.9% (1.6% placebo)	NR	NR	Subjects with lowest blood pressure experienced greatest cardiovascular benefit
CIBIS-II[12]	Bisoprolol	NR	NR	SBP < 100 mm Hg	Less hospitalizations for hypotension in bisoprolol arm (3 vs 11; $P = .03$)
MERIT-HF[13]	Metoprolol	NR	SBP decreased less than placebo (–2.1 vs 3.5; $P = .013$)	Supine SBP < 100 mm Hg	Relative-risk of primary outcome was lower in the lower SBP tertile; < 1% discontinuation due to hypotension
ATLAS[14]	Lisinopril	11% (high-dose group), 7% (low-dose group)	SBP decreased 4.4 mm Hg more in the high-dose group vs low-dose group; $P < .001$	No predefined numeric threshold for definition	0.6% (low-dose group) and 0.8% (high-dose group) discontinuation due to hypotension
Val-HeFT[15]	Valsartan	NR	At 1-year, SBP 5.2 mm Hg lower, vs 1.3 mm Hg lower with placebo	Titration required standing SBP ≥ 90 mm Hg, absence of symptomatic hypotension, and serum creatinine concentration < 2.0 mg/dL or < 50% higher than baseline concentration	1.3% (0.8% placebo) discontinuation due to hypotension; $P = .124$
CHARM-Alternative[16]	Candesartan	14.1% (11.7% placebo)	SBP 4.4 mm Hg lower vs placebo	None	3.7% (placebo 0.9%) discontinuation due to hypotension; $P < .0001$
PARADIGM-HF[17]	Sacubitril-valsartan	14% symptomatic (9.2% enalapril), 2.7% symptomatic with SBP < 90 mm Hg (1.4% enalapril)	SBP 3.2 mm Hg lower vs enalapril; $P < .001$	SBP < 100 mm Hg at screening, SBP < 95 mm Hg at randomization, or symptomatic hypotension	Double run-in period, likely leading to underestimation of risks; 0.9% (0.7% with enalapril) discontinuation due to hypotension
PIONEER-HF[18]	Sacubitril-valsartan	15% symptomatic (12.7% enalapril)	NR	SBP < 100 mm Hg for preceding 6 hours	2.5% (2.5% with enalapril) rate of discontinuation due to hypotension
TRANSITION[19]	Sacubitril-valsartan	12.7% predischarge, 9.5% postdischarge	NR	SBP < 100 mm Hg for preceding 6 hours	0.7% rate of discontinuation due to hypotension; SBP ≥ 120 mm Hg was predictor of successful titration
EPHESUS[20]	Eplerenone	NR	No significant difference	None	Mean blood pressure increased by 5 mm Hg in the eplerenone group (vs 8 mm Hg in the placebo); $P < .01$
EMPHASIS-HF[21]	Eplerenone	3.4% (2.7% placebo)	SBP 2.5 mm Hg lower, vs 0.3 with placebo	None	NR
DAPA-HF[22]	Dapagliflozin	0.3% (0.5% placebo) asymptomatic and 0.1% (0.2% placebo) symptomatic	SBP 1.92 mm Hg lower, vs 0.38 with placebo; $P = .002$	SBP < 95 mm Hg	NR
EMPEROR-Reduced[23]	Empagliflozin	9.4% (8.7% placebo) asymptomatic and 5.7% (5.5% placebo) symptomatic	SBP 2.4 mm Hg lower, vs 1.7 with placebo	Symptomatic hypotension and/or SBP < 100 mm Hg at screening	Baseline SBP and the risk of primary end points were inversely related

HF = heart failure; NR = not reported; SBP = systolic blood pressure

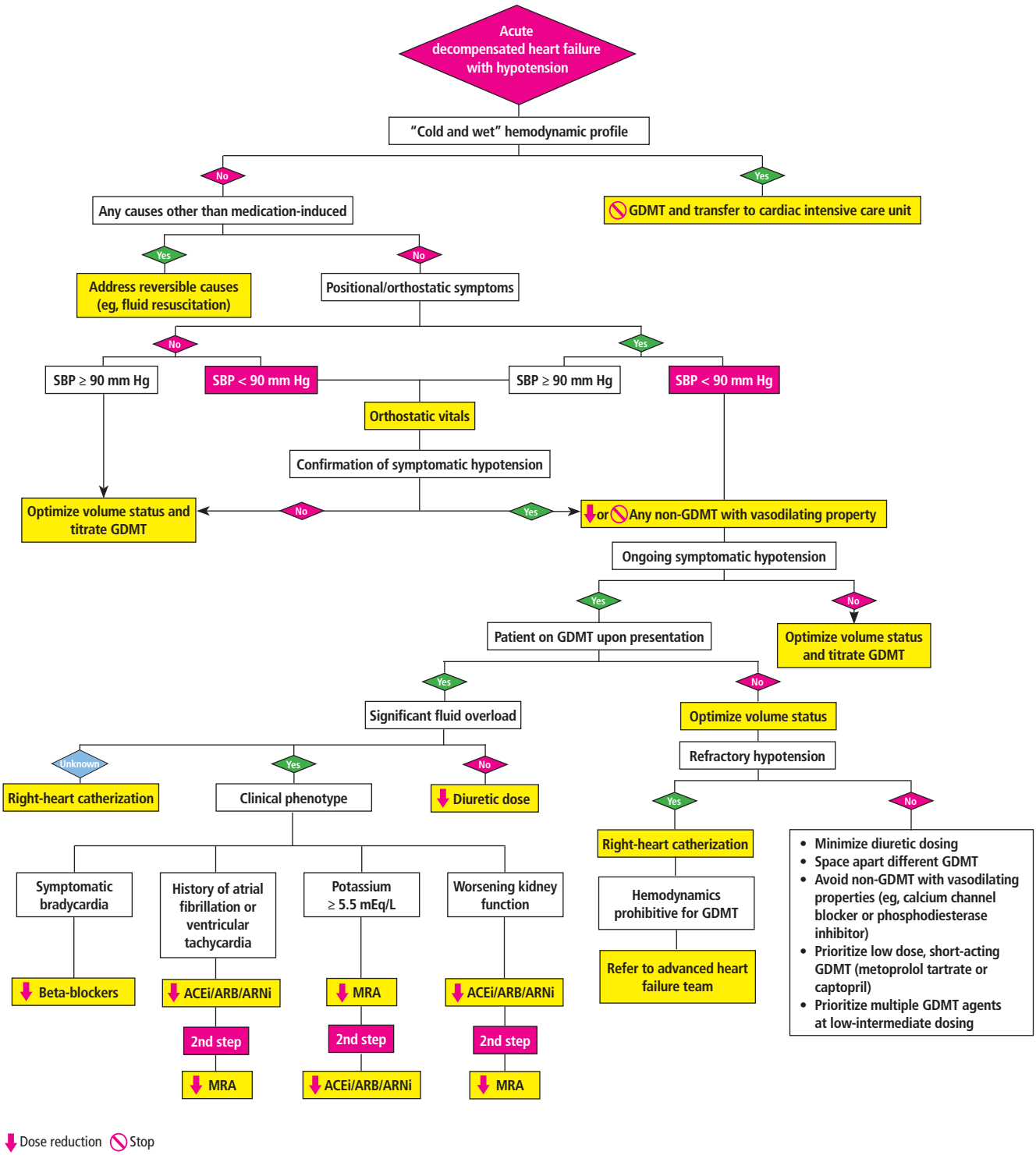

Figure 1. Management algorithm for in-hospital hypotension in patients with acute decompensated heart failure.

ACEi = angiotensin-converting–enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin-receptor–neprilysin inhibitor; GDMT = guideline-directed medical therapy; MRA = mineralocorticoid receptor antagonist; SBP = systolic blood pressure

ical hypoperfusion may become apparent, and patients should be readily transferred to an intensive care unit.

Asymptomatic hypotension

The approach to hypotension in patients with acute decompensated heart failure needs to be tailored to patient-specific factors. For example, an SBP of 90 mm Hg would not be disproportionately low in a patient with a 10% ejection fraction in the absence of signs of hypoperfusion, whereas an SBP of 130 mm Hg may represent a relative hypertensive urgency. Alternative causes of hypotension (eg, dehydration, overdiuresis, gastrointestinal bleeding, arrhythmia) should be considered and addressed before systematically decreasing guideline-directed medical therapy.

We would not initiate radical interventions in patients with asymptomatic or nonsevere hypotension (SBP 90 mm Hg or greater), as most patients with heart failure can tolerate guideline-directed medical therapy irrespective of low blood pressure measurements as long as volume status is adequately optimized. Transient asymptomatic blood pressure drops are common during guideline-directed medical therapy dosing but typically resolve with heart failure improvement. Determining association between low SBP and functionally limiting symptoms (eg, dizziness) is essential before initiating down-titration of guideline-directed medical therapy and can be readily assessed with orthostatic vitals.

Symptomatic hypotension

In severe (SBP less than 90 mm Hg) or symptomatic hypotension, any drug that lowers blood pressure and is otherwise not indicated in patients with heart failure (eg, calcium channel blockers) should be immediately stopped. Lastly, in case of refractory hypotension, diuretics may also be tapered in the absence of prominent congestion. Volume assessment may frequently be challenging, and it would be reasonable to consider right-heart catheterization for a more accurate assessment.

INITIATION OF GUIDELINE-DIRECTED MEDICAL THERAPY

Hospitalization of patients with acute decompensated heart failure provides an opportunity to initiate and continue guideline-directed medical therapy before discharge. Nonetheless, prolonging the hospital stay for optimization of guideline-directed medical therapy may not be cost-effective, and long-term benefits are only realized through outpatient adherence.[24] Accordingly, we do not recommend the extended conventional approach to guideline-directed medical therapy optimization (ie, the guideline-directed medical therapy sequence followed in clinical trials), but rather advocate for rapid escalation of guideline-directed medical therapy owing to the following reasons.[24]

- The addition of multiple agents has been shown to provide substantially more benefit, even at lower-than-target doses, compared with up-titrated single agents[24,26]
- The beneficial effects of each class of guideline-directed medical therapy are independent of others[24]
- Acute decompensated heart failure represents a high-risk period for patients with associated high morbidity and mortality, and guideline-directed medical therapy reduces adverse events as early as 30 days after readmission, thereby minimizing delay in benefits[24]
- Prescription of guideline-directed medical therapy at the time of hospital discharge increases adherence in the outpatient setting.[24]

Early initiation of guideline-directed medical therapy in hypotensive patients with "warm and wet" hemodynamic profiles is generally feasible.[24] However, patients who remain hypotensive despite optimization of volume status or those who develop disproportionately worse kidney function when attempting guideline-directed medical therapy titration may benefit from right heart catheterization-guided management.[27,28] According to in-hospital initiation trials, guideline-directed medical therapy should be initiated once SBP is stable for 6 hours (ie, no increase in the intravenous diuretic dose for 6 hours, no intravenous vasodilators including nitrates within the prior 6 hours, and no intravenous inotropic drugs for 24 hours).[24,29,30]

Our approach

SGLT-2 inhibitors are very well tolerated in acute decompensated heart failure because of negligible hypotensive effects, but their natriuretic properties may require diuretic dose reduction.[31] Likewise, mineralocorticoid receptor antagonists have minimal effects on blood pressure.[32] In our experience, mineralocorticoid receptor antagonist dose reductions or alternate day dosing can be considered with potassium levels of at least 5.5 mEq/L. Beta- blockade and aldosterone antagonism—via ARN inhibitors, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs)—have

shown the greatest impact on morbidity and mortality in patients with acute decompensated heart failure and should be first-line in stabilized patients with heart failure.[33] However, we would recommend introducing target-dose mineralocorticoid receptor antagonists and SLGT-2 inhibitors first in acute decompensated heart failure with symptomatic or clinically significant hypotension.

While in-hospital ARN inhibitors appear both effective and safe even with lower baseline SBP levels during acute decompensated heart failure,[34] beta-blockers have less pronounced afterload-reducing properties.[35] The presence of active ischemia, tachyarrhythmias, or specific cardiomyopathies (eg, cardiac amyloidosis) may also favor preferential use of beta-blockers.

Once the patient with hypotensive acute decompensated heart failure is already improving clinically, we would start a low dose of short-acting beta-blockers, such as metoprolol tartrate, which lacks the alpha-blocking properties of carvedilol, followed by gradual titration. If hypotension is suspected to be caused by a low cardiac output state, beta-blockers should be deferred to allow for compensatory tachycardia, and aldosterone antagonism via ACE inhibitors, ARBs, or ARN inhibitors may be carefully trialed first. Short-acting ACE inhibitors (eg, captopril) may be useful during the initial titration phase. To further minimize risk of recurrent hypotension during guideline-directed medical therapy titration, minimization of diuretics and appropriate spacing of guideline-directed medical therapy dosing are helpful.

Kidney function may deteriorate during early initiation of guideline-directed medical therapy compounded by intravenous diuretics.[24] Nevertheless, renal function often stabilizes over time, and guideline-directed medical therapy has proven benefits even with an estimated glomerular filtration rate of 15 mL/minute/1.73 m^2 in the context of chronic kidney disease. Initiation of ARN inhibitors or SGLT-2 inhibitors require higher estimated glomerular filtration rates.[24]

CONTINUATION OF THERAPY IN PATIENTS WITH HYPOTENSION AND ACUTE DECOMPENSATED HEART FAILURE

On the other hand, guideline-directed medical therapy down-titration should be considered once reversible causes have already been addressed. It is worth noting that abrupt withdrawal of beta-blockers, ACE inhibitors, ARBs, or ARN inhibitors may lead to clinical decline, and therefore should never be done in the absence of symptomatic hypotension or end-organ damage. As a rule of thumb, medications with less benefit for mortality rates (eg, hydralazine, isosorbide, or mineralocorticoid receptor antagonist) should be temporarily stopped first.

Beta-blockers should be temporarily stopped in the presence of symptomatic bradycardia, while aldosterone antagonists (mineralocorticoid receptor antagonists, ACE inhibitors, ARBs, or ARN inhibitors) may be stopped mainly in the setting of acute kidney injury or potassium of at least 5.5 mEq/L. Similarly, a history of arrhythmias should warn against beta-blocker interruption in favor of an ACE inhibitor, ARB, or ARN inhibitor taper. A similar approach to these common heart failure phenotypes has been proposed also for patients with ambulatory heart failure.[35] Regardless of the clinical phenotype, arranging for early post-discharge follow-up for ongoing medication titration is mandatory for long-term success.

THE BOTTOM LINE

It is important to recognize that intolerance to guideline-directed medical therapy remains a poor prognostic indicator, and referral to the advanced heart failure teams would be warranted to explore candidacy for advanced therapies for patients.

Risk-stratifying patients with acute decompensated heart failure by focusing on avoidance, early recognition, and management of symptomatic and clinically significant hypotension results in the most promising outcomes for these patients.

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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REVIEW

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Portopulmonary hypertension: A focused review for the internist

ABSTRACT

Portopulmonary hypertension, ie, pulmonary arterial hypertension in a patient with portal hypertension, affects transplant eligibility and has a poor prognosis. The pathogenesis remains an area of active research, with various mechanisms proposed. Diagnosing it requires a detailed history, physical examination, laboratory tests, and echocardiographic evaluation, followed by a careful hemodynamic assessment.

KEY POINTS

Suspect portopulmonary hypertension in patients with portal hypertension and chronic liver disease who have dyspnea on exertion, chest pain, or exertional syncope or near-syncope.

Patients awaiting liver transplant should be screened for portopulmonary hypertension at least annually, although the optimal interval is unknown.

Transthoracic echocardiography is the best screening tool, but the diagnosis of portopulmonary hypertension requires right heart catheterization showing precapillary pulmonary hypertension in the context of increased portal pressure.

Targeted pulmonary vasodilator therapy and liver transplant are the main treatment options, and pulmonary vasodilator therapy may make a patient eligible for a liver transplant who might have been excluded owing to elevated pulmonary vascular resistance.

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For reasons that are not entirely clear, some patients who have portal hypertension go on to also have pulmonary arterial hypertension, a grim but fortunately rare combination called *portopulmonary hypertension*.[1] Portopulmonary hypertension is important to recognize, both because it has a poor prognosis and because it can affect a patient's eligibility for liver transplant.

This article reviews the key aspects of screening, diagnosis, and treatment of patients with portopulmonary hypertension and highlights the various pulmonary hemodynamic patterns encountered in patients with liver disease.

PORTAL AND PULMONARY HYPERTENSION

Portal hypertension is characterized by a high pressure gradient (> 5 mm Hg) between the portal venous system and the hepatic veins.[2] It is usually caused by liver cirrhosis, although noncirrhotic causes such as congenital hepatic fibrosis, sarcoidosis, and schistosomiasis are occasionally seen. It can be recognized clinically by its classic signs and sequelae such as gastroesophageal varices, portal hypertensive intestinal vasculopathies, ascites, spontaneous bacterial peritonitis, hepatic hydrothorax, and hepatorenal syndrome.[3]

Pulmonary arterial hypertension has a specific hemodynamic profile called *precapillary pulmonary hypertension*, defined by the following[4]:

- Mean pulmonary artery pressure greater than 20 mm Hg
- Pulmonary artery wedge pressure 15 mm Hg or less

- Pulmonary vascular resistance at least 3 Wood units (WU); in 2022, the European Society of Cardiology and the European Respiratory Society[5] lowered this to greater than 2 WU, but the clinical implications of this change in portopulmonary hypertension remain unclear.

PORTOPULMONARY HYPERTENSION IS UNCOMMON

The exact prevalence of portopulmonary hypertension in the United States is difficult to determine, but it is not common.[6–8] McDonnell et al[9] reported that patients with hepatic cirrhosis had a prevalence of pulmonary arterial hypertension of 0.73%. In the United States and Europe, the prevalence of pulmonary arterial hypertension ranges from 15 to 50 per million, with portopulmonary hypertension accounting for 5% to 15% of cases.[10] In a prospective study of 1,235 patients undergoing liver transplant in the United States, approximately 5% met the criteria for portopulmonary hypertension.[11]

The incidence of portopulmonary hypertension will likely increase as our population ages and as the prevalence of cirrhosis increases. In North America, the prevalence of cirrhosis has increased 1.5-fold to 2-fold over the past 2 decades.[12]

MECHANISMS PROPOSED

The pathophysiology of portopulmonary hypertension remains unclear but may involve several factors, including the following:

Genetic predisposition. Several genetic variants are thought to play a role, including single-nucleotide polymorphisms in the genes coding for estrogen receptor 1, aromatase, phosphodiesterase 5, angiopoietin 1, and calcium-binding protein A4.[13,14]

Hyperdynamic circulation. Patients with chronic liver disease and cirrhosis have high cardiac output and low systemic vascular resistance. This hyperdynamic circulatory state may contribute to higher pulmonary vascular shear stress (frictional force of blood flow on the endothelium),[15] which may injure endothelial cells and activate genes that participate in vascular remodeling.

Inflammation. Bacteria can enter the portal circulation through disruptions in the intestinal barrier. Bacterial lipopolysaccharides can activate Toll-like receptors on immune cells, causing them to release inflammatory cytokines such as interferon gamma and interleukin 6, which have been implicated in the pathogenesis of pulmonary arterial hypertension.[15,16]

TABLE 1
Features suggesting portopulmonary hypertension in patients with cirrhosis

History
Dyspnea, fatigue, chest pain
Syncope, presyncope
Weight gain
Lower-extremity swelling
Ascites
Clinical evidence of portal hypertension, eg, variceal hemorrhage, portal gastropathy, hepatic hydrothorax, ascites
Physical examination
Jugular vein distention
Wide, split second heart sound, with loud pulmonic component
Tricuspid regurgitation murmur
Parasternal heave
Hepatomegaly, pedal edema, ascites
Signs of cirrhosis: spider angiomata, jaundice, gynecomastia, caput medusa, palmar erythema, ascites, hepatosplenomegaly
Imaging and electrocardiography
Computed tomography: main pulmonary artery-to-ascending-aorta ratio ≥ 1, dilation of right atrium and ventricle
Electrocardiography: signs of right ventricular strain, right axis deviation, right atrial abnormality (P pulmonale), incomplete or complete right bundle branch block
Hepatic vein catheterization diagnostic of portal hypertension: hepatic venous pressure gradient ≥ 6 mm Hg
Echocardiography
Enlarged right atrial area (> 18 cm^2)
Reduced right ventricular fractional area change (< 35%)
Flattened interventricular septum
D-shaped left ventricle
Right ventricular/left ventricular basal diameter > 1
Peak tricuspid regurgitation jet velocity > 2.8 m/s
Right ventricular systolic pressure ≥ 45 mm Hg
Decreased tricuspid annular plane systolic ejection (< 18 mm)
Pulmonic insufficiency
Pulmonary artery diameter ≥ 25 mm
Inferior vena cava diameter > 21 mm with decreased respirophasic variation

Imbalance of vasoconstrictive and vasodilatory mediators. Portosystemic shunts develop as a result of portal hypertension.[17] These shunts may allow vasoactive substances in the blood to evade hepatic metabolism and enter the pulmonary circulation, causing vasoconstriction and endothelial remodeling.[15] In addition, levels of specific mediators such as bone morphogenetic proteins 9 and 10, which are responsible for maintaining vascular quiescence, have been found to be lower in patients with portopulmonary hypertension than in healthy controls.[18,19]

TABLE 2
Pulmonary hemodynamic patterns in patients with liver disease

Hemodynamic abnormality	Mean pulmonary artery pressure	Pulmonary artery wedge pressure	Cardiac output	Pulmonary vascular resistance
Volume overload	↑	↑↑	↔	↔
Hyperdynamic state	↑	↔	↑↑	↔
Portopulmonary hypertension	↑↑	↔	↔↓	↑↑
Volume overload and hyperdynamic state	↑↑	↑↑	↑↑	↔
Volume overload and portopulmonary hypertension	↑↑	↑↑	↔↓	↑↑
Volume overload, hyperdynamic state, and portopulmonary hypertension	↑↑	↑↑	↑↑	↑↑

↑= elevated; ↑↑= very elevated; ↔ = normal; ↔↓ = normal or low

WHEN TO SUSPECT PORTOPULMONARY HYPERTENSION

In general, portal hypertension precedes the development of portopulmonary hypertension by several years.[20] Suspect portopulmonary hypertension in patients with portal hypertension and chronic liver disease who have dyspnea on exertion, chest pain, or exertional syncope or near-syncope (**Table 1**). Patients may also present with signs suggesting right heart failure such as jugular venous distention, edema, ascites, a second heart sound that is wide and split, and a murmur of tricuspid regurgitation.[21]

SCREEN WITH TRANSTHORACIC ECHOCARDIOGRAPHY

Patients with portal hypertension, particularly those being evaluated for liver transplant, should be screened for portopulmonary hypertension with transthoracic echocardiography.[5] The right ventricular systolic pressure as estimated by echocardiography can differ widely from that measured directly by right heart catheterization.[11] Patients awaiting liver transplant should be screened for portopulmonary hypertension with echocardiography at least annually, although the optimal interval is unknown.[5]

DISTINCT HEMODYNAMIC PATTERNS IN LIVER DISEASE

In patients with liver disease, 3 hemodynamic abnormalities can exist alone or in combination, and some patients have all 3 (**Table 2**)[1]:

- Hyperdynamic circulation due to splanchnic vasodilation and low systemic vascular resistance
- Volume overload from secondary hyperaldosteronism
- Portopulmonary hypertension due to increased pulmonary vascular resistance.

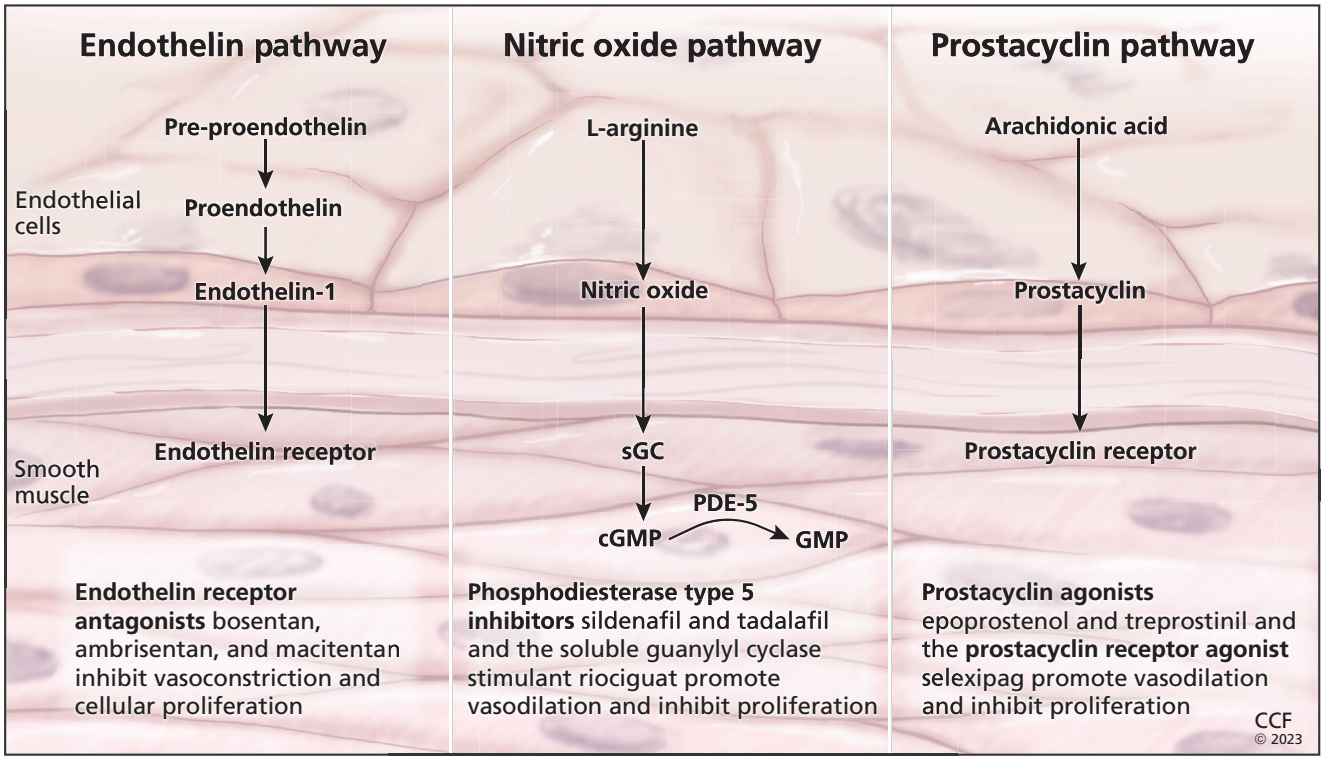

Figure 1. Mechanism of action of pulmonary hypertension medications.

cGMP = cyclic guanosine monophosphate; GMP = guanosine monophosphate; PDE-5 = phosphodiesterase type 5; sGC = soluble guanylyl cyclase

Right heart catheterization is essential for identifying the predominant hemodynamic pattern.

Caveats

Although a hyperdynamic state is inherent in liver disease, it can also be caused or exacerbated by conditions such as anemia, obesity, thiamine deficiency, systemic arteriovenous shunts, and hyperthyroidism.[22] Similarly, a volume overload state can be present in patients with concomitant renal disease or left heart failure (systolic or diastolic, or both). And precapillary pulmonary hypertension, suggestive of portopulmonary hypertension, can also be seen in patients with scleroderma, congenital heart disease, drug or toxin exposure, lung diseases, hypoxia, chronic thromboembolic disease, and sarcoidosis.[5]

IMPLICATIONS FOR LIVER TRANSPLANT

Patients with hyperdynamic circulation and volume overload can undergo liver transplant without pulmonary hypertension therapies. However, liver transplant is contraindicated in patients with portopulmonary hypertension who have persistently elevated pulmonary vascular resistance despite pulmonary hypertension treatment. In 2021, the Organ Procurement and Transplantation Network modified its criteria and now allows liver transplants for patients with portopulmonary hypertension with either of the following 2 hemodynamic patterns after treatment:

- Mean pulmonary artery pressure less than 35 mm Hg and pulmonary vascular resistance less than 5 WU
- Mean pulmonary artery pressure 35 mm Hg to 44 mm Hg and pulmonary vascular resistance less than 3 WU.[23]

Although the 2019 World Symposium on Pulmonary Hypertension decreased the mean pulmonary arterial pressure threshold for the diagnosis of pulmonary hypertension from 25 mm Hg or higher to higher than 20 mm Hg,[4] and the 2023 guidelines lowered the pulmonary vascular resistance threshold from 3 or more WU to more than 2 WU,[5] inclusion criteria in studies of portopulmonary hypertension were based on the older definitions.[24] The current hemodynamic criteria for portopulmonary hypertension remain the following:

- Mean pulmonary artery pressure greater than 20 mm Hg

- Pulmonary artery wedge pressure 15 mm Hg or lower
- Pulmonary vascular resistance 3 WU or greater.[4]

MANAGEMENT

Important goals of therapy include symptom relief and improvements in functional capacity and quality of life. General management includes supplemental oxygen for hypoxemia (resting, exercise-induced, or nocturnal), diuretics for fluid overload, and an exercise program. Specific treatment includes pulmonary vasodilator therapy and, ideally, liver transplant once the pulmonary hemodynamic profile is optimized.[25]

Medications for pulmonary arterial hypertension

Medications specifically for pulmonary arterial hypertension help reduce pulmonary vascular resistance while improving right ventricular function.

Importantly, these medications reduce pulmonary vascular resistance more than they decrease the mean pulmonary artery pressure because they also increase cardiac output, which can partially offset the expected improvement in mean pulmonary artery pressure.[26] In the Portopulmonary Hypertension Treatment With Macitentan—a Randomized Clinical Trial (PORTICO),[27] patients treated with macitentan had a decrease in pulmonary vascular resistance of 37% at 12 weeks, while the mean pulmonary artery pressure dropped 14% and the cardiac index increased 19%.

A unique role of pulmonary arterial hypertension therapies in patients with portopulmonary hypertension is to facilitate liver transplant. A meta-analysis of 26 observational and case-controlled studies in 1,019 patients showed that pulmonary hypertension therapies in patients with portopulmonary hypertension improved their pulmonary hemodynamic numbers, and more importantly, 44% became eligible for liver transplant.[28]

Current drugs for pulmonary arterial hypertension belong to several classes (**Figure 1**)[25,29]:

- Prostacyclin agonists: treprostinil and epoprostenol
- Prostacyclin receptor agonist: selexipag
- Endothelin receptor antagonists: bosentan, ambrisentan and macitentan
- Phosphodiesterase type 5 inhibitors: sildenafil and tadalafil
- Guanylyl cyclase stimulants: riociguat.

All the above PAH-specific drugs are metabolized in the liver, except for epoprostenol, which is rapidly hydrolyzed in blood. Individual medications in these classes have different dosing requirements in patients with cirrhosis. A detailed description of their use in the context of liver cirrhosis was previously published by our group.[25]

Calcium channel blockers are generally not used in patients with portopulmonary hypertension because they can worsen hypotension and exacerbate portal hypertension.[30]

In case reports and small case series, patients with portopulmonary hypertension showed improvements in their pulmonary hemodynamics with pulmonary hypertension therapies. A prospective cohort study examined 637 patients with portopulmonary hypertension, of whom 90% were treated with pulmonary arterial hypertension-specific therapies (74% received monotherapy), resulting in significant improvement in functional class and hemodynamic parameters. Notably, 63 patients underwent liver transplant, of whom 60 (95%) were on pulmonary hypertension therapies as a bridge to transplant.[31] Furthermore, a retrospective study of 21 patients with portopulmonary hypertension showed that early initiation of parenteral epoprostenol therapy allowed 52% of them to become eligible for liver transplant within 1 year.[32]

Unfortunately, the side effects of pulmonary arterial hypertension-specific therapies often overlap with signs and symptoms of liver disease such as nausea, vomiting, anorexia, and edema, limiting the aggressiveness of this treatment.[25]

Only a few studies have tested the impact of pulmonary arterial hypertension therapies in patients with portopulmonary hypertension (**Table 3**).[27,33–36] At the time of this writing, only 1 randomized controlled trial in portopulmonary hypertension (PORTICO)[27] has compared a pulmonary arterial hypertension therapy (macitentan) and placebo. The Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1[33] randomized patients with pulmonary arterial hypertension to riociguat vs placebo and included a subgroup of patients with portopulmonary hypertension.[33–35] In addition, there is an open-label observational trial in portopulmonary hypertension using ambrisentan.[36] In general, patients with portopulmonary hypertension are excluded from trials in pulmonary arterial hypertension owing to hepatic safety concerns and unpredictable blood levels of medications in the context of chronic liver failure.

Patients with suspected or known portopulmonary hypertension should be referred to a pulmonary hypertension center of excellence with multidisciplinary care, as their care is complex. The medications are poorly tolerated and need frequent changes in type and dosage, and patients need serial evaluations and

TABLE 3
Trials of treatment of portopulmonary hypertension

Portopulmonary Hypertension Treatment WIth Macitentan—a Randomized Clinical Trial (PORTICO)[27]

Design: Multicenter, randomized, double-blind, placebo-controlled trial of macitentan 10 mg by mouth once daily (n = 43) vs placebo (n = 42) for 12 weeks.

Inclusion and exclusion criteria: Adults age ≥ 18 with portopulmonary hypertension, 6-minute walking distance ≥ 50 m, pulmonary vascular resistance > 320 dynes·sec·cm^{-5}; excluded patients with Model for End-stage Liver Disease score ≥ 19 or Child-Pugh class C liver disease.

Results: 35% reduction in pulmonary vascular resistance in macitentan group compared with placebo.

Comments: No hepatic safety concerns; more adverse effects (such as peripheral edema) in the macitentan group.

Subgroup analysis from Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (PATENT-1) and PATENT-2[33–35]

Design: Multicenter, randomized, double-blind, placebo-controlled trial of riociguat up to 2.5 mg 3 times daily vs placebo for 12 weeks in 443 patients with pulmonary arterial hypertension (PATENT-1), of whom 13 had portopulmonary hypertension, with open-label extension in 396 patients who had no side effects (PATENT-2).

Inclusion criteria. Adults age ≥ 18, pulmonary arterial hypertension due to any cause, never treated or treated with endothelin receptor antagonist or prostacyclin analogue (except intravenous).

Results: Improvement in 6-minute walking distance (+ 48 meters with riociguat compared with +3 meters with placebo)
Secondary end point: Improvement in World Health Organization functional class
Sustained effect noted at the end of 2 years in PATENT-2.

Comments: No hepatic safety concerns, but dose adjustment needed; peripheral edema and headache were common adverse effects.

Open-label trial of ambrisentan[36]

Design: Open-label comparison of ambrisentan 5 mg once daily (titrated up to 10 mg once daily at or after week 4 if tolerated) for 24 weeks (n = 23), followed by long-term extension for 24–28 weeks (n = 19).

Inclusion criteria: Adults age ≥ 18 with portopulmonary hypertension, Child-Pugh class A or B, alanine aminotransferase and aspartate aminotransferase levels less than 5 times the upper limit of normal.

Results: No change in 6-minute walking distance, improvement in pulmonary vascular resistance (7.1 ± 5 vs 3.8 ± 1.8 WU, $P < .001$).
Secondary end points: improvement in World Health Organization functional class, right atrial pressure, mean pulmonary artery pressure, and cardiac index.

Comments: Peripheral edema and headaches were common side effects.

treatment optimizations to achieve or maintain eligibility for liver transplant.

PORTOPULMONARY HYPERTENSION HAS A POOR PROGNOSIS

The 5-year mortality rate exceeds 60% even with treatment,[37] and many patients die of complications of their liver disease.[38] In the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management, patients with portopulmonary hypertension had lower survival rates than those with idiopathic or familial pulmonary arterial hypertension (67% vs 85% at 2 years, and 40% vs 64% at 5 years).[39]

In a multivariable model of portopulmonary hypertension in patients from our institution, the Model for End-stage Liver Disease-Na score, resting heart rate, and hepatic encephalopathy were independent predictors of death, while the severity of portopulmonary hypertension did not predict pretransplant mortality risk.[37] Similarly, other investigators showed that severity of cirrhosis negatively affected outcomes,[40] and that the prognosis for patients with portopulmonary hypertension prognosis is poor if they do not receive a liver transplant, despite the use of therapies for pulmonary arterial hypertension.[41] Patients with portopulmonary hypertension do better after liver transplant, with improvement in hemodynamics and decreased need for pulmonary vasodilators.[42] Therefore, efforts should focus on facilitating liver transplant whenever possible.[25,36]

It is essential to differentiate portopulmonary hypertension from other types of pulmonary hyper-

tension, as postcapillary pulmonary hypertension does not appear to have a negative impact on survival after liver transplant.[43]

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