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Decongesting heart failure with diuretics: Easier to prescribe than to fully understand

The clinical hallmark in patients with congestive heart failure (HF) is the presence of excess fluid volume, due at least in part to a cardiac etiology. Clinical HF includes pulmonary and other organ congestion, gravity-dependent soft-tissue edema, and ascites. In severe HF, volume expansion can be accompanied by organ hypoperfusion. Given the obvious link between volume expansion and symptoms, fluid removal has historically been at the top of the therapeutic to-do list. Over time, the list has included phlebotomy, mercurials, loop diuretics, dialysis, hyperfiltration, “unloading therapies,” and therapies that target physiologic pathways. The hope for finding the magic inotrope, including digoxin and dobutamine compounds, has not been fulfilled.

Current options and guidelines for treatment of the patient with HF include use of antagonists to a number of physiologic pathways that are upregulated in response to decreased cardiac function in an ultimately counterproductive way. Large-scale clinical trials support the use of specific drugs that target renin-angiotensin, adrenergic, vasopressin, and aldosterone pathways. A recent addition to this list are drugs that inhibit the sodium-glucose cotransporter 2 (SGLT-2) molecule. SGLT-2 inhibitor drugs have diuretic activity, but likely have additional extrarenal effects. As effective as these drugs have been in clinical trials, there is more to be learned about them and their interaction with traditional diuretics in the setting of decompensated HF.

The use of an intimidating cocktail of drugs, which is now standard of care for patients with chronic HF, is based on solid clinical trial data. Although much less emphasized and the subject of fewer landmark clinical studies, diuretics are still a mainstay in the treatment paradigm, particularly for patients with acute decompensated HF. Despite all the newer drugs and advanced treatment strategies for chronic HF, acute decompensated HF remains an extremely common cause of hospital admission and subsequent readmission. The dosing of diuretics in the acute setting has historically been empiric and experience-based, and the strategy for transition from intense inpatient diuresis to baseline diuretic dosing at the time of discharge is equally so. Initial diuresis is often complicated by some degree of diuretic resistance, and confounders in the discharge management process have included interpreting and managing the frequently elevated postdiuresis creatinine level and concerns regarding postdiuresis sodium retention.

Over the past decade, studies have provided pragmatic guidance for utilizing diuretics in patients with decompensated HF. As discussed by Mirzai et al1 in this issue of the Journal, the DOSE (Diuretic Optimization Strategies Evaluation) study2 provided strong supportive evidence for rapid and aggressive use of intravenous loop diuretic therapy—2.5 times the chronic oral outpatient dose given intravenously, followed by rapid and significant dose escalation. But not all patients respond to this dosing regimen, even after the suggested doubling of the dose in 2 hours. Mirzai et al offer several pragmatic solutions to this clinically challenging scenario in the diuretic-resistant patient. They and others have suggested following the urinary sodium level as well as urine volume, but the timing of sampling and logistics of this approach can be problematic.

Digging deeper into the pathophysiology of diuretic resistance3 reveals several complex interacting pathways. Not surprisingly, many of these have been targeted by drugs included in the current treatment guidelines for chronic HF. But none of these pathways can fully explain or be used to
safely reverse diuretic resistance. Nor do they completely explain the phenomenon of postdiuresis sodium avidity, a potential component of resistance that in healthy humans seems at least in part a reactive response to renal sensing of relative volume depletion. A recent study questioned whether the postdiuresis renal sodium avidity response occurs in patients with chronic HF who likely remain somewhat volume-overloaded, even after initial aggressive diuresis. In an accompanying editorial, Martens et al highlighted the possibility that the kidneys of some patients with chronic HF acquire a sodium-retentive (avid) phenotype, and discuss several hemodynamic mechanisms by which this occurs. Future studies of pathway-targeting pharmacologic approaches may help elucidate this.

Just as the myocardium undergoes structural and biochemical remodeling in the setting of chronic HF, so may the kidney. Perhaps there are epigenetic factors at play that may attenuate the benefit from hemodynamic, neurohumoral, and pharmacologic interventions and complicate the interpretation of short-term studies. Possible evidence that not all of the hemodynamic adjustments to HF and aggressive diuresis are transient comes from the observation that rats treated with loop diuretics respond with significant hypertrophy of the distal tubules, with accompanying enhanced sodium reabsorption.

The article by Mirzai et al in this issue prompted me to do some background reading, including rummaging through files of photocopied papers with my handwritten notes, some dating back to my residency. Yes, Dr. Laurence Beck, if I had paid more attention back then at your conferences, which frequently included strikingly lucid explanations of complicated renal physiology, my understanding would have come easier now. And I fully appreciate the lasting impact you had on many of us as our former program director. If it hadn’t been for you, I’d not likely have found this topic to be as intriguing as I do now, more than 40 years after listening to your teachings. A great educator does indeed impart gifts that keep on giving.

Brian F. Mandell, MD, PhD
Editor in Chief

2022

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PRACTICAL MANAGEMENT OF STROKE
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MULTIDISCIPLINARY COLORECTAL ONCOLOGY COURSE: A CASE-BASED APPROACH
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MASTERING THE MITRAL VALVE
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February 2–5
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ADVANCES IN CONGENITAL HEART DISEASE SUMMIT
February 16–18
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PAIN MANAGEMENT SYMPOSIUM
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Charleston, SC

COMPREHENSIVE CARE FOR THE LIFETIME TREATMENT OF ADULT CONGENITAL HEART DISEASE
March 31–April 1
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COMPREHENSIVE, LIFELONG, EXPEDITIOUS (CLE) CARE OF AORTIC DISEASE
September 22–23
Cleveland, OH

GLOBAL EP
September 29–30
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A 46-year-old woman presented with a 3-month history of progressive fatigue and shortness of breath. She had a history of uterine fibroids with heavy menstrual bleeding but had missed her gynecologic follow-up examination 2 years earlier. Physical examination revealed facial and conjunctival rim pallor, blue sclera (Figure 1A) with conjunctival rim pallor, and koilonychia. Laboratory tests were hemoglobin 4.0 g/dL (reference range 12–16), hematocrit 16.7% (37–47), mean corpuscular volume 54.8 fl (80–98), serum ferritin 0.8 ng/mL (24–307), and transferrin saturation 2.8% (20%–50%). Iron deficiency anemia was diagnosed.

The patient received a blood transfusion and began taking iron supplements. Her uterine fibroids were treated with oral gonadotropin-releasing hormone antagonists. Three months later, her symptoms and physical findings, including the blue sclera (Figure 1B), had resolved, and her hemoglobin and ferritin levels had normalized.

Blue sclera is a common and useful finding of iron deficiency but is often overlooked. In 1908, Sir William Osler first described a blue discoloration of the sclera as a symptom of anemia in young girls and wrote that the eyes “have a peculiar brilliancy and the scleroties are of a bluish color”.i Kalra et al subsequently found that blue sclera is more common in patients with iron deficiency anemia (87%) than in those with other types of anemia (7%). In adult patients, blue sclera reportedly has 87% to 89% sensitivity and 64% to 94% specificity for iron deficiency anemia and iron deficiency (ie, anemia need not always be present).2,3 Blue sclera has been reported in other conditions, albeit rarely, including rheumatoid arthritis, myasthenia gravis, and long-term steroid therapy.2 Its pathogenesis is thought to involve thinning of the collagen fibers of the sclera due to iron deficiency, which allows the bluish color of the underlying uvea to become visible.

Figure 1. (A) Bluish sclera with peculiar brilliancy and pale skin at presentation. (B) Normalized sclera color 3 months after iron supplementation therapy.

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DISCLOSURES

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

REFERENCES


Address: Yasuhiro Kano, MD, Department of General Internal Medicine, Tokyo Metropolitan Tama Medical Center, 2-8-29 Musashidai, Fuchū, Tokyo 183-8524, Japan; yasuhiro.kano.21@gmail.com
Scaly plaques in a malnourished patient

A 30-year-old man presented following an episode of loss of consciousness. He appeared to be malnourished and was known to have a history of alcohol use disorder complicated by cirrhosis. He also had a 1-year history of widespread pruritic rash.

Examination noted well-demarcated pink plaques with cracked scales resembling a riverbed on the scalp, lateral neck, right abdomen, and the dorsal surface of both hands (Figure 1) and forearms, as well as on the feet, inner thighs, and scrotum. There was no involvement of the axillae, interdigital finger and toe web spaces, periungual skin, mons pubis, or umbilicus. Because of the patient’s long-standing history of alcohol use disorder and the presence of chronic rash, malnutrition and nutritional deficiency were suspected.

Laboratory testing revealed the following:
- White blood cell count 19.9 × 10⁹/L (reference range 4.5–11)
- Hemoglobin 8.6 g/dL (14–18)
- Mean corpuscular volume 96.2 fl (80–100)
- Serum zinc 35 μg/dL (70–150)
- Serum alkaline phosphatase (ALP) 735 IU/L (44–147)
- Chromium 0.44 μg/L (≤ 1.4)
- Albumin 1.8 g/dL (4.1–5.1)
- Serum copper within normal limits
- 4th-generation human immunodeficiency virus (HIV) antigen/antibody test nonreactive.

The markedly low serum zinc and the characteristic location of the rash in a patient with long-standing alcohol use disorder and cirrhosis confirmed the diagnosis of acrodermatitis enteropathica. The low serum zinc level is diagnostic, but the test may take many days to return a result. ALP is decreased in acrodermatitis enteropathica as zinc is a cofactor for ALP activity. The ALP will return a result sooner than the serum zinc level. In our patient, the ALP was elevated due to his cirrhosis.

■ TREATMENT

Treatment of acrodermatitis enteropathica typically involves long-term daily zinc supplementation with oral zinc gluconate or zinc sulfate. Our patient was prescribed zinc sulfate 1.5 mg/kg/day. Skin care included topical petrolatum. In 3 weeks, his zinc level had risen from 35 μg/dL to within normal limits at 80 μg/dL, with near resolution of the plaques (Figure 2).

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ACRODERMATITIS ENTEROPATHICA: KEY FEATURES

Acrodermatitis enteropathica is caused by zinc deficiency, and cutaneous findings include sharply demarcated, symmetric erythematous patches and plaques with erosions and scale-crust of the perioral region, genitals, and distal extremities.1 The classically described clinical triad consists of dermatitis, alopecia, and diarrhea, although our patient had no signs of the latter two conditions.

Zinc deficiency may be inherited or acquired.2 Acquired acrodermatitis enteropathica may be secondary to decreased nutritional zinc intake, impaired absorption, or increased gastrointestinal excretion.1 Risk factors for decreased intake include alcoholism, long-term total parental nutrition, vegetarian diets, and diets high in mineral-binding phytates.1,3 Patients with impaired absorption or increased excretion include those with intestinal malabsorption, liver disease, renal disease, Crohn disease, cystic fibrosis, and a history of gastric bypass surgery.2,3

The diagnosis of acquired acrodermatitis enteropathica is largely based on clinical presentation and supported by a serum zinc less than 50 μg/dL. Skin biopsy is rarely necessary but can be diagnostic of a nutritional-deficiency dermatitis that is not specific to acrodermatitis enteropathica. Histopathologic study reveals pallor and ballooning of the keratinocytes in the upper epidermis.6

THE DIFFERENTIAL DIAGNOSIS IN ADULTS

Other diagnoses considered include pellagra, crusted scabies, and an eczematous dermatitis such as atopic or contact dermatitis. Although cracking and fissuring may be seen in patients with chronic eczematous dermatitis, involvement of the distal extremities, face, and groin are classic for acrodermatitis enteropathica. Alcohol use disorder is a common etiology of pellagra, but pellagra typically involves sun-exposed areas, with findings that include a hyperpigmented rash with scale crust and a shiny shellac-like surface along dermatomes C3 and C4 (the Casal collar or necklace).

Crusted scabies is more commonly seen in patients who are immunocompromised, classically in those with HIV. The plaques of crusted scabies are more hyperkeratotic, with a pumice-stone appearance with a distinctive erythema, and they tend to involve the digital interweb spaces, periungual skin, and axillae, which were spared in this patient.

REFERENCES


Address: Allison Zarbo, MD, Department of Dermatology, Henry Ford Health System, 3031 West Grand Boulevard, Detroit, MI 48202; azarbo2@hfhs.org.
Mucormycosis presenting as dental pain

A 19-year-old Indian female was referred to the emergency department by her dentist. She had presented to the dentist with 15 days of constant pain in the left premolar tooth, describing the pain 8 out of 10 and radiating to the left cheek. The dentist performed a root canal procedure, which did not resolve the pain, and 1 week after the procedure she developed mobility in her left upper teeth and sinus discharges on the upper buccal mucosa.

On presentation in the emergency department, the patient said that she had recovered from COVID-19 about 2 weeks earlier and had been treated with dexamethasone. Evaluation in the emergency department showed that she was hemodynamically stable and afebrile. The left side of her face was tender to palpation. On oral examination, mobility of the left upper teeth was noted, with purulent discharge on the upper buccal mucosa (Figure 1).

Results of a complete blood cell count and basal metabolic panel were unremarkable. Magnetic resonance imaging with contrast revealed markedly...
MUCORMYCOSIS

inflamed and hypertrophic mucosa of the left maxillary sinus cavity (Figure 2). The left maxillary bone was noted to be necrotic and nonenhancing (Figure 3). The findings on oral examination and imaging raised concern for mucormycosis, and the patient was referred for emergency surgery.

She underwent thorough debridement and left subtotal maxillectomy. Intraoperatively, the left maxillary sinus cavity could be seen to communicate with the buccal vestibule (Figure 4). Microscopic examination of the excised tissue demonstrated hyphae of irregular width and branching angles of 90 degrees. A diagnosis of maxillary mucormycosis invading into the buccal vestibule was made. The patient was started on amphotericin B, and at 4 weeks after surgery, she had improved completely.

MUCORMYCOSIS: SYMPTOMS, DIAGNOSIS, AND TREATMENT

Mucormycosis is an infection caused by filamentous molds that commonly affect immunocompromised patients such as those with cancer or uncontrolled diabetes. In 2021, a systematic review found numerous cases of invasive fungal infection and mucormycosis reported in patients with COVID-19. This has been attributed to diabetes as a common predisposing comorbidity and to treatment with steroids. Our patient was healthy at baseline. We believe that her treatment with steroids and her immunocompromised state secondary to COVID-19 may have predisposed her to mucormycosis.

Our patient had initial symptoms 25 days after COVID-19 infection, which aligns with the already available literature. Several hospitals in India have opened outpatient departments for mucormycosis to monitor COVID-19-recovered patients from 10 days to 6 weeks, when they are most vulnerable to the fungal infection.

Symptoms

Initial symptoms of mucormycosis are paresthesia and swelling over the face, nasal congestion and discharge, fever, headache, and lethargy, which are similar to symptoms of sinusitis and periorbital cellulitis. However, the appearance of black lesions on the nasal bridge or upper inside of the mouth that are progressively increasing in number or size and associated pulmonary symptoms like cough, chest pain, and dyspnea in a patient with diabetes or immunosuppression should raise a strong suspicion for maxillary mucormycosis. Nevertheless, in rare cases, dental pain can also be a presenting feature of maxillary mucormycosis.

As this disease is rapidly progressive, early diagnosis is crucial in the prognosis of the patient. Fortunately, our patient’s dentist was able to recognize this alarming sign on the second visit and transfer the patient for an emergency evaluation.

Diagnosis and treatment

Microscopic examination of excised tissue in mucormycosis shows hyphae of irregular width and branching angles of 90 degrees. On histopathology, the invasive disease is characterized by prominent infarcts and angioinvasion. Rapid identification of invasive mucormycosis is necessary to minimize the mortality
and morbidity of this disease. Thus, it is worthwhile for clinicians to be able to rapidly identify the characteristics of hyphae of mucormycosis.

It is pertinent to mention that mucormycosis is not contagious. A person can get mucormycosis through contact with fungal spores in the environment. For example, the lung or sinus forms of the infection can occur after someone inhales spores from the air.

Treatment includes immediate hospitalization, surgical debridement and systemic antifungal therapy. The liposomal formulation of amphotericin B (AmBisome) is the drug of choice based on efficacy and safety data.

■ TAKE-HOME MESSAGE

Our patient’s case illustrates the need for early diagnosis and urgent debridement for better outcomes. Mucormycosis should be considered in the differential diagnosis for any patient presenting with dental pain in the setting of recent COVID-19 infection.

■ DISCLOSURES

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

■ REFERENCES


Address: Pankaj Garg, MS, MBBS, Department of Surgery, Indus International Hospital, 1043, Sector 15, Panchkula, Haryana 134113, India; drgargpankaj@yahoo.com
Primary care clinicians face the almost overwhelming task of staying abreast of current research in the various medical disciplines and assessing it for clinical implications. This challenge, in turn, creates knowledge and competency gaps in many primary care clinicians.

This CME-certified, live symposium is designed to review best practices that highlight the latest therapies, procedures, and diagnostics in primary care. You will be offered updates on treatment strategies for common conditions, including diabetes, weight management, adult ADHD, and depression, as well as reviews of the latest in heart failure, chronic nausea, and dysautonomia & POTS syndrome. In addition, our program will incorporate conversations on PreP and HIV, shared decision making in older adults with multiple chronic comorbidities, and how changes in the construct of race in medical care impact clinical practice (kidney disease).

Learn How To
- Summarize the most recently published data from research and clinical trials and discuss their clinical implications for primary care medicine.
- Integrate a model for shared decision-making for older adults with multiple chronic comorbidities.
- Critically review the evidence on pre-exposure prophylaxis for HIV and AIDS.
- Discuss the impact of a patient’s race on the management of kidney disease.
- Review the clinical implications of recently published research on topical areas of interest to primary care practitioners, including diabetes, weight management, adult attention deficit disorders, treatment-resistant depression, heart failure, delayed gastric emptying, and dysautonomia conditions.

Who Should Attend
This activity is designed for family physicians, general internists, nurses, nurse practitioners, physician assistants, and other health care professionals who have an interest in primary care.
Q: How do I interpret and use quantitative buprenorphine and norbuprenorphine urine levels?

A patient returns to the outpatient clinic for follow-up of buprenorphine treatment of opioid use disorder. Buprenorphine confirmatory testing at the last visit had shown a urine buprenorphine level greater than 2,000 ng/mL and a urine norbuprenorphine of 220 ng/mL. How do I interpret these results, and when should I order quantitative buprenorphine confirmatory testing?

Given the cost, quantitative testing should be ordered thoughtfully, and only when the results would change clinical management. Confirmatory buprenorphine testing of urine samples can be useful in outpatient settings where buprenorphine dosing is not directly observed, as in most primary care clinics that offer treatment of opioid use disorder (OUD). Such testing can offer advantages beyond point-of-care immunoassays, including providing confidence to the clinical team on buprenorphine dosing and identification of previously unknown or undisclosed barriers to treatment success. Retaining and engaging the patient in effective treatment should remain the ultimate goals of testing.

BUPRENORPHINE METABOLISM AND LABORATORY ASSESSMENT

Because of its extensive first-pass metabolism by the liver if taken orally, buprenorphine is used sublingually, buccally, via a subcutaneous implant, or via depot injection. Buprenorphine is primarily metabolized by hepatic cytochrome P450 3A4 (CYP3A4) to its active metabolite norbuprenorphine. Buprenorphine and norbuprenorphine are eliminated primarily via the biliary system, with 10% to 30% excreted in urine. Drugs or conditions that inhibit or induce CYP3A4 and genetic polymorphisms affecting CYP3A4 can diminish or enhance buprenorphine metabolism.

A buprenorphine film or tablet can be dipped in or submerged into a urine sample to alter the result (“urine spiking”). In such cases, common indicators of urine specimen integrity (temperature, pH, specific gravity, creatinine, and nitrites) can still be within normal limits, and the result of a point-of-care immunoassay would be positive for buprenorphine. Confirmatory testing provides quantification of urinary buprenorphine and norbuprenorphine, as well as naloxone if ordered, using gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry. Both buprenorphine and norbuprenorphine can be detected in urine for 2 to 4 days and possibly longer in people who are taking buprenorphine chronically.

Although higher doses of buprenorphine generally result in higher plasma levels and creatinine-normalized urine levels of buprenorphine and norbuprenorphine, there is wide variability between individuals.

Given the individual variability of these levels and the variability in the severity of OUD, these quant-
titative buprenorphine and norbuprenorphine levels have no proven or apparent role in reliably indicating
the dose that has been taken recently, nor do they
help determine the effective buprenorphine dose. The effective dose remains a clinical decision. How-
ever, quantitative test results can provide reassurance
that at least some amount is being taken.

### HOW TO INTERPRET BUPRENORPHINE

**CONFIRMATORY TESTING**
The buprenorphine level, norbuprenorphine level, and the norbuprenorphine-to-buprenorphine ratio are important when interpreting results.

Table 1 shows patterns of quantitative levels of buprenorphine and norbuprenorphine and associated differential diagnoses for patients taking sublingual or buccal buprenorphine. These values may not apply to patients receiving extended-release injectable or implantable formulations of buprenorphine.

### Sample scenarios for interpreting test results
The test results reported in Table 1 can be interpreted as follows:

- **Scenario 1:** The values tell us that buprenorphine has been taken recently, but we cannot draw conclusions about the amount taken.
- **Scenario 2:** The values are low. While there is no agreed-upon threshold for “low” values, the upper limit of the lowest quartile among several studies was 20 ng/mL for buprenorphine and 45 ng/mL for norbuprenorphine, although other studies have considered less than 100 ng/mL to be low. Low values may be consistent with adherence, given individual variation, but it is reasonable in this setting to engage the patient in exploratory discussions related to dosing consistency, sublingual or buccal technique, and medication interactions.
- **Scenario 3:** In general, the ratio of norbuprenorphine to buprenorphine is often greater than 1, but there is significant individual variability. The
ratio appears independent of dose but dependent on the time since the most recent dose, because plasma and urine levels of buprenorphine rise and fall faster than those of norbuprenorphine. The pattern of a positive but low urinary buprenorphine and a lower or negative norbuprenorphine can arise with dosing of buprenorphine for the first time in days only hours (often 0.5 to 2 hours) before providing the urine sample.

• **Scenarios 4 and 5:** Buprenorphine levels are high, while norbuprenorphine levels are low or negative. Several studies suggest a ratio of norbuprenorphine to buprenorphine of less than 0.02 as a threshold for identifying urine spiking, based on data outliers. In another study, with subsequent patient confirmation of urine spiking as a reference, a norbuprenorphine-buprenorphine ratio of 0.26 or less provided maximal sensitivity but low specificity (58%) for urine spiking, while buprenorphine concentrations of 700 ng/mL or greater had a specificity of 85% and sensitivity of 77%. Elevated urine naloxone levels with thresholds of at least 200 ng/mL are often seen with parenteral use of buprenorphine-naloxone or urine spiking with buprenorphine-naloxone. When any of these indicators is present, it is reasonable to consider urine spiking and explore this possibility with the patient. Positive levels of norbuprenorphine likely suggest recent dosing of at least some amount, even in the presence of indicators of urine spiking. However, it is unknown whether low levels of norbuprenorphine in cases otherwise suggestive of urine spiking represent recent dosing or spontaneous formation of norbuprenorphine in vitro from high concentrations of unconsumed buprenorphine.

**Case example revisited**

In the opening case, the buprenorphine level of greater than 700 ng/mL, the positive norbuprenorphine level, and a low norbuprenorphine-buprenorphine ratio (0.11) suggest recent dosing of some amount of buprenorphine and the possibility of urine spiking with unconsumed buprenorphine (scenario 5).

**MOTIVATIONS FOR URINE SPIKING**

Patients may engage in urine spiking for various reasons. They may have missed doses, lost medication, or diverted some or all of their buprenorphine to help others or for financial reasons, and they may fear the perceived consequences of providing a urine sample negative for buprenorphine. Some may be taking their buprenorphine as prescribed but fear consequences of nonprescribed drug use and thus spike a diluted or acquired urine specimen. In one study, patients who provided spiked urine samples had significantly lower treatment retention rates (defined in this study as adherence to the treatment program until data collection ended) after this finding was discussed with them. Given mortality rates with untreated OUD, it is imperative to approach conversations about urine spiking from a place of empathy for the patient, acknowledging that urine spiking may often reflect treatment struggles and the need for more support. Creating a psychologically safe space for patients, inviting the patient to share treatment-related struggles, and transparency about urine testing are components of effective care and, in our experience, may reduce urine spiking. Retaining patients in care and identifying barriers to effective treatment should be the goals of these conversations.

**Indicators of urine spiking include high buprenorphine levels and low norbuprenorphine-buprenorphine ratios**

**THE BOTTOM LINE**

Quantitative buprenorphine and norbuprenorphine testing can be useful in outpatient settings where dosing is not observed. It is reasonable to order it once in the first months of buprenorphine treatment and then periodically (eg, every 3 to 6 months) for patients whose OUD is not in remission, while being transparent with the patient about when urine samples are tested. The levels cannot be used to draw conclusions about dosing amounts but may help identify previously unknown or undisclosed barriers to treatment.

Interpreting the results based on the current evidence and acknowledging their limitations, along with an inquisitive, nonjudgmental communication style, can identify barriers to treatment and enhance clinical care in a way that point-of-care immunoassays cannot.

**Acknowledgment:** We are grateful to Dr. Petrie Rainey of the Department of Laboratory Medicine, University of Washington, Seattle, for the insightful comments on earlier drafts related to laboratory measurements of buprenorphine and norbuprenorphine.

**DISCLOSURES**

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

REFERENCES


Address: Richard C. Waters, MD, MSc, Housing & Street Outreach Programs, Neighborcare Health, 1930 Post Alley, Seattle, WA 98101; rcwaters@gmail.com

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Q: How do we maximize diuresis in acute decompensated heart failure?

A: IN PATIENTS WITH ACUTE DECOMPENSATED heart failure (ADHF), the initial diuretic regimen should maximize intravenous loop diuretics based on urine output or spot urine sodium. Combination therapy can be used if diuretic resistance occurs.

ADHF accounts for more than 1 million hospitalizations per year in the United States, and inadequate diuresis is a common cause of readmissions and higher mortality. In the absence of cardiogenic shock, ADHF manifestations are driven primarily by expansion of extracellular fluid volume, leading to elevated cardiac filling pressures and congestion (edema, dyspnea, and orthopnea). Despite the evidence supporting guideline-directed medical therapy, studies guiding diuresis are limited.

**LOOP DIURETICS**

Loop diuretics are the cornerstone of ADHF management. Their early administration is linked to lower in-hospital mortality rates. Furosemide, torsemide, and bumetanide are the most used (Table 1). Torsemide and bumetanide have better bioavailability than furosemide, and data suggest torsemide superiority, given its possible improved outcomes and mitigation of cardiac fibrosis.

**Initial dosing**

Loop diuretics have a steep dose-response curve with little natriuretic effect until an individualized threshold is reached, and maximum natriuretic effect once the ceiling dose is achieved (Figure 1). Dose increases beyond the ceiling may increase the duration of natriuresis rather than the rate by maintaining the diuretic concentration above the threshold for longer. The dose-response relationship is log-linear, meaning the dose should be adjusted in a logarithmic fashion (eg, an increase from 20 mg to 40 mg is greater than 220 mg to 240 mg).

Regarding initial dosing, the DOSE trial (Diuretic Optimization Strategies Evaluation) found better symptom improvement with aggressive intravenous loop diuretic dosing 2.5 times the total daily oral dose compared to a numerically equal dose. There is conflicting evidence about the relationship between diuretic dosing, renal dysfunction, and clinical outcomes. In general, to avoid premature cessation of diuretic therapy, doubling of creatinine or an increase greater than 1 mg/dL (instead of > 0.3 mg/dL) has been suggested as true renal dysfunction requiring further workup.

Recent data suggest that using urine output and spot urine sodium to predict short-term responsiveness to intravenous loop diuretics in ADHF permits more timely adjustments to therapy (Figure 2). With this approach, if the goal of a urine output of more than 150 mL/hour or a urine sodium greater than 50 to 70 mEq/L is not achieved at 2 hours after the initial dose, the dose should be doubled and the parameters rechecked 2 hours after the repeat dose until the goals are met. When the goals are met, the same dose can be administered every 6 to 12 hours until volume overload resolves. Continuous furosemide infusion is also commonly used in refractory cases, given favorable pharmacodynamics with concentration maintenance above the threshold. The DOSE trial showed no difference in efficacy between...
continuous and intermittent dosing, but loading doses were not given at infusion initiation.5

DIURETIC RESISTANCE

Diuretic resistance is defined as persistent congestion with inadequate response to escalating diuretic doses.1 Although there is no consensus on a precise metric, the inability to meet short-term urine sodium goals (Figure 2) can predict diuretic resistance. The proposed quantitative definition is failure to increase urine sodium by 90 mEq/L despite high-dose oral furosemide (160 mg twice daily or equivalent) over 3 days.7

Loop diuretics achieve their effect primarily by secretion into tubular fluid by proximal organic anion transporters, a process dependent on renal blood flow and serum pH.7 The response to loop diuretics may be diminished due to genetic polymorphisms altering transport and metabolism,8 low absorption from gut edema (as may occur with oral furosemide), low plasma protein content (> 90% protein-bound), and low renal function or perfusion (particularly with nonsteroidal anti-inflammatory drugs or possibly aspirin).3 Dietary sodium restriction nonadherence must also be ruled out since postdiuretic sodium retention can mimic true diuretic resistance.3 Renin-angiotensin system activa-
tion may also contribute, but distal tubular cell hypertrophy with increased sodium resorption is emerging as the primary mechanism of diuretic resistance.\(^3\)

**OPTIONS FOR AUGMENTING DIURESIS**

Several options exist to augment diuresis. However, most experts recommend delaying combination therapy until loop diuretic dosing is optimized (Figure 2), to avoid risks of renal dysfunction and electrolyte abnormalities.\(^3\)

**First-line therapy: thiazide diuretics**

Thiazide diuretics overcome the increased sodium avidity of the distal convoluted tubule that occurs with chronic loop diuretic use.\(^5,9\) Commonly used thiazide diuretics are metolazone and hydrochlorothiazide, but other options have similar efficacy and adverse-event rates (Table 1).\(^9\) The current guidelines for thiazide use are based on small studies\(^3,9\) and the CARRRESS-HF trial (Cardiorenal Rescue Study in Acute Decompensated Heart Failure),\(^10\) where thiazides used in a stepwise pharmacologic algorithm were compared with ultrafiltration.

**Second-line therapy: acetazolamide, potassium-sparing diuretics**

Although a poor diuretic on its own, the carbonic anhydrase inhibitor acetazolamide has been shown to augment the loop diuretic effect through decreased sodium bicarbonate reabsorption in the proximal tubules (Table 1).\(^9\) This allows more sodium delivery to the loop of Henle, but tolerance develops after 72 hours.\(^1\) Acetazolamide also has intrinsic renal vasodilatory effects and blocks the pendrin system of chloride-bicarbonate exchange in the distal nephron.\(^1,11\) Combination therapy with acetazolamide has shown greater decongestion success compared with loop diuretics alone in the recent ADVOR trial (Acetazolamide in Decompensated Heart Failure With Volume Overload),\(^12\) without significant differences in adverse events or the secondary end points of death or rehospitalization.

The potassium-sparing diuretics amiloride and triamterene inhibit distal epithelial sodium channels in the collecting duct. Anecdotal evidence suggests amiloride can result in decongestion, but randomized clinical trials are lacking, and these medications can lead to severe hyperkalemia.\(^2\) Spironolactone works on a separate receptor to cause mild natriuresis, and it reduces potassium wasting of loop and thiazide diuretics. Data are limited regarding its synergistic use with loop diuretics in ADHF. The ATHENA-HF trial (Aldosterone Targeted Neurohormonal Combined With Natriuresis Therapy in Heart Failure)\(^13,14\) found no difference in outcomes with this regimen; however, the patient sample did not exhibit diuretic resistance, and the 4 days of therapy may have been inadequate for response (spironolactone is a prodrug).

**Alternatives**

**Tolvaptan.** Vasopressin levels are increased in heart failure, worsening fluid retention. The selective V\(_2\) vasopressin receptor antagonist tolvaptan blocks distal tubule reabsorption of free water. It has been shown to improve filling pressures when combined with loop diuretics. It may be preferable in patients with hyponatremia and kidney dysfunction, but no improved outcomes have been seen.\(^13\) A moderate-sized cohort study comparing metolazone, chlorothiazide, and tolvaptan has shown excellent weight loss with no significant difference between the groups.\(^15\) Conivaptan has also demonstrated promising diuresis augmentation in heart failure without adverse renal or hemodynamic effects.\(^16\)

**Sodium-glucose cotransporter 2 inhibitors** decrease proximal sodium absorption. Strong evidence from clinical trials shows significant diuresis

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**FIGURE 1.** Loop diuretic dose-response curves in patients with heart failure (green line) and without heart failure (blue line). Heart failure shifts the curve down and to the right, translating to the need for higher doses of diuretics to achieve the same degree of diuresis and decreased maximal diuretic response.

\[
\text{FE}_{\text{Na}} = \text{fractional excretion of sodium}
\]

Based on data from reference 2.
FIGURE 2. Algorithm for initiation (day 1) of diuretic titration in patients with acute decompensated heart failure.

*aHigher dose for reduced glomerular filtration rate.

*bSee Table 1 for maximum recommended total daily dosing.

IV = intravenous; \( U_{Na} \) = urine sodium; UOP = urine output

Based on data from references 1 and 2.
with renoprotection and improved heart failure outcomes, but coadministration with loop diuretics has not been studied.1

**Hypertonic saline.** Intravenous hypertonic saline has been shown to augment diuresis by improving renal perfusion by osmotic “pulling” of free water into the intravascular space and by improving the loop diuretic effect through better sodium delivery to the loop of Henle.13 It also improves inotropy through myocardial stimulation.1 This method has been associated with reduced mortality rates, hospital length of stay, and treatment cost compared with furosemide alone.1

**Ultrafiltration.** Methods such as ultrafiltration can be used in congestion that is refractory to medical therapy. Outpatient peritoneal dialysis has been described for advanced heart failure with cardiorenal syndrome.15 However, there is no evidence favoring ultrafiltration over loop diuretics as first-line therapy.2

**Hemodynamic evaluation.** An invasive hemodynamic evaluation should be considered in hospitalized patients who have refractory symptoms despite adequate diuresis, worsening renal failure with increasing diuretics, or repeated hospitalization.17 Wireless implantable pulmonary artery pressure monitors showed promising results in the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III HF Patients) trial,18 in which patients with persistent symptoms who were randomized to receive a monitor had a 28% relative reduction in heart failure hospitalization rates.

### THE BOTTOM LINE

ADHF is a major source of healthcare spending in the United States, with many hospital discharges complicated by readmissions due to inadequate diuresis. The initial goal should always be to maximize loop diuretic therapy using urine output or urinary sodium for guidance. Combination therapy can be used when patients respond poorly to escalating loop diuretic doses.

### DISCLOSURES

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

### REFERENCES


Address: Heba Wassif, MD, MPH, Department of Cardiovascular Medicine, Heart, Vascular, and Thoracic Institute, J2-4, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; wassilf@ccf.org
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Q: Atrial fibrillation: Rate control or rhythm control?

A: ATRIAL FIBRILLATION CAN BE MANAGED by either a rate control or a rhythm control strategy. Data as to which provides better clinical outcomes have been mixed.

Until now, rate control has been preferred, in view of the side effects of antiarrhythmic drugs and the noninferiority of rate control that was demonstrated in multiple studies. However, rate control as the primary approach is now in question, and the pendulum is swinging in favor of rhythm control.

For patients with atrial fibrillation, the 3 principal goals of therapy are to control symptoms, prevent thromboembolism and stroke, and prevent tachycardia-mediated cardiomyopathy. Maintaining sinus rhythm has many benefits, as it is more physiologic and maintains atrioventricular synchronicity with improved ventricular filling through “atrial kick,” thereby improving exercise tolerance, relieving symptoms better, and preventing structural and electrical remodeling. Therefore, even if direct evidence from randomized clinical trials is lacking in many types of patients, given the unpredictable long-term adverse effects of atrial fibrillation, rhythm control is generally the goal. Another factor pushing us in that direction is modern technology such as pulsed-field ablation, which has shown benefits and safety in preclinical and clinical studies.

EVIDENCE FAVORING RATE CONTROL

Several landmark trials formed the basis of current guidelines for treating atrial fibrillation.

The AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management), published in 2002, was one of the first large randomized controlled trials to compare rate control and rhythm control. It found no difference in survival outcomes between the strategies, and rates of hospitalization and adverse drug effects were significantly lower with rate control. In both study groups, most strokes occurred after warfarin was stopped or when the international normalized ratio was subtherapeutic. The mean age of the patients was 70, and therefore these results may not be applicable to younger patients.

The STAF study (Strategies of Treatment of Atrial Fibrillation) yielded results similar to those of the AFFIRM trial in terms of both survival and hospitalizations.

The PIAF trial (Pharmacological Intervention in Atrial Fibrillation) showed no significant difference in symptom improvement between the treatment groups, but the rhythm control group had more hospital admissions.

The RACE study (Rate Control vs Electrical Cardioversion for Persistent Atrial Fibrillation) found more cardiovascular deaths and hospitalizations for congestive heart failure with rate control, while thromboembolic events, drug side effects, and pacemaker implantation were more frequent in the rhythm control group.

Of note, most of these trials were designed to evaluate the noninferiority of rate control compared with rhythm control, not superiority. Another consideration is that these trials were conducted almost 20 years ago, and rhythm control strategies—in particular, ablation—have since evolved.
EVIDENCE FAVORING RHYTHM CONTROL

Rhythm control strategies include antiarrhythmic drug therapy and catheter ablation.

The EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial)\(^9\) reported that in patients with a diagnosis of atrial fibrillation within the past year and concomitant high-cardiovascular-risk conditions, treatment with drugs or catheter ablation was associated with lower risks of death from cardiovascular causes, stroke, or hospitalization for heart failure or acute coronary syndrome than usual care. Furthermore, there was no significant difference in length of hospital stay between the groups. The favorable results for rhythm control were likely due to including catheter ablation along with antiarrhythmic drugs as a rhythm control treatment.

The Get With The Guidelines—Heart Failure registry\(^10\) study found that rhythm control was associated with lower risk of death at 1 year in patients age 65 and older with atrial fibrillation and heart failure with preserved ejection fraction.

Shojae et al\(^11\) found that, in patients who presented to the emergency department in rapid atrial fibrillation, amiodarone was superior to digoxin with regard to treatment success and quicker onset of action.

Delle Karth et al\(^12\) compared amiodarone vs diltiazem in critically ill patients and found equivalent outcomes with either drug. However, more patients had to discontinue diltiazem therapy due to hypotension.

EVIDENCE ON CATHETER ABLATION VS MEDICAL THERAPY

Numerous randomized controlled trials have compared catheter ablation and medical therapy for

<table>
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rhythm control in atrial fibrillation.

The CASTLE-AF (Catheter Ablation for Atrial Fibrillation With Heart Failure)\(^{13}\) and AATAC (Ablation vs Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device)\(^{14}\) trials included patients with atrial fibrillation and left ventricular systolic dysfunction. They showed that catheter ablation was associated with significantly lower rates of death from any cause or of hospitalization for worsening heart failure compared with medical therapy. CASTLE-AF compared catheter ablation vs medical therapy for rate or rhythm control, whereas AATAC compared catheter ablation vs amiodarone.

The CABANA trial (Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation)\(^{15}\) included patients with and without left ventricular systolic dysfunction and an overall healthier cohort than in CASTLE-AF and AATAC. Catheter ablation did not show a significant reduction in death, disabling stroke, serious bleeding, or cardiac arrest compared with medical therapy at 12 months. These results were thought to be affected by lower-than-expected event rates and high crossover rates in the study. Per-protocol analyses, as opposed to intention-to-treat analyses, showed significant benefit with catheter ablation vs drug therapy with regard to both the primary and secondary end points. On subgroup analysis, the maximal benefit of catheter ablation was in younger patients.\(^{16}\)

D’Angelo et al\(^{17}\) performed a retrospective study and found results comparable to those of CABANA, with early referral for catheter ablation showing better outcomes as opposed to late referral.

The STOP-AF First\(^{18}\) and EARLY-AF (Early Aggressive Invasive Intervention for Atrial Fibrillation)\(^{19}\) trials found lower rates of recurrence of arrhythmia with cryoablation than with antiarrhythmic drug therapy.

Asad et al\(^{20}\) performed a meta-analysis of the above-mentioned studies and several others comparing catheter ablation vs medical therapy for atrial fibrillation. The rate of all-cause mortality was lower with catheter ablation, a difference that was primarily driven by patients with atrial fibrillation and heart failure with reduced ejection fraction from the CASTLE-AF trial. Moreover, there were significant reductions in cardiovascular hospitalizations and recurrence of atrial arrhythmia with catheter ablation in patients both with and without heart failure.

### INDIVIDUALIZED THERAPY

The choice of therapy should be individualized, as summarized in (Table 1).

**Rate control** with a beta-blocker or calcium channel blocker may be preferred in patients with asymptomatic atrial fibrillation (whether paroxysmal, persistent, or permanent) and in patients in whom rhythm control may not be a good option, such as elderly patients, patients with long-standing atrial fibrillation, and those with markedly enlarged left atria. Calcium channel blockers are best avoided in patients with heart failure.

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**Since its invention, ablation has demonstrated the best outcomes with regard to mortality and morbidity**

---

**Rhythm control**

Rhythm control may be preferable in patients who are younger, are at high cardiovascular risk, or have heart failure, or in patients for whom rate-control therapy has failed.

**Cardioversion** can restore sinus rhythm and can be repeated multiple times if unsuccessful at first. It can be used for patients with symptoms or with newly diagnosed atrial fibrillation. To lessen the risk of thromboembolism, patients must have had atrial fibrillation for less than 48 hours, must have been on anticoagulation for at least 3 weeks, or must undergo transesophageal echocardiography to rule out thrombus before cardioversion.\(^{21}\)

**Antiarrhythmic drug therapy.** Occasionally, certain antiarrhythmic drugs may need to be started in the hospital to ensure patient safety, as they can lead to life-threatening arrhythmias. Amiodarone and dronedarone have the least-cardiotoxic adverse effects compared with other antiarrhythmic drugs. However, amiodarone has significant systemic effects, including liver, lung, and thyroid toxicity. Dronedarone has a better systemic adverse-effect profile than amiodarone, but it is associated with hepatotoxicity.

Dronedarone cannot be used in patients with heart failure, as a higher mortality rate has been reported in this subgroup when given dronedarone.\(^{22}\) Moreover, the PALLAS study (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy)\(^{23}\) found that dronedarone was associated with higher rates of stroke, cardiovascular death, and readmission when used to treat permanent atrial fibrillation.
Amiodarone is the most commonly prescribed antiarrhythmic drug for atrial fibrillation, and when compared with other antiarrhythmics, including sotalol, dronedarone, propafenone, and flecainide, it was the most effective in maintaining sinus rhythm. Amiodarone, sotalol, and dofetilide can be safely used in patients with structural heart disease, but caution is advised for other antiarrhythmic drugs.

Propafenone and flecainide are good options in patients without structural heart disease.

Catheter ablation. Since its invention, ablation has demonstrated the best outcomes with regard to patients without structural heart disease.


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A 65-year-old man with melena and a blood disorder

A 65-year-old man presented to the emergency department after having 3 black, tarry bowel movements in the last 24 hours. He had had another episode of melena 4 months earlier, in which upper endoscopy had revealed esophagitis.

For the past 3 years he had chronic anemia related to primary myelofibrosis. The diagnosis had been confirmed by bone marrow biopsy that showed increased cellularity (70%–80%), 1.4% blasts, myelofibrosis (graded MF-3 on a scale of MF-0 to MF-3), normal karyotype, BCR/ABL-negative, and JAK2-positive. He was being treated with epoetin alfa and ruxolitinib for this condition and needed blood transfusions every other week. His last transfusion had been earlier in the day of the bleeding, and his hemoglobin level at that time was 7.6 g/dL (reference range 13.2–16.6).

The patient also had hypertension, stage 3 chronic kidney disease, vertigo, and gout. Asked whether he was taking any drugs that could predispose to bleeding such as anticoagulants, antiplatelet agents, nonsteroidal anti-inflammatory drugs, or selective serotonin reuptake inhibitors, he said he was not.

■ PRIMARY MYELOFIBROSIS: A NEOPLASM OF BONE MARROW

1 Which of the following is the most common cause of death in patients with primary myelofibrosis?

☐ Bleeding
☐ Cardiovascular complications
☐ Leukemic transformation
☐ Infection

Primary myelofibrosis is a chronic myeloproliferative neoplasm. Its clinical manifestations are nonspecific and include fever, fatigue, weight loss, and night sweats. In the absence of symptoms, it is usually discovered in a workup for anemia, splenomegaly, or hepatomegaly. Primary myelofibrosis is classified as either overtly fibrotic or prefibrotic.

The World Health Organization lists 3 major and 5 minor criteria for diagnosis:

Major criteria:

- Megakaryocyte changes
- JAK2, CALR, or MPL mutations or clonal markers on bone marrow analysis
- Exclusion of other myeloid neoplasm diagnoses.

Minor criteria:

- Anemia not otherwise explained
- Leukocytosis
- Palpable splenomegaly
- Increased serum lactate dehydrogenase
- A leukoerythroblastic blood smear, confirmed in 2 consecutive determinations.

The diagnosis of overt primary myelofibrosis is established if all 3 major criteria and 1 minor criterion are met.

Causes of death

The most common causes of death in patients with primary myelofibrosis are leukemic progression, responsible for up to 20% of deaths, followed by cardiovascular complications, infection, and bleeding.

There are validated prognostic scoring tools for primary myelofibrosis. Age older than 65, severity of anemia, degree of leukocytosis, number of circulating blasts, and presence of constitutional symptoms are associated with worse survival rates.

■ CASE CONTINUED: INITIAL EVALUATION

The patient was awake, oriented, and able to provide...
MELENA

a coherent medical history. He appeared mildly malnourished but with a good general appearance. His pulse was 104 beats per minute and his blood pressure was 136/57 mm Hg. His spleen was palpable, and the rims of his conjunctiva were mildly pale. On rectal examination, his stool was black and tarry. No spider angiomas or jaundice was noted on physical examination, and there were no signs of ascites on abdominal examination.

Results of a complete blood cell count and other initial laboratory tests were as follows:

- Hemoglobin 6.6 g/dL (reference range 13.2–16.6)
- Hematocrit 20.8% (38.3%–48.6%)
- Mean corpuscular hemoglobin 28.4 pg (25.4–32.7)
- Red blood cell count $2.32 \times 10^{12}$/L (4.35–5.65)
- Red cell distribution width 26.9% (11.8%–14.5%)
- White blood cell count 12.9 $\times 10^9$/L (3.4–9.6)
- Platelet count 210 $\times 10^9$/L (135–317).
- Glomerular filtration rate 55 mL/min/1.73 m\(^2\) body surface area (> 60)
- Serum creatinine 1.39 mg/dL (0.74–1.35)
- Total bilirubin 1.3 mg/dL (≤ 1.2)
- Sodium 140 mmol/L (135–145)
- Potassium 4.7 mmol/L (3.6–5.2)
- Chloride 105 mmol/L (98–107)
- Blood urea nitrogen 29 mg/dL (8–24)
- Prothrombin time 17.5 seconds (11.6–14.7)
- International normalized ratio 1.4 (0.8–1.1).

The patient received 2 units of packed red blood cells and an intravenous proton-pump inhibitor.

Does the patient need to be admitted?

Which of the following would not influence the decision whether to admit the patient to the hospital or perform an outpatient workup?

- Melena
- Low hemoglobin level
- Tachycardia
- Splenomegaly

Scoring systems are available to help determine the need for hospitalization in patients with upper gastrointestinal bleeding.

The Glasgow-Blatchford score is recommended by the International Consensus Group guideline.\(^5\) This 23-point score is based on sex, pulse, systolic blood pressure, blood urea nitrogen, hemoglobin, chronic liver disease, chronic heart disease, melena, and syncope.\(^6\) A score of 0 or 1 is associated with a very low risk of rebleeding, death, or need for urgent endoscopic intervention.\(^7\)

The Rockall score, also commonly used,\(^8\) is based on clinical components (age, blood pressure, heart rate, and comorbidities) and endoscopic findings (diagnosis and bleeding stigmata). However, it is less accurate than the Glasgow-Blatchford score.\(^9,10\)

The Glasgow-Blatchford score has been proven for assessing the need for intervention for both variceal\(^11\) and nonvariceal bleeding.\(^12\) Different studies confirmed its accuracy in predicting outcomes.\(^7,10,13\)

A modified Glasgow-Blatchford score, which omits the subjective components (comorbidities, melena, and syncope), has also been shown to perform well.\(^14\) These scores do not consider splenomegaly.

The patient had no history of liver disease, heart failure, or recent syncope or presyncopal symptoms. His calculated Glasgow-Blatchford score was 12. He was admitted to the hospital for further evaluation and upper endoscopy.

Case continued: Upper endoscopy performed

In view of the patient’s worsening anemia, upper endoscopy was performed. Findings included 5 columns of spurting, large varices (> 5 mm, grade 3 on a scale of 3) in the lower third of the esophagus (Figure 1A), and red, dilated venules (ie, the “red wale” sign). No varices were seen in the stomach, although there was a substantial amount of clotted blood in the gastric fundus and body, which could have hidden any varices there. Six bands were placed (Figures 1B, 1C), which partially eradicated the esophageal varices, and the patient was started on octreotide by continuous infusion for 72 hours. Intravenous ceftriaxone 1 g was administered approximately 4 hours after the patient presented to the emergency room, and he received 1 g daily on subsequent days. He had no further episodes of melena during the hospitalization, and he was discharged after 4 days.

Management of esophageal varices

Which option is the best next step in managing esophageal varices after hospitalization?

- A beta-blocker and follow-up endoscopy in 1 to 4 weeks
- Abdominal ultrasonography and repeat endoscopy in 1 week
- A transjugular intrahepatic portosystemic shunt
- Abdominal ultrasonography and upper endoscopy in 4 to 8 weeks

Hemostasis in esophageal variceal bleeding should
preferably be achieved with variceal band ligation. Sclerotherapy should usually be avoided but may be necessary if visualization is difficult or if there is extensive scarring from previous banding.

The management goals for a patient with acute variceal hemorrhage are to avoid complications and reduce the risk of rebleeding. Red, dilated venules (ie, the red wale sign) and are considered the endoscopic sign with the highest risk of rebleeding.

Secondary prophylaxis after an episode of variceal bleeding can lessen the risk of death. Initial management includes noncardioselective beta-blockers such as propranolol, nadolol, and carvedilol. These medications reduce the risk of esophageal hemorrhage and slow the rate of growth of varices. The dosage should be titrated to the highest dose tolerated or to a reduction in the resting heart rate by 25% or as low as 55 beats per minute. Our patient was started on carvedilol 6.25 mg daily.

The American Association for the Study of Liver Diseases recommends upper endoscopy every 2 to 8 weeks until the varices are eradicated, again 3 to 6 months after eradication, and then every 12 months. Ultrasonography is recommended in the acute setting to investigate new or worsening ascites in patients with bleeding esophageal varices, if there is suspicion of portal vein thrombosis, or to investigate portal hypertension if there is no known history of liver disease.

In patients with advanced cirrhosis (Child-Pugh class B or C), placement of a transjugular intrahepatic portosystemic shunt within the first 3 days after presentation was shown to reduce the risks of further bleeding and death at 1 year. In general, the major drawback of this treatment is overt hepatic encephalopathy, which occurs in about one-third of patients. It should be therefore reserved for select cases. In the setting of bleeding esophageal varices, the ideal candidate for shunt placement within the first 3 days of presentation would have no history of hepatic encephalopathy, no history of heart failure or tricuspid valve regurgitation, no signs of sepsis, no pulmonary hypertension, and no significant coagulopathy.

CASE RESUMED: FURTHER INVESTIGATION

Abdominal ultrasonography was done to evaluate for hepatic or portal vein thrombosis. The liver was normal in appearance, and blood flow was normal on Doppler studies. The spleen was markedly enlarged (measuring 24.5 cm), and there was mild ascites. Four weeks after discharge, upper endoscopy was performed again and revealed several varices in the esophagus. The varices were medium-sized (grade 2 on a scale of 3) and not bleeding, and there were no stigmata of recent bleeding and no red wale signs. Three bands were placed in the distal 5 cm of the esophagus. The mucosa of the stomach was diffusely mildly congested, with apparent extrinsic compression along the greater curvature of the gastric body. In the second portion of the duodenum, the mucosa appeared swollen with the suggestion of “ropey” protuberances.

Since Doppler ultrasonography did not show any obvious portal vein thrombosis, magnetic resonance imaging of the abdomen was performed to evaluate the etiology of the esophageal varices. This showed cirrhotic liver morphology and hepatic iron deposition (likely related to transfusions or iron therapy), without suspicious liver lesions. The hepatic vasculature was patent, with conventional arterial anatomy and large main portal and splenic veins. Portal hyper-
tension with moderate ascites and venous collaterals including gastroesophageal varices were present. The spleen was markedly enlarged, measuring 22.5 cm.

### Etiology of Portal Hypertension

**Presinusoidal causes**
- Idiopathic noncirrhotic portal hypertension
- Biliary diseases (primary biliary cirrhosis, primary sclerosing cholangitis)
- Neoplastic and nonneoplastic occlusion of the portal vein
- Schistosomiasis
- Polycystic disease
- Arteriovenous fistulas
- Congenital hepatic fibrosis

**Sinusoidal causes**
- Drug-induced
- Alcoholic liver damage
- Nonalcoholic steatohepatitis
- Viral hepatitis
- Amyloid
- Infiltrative diseases
- Visceral leishmaniasis
- Gaucher disease
- Acute fatty liver of pregnancy

**Postsinusoidal causes**
- Budd-Chiari syndrome
- Veno-occlusive disease
- Hypervitaminosis A
- Primary vascular malignancies
- Epithelioid hemangiendothelioma and angiosarcoma

**Cirrhosis accounts for most cases of portal hypertension in Western countries.**

Noncirrhotic causes account for less than 10% of cases, and they present with normal synthetic liver function and normal to mildly elevated hepatic venous pressure gradient. Common causes of noncirrhotic portal hypertension include Budd-Chiari syndrome, portal vein thrombosis, and idiopathic portal hypertension. Schistosomiasis, a disease caused by parasitic worms lodging in the liver, is common in Africa and other tropical areas but not in the United States.

Causes of portal hypertension are divided according to their anatomic location. Prehepatic and posthepatic causes differ from intrahepatic disorders in that they do not directly involve the liver. These disorders cause a disruption in the hepatic vascular system that leads to increased pressure in the portal venous system.

Intrahepatic causes are categorized according to where the obstruction is in relation to the sinusoids, ie, presinusoidal, sinusoidal, or postsinusoidal (Table 1), although many of them can affect more than one vascular compartment.

Idiopathic portal hypertension has been reported worldwide, but mainly in developing countries, the Indian subcontinent, and Japan. By definition, the cause is unknown, but studies have found associations with other conditions including immunologic disorders, genetic diseases, human immunodeficiency virus infection, and exposure to drugs and toxins.

Noninvasive diagnostic approaches such as liver imaging modalities are useful, but the differential diagnosis to determine the cause of the portal hypertension relies on thorough interpretation of the liver biopsy.

### CASE RESUMED: BIOPSY

The patient’s cirrhosis was presumed to be secondary to iron deposition. Results of iron studies were as follows:
- Ferritin level 1,227 µg/L (24–336)
- Iron 156 µg/dL (50–150)
- Total iron binding capacity 165 µg/dL (250–400)
- Percent saturation > 90% (14%–50%).

However, the patient’s levels of liver enzymes and albumin were within normal limits. We decided to confirm the diagnosis of cirrhosis and further investigate its etiology with pathologic examination. Transjugular liver biopsy was performed, and during the procedure the corrected sinusoidal pressure gradient was 10 mm Hg, indicating sinusoidal portal hypertension. Pathologic study of the sampled tissue revealed extramedullary hematopoiesis, ie, production of blood cells outside of the bone marrow, and no significant fibrosis on trichrome staining. The combination of portal hypertension with patent portal and hepatic veins and no cirrhosis on liver biopsy led to the diagnosis of noncirrhotic intrahepatic portal hypertension.
EXTRAMEDULLARY HEMATOPOIESIS

What are the organs most often affected by extramedullary hematopoiesis?

- Liver and spleen
- Kidney and adrenal glands
- Lungs and pleura
- Breasts

Patients with primary myelofibrosis can develop anemia and hepatosplenomegaly due to ineffective erythropoiesis and extramedullary hematopoiesis. In extramedullary hematopoiesis, hematopoietic stem cells escape from the bone marrow, travel through the bloodstream, and infiltrate other organs. In most reported cases, the organs affected were the liver and spleen, but extramedullary hematopoiesis can also affect the kidneys, adrenal glands, lymph nodes, lungs, pleura, skin, breasts, dura mater, ovaries, thymus, gastrointestinal tract, and central nervous system.

In the liver, hematopoietic cells obstruct the sinuses, resulting in portal hypertension. This can be managed by placing a transjugular portosystemic shunt to alleviate the symptoms, especially in patients presenting with recurrent variceal bleeding and refractory ascites.

FURTHER MANAGEMENT AND OUTCOME

On portal pressure measurement, the corrected sinusoidal gradient was a mean of 10 mm Hg, indicating sinusoidal portal hypertension. Portal hypertension has been described in patients with recurrent variceal bleeding. portal hypertension should be considered.

Secondary prophylaxis after esophageal variceal bleeding is important to improve outcomes and reduce mortality.

REFERENCES


infiltration from extramedullary hematopoiesis and fibrosis.

Therefore, the hematology care team decided to perform allogeneic stem cell transplant. On post-transplant day 12, the patient’s course was complicated by cytokine release syndrome, frequent diarrhea, hyperbilirubinemia with interval development of ascites, and stress cardiomyopathy. He was admitted to the intensive care unit for management of septic shock secondary to candidemia and Candida krusei peritonitis. Sepsis was further complicated by acute hypoxic respiratory failure, acute kidney injury, severe pulmonary edema, and episodes of pulseless electrical activity. After a conversation with the family, the patient was taken off life-support and pronounced dead.

TAKE-HOME POINTS

- All patients with gastrointestinal bleeding should be thoroughly evaluated.
- The Glasgow-Blatchford score is a useful tool to assess the need for hospitalization in patients with gastrointestinal bleeding.
- In a patient with esophageal varices and no history of liver disease, noncirrhotic causes of portal hypertension should be considered.
- Secondary prophylaxis after esophageal variceal bleeding is important to improve outcomes and reduce mortality.

DISCLOSURES

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


Address: Bhaumik Brahmbhatt, MD, MBBS, Division of Gastroenterology and Hepatology, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224; Brahmbhatt.Bhaumik@mayo.edu
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Diagnostic stewardship for urinary tract infection: A snapshot of the expert guidance

ABSTRACT

The urine culture, the cornerstone for laboratory diagnosis of urinary tract infection (UTI), is associated with a high frequency of false-positive and false-negative results, and its diagnostic threshold is debated. Urine culture takes 2 to 3 days to result, and antibiotics are often initiated while awaiting final culture readings. Further, asymptomatic bacteriuria—the presence of bacteria in urine in the absence of UTI symptoms—generally does not warrant treatment. The authors review current expert guidance on the use of urine culture, including approaches to ordering, processing, and reporting of urine cultures, with the goal of reducing unnecessary antibiotic use and misdiagnosis of UTI.

KEY POINTS

Appropriate ordering of urine culture involves documentation of proper (eg, clean-catch) collection, and testing only patients with documented signs and symptoms of UTI.

Examples of inappropriate practice are the inclusion of culture in standard order sets (emergency department, hospital admission, preoperative, altered mental status, and falls assessment), and ordering a urine culture in response to a change in urine characteristics.

The consensus panel guidance reemphasizes generally accepted principles: ie, that even cultures with uropathogen growth greater than 100,000 colony-forming units (CFU)/mL do not require treatment in patients without symptoms, and that true UTI may be associated with uropathogen growth less than 100,000 CFU/mL.
CLINICAL SETTING

The guidance relates to urine culture diagnostic stewardship in both outpatient and inpatient settings and specifically addresses the emergency department, inpatient, ambulatory, and long-term care practice settings.

INTENDED AUDIENCE

This review is intended for clinicians who diagnose and treat UTI, and for those who perform or report urine studies. These include general practitioners, emergency medicine physicians, infectious disease physicians, geriatricians, and laboratory medicine medical directors. This review is also intended for urologists, for whom the discussion of exceptions to the guidance in urological patient cohorts is particularly relevant.

WHO WROTE THE GUIDELINES?

The guidance includes 18 general statements written by an expert panel chosen from geographically diverse practice settings. The panel included 15 individuals with specialization in healthcare epidemiology and quality improvement, medical informatics and decision support, infectious diseases, clinical microbiology, antimicrobial stewardship, and urology, and with expertise in UTI management, diagnostic stewardship, clinical microbiology, and infection prevention. Thirteen of the 15 panelists were physicians, and 10 of those were infectious disease physicians. No clinical pathologists trained and board-certified in the general practice of laboratory medicine were on the panel.

The guidance panel reviewed relevant literature on diagnostic stewardship from electronic databases to generate a final list of clinical questions to guide the development of survey questions for use in the modified Delphi process. A modified Delphi approach using the RAND/UCLA Appropriateness Method was used to determine best practices in diagnostic stewardship relating to urine culture. Guidance panel experts ranked their recommendations on a Likert scale, and subsequently met to further discuss points of disagreement. A second round of review was performed, and the final body of guidance statements was generated.

WHAT ARE THE MAIN RECOMMENDATIONS?

Key points of the guidance are summarized in Table 1. The main recommendations focus on optimizing urine culture diagnostic stewardship and antibiotic stewardship. The recommendations are broadly classified by ordering, processing, and reporting of urine cultures, along with associated appropriate and inappropriate practices.

Ordering urine cultures

Appropriate practice for ordering a urine culture includes documentation of signs or symptoms (Table 2) of UTI in order to obtain a urine culture, to replace stand-alone urine culture orders with a “reflex-culture” protocol (ie, when urinalysis and urine culture are ordered together, the culture is per-

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**TABLE 1**

Ordering, processing, and reporting urine cultures: Key points of the expert guidance

<table>
<thead>
<tr>
<th>Stage</th>
<th>Appropriate practices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ordering</td>
<td>Require documentation of proper (eg, clean-catch) collection</td>
</tr>
<tr>
<td></td>
<td>Only test patients with documented signs and symptoms of urinary tract infection</td>
</tr>
<tr>
<td>Processing</td>
<td>Use a reflex-culture protocol when possible, so urine without inflammatory markers (ie, white blood cells) is not cultured, as this helps prevent microbial characterization and inappropriate treatment of asymptomatic bacteriuria</td>
</tr>
<tr>
<td></td>
<td>Do not routinely work up any isolates when more than 2 types of bacteria are recovered by culture</td>
</tr>
<tr>
<td>Reporting</td>
<td>Optimize laboratory reporting:</td>
</tr>
<tr>
<td></td>
<td>• Include a disclaimer that high colony counts can be present in asymptomatic bacteriuria</td>
</tr>
<tr>
<td></td>
<td>• “Nudge” prescribers not to treat asymptomatic bacteriuria or mixed growth</td>
</tr>
<tr>
<td></td>
<td>• Clearly define identified isolates as uropathogen or probable skin contaminant</td>
</tr>
<tr>
<td></td>
<td>• Use antibiotic cascade reporting, which does not report fluoroquinolones as first-line antibiotics</td>
</tr>
</tbody>
</table>

Based on information in reference 1.
formed only if urinalysis criteria are met) based on urinalysis results, and to automatically cancel repeat urine cultures within 5 days of a positive culture, if during the same hospital admission.

Inappropriate practice is the inclusion of culture in standard order sets (emergency department, hospital admission, preoperative, altered mental status, and falls assessment), or ordering urine cultures in response to a change of urine characteristics.

Processing urine cultures

Appropriate practice includes using an elevated white blood cell count on urine microscopy as a criterion for reflex culture when a urine culture is ordered by a clinician. Further, the collection method (eg, midstream clean catch, indwelling catheter, in-and-out straight catheterization) should be documented before processing cultures.

Inappropriate practice includes automatically obtaining reflex cultures based on urinalysis results in cases where a urine culture was not specifically requested.

Reporting urine cultures

Appropriate practice should include urine culture reports informing clinicians that counts greater than 100,000 colony-forming units (CFU)/mL may not represent true infection in the absence of symptoms, and reminding clinicians not to treat asymptomatic bacteriuria or mixed flora. Further, the culture report should differentiate between typical uropathogens and contaminants. Identification and susceptibility testing of isolates should not be routinely reported when more than 2 unique bacterial isolates are present in culture.

For example, our clinical laboratory provides the following comments along with results of cultures with growth of 3 or more organisms: Mixed microbiota. No further workup. Mixed microbiota can be due to urine contamination with skin bacteria at time of collection or presence of a long-term urinary catheter. If a new culture is needed, please consider re-education of the patient on proper midstream collection technique or straight catheterization for urine collection.

An additional appropriate practice, termed cascade reporting, is that antibiotics recommended by the Infectious Diseases Society of America (IDSA) should be preferentially reported if an organism is susceptible, and fluoroquinolone susceptibilities should be withheld unless there is resistance to preferred oral antibiotics.

Inappropriate practice would include suggesting not to treat if less than 100,000 CFU/mL of bacteria is recovered in culture, and withholding culture information and waiting for the prescriber to contact the clinical microbiology lab to release the results.

What is different from previous guidelines?

The goal of the current guidance is different from the IDSA/American Society for Microbiology (ASM) guidelines in that the focus is the best implementation of urine testing for the optimal treatment for UTI. It seeks to provide system-based guidance to influence diagnostic stewardship on a large scale.

The 2018 IDSA/ASM “Guide to utilization of the microbiology laboratory for diagnosis of infectious diseases,” which includes urine culture guidance, does not disagree with any of the guidance offered by Claey s et al, but it does offer additional points. The IDSA/ASM guide states that urine should be placed in boric acid (“gray-top”) preservative tubes if transported at room temperature. Alternatively, urine can be refrigerated after collection and during transport, or urine can be inoculated within 30 minutes of collection if not refrigerated and not preserved with boric acid. The IDSA/ASM guide also states that a reflex-culture protocol based on pyuria should be a locally approved policy.
The guidance by Claeyts et al does not address preanalytical considerations to prevent bacterial overgrowth during transport. Preanalytical practice effectiveness is systemically reviewed elsewhere. Additionally, it is beyond the scope of the guidance to inform as to how to create and implement a reflex-culture approach at a local level.

What is the Expected Clinical Impact?
The clinical impact of the guidance can be stratified into 2 main categories: reduction in unnecessary antibiotic use, which is good antimicrobial stewardship practice, and cost avoidance through decreased urine culture testing and inappropriate therapy, which is good diagnostic stewardship practice.

Reduction in Antibiotic Overuse
Antibiotic exposure is a known strong risk factor for antibiotic-resistant UTI and other infections. Antibiotic use is associated with increased resistance at the population level. Antibiotic exposure is also associated with increased risk for Clostridioides difficile colitis and vulvovaginal candidiasis due to disruption of the healthy microbiome. Thus, reducing the unnecessary use of antibiotics is a critical aspect of delaying and minimizing the emergence of resistance and reducing collateral pathology. The guidance by Claeyts et al provides actionable measures to reduce unnecessary antibiotic use during each stage of the urine culture process, ie, ordering, processing, and reporting.

Recommended measures are provided to avoid unnecessary detection and treatment of asymptomatic bacteriuria. In one study, about 70% of patients with asymptomatic bacteriuria were treated with antibiotics, despite the lack of benefit and the discordance with existing guidelines. The current recommendation is that the clinician be prompted to document signs and symptoms of infection when requesting a urine culture. The assignment of a symptom complex to a culture is designed to reduce testing in the absence of UTI symptoms and, thus, to subsequently reduce unnecessary treatment of asymptomatic bacteriuria. Further guidance designed to limit treatment of asymptomatic bacteriuria includes the recommendation that culture reports remind, or “nudge,” clinicians to not treat asymptomatic bacteriuria, and that even high colony counts (> 100,000 CFU/mL) may not represent true infection in the absence of signs and symptoms.

Further, the guidance provides a strategy to decrease the time and resources required to achieve a final laboratory result by screening with urinalysis before culture. A urine culture generally takes 2 or more days to return a result with antibiotic susceptibility test interpretations. However, if a reflex-culture protocol is employed as the guidance recommends, the time to final result would often be significantly reduced, and culture would be obviated. This practice could lead to a reduction in unnecessary antibiotic use.

Cost Reduction
In 2019, there were more than 36 million hospitalizations in the United States. It is estimated that about 27% of hospitalizations are associated with a urine culture. At about $10 per culture (based on the Medicare clinical laboratory fee schedule CPT code 87086), this translates to almost $100 million annually in the inpatient setting alone. These data, coupled with the large quantity of urine cultures obtained in the emergency, ambulatory, and long-term care settings, underscore the opportunity for cost avoidance associated with a reflex-culture protocol. Further cost savings would be associated with the reduction in treatment of asymptomatic bacteriuria.

Do other Societies Agree or Disagree?
The main tenet of nontreatment of asymptomatic bacteriuria described in the guidance by Claeyts et al is agreed upon by other major societies. IDSA, the American Urological Association (AUA), and the European Association of Urology (EAU) agree that asymptomatic bacteriuria should generally not be treated outside the context of pregnancy or prior to a subset of urologic interventions. The guidance is also corroborated by the American Board of Internal Medicine’s Choosing Wisely health-education campaign, which recommends not obtaining urine cultures in the absence of symptoms and not treating asymptomatic bacteriuria. The IDSA/ASM guide to laboratory testing recommends that a reflex-culture policy be established locally.

Existing guidelines vary as to the cutoff for uropathogen growth on standard culture. For example, the US Centers for Disease Control and Prevention requires at least 100,000 CFU/mL on urine culture to meet its criteria for diagnosis of UTI. Conversely, the IDSA/ASM guidelines have a more flexible threshold and include growth less than 100,000 CFU/mL.

Fluoroquinolones
Similar to the guidance by Claeyts et al, the guidelines from the IDSA, AUA, and EAU emphasize that fluoroquinolones should be avoided in uncomplicated...
cystitis. For example, the IDSA/European Society for Microbiology and Infectious Diseases guidelines note that fluoroquinolones are highly efficacious but have the propensity for significant off-target effects and should be reserved for uses other than acute cystitis, and should be considered an alternative rather than a first-line regimen. The EAU guidelines state that fluoroquinolones should not be used to treat uncomplicated cystitis, and the AUA guidelines note that the serious adverse effects associated with fluoroquinolones including tendonitis, tendon rupture, QT interval prolongation, and C difficile infection generally outweigh the benefits in uncomplicated UTI. Of note, the IDSA, AUA, and EAU recommendations do not necessarily apply to patients with complicated UTI (eg, aberrant anatomy, foreign body) or compromised immunity.

**HOW WILL THIS CHANGE DAILY PRACTICE?**

Most of the statements in the Claeys et al guidance are generally accepted good practice. However, the guidance also adds weight to the increasingly common practice of using a reflex-culture approach to prevent the culture of urine specimens in which no inflammation is present (ie, no white blood cells).

The guidance deemphasizes the traditional cutoff of 100,000 CFU/mL as a diagnostic criterion for UTI, which is consistent with IDSA’s previous deemphasis of this cutoff. The cutoff of 100,000 CFU/mL was developed based on a population with pyelonephritis and has since proven to be inadequate. The current guidance reemphasizes generally accepted principles, ie, that even cultures with uropathogen growth of greater than 100,000 CFU/mL do not require treatment in patients without symptoms, and that true UTI may be associated with uropathogen growth of less than 100,000 CFU/mL.

The framework provided for the stewardship of fluoroquinolone use may reduce prescription of this drug class. In 2016, the US Food and Drug Administration added a boxed warning to fluoroquinolones due to their association with tendonitis and tendon rupture. However, there is evidence that the boxed warning has had little effect on prescription patterns of fluoroquinolones for uncomplicated UTI, and little effect on the high rates of fluoroquinolone resistance. We believe that one of the greatest impacts of the current guidance could be in reversing these trends in daily practice by encouraging laboratories to avoid reporting fluoroquinolones as routine, first-line antibiotics for UTI.

**SPECIAL CONSIDERATIONS: WHEN WOULD THE GUIDANCE NOT APPLY?**

The guidance by Claeys et al does not apply to a number of clinical scenarios. Children, pregnant patients, renal transplant recipients, and severely immunocompromised patients were specifically excluded. However, screening for and treatment of asymptomatic bacteriuria is indicated in pregnancy, and the benefits of treatment may outweigh the risks.

**Considerations for patients with urologic conditions**

Screening for and treating asymptomatic bacteriuria is indicated prior to urologic surgical procedures that involve manipulation of the upper urinary tract or that cause mucosal trauma, and the benefits of treatment may outweigh the risks.

For patients who have a urinary catheter or who require intermittent catheterization, and for patients with neurogenic lower urinary tract dysfunction or bowel interposition in the urinary tract (eg, ileal conduit, neobladder), the utility of a reflex-culture approach has not been empirically established. Further, the IDSA guidance for catheter-associated UTI states that pyuria should not be used to differentiate between catheter-associated UTI and asymptomatic bacteriuria. UTI symptoms in these patients may be subtle and variable and can include increased spasticity, autonomic dysreflexia, and a sense of unease. Symptoms must be considered in the context of the physical examination and urine studies, especially given that the urine of these patients is generally chronically colonized with bacteria.

**Other patients under urologic care**

Urine cultures with complete antimicrobial susceptibility profiles may be required in urologic patients regardless of urinalysis results. Such circumstances may include contexts prior to or following urologic procedures, as well as cases of suspected prostatitis, epididymoorchitis, fistulae, or recurrent UTI.

The clinical appropriateness of performing cultures for urology patients should be at the discretion of the supervising urologist or urology practitioner, and stand-alone cultures should not be reverted to reflex culture in urologic patients without prior discussion with the urology team. Similarly, a culture within 5 days of another culture should not be cancelled in a urologic patient before a discussion with the team requesting the culture. Such a culture may be necessary in the context of refractory symptoms, to assess the possibility of recurrent infection or continued contamination. In urologic patients, species-level
DIAGNOSTIC STEWARDSHIP FOR URINARY TRACT INFECTION

identification and antimicrobial susceptibility testing of all isolates grown in urine may be necessary before endourologic procedures, even in cases of more than 2 organisms, as polymicrobial interactions can play a role in urologic infection, and so this should be left to the discretion of the urology team.

In select cases of UTI, fluoroquinolone use is appropriate. For example, the EAU guidance states that fluoroquinolones are an effective oral regimen for uncomplicated pyelonephritis. Further, fluoroquinolones often exhibit excellent penetration of the prostate and thus are associated with significant benefit, particularly if there is suspicion for prostatitis, or in patients with febrile or recurrent UTI with prostatic involvement. Thus, fluoroquinolone susceptibilities must be reported in such cases.

Other considerations
In daily practice, a balance must be achieved between diagnostic stewardship and clinical practicality. For example, the guidance places additional ordering demands on the clinician, and there should be a method in place to rapidly designate an exception to the laboratory that processes the specimens. A series of “hard stops” for the clinician when placing orders may lead to inappropriate care when such hard stops are not applicable, as in the exceptional circumstances discussed above.

In early urosepsis, a subset of patients may not be able to describe symptoms, but changes in behavior or mental status may be witnessed or reported. Even in the absence of a catheter, the completion of a urine culture with antimicrobial susceptibility testing should be based on clinical discretion.

In some patients with catheters, UTI may present with fever without septic shock, particularly in those unable to communicate, and thus urine culture should be processed at the discretion of the requesting clinician.

Recently, machine learning has been shown to improve antimicrobial stewardship. Specifically, the use of machine learning-generated antibiotic recommendations was associated with minimization of antimicrobial resistance. As these models mature and undergo further validation, their integration within antimicrobial and diagnostic stewardship is poised to lead to further reduction in antibiotic overuse, antimicrobial resistance, and financial burden to patients and the healthcare systems.

REFERENCES


DISCLOSURES

Dr. Rhoads reports work as advisor or review panel participant with BD Diagnostics, Luminex, Roche Diagnostics, Tails Biomedical, and Thermo Fisher Scientific; teaching and speaking with Cepheid; and research (principal investigator) with bioMerieux, Cepheid, Cleveland Diagnostics, Hologic, Luminex, Qiagen, Specific Diagnostics, Thermo Fisher Scientific, and Vela Diagnostics. Dr. Werneburg reports no relevant financial relationships which, in the context of his contributions, could be perceived as a potential conflict of interest.

Cardiovascular Update for the Primary Care Provider

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A 22-year-old woman was brought to the emergency department after her parents had noted she had been behaving more and more strangely for the past 2 to 3 weeks, being irritable and secluding herself in her room. They had called emergency medical services after noticing that 4 amitriptyline tablets were missing from her father’s prescription bottle and after hearing her make nonsensical statements. The patient had recently lost a close friend to drug overdose, and her parents had attributed her behavior changes to this stressor.

The patient had also been complaining of gradual-onset and progressive headache and neck and back pain for 3 weeks. She described it as a constant, aching sensation of moderate intensity that over the past week had begun to wake her from sleep. She denied any sensory or motor disturbances, changes in vision, fever, trauma, or sick contacts. She had been taking acetaminophen, naproxen, and tizanidine.

INITIAL EXAMINATION

Her blood pressure was 111/55 mm Hg, pulse rate 55 beats per minute, temperature 97.4°F (36.3°C), respiratory rate 16 breaths per minute, and oxygen saturation 100% by pulse oximetry on room air. She was alert but uncooperative and answered questions inappropriately.

Her ears, eyes, nose, and throat were unremarkable. Breath sounds were clear throughout both lungs. Her heart rate and rhythm were normal with no murmurs, rubs, or gallops. Her abdomen was soft and nontender. Her cranial nerve examination was normal. She had normal strength (5 on a scale of 5) and intact sensation in all extremities. Her neck had full range of motion, but she said it hurt, worst during flexion.

Results of a comprehensive metabolic panel including liver function tests, complete blood cell count with differential, ethanol level, acetaminophen level, urine beta-human chorionic gonadotropin, urinalysis, and urine toxicology were normal, but her urine was positive for tetrahydrocannabinol.

Magnetic resonance imaging (MRI) of the head with and without contrast was obtained and revealed a 1.2-cm nonhemorrhagic ring-enhancing lesion within the insular pole of the left frontal lobe with...
adjacent subcortical vasogenic edema, without restricted diffusion (Figure 1).

■ RING-ENHANCING BRAIN LESIONS

Which of the following brain tumors typically presents with ring-enhancing lesions on MRI and therefore would be the most likely in our patient, if she has a brain tumor?

- Low-grade glioma
- Meningioma
- Germ cell tumors
- Glioblastoma

Ring-enhancing lesions have a broad differential diagnosis that includes malignancy, demyelinating lesions, infection, and subacute infarction. Certain characteristics can help distinguish the likely etiology of central nervous system lesions. For example, pyogenic brain abscesses typically present with restricted diffusion while malignant lesions typically do not.1

Among the choices given, this patient’s MRI characteristics would be most consistent with glioblastoma. Glioblastoma typically presents with ring enhancement due to central necrosis, without restricted diffusion.2 However, glioblastoma also usually has thick, irregular borders, which our patient’s MRI did not show.

■ CASE CONTINUED: WORKUP FOR FEVER AND INFECTIOUS DISEASES

The neurosurgery department was consulted for a possible brain tumor. However, on her fourth day in the hospital, the patient became febrile for the first time during the hospitalization, and her temperature was 102.6°F (39.2°C).

We elicited further history from her parents. She had no fever or febrile symptoms before admission. She had grown up in the Ohio River valley and lived with her father, who was divorced from her mother. She had no pets at home and no recent infections or dental manipulations. She drank socially on weekends and consumed marijuana “gummies” on rare occasions. She had no history of recent travel and had never traveled outside of the United States. Her father had recently been released after a year in prison.

Despite the indeterminate MRI findings, her fever put cerebral abscess higher on the differential diagnosis, prompting her physicians to begin empiric antibiotic therapy and perform a lumbar puncture.

■ CHOOSING AN ANTIBIOTIC REGIMEN

Which of the following is the most appropriate empiric regimen for suspected cerebral abscess?

- Vancomycin and piperacillin-tazobactam
- Cefepime and metronidazole
- Ceftriaxone and metronidazole
- Vancomycin and metronidazole

Brain abscess is often the result of seeding from oral, otic, or sinus sources, making streptococcal species the most common isolates.3 Empiric coverage is based on the typical flora from these locations, including streptococcal species, gram-negative organisms, and anaerobic pathogens.

Antibiotics that cover methicillin-resistant Staphylococcus aureus, such as vancomycin, could be considered in a postoperative setting or if hematogenous seeding from bacteremia is suspected.

Pseudomonas infection is uncommon except after surgery or in head trauma.4 Thus, it is not necessary to empirically cover them, for example, with piperacillin-tazobactam or cefepime.

The best regimen of those presented above is ceftriaxone and metronidazole, which provides adequate coverage of streptococcal species and anaerobes. However, we chose to add vancomycin in this patient’s case in addition to ceftriaxone and metronidazole due to the unclear etiology of the possible abscess and the severity of the patient’s illness.

■ CASE CONTINUED: CEREBROSPINAL FLUID STUDIES

Testing for human immunodeficiency virus infection was negative.

On hospital day 5, lumbar puncture with cerebrospinal fluid analysis yielded the following values:

- Opening pressure 480 mm H2O (reference range 50–200)
- White blood cell (WBC) count 343 × 106/L (reference range 0–5), with 71% lymphocytes and 27% neutrophils
- Glucose level 26 mg/dL (reference range 40–70 mg/dL)
- Protein 286 mg/dL (reference range 15–45 mg/dL).

■ INTERPRETING THE CEREBROSPINAL FLUID FINDINGS

Which of the following cerebrospinal fluid findings would most strongly indicate bacterial meningitis?
WBC count 800 × 10⁶/L with neutrophilic predominance, glucose 21 mg/dL, protein 110 mg/dL

WBC count 200 × 10⁶/L with lymphocytic predominance, glucose 48 mg/dL, protein 90 mg/dL

WBC count 900 × 10⁶/L with lymphocytic predominance, glucose 34 mg/dL, protein 180 mg/dL

WBC count 800 × 10⁶/L with lymphocytic predominance, glucose 19 mg/dL, protein 160 mg/dL

Analyzing the cerebrospinal fluid is a key part of evaluating suspected meningitis. Bacterial meningitis typically manifests with very elevated WBC counts with neutrophilic predominance, low glucose, elevated protein, and elevated opening pressure. Therefore, the first answer choice above is correct. In contrast, viral infections typically manifest with moderately elevated WBC counts with lymphocytic predominance, elevated protein, normal glucose, and normal or modestly elevated opening pressure.

Our patient’s results were not typical of either of these presentations. While bacterial meningitis should still be considered, the cerebrospinal fluid findings and subacute presentation were more consistent with atypical infection, perhaps with a fungus or *Mycobacterium* species.

**CASE CONTINUED: HER CONDITION WORSENS**

A number of tests were ordered and yielded negative results. These included blood cultures, cerebrospinal fluid cultures, cerebrospinal fluid cytology, leukemia panel, lymphoma panel, potassium hydroxide smear, Gram stain, *Toxoplasma* polymerase chain reaction testing, meningitis polymerase chain reaction panel (including *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, cytomegalovirus, enterovirus, herpes simplex virus 1, herpes simplex virus 2, human herpesvirus 6, human parechovirus, varicella zoster virus, and *Cryoptococcus neoformans/gattii*), antineutrophil cytoplasmic antibody panel, Lyme antibody, 1,3 beta-glucan (a test for fungal cell wall elements), and a screening test for syphilis.

Although the patient had no pulmonary symptoms or signs, results of chest radiography to uncover supporting evidence of infection or malignancy were interpreted as normal (Figure 2).

On hospital day 6, the patient began reporting a worsening headache associated with blurred vision. She continued to exhibit irritability, intermittently refusing testing and nursing interventions. Her confusion and somnolence worsened. No additional fever was recorded. Cardiopulmonary examinations and peripheral neurologic examinations were normal. The development of disconjugate gaze and esotropia indicated left abducens nerve palsy. Optic disc margins were crisp. Repeat lumbar puncture again demonstrated elevated opening pressure, lymphocytosis, and elevated protein.

Acetazolamide was given to treat the increased intracranial pressure. Her serum sodium began trending downwards at this time and would remain at approximately 130 mg/dL.

Repeat MRI on hospital day 8 revealed several new foci of restricted diffusion compatible with acute infarcts. She underwent transesophageal echocardiography and computed tomography of the chest, abdomen, and pelvis, which showed no signs of pulmonary, cardiac, lymphatic, or skeletal disease. Skin examinations were negative for rashes, nodules, or lesions. Testing for histoplasmosis (by serum antibody testing and antigen enzyme immunoassay), blastomycosis, *Coccidioides*, and antiphospholipid antibody panel were negative. Cerebrospinal fluid tests for *Mycobacterium tuberculosis* by polymerase chain reaction, acid-fast stain, and acid-fast culture were negative. However, a blood test for *M tuberculosis* (T-SPOT) returned positive on hospital day 10.

Before this blood test result was available, her condition worsened on hospital day 10 with lethargy and near-total loss of vision in her left eye. Repeat computed tomographic angiography of the head and neck with transcranial Doppler revealed narrowing in both middle cerebral arteries with mild spasm in the left anterior cerebral artery. At this point, the patient was started on dexamethasone and was transferred to a tertiary care facility.

Figure 2. Chest radiography showed no airspace abnormalities or hilar abnormalities.
CONFUSION IN A 22-YEAR-OLD WOMAN

Approximately 2 days after transfer, her clinical condition deteriorated further. She was started on levetiracetam for suspected seizures and was intubated for her inability to protect her airway. She was treated broadly with amphotericin, rifampin, isoniazid, pyrazinamide, and ethambutol in addition to ceftriaxone and metronidazole. An external ventricular drain was placed to decrease her intracranial pressure.

A third MRI showed worsening basilar leptomeningeal enhancement with a persistent peripherally enhancing lesion (Figure 3). Another lumbar puncture was done. Cerebrospinal fluid antigen and antibody testing for histoplasmosis were negative. Repeat acid-fast stain and a nucleic acid amplification test for M tuberculosis (Xpert MTB/RIF assay) were negative. Metagenomic next-generation sequencing detected M tuberculosis complex, but below threshold levels for a confirmed positive result. DNA probe of cerebrospinal fluid culture ultimately confirmed the diagnosis of tuberculous meningitis approximately 2 weeks after the sample was obtained.

The patient’s intracranial pressure was controlled with barbiturate coma, hypothermia, and paralytics. Despite these interventions, her clinical status did not improve due to extensive cerebral infarcts (Figure 4). She was subsequently transferred to hospice care and died approximately 5 weeks after her initial presentation.

Figure 3. Two weeks later, with the patient’s condition continuing to worsen, magnetic resonance imaging showed bulky leptomeningeal enhancement (arrows), most prominent at the basal surface of the cerebrum, with a peripherally enhancing 1.2-cm lesion at the left sylvian fissure (arrowhead).

TUBERCULOUS MENINGITIS AND VASCULOPATHY

Tuberculosis is often called “the Great Imitator” due to its ability to mimic the clinical presentation of many diseases. In the United States, the prevalence of tuberculosis is low, and extrapulmonary tuberculosis occurs primarily in adults with reactivation disease. Cases of tuberculous meningitis are increasingly rare in the United States, with only 74 cases reported in 2018. However, when it does occur, it is devastating. Short-term mortality rates range from 20% to 69% with standard antituberculosis therapy, and the disease is fatal without treatment. It is estimated that more than half of those affected by tuberculous meningitis die or have permanent disability despite antituberculosis treatment. The morbidity and mortality underscore the importance of early recognition.

Clinically, tuberculous meningitis can be very difficult to diagnose. A history of an immunocompromised state such as human immunodeficiency virus infection or travel to endemic areas is often present. Among patients with tuberculosis, those with human immunodeficiency virus infection have a fivefold higher likelihood of central nervous system dissemination compared with those without. However, as our patient’s case demonstrates, risk factors are not always present. The patient’s father’s incarceration
presents a clue, but it is unclear if that was truly the source of her infection. Presentation with neurologic manifestations without prior history of tuberculosis is relatively uncommon, representing as few as 10% of cases in one series.⁸

**Clues to tuberculous meningitis**

Some clinical features can point to tuberculous meningitis. Many patients present with a subacute febrile illness that includes malaise and headache. Over a period of weeks to months, the disease progresses and causes meningismus, worsening headache, confusion, and abnormal behavior or personality changes, sometimes accompanied by cranial nerve abnormalities.⁹

Our patient’s parents believed that her behavioral or personality changes were related to suffering the loss of a close friend. This history, her uncooperative behavior, and our suspicion of substance abuse were red herrings. Further, she had no fever, leukocytosis, or other overt infectious symptoms. Her neck and back pain were attributed to other possible causes, contributing to a delay in diagnosis.

**Prodromal, meningitic, and paralytic phases**

Untreated, tuberculous meningitis will continue to progress and cause stupor, coma, seizures, and often death. Based on this progression of symptoms, tuberculous meningitis is often said to have 3 phases: prodromal, meningitic, and paralytic. These 3 phases parallel the 3 stages of severity of the illness based on mental status and neurologic signs: fully conscious with no focal defects; conscious but with inattention, confusion, lethargy, and focal signs; and stuporous or comatose, with multiple cranial nerve palsies or complete hemiparesis or paralysis.⁹ Even when treated appropriately, tuberculous meningitis often paradoxically deteriorates before it improves, resembling a reaction like the immune reconstitution syndrome.¹⁰

**Associated vasculitis and stroke**

Vasculitis leading to stroke can also occur, usually during the paralytic phase, and accompanies 15% to 57% of cases of tuberculous meningitis.¹¹ In such cases, leptomeningeal inflammation and exudate surround the arteries as they traverse the area. The artery most commonly affected by stenosis due to this inflammation is the middle cerebral artery, causing downstream infarcts at perforators and terminal cortical branches. The area most commonly involved is the basal ganglia, particularly the area supplied by the lateral lenticulostriate arteries.¹² Branches from the anterior cerebral artery are also commonly involved. This distribution of vasospasm is consistent with the

*Figure 4*. One month after presentation, shortly before the patient died, magnetic resonance imaging showed multifocal areas of patchy parenchymal restricted diffusion that were not associated with localized pathologic enhancement. These features raised suspicion for acute infarction along the genu and body of the corpus callosum, left corona radiata and corpus striatum, juxta-cortical left frontal operculum, left temporal stem and anterior temporal white matter, right anterior temporal white matter, anterior commissure and fornix columns, right posterior limb internal capsule, right hippocampal body, left cingulate gyrus, and left parietal convexity.
distribution seen in our patient, involving bilateral middle cerebral artery stenosis and left anterior cerebral artery stenosis. Vasculopathy can be a large contributor to the severity of illness, with cerebral infarction an independent predictor of death in tuberculous meningitis.13

Our patient’s diffuse infarctions sealed her fate. Her infarctions involved the left precентрal and post-central gyri, left superior and inferior parietal lobules, and dorsal aspect of the left superior middle frontal gyri, suggesting extensive disease in the left middle cerebral artery. In addition, she had infarcts at the lentiform nucleus, left caudate head, genu body and splenium of the corpus callosum, posterior limb of each internal capsule and underlying cerebral peduncles, the basis pontis, the right precentral and postcentral gyri, right opercular cortex, right insular cortex, left precuneus, and the subcortical white matter of both temporal poles.

**SUSPECTING AND DIAGNOSING TUBERCULOUS MENINGITIS**

Subacute meningitis with middle cerebral artery distribution vasospasm and basilar leptomeningeal enhancement should raise suspicion for possible tuberculous meningitis.14 However, these often only present in later stages of the disease. Furthermore, they are not specific to tuberculous meningitis. Viral and fungal infections can have a similar clinical presentation, emphasizing the importance of early and accurate diagnostic testing. Testing for histoplasmosis was especially pertinent for this patient, who lived in the Ohio River valley. Evaluation for histoplasmosis optimally includes urinary antigen testing, which is more sensitive than serum antigen or antibody testing.15 Cerebrospinal fluid testing can also be considered, with less robust data suggesting sensitivity around 85% to 98%.15,16

Traditional diagnostic tests for tuberculosis such as acid-fast bacillus smear and culture have low sensitivity for tuberculous meningitis. Thwaites et al17 reported sensitivities of 52% for smear and 64% for culture. Culture is also less clinically useful, as M tuberculosis can take weeks to grow on culture. Our patient had 2 sets of negative acid-fast bacillus smears and cultures, both obtained in the third phase of tuberculous meningitis. One was obtained before starting antibiotics directed at M tuberculosis, which should have made for optimal test results.

The poor sensitivity and the delay in diagnostic results can be mitigated with ancillary molecular diagnostic testing. Nucleic acid amplification can provide rapid results, if it is available. The most utilized is polymerase chain reaction, offering a sensitivity around 82%.18 While it is not approved by the US Food and Drug Administration for testing cerebrospinal fluid samples, it can improve diagnostic yield compared with traditional methods and provides results much more rapidly than culture.

**CASE CONCLUSION, LESSONS LEARNED**

This patient’s case involved a unique scenario of negative cerebrospinal fluid polymerase chain reaction testing but still high clinical suspicion for tuberculous meningitis, as well as positive blood testing. Factors such as a low-volume cerebrospinal fluid sample, testing early in the course of disease, and low pathogen burden can increase the likelihood of false-negative results. However, none of these were apparently involved in this patient’s case.

When further testing is indicated due to high clinical suspicion and negative results on polymerase chain reaction testing, other molecular diagnostic testing options include metagenomic next-generation DNA sequencing, DNA-probe testing, and the Xpert MTB/RIF assay or Xpert Ultra MTB/RIF assay. In such scenarios, next-generation DNA sequencing can offer an improved diagnostic sensitivity compared with polymerase chain reaction testing, acid-fast bacillus smear, and culture.19 In our patient’s case, it was the first test to detect M tuberculosis in the cerebrospinal fluid, which was later confirmed with DNA-probe testing of the culture weeks later. Clinically, the next-generation DNA sequencing was able to help provide earlier guidance about the need and direction of further testing.

Ultimately, patients without classic risk factors or pulmonary disease pose a significant challenge for clinicians to diagnose tuberculous meningitis. A clinical presentation involving subacute meningitis with cerebrospinal fluid studies indicating increased intracranial pressure and lymphocytic pleocytosis with low glucose should raise suspicion for tuberculous meningitis, but these signs are nonspecific.20 Depending on disease severity and progression, MRI findings indicating vasculopathy or meningeal enhancement with predilection of the basal cisterns may also be present.

Traditional acid-fast bacilli smear and culture have poor sensitivity that can be improved with
molecular diagnostic testing. As demonstrated in this patient’s case, the tuberculosis blood test and other serologic tests can help augment cerebrospinal fluid studies, as the latter can be less sensitive. In addition, when high clinical suspicion for tuberculous meningitis is present, metagenomic next-generation DNA sequencing and DNA-probe testing should be considered, as they improve overall sensitivity of cerebrospinal fluid results.

Finally, our patient’s case emphasizes the importance of early antimicrobial therapy against M. tuberculosis, in view of the disease’s high rates of morbidity and mortality.

■ DISCLOSURES

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

■ REFERENCES


■ TEACHING POINTS

- Tuberculous meningitis should be considered in the differential diagnosis of subacute meningitis and is associated with a poor prognosis.
- Vasculopathy leading to cerebral infarction is common with tuberculous meningitis.
- Diagnostic confirmation can be difficult in tuberculous meningitis due to delay in culture results. Thus, molecular diagnostics should be considered to help confirm the diagnosis early.
- Empirc therapy should be started early when tuberculous meningitis is suspected, in view of its high mortality rate when left untreated.

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Address: Brian Elliott, MD, Department of Internal Medicine, Boonshoft School of Medicine, Wright State University, 128 E Apple Street, Weber CHE Building, Floor 2, Dayton, OH 45409; brian.elliott@wright.edu

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The role of GLP-1 receptor agonists in managing type 2 diabetes

In the August 2022 issue, an error appeared in Nachawi N, Rao PP, Makin V. The role of GLP-1 receptor agonists in managing type 2 diabetes. Cleve Clin J Med 2022; 89(8):457–464. doi:10.3949/ccjm.89a.21110. In Table 1, the frequency of administration of tirzepatide is once weekly, not once daily. Additional available tirzepatide doses have also been added. The corrected Table 1 appears below:

**TABLE 1**
Glucagon-like peptide-1 receptor agonists approved for use in the United States

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available doses</th>
<th>Frequency and route</th>
<th>Dose approved for weight management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>5 μg, 10 μg</td>
<td>Twice daily subcutaneously</td>
<td>Not approved</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>0.6 mg, 1.2 mg, 1.8 mg</td>
<td>Once daily subcutaneously</td>
<td>0.6 mg once daily for 1 week, increase by 0.6 mg daily at weekly intervals to a target dose of 3 mg once daily</td>
</tr>
<tr>
<td>Exenatide extended-release</td>
<td>2 mg</td>
<td>Once weekly subcutaneously</td>
<td>Not approved</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>0.75 mg, 1.5 mg, 3 mg, 4.5 mg</td>
<td>Once weekly subcutaneously</td>
<td>Not approved</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>0.25 mg, 0.5 mg, 1 mg, 2 mg</td>
<td>Once weekly</td>
<td>Titrate every 4 weeks: 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2.4 mg once weekly</td>
</tr>
<tr>
<td>Semaglutide, oral</td>
<td>3 mg, 7 mg, 14 mg</td>
<td>Once daily by mouth</td>
<td>Not approved</td>
</tr>
<tr>
<td>Liraglutide-insulin degludec</td>
<td>0.36 mg-10 U, 0.5 mg-16 U</td>
<td>Once daily subcutaneously</td>
<td>Not approved</td>
</tr>
<tr>
<td>Lixisenatide-insulin glargine</td>
<td>5 μg-15 U, 10 μg-30 U</td>
<td>Once daily subcutaneously</td>
<td>Not approved</td>
</tr>
<tr>
<td>Tirzepatide</td>
<td>2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg</td>
<td>Once weekly subcutaneously</td>
<td>Not approved</td>
</tr>
</tbody>
</table>

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